VETERINARY PHARMACOLOGY, TOXICOLOGY & THERAPEUTICS

Pharmacology Notes

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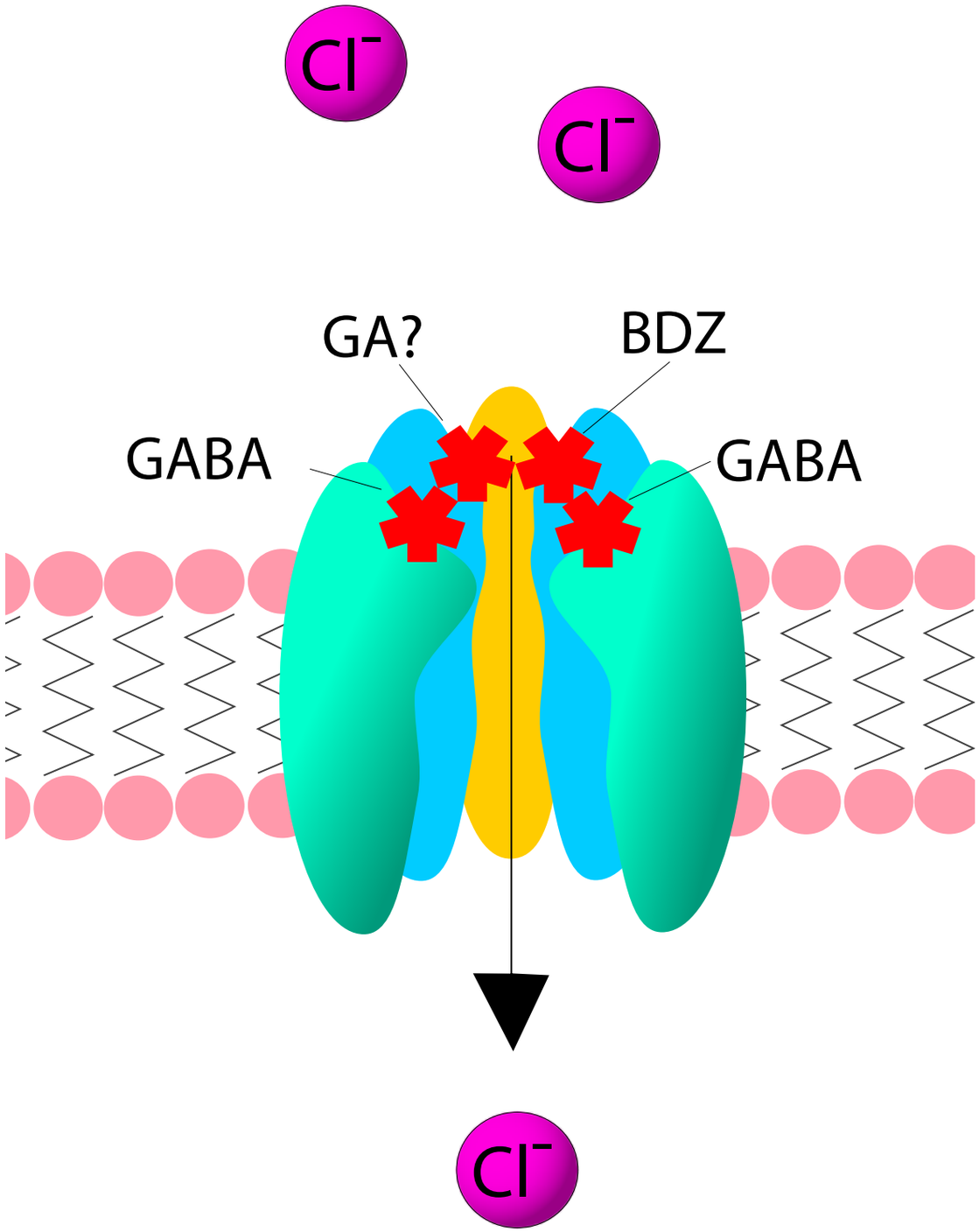
Chapter 1

Basics

This part covers the molecular basis of drug action, drug receptor interactions and basic toxicology.



The $GABA_A$ receptor, the main inhibitory mechanism in the CNS.

Basic stuff

Basic stuff

☑ Drugs can have many names - learn the approved name.

Definitions

Pharmacology = the study of drugs - from φαρμακον - drug, medicine or poison!

Drug = any substance which can affect a biological system. The original definition was “dried herb”; in the USA, “drugs” are what drug addicts use, anything else tends to be a “pharmacologic agent”.

Pharmacodynamics = what the drug does to the animal

Pharmacokinetics = what the animal does to the drug, or strictly speaking, the movement of drugs within the body.

Pharmacy = the science of the preparation of drugs

Therapeutics = the treatment of disease. This is more of an art than a science - there is usually no single right way to treat disease in an individual animal (despite the impression you may get from some people!). There are usually plenty of wrong ways though; a knowledge of pharmacology can avoid most of these.

Toxicology = the study of poisons

Pharmacopoeia = an official list of drug preparations, principally concerned with purity standards. You may see a drug name followed by the letters BP or USP indicating that it was made to the standards specified in the British Pharmacopoeia or the United States Pharmacopoeia.

None of these definitions is exact - you may well see different definitions in some books.

Drug names

This is a constant source of confusion since every drug may have several different names.

You will be expected to know the drug by its approved name but you may come across the other names in scientific papers or advertising literature. Some older drugs have different approved names in different countries; eg, the drug known as pethidine in most countries is called meperidine in the USA. This can lead to confusion when reading textbooks! New Zealand usually uses BANs, although Britain is supposed to have changed over to INNs. The change in the UK caused several

deaths when people were given ephedrine instead of epinephrine so they have gone back to calling it adrenaline!

Drugs take a long time and a lot of money to develop and win government approval. The drug companies thus patent new drugs which gives them exclusive rights to sell the drugs for a specific length of time (15 - 20 years). They advertise the drug under their trade name in the hope that vets will continue to think of the drug by the trade name after the patent expires and other firms are allowed to make and sell the drug (under different trade names). Drugs which have been around for a while and for which there is a big market will be made by several different companies and have several different trade names, eg xylazine is sold as "Bomazine", "Reazine", "Thiazine" and "Xylase" as well as the original preparation "Rompun". (Trade names vary from country to country, these are just the ones in NZ.) On the other hand, old and cheap drugs (on which there is very little profit to be made) are usually sold by their approved names eg, morphine chloride (BP). The (BP) means that it has been made to standards specified in the British Pharmacopoeia. You may also see USP, USNF (national formulary) and Eur P.

The approved name of a drug can be found if you know any of the other names by looking in the Merck Index (in the library). (This is a different book from the Merck (Veterinary) Manual.)

Approved names are by convention in lower case: trade names are capitalised.

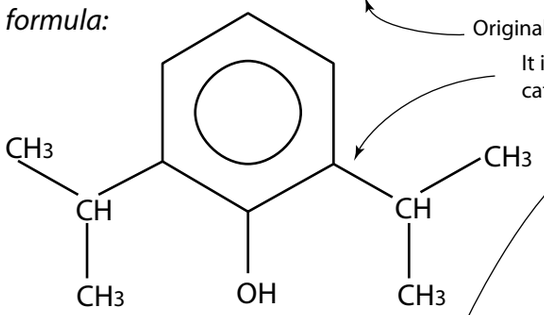
Learn the approved name!

DIAGRAM 1.1.1 Drug names

drug company number: **ICI 35 368**

Originally developed by ICI (now AstraZeneca).

formula:



It is sometimes useful to know a drug's structure: cats can have problems metabolising phenols.

There are two different international classifications for chemical names, IUPAC &CA

Chemical Abstracts Service Registry No. A unique no. applied by the American Chemical Society for use in their chemical database. Not much use to pharmacologists.

In the past drugs were approved by several different bodies, so older drugs may have different British Approved Names or United States Adopted Names. They are all supposed to be approved by the WHO now and have International Non-proprietary Names although these can be provisional (pINN) or recommended (rINN).

chemical name: **2,6 di-isopropylphenol**
2,6 bis(1 methylethyl)phenol

CAS number: **2078-54-8**

approved name: **propofol**

trade names:

veterinary: **"Rapinovet"** (Schering-Plough)
"Aquafol" (Parnell)

human: **"Diprivan"** (AstraZeneca)
"Propofol Inj" (Baxter)
"Propofol Inj" (Abbott)
"Recofol" (Pacific)

Propofol (the active ingredient) is formulated in a suitable vehicle for injection into animals. The original vehicle was a soya bean lipid emulsion. It was then sealed into vials and has different labels stuck on it for human or veterinary use (Diprivan or Rapinovet). Since the patent ran out, other companies are now making and selling propofol in different formulations, eg Aquafol is an aqueous solution.

Learn the approved name!

Therapeutic principles

All drugs have unwanted effects - you must balance the benefits against the dangers before you give any drugs to animals. In some cases, for instance anaesthetics given to allow surgery, the benefits are obvious: this is not always the case. There are no figures for veterinary medicine, but in the USA, medication errors kill 98,000 people a year - more than road traffic accidents.

In general, it is best to give the minimal amount of drug necessary to allow the animal to heal itself.

Outline of decision making process

- What is the diagnosis? As specific as possible.
- What organ systems are affected? Symptomatic treatment may be necessary.
- Is drug treatment necessary?
- What do you want the drug to do? This must be precise.
- What drug does this?
- What else may the drug do? Do you need to give other drugs to control these side effects? Will it harm the animal's owner or the environment?
- How much drug will you give and for how long?
- What route of administration will you use?
- How will you monitor the drug's effectiveness?
- What will you do if the drug doesn't work?
- Is the drug you chose available (and legal)?
- What are the witholding times? (in food animals)
- Is it expensive and is there something cheaper that works as well?

- Are the benefits of using the drug likely to be greater than the risks?

There will never be a single right answer to all these questions, but by the time you finish your course you must be able to decide rationally which drugs to use in any particular animal

Drug development

The process of drug development has changed a lot over the years and is now highly (over?) regulated - see the Law chapter for details. Every statement about the regulation of veterinary medicines in NZ has to contain caveats, but here is a very generalised overview.

All medicines, both human and veterinary, go through the same process, but most modern veterinary drugs are rejects from the human medicine process. The basic requirements are that a drug is effective and safe. The process of showing this usually starts off at the molecular level with binding studies, although there is a trend to try to predict these using computed algorhythms. From there, the drug progesses to cellular responses, then physiological responses in vitro then in vivo in laboratory animals. Some of these lab animals may be target animals as far as we are concerned, as dogs, cats and (rarely) sheep and pigs are sometimes used. This whole process is sometimes called the preclinical phase. Phase 1 is testing in healthy volunteers (people) or conscripts (animals)to study safety and pharmacokinetics. Phase 2 is testing in patients with the disease to be treated to establish efficacy and dose. Phase 3 is similar but much larger multi-centre studies of the final formulation. If it still looks good, the drug can then be sold and Phase 4 covers post-marketing surveillance for rare problems. If a drug company has spent lots of money testing a medicine for human use and it fails for some reason, there is a big incentive to develop it for veterinary use and recover at least some of the cost. The only area where veterinary medicines are ahead is anthelmintics.

Drug action

Drug action

- ☑ Most drugs act at receptors
- ☑ There are four families of receptors: ionotropic, metabotropic, tyrosine kinase and nuclear
- ☑ Drugs can bind to receptors to produce a full response (full agonists), a partial response (partial agonists), no response (antagonists) or a negative response (inverse agonists)
- ☑ Drugs which occupy a receptor stop other drugs from binding
- ☑ Drugs can also act at ion channels, enzymes,

To produce an effect, drugs must get from the site of administration to the site of action (pharmacokinetics) where they may produce an effect in a number of ways. The molecular targets for drugs are:

- receptors
- ion channels
- enzymes
- carrier molecules
- some drugs also have a non specific effect.

Anything which binds to a recognition site is sometimes called a ligand. (A ligand may not produce an effect, but if it occupies enough recognition sites, it may prevent an active drug from binding.)

No drug is completely specific and many drugs have lots of different effects, which are often produced by different mechanisms. That's part of the fun of pharmacology!

How receptors work

Receptors are specific recognition sites for endogenous chemical messengers, usually neurotransmitters or hormones. About 70% of drugs in current use act on receptors, either by mimicing the effect of the endogenous substance or blocking its access to the receptor.

There are four main families of receptors:

•**ionotropic** receptors (ligand gated ion channels). The receptor is on the ion channel and activation makes the ion channel open in milliseconds, used for fast synaptic transmission, eg nicotinic acetylcholine receptors.

•**metabotropic** receptors (G protein coupled receptors) The receptor is coupled to the effector enzyme or ion channel by a G protein, used for slower (seconds) secretory and smooth muscle functions, eg muscarinic acetylcholine receptors.

•**tyrosine kinase coupled** receptors. The receptor is on the enzyme and activation takes minutes, mainly involved in controlling cell growth etc, eg insulin receptors.

•**steroid** receptors in the nucleus which affect gene transcription, effects are produced as a result of new protein production so are slow (hours), eg oestrogen receptors.

The first three types are all cell membrane proteins, steroid receptors can either be in the cytosol or nucleus. Receptors are being destroyed and replaced all the time; receptor numbers can either increase (up regulation) or decrease (down regulation), usually in response to changes in the amount of ligand around.

Ionotropic receptors

These are a group of four or five proteins embedded in the cell membrane forming a pore. When the drug binds to the receptor, it causes a change in shape of one or more of the proteins which opens the pore and allows ions (usually sodium, potassium or calcium) through. The pore usually opens in a fraction of a millisecond and closes after several milliseconds, so this type of receptor is used for fast neurotransmission. An example is the nicotinic acetylcholine receptor; several clinically important drugs act at these receptors in the neuromuscular junction.

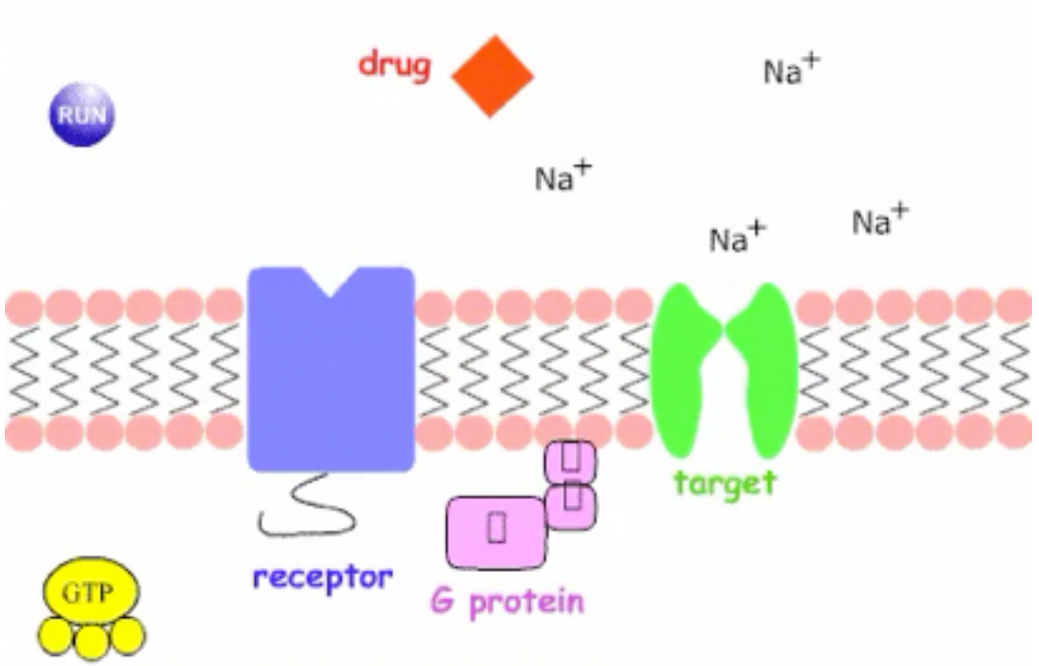
MOVIE 1.1 Ionotropic receptor

Ionotropic receptor, eg, nicotinic acetylcholine receptor. When the drug binds to the receptor, the gate opens and ions rush through (usually in). The ions are mainly Na+ in nAChRs, these depolarise the post synaptic membrane.

G protein coupled receptors

These receptors are also proteins embedded in the cell membrane. They have seven transmembrane regions, with tails on the inside and outside (so are occasionally classified as 7TM receptors). When the drug binds to the outside, this causes a change in shape on the inside which allows a G protein to bind to this end of the protein. The G proteins are normally not attached to the receptor, they seem to move around the inner side of the cell membrane interacting with various proteins. After they bind to the receptor they take up GTP (hence G protein) which gives them enough energy to move to a target enzyme. Different types of G protein can then activate or inhibit the enzyme. For instance, Gi inhibit and Gs stimulate the

MOVIE 1.2 G protein coupled (metabotropic) receptor



There are several different G proteins and lots of effectors, so the results of activation can be varied.

enzyme adenylate cyclase, which produces the second messenger cAMP; Gq stimulates phospholipase Cb, which produces IP3. There are at least 17 more variants. In some circumstances, the βγ subunit can even regulate enzymes. A drug binding to the receptor may activate more than one type of G protein leading to different effects, eg detomidine and xylazine both bind to a2 receptors, but have some different effects in cattle. This may be cased by different G protein coupling.

A number of toxins (pertussis toxin, cholera toxin, various wasp venoms) interact with the G proteins but there are no useful drugs yet which do so, although some drugs intract with G proteins as a side effect, eg suramin (used to kill trypanosomes) and benzalkonium (an antiseptic).

G protein coupled receptors often group together in dimers or oligomers, or are associated with other proteins - receptor activity modifying proteins (RAMPs - biochemists love their acronyms). This may help to explain why the same drug can have different effects in different tissues.

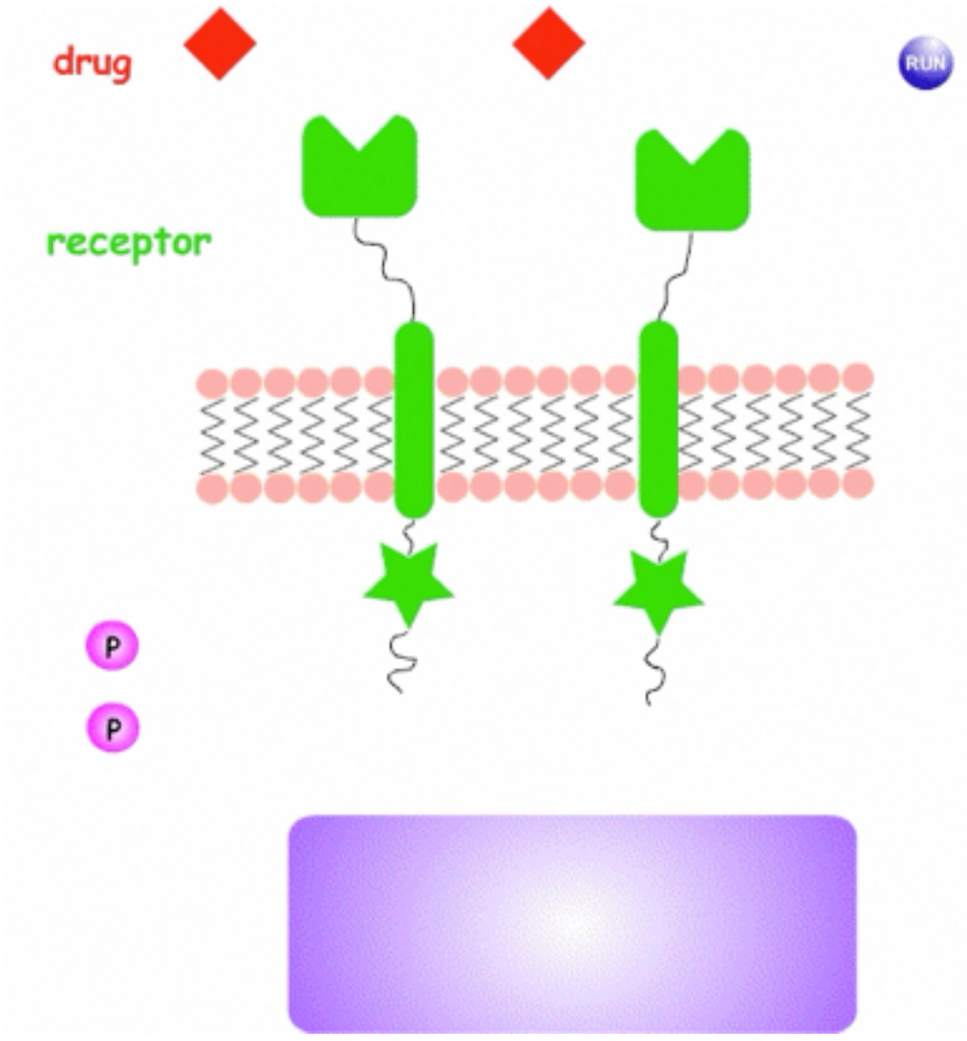
Kinase linked receptors

Some drugs can activate the target enzymes directly. The receptor / enzyme has a protein kinase (usually tyrosine kinase) domain. This phosphorylates and thus activates proteins, which then activate the effectors. The receptors often work in pairs, and possibly larger numbers. The effectors can be other enzymes, transport proteins, ion channels, contractile proteins, etc. Knowledge of all the intermediate steps is still sparse, but they may well be a target for future drugs.

Kinase linked receptors are used by insulin and various cytokines and growth factors.

Guanylate cyclase linked receptors are very similar.

MOVIE 1.3 Tyrosine kinase coupled receptors

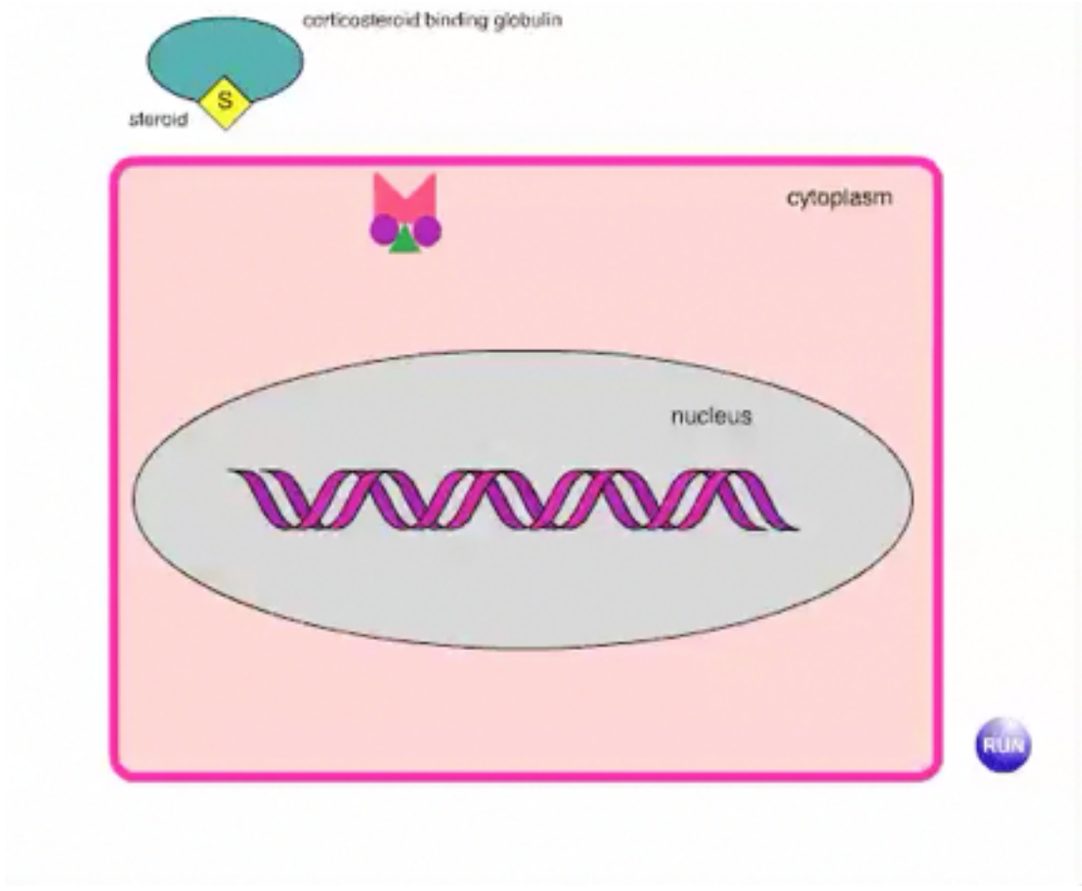


Two receptors are usually involved, effects appear in minutes to hours.

Nuclear receptors

Despite the name, some of these, eg steroid receptors, are actually in the cytoplasm, but they all act to alter gene transcription and thus protein production. As well as steroids (including sex hormones), thyroid hormone receptors fall into this class.

MOVIE 1.4 Nuclear (steroid) receptor



Receptor for corticosteroids. The transcription of a wide variety of proteins may be stimulated or inhibited, leading to a slow but widespread effect.

Receptor Subtypes

Most receptors can produce slightly different effects or bind drugs with slightly different affinity in different species and different tissues (beware of rat papers). These differences are often assigned to subgroups of receptors which are then given different numbers (by different people). Sometimes there is no agreement on whether these subtypes really exist or are just experimental artefacts.

For instance; adrenergic receptors are commonly divided into α and β receptors, since these are completely different types of receptors, but both are activated by adrenaline. They can be subdivided into α1 α2 β1 and β2 receptors. These can be further subdivided, eg α2A α2B α2C α2D etc. However, α2A receptors in humans are identical to α2D receptors in the rat, and there are several more α2 receptors which have been cloned and have slightly different amino acid sequences (but no names as yet). You are only expected to know about the subtypes which are clinically important, so please do not get confused!

Receptor subtypes are not just a pharmacological fad: if subtype specific drugs can be developed, it may be possible to produce drugs with specific effects, ie no side effects. Adrenaline, which acts at all adrenergic receptors, is not much use as a sedative because of its cardiovascular side effects, whereas medetomidine, a reasonably specific α2A agonist, is a clinically useful sedative.

Traditionally, receptors have been characterised by studying the effects of drugs which are thought to act at those receptors. Increasingly, receptors are found by isolating and sequencing proteins at random, those with a similar sequence to known receptors are also assumed to be receptors. They are then put into or knocked out of transgenic mice to see what they do. This often produces surprising results which are difficult to interpret, but the art is still in its infancy.

Other drug actions

Ion channels

Some drugs block ion channels (usually voltage gated channels) by physically clogging up the channel, eg local anaesthetics such as lignocaine. The drug may also modulate the opening or closing of the channel, eg dihydropyridine calcium channel blockers.

Enzymes

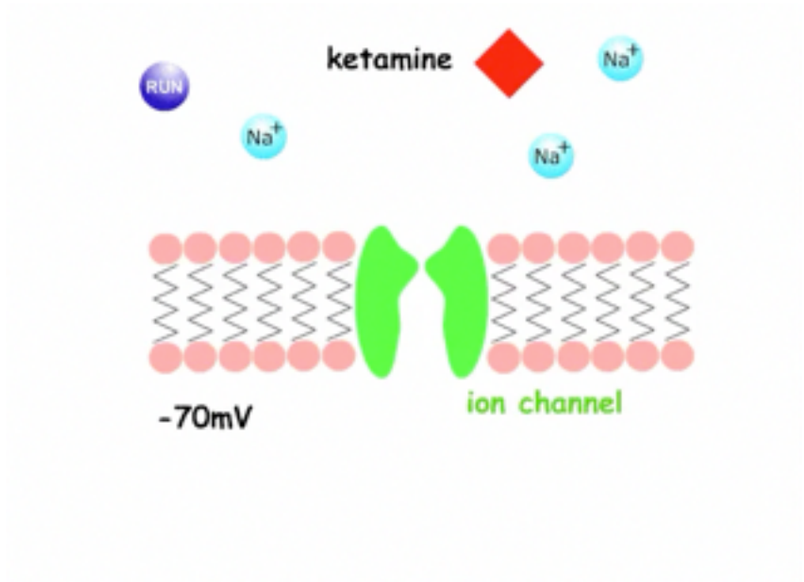
Many drugs affect enzyme function, usually by acting as an analogue of the enzyme substrate which competes with the real substrate for the active sites on the enzyme, eg organophosphate sheep dips compete with acetylcholine for the binding sites on the enzyme acetylcholinesterase (a).

Drugs may also act as false substrates (b) where an abnormal metabolite is produced, eg, fluorouracil, an anticancer drug, or as a prodrug (c) where the drug must be metabolised to be active, for instance, many angiotensin converting enzyme inhibitors used to treat heart failure.

Carrier molecules

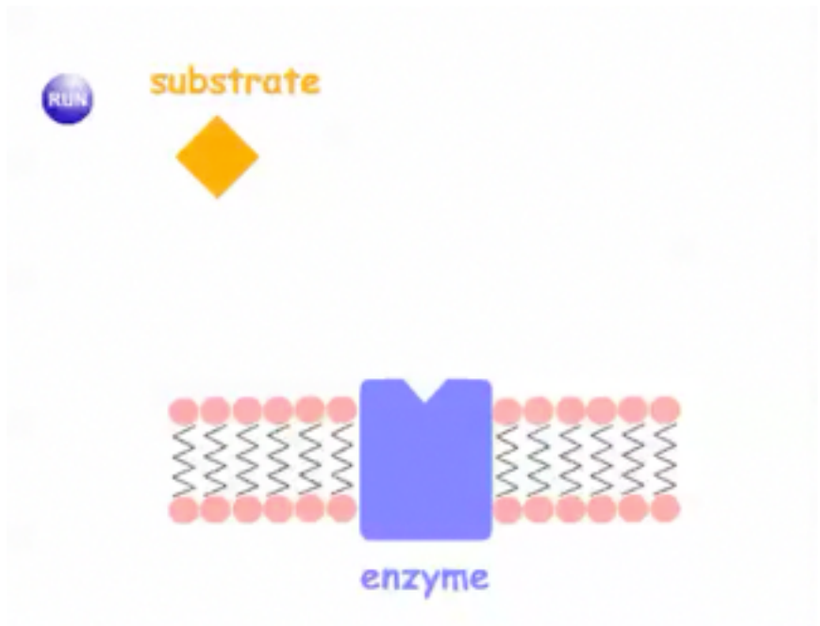
Some small polar molecules do not cross cell membranes easily and carrier proteins are used to get them into cells. This may be the means of removing the mole-

MOVIE 1.6 Ion channel blocker



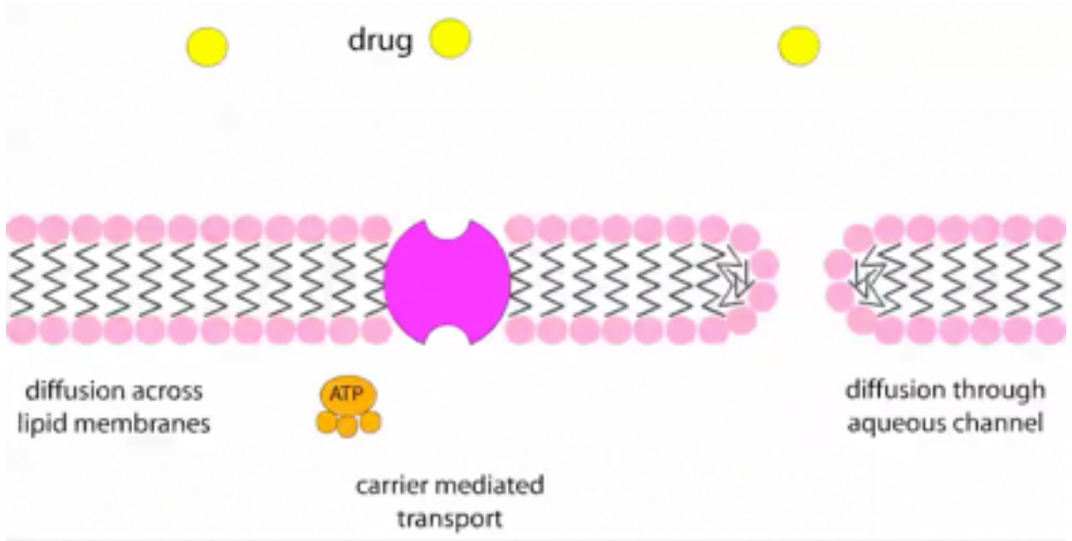
Note that these are different from ionotropic receptors!

MOVIE 1.5 Drug - enzyme interactions



cule from its site of action and so ending its action, eg 5HT is taken up into neurones: drugs which block this process prolong its action, eg fluoxetine (Prozac), a

MOVIE 1.7 Carrier molecules



Some carrier molecules, such as PGp, are important in pushing drugs out of cells.

Specific Serotonin Reuptake Inhibitor used as an antidepressant in people and to modify the behaviour of dogs and cats.

Non-specific drug targets

Some drugs produce an effect by a non specific physical means, eg, osmotic diuretics, radioactive iodine for hyperthyroidism.

Most drugs, particularly older drugs, are not specific for one receptor system or even one type of action - they have lots of side effects. For instance, chlorpromazine (a very old sedative) was originally given the trade name “Largactil” because it had such a large range of actions.

Drug - receptor interactions

A drug may be classified according to its interaction with the receptor:

•an **agonist** will bind to a receptor and mimic the effect of the endogenous ligand (nb endogenous ligands have not yet been found for all receptors, but they are assumed to exist). For instance, fentanyl will bind to μ opioid receptors, for which the endogenous ligand is probably endomorphan.

•an **antagonist** will bind to the receptor but do nothing on its own. However, it will stop an agonist binding and thus block the effects of an agonist. Most antagonists are competitive, ie they compete with the agonist for the receptor. This means that adding more agonist will push the competition in favour of the agonist. The diagram below shows this - it is still possible for the agonist to produce its effect in the presence of the antagonist, but more agonist is needed (compare concentrations A and B below which produce the same effect). For instance, naloxone will antagonise the effects of fentanyl at the μ receptor. A few antagonists bind irreversibly to the receptor, adding more agonist then has no effect.

•a **partial agonist** will bind to the receptor but not produce as big an effect as a full agonist. It will still occupy the receptor and prevent a full agonist getting there so in the presence of a full agonist it acts as a partial antagonist, eg, pentazocine at the μ receptor.

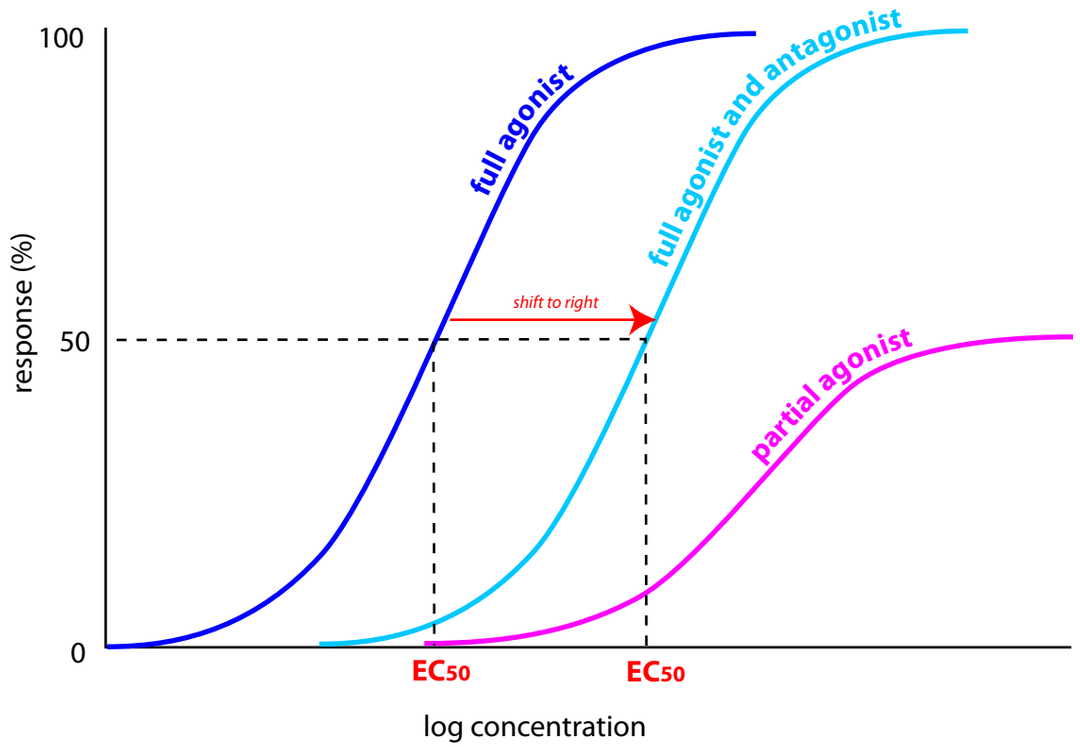
•an **inverse agonist** binds to the receptor to produce the opposite effect to an agonist. There are very few examples of these, and none are used clinically.

The potency of an agonist depends on two factors: its affinity (the tendency to bind to the receptors) and its efficacy (the ability to produce effects after binding). Full agonists have high efficacy, partial agonists have a lower efficacy and antagonists have zero efficacy.

If a full agonist can produce a maximal response in a tissue without occupying all the receptors, the tissue possesses spare receptors or a receptor reserve. This often happens with smooth muscle, and appears to be a way of economising on endogenous ligand. Changes in the amount of endogenous ligand (usually as a result of disease) will lead to changes in receptor numbers over hours to days. This will in turn affect the results of giving a normal dose of drug acting on these receptors.

Some drugs appear to act as antagonists to other drugs when given to animals. This can happen by:

DIAGRAM 1.2.1 Concentration response curves



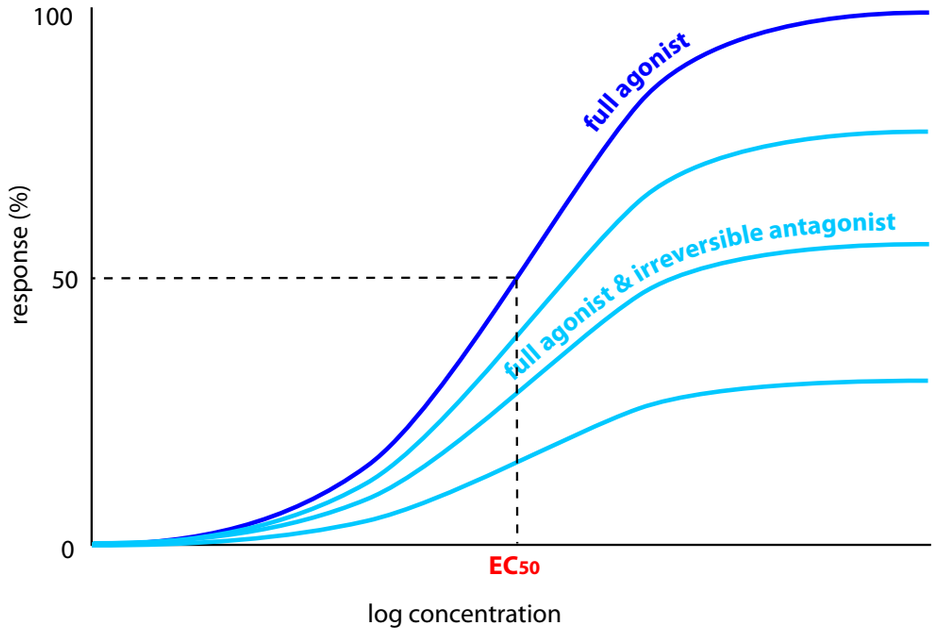
These are usually plotted semi-logarithmically.

- **chemical antagonism** - where the two drugs react chemically to inactivate each other, eg penicillin and streptomycin.
- **pharmacokinetic antagonism** - the "antagonist" reduces the concentration of the agonist at its site of action by interfering with its absorption, distribution, metabolism or elimination. Fairly common, eg, phenobarbitone increases metabolism of many drugs.
- **physiological antagonism** - the drugs have opposite effects and cancel each other out. Fairly common, eg, histamine increases gastric secretion while a proton pump inhibitor such as omeprazole decreases it by a different mechanism.

When drugs are given long term, the effects sometimes decrease over time. This is usually called tolerance in whole animals, desensitisation or tachyphylaxis in vitro and is usually undesirable. There are a number of ways this can happen:

- the number of receptors can change (downwards) (hours to days).
- the receptors may change so that binding the drug no longer produces an effect (minutes).

DIAGRAM 1.2.2 Concentration response curve



Concentration response curve for a full agonist in the presence of an irreversible antagonist.

- sometimes mediators are depleted (minutes to days).
- the drug may be metabolised faster (days to weeks).
- the animal may adapt to the effect of the drug and learn to function normally (days to weeks).

This subject is clinically important but not well understood.

The EC50.

It is sometimes useful to be able to compare drugs objectively and a variety of terms to which numbers can be attached are used.

The EC50 is the concentration at which a drug produces 50% of its maximal effect. This only applies to in vitro preparations since the drug concentration cannot usually be measured in patients at the site where it is thought to act. (IC50 is the concentration where 50% inhibition occurs.)

The ED50 is the dose at which a drug produces a quantal response in 50% of animals; eg. the minimal alveolar concentration of an anaesthetic is the dose (despite the name) which stops 50% of animals responding to a supramaximal stimulus (often skin inciscion).

ED50 and EC50 are not interchangeable, and do not mean the same thing.

The LD50 is the dose which kills 50% of animals; ie, a specific type of ED50.

The therapeutic index is the ratio of LD50 : ED50. A high therapeutic index indicates a safe drug, a drug such as digoxin has a therapeutic ratio close to one! It is rarely ethically justifiable to kill animals to work out the LD50, so the dose which is toxic to 50% is sometimes used instead. However, toxicity is not really a quantal effect, so this approach has not caught on yet. In people, the number needed to harm (NNH) is sometimes used. This is the number of patients who would have to be treated to see serious side effects in one case.

Some types of toxicity are not related to dose (they are usually immune mediated) and the therapeutic ratio gives no useful info about these.

DIAGRAM 1.2.3 EC50

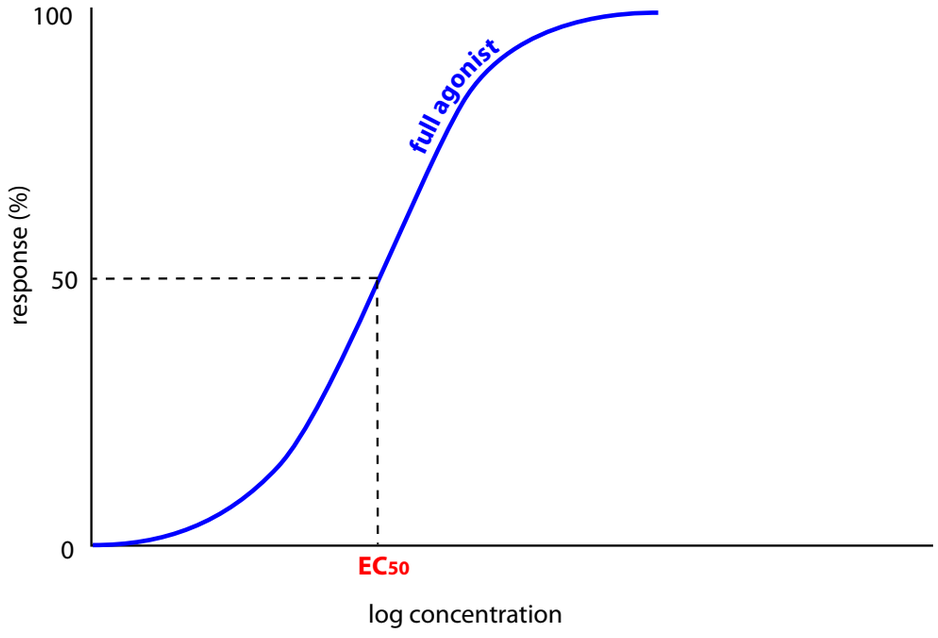
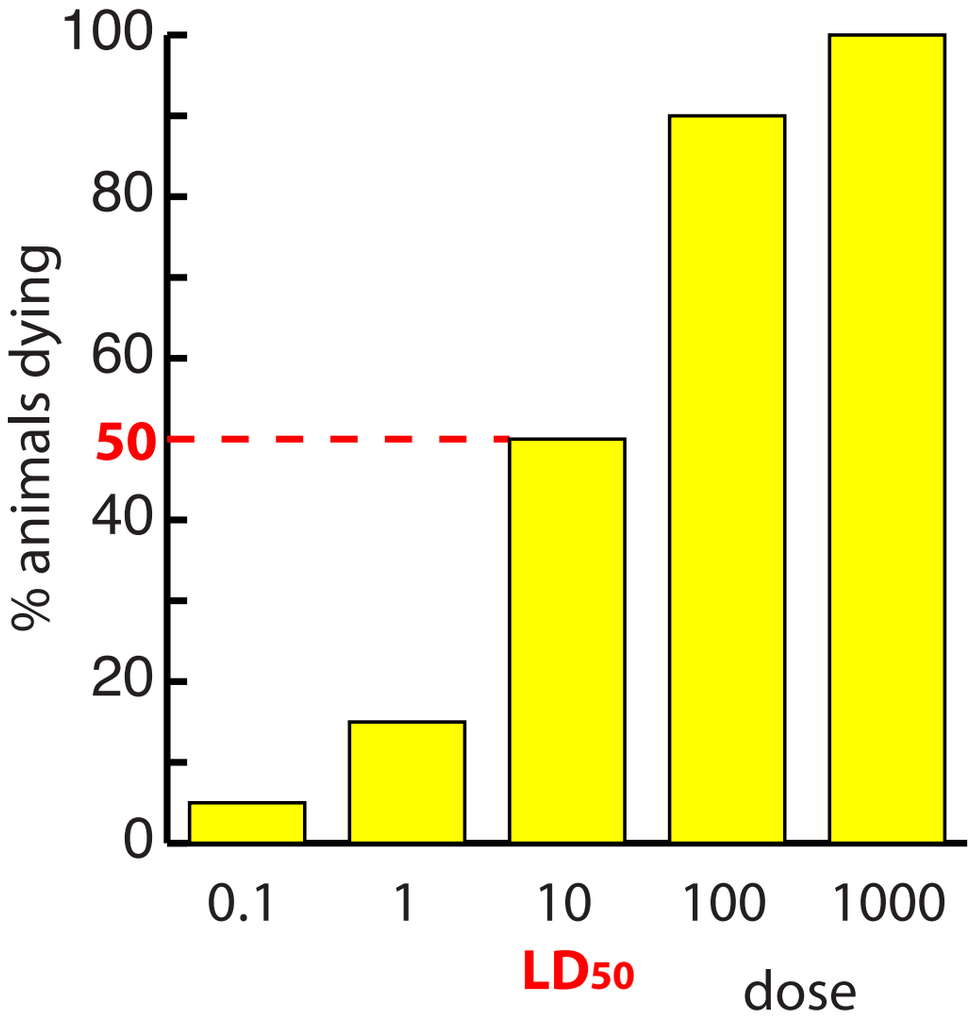


DIAGRAM 1.2.4 ED50



The LD50 is a special sort of ED50.

SECTION 3

Measurement

Measurement

☑ This section is for interest only!

☑ It is included as information from current *in vitro* models is only tenuously connected to what happens in animals.

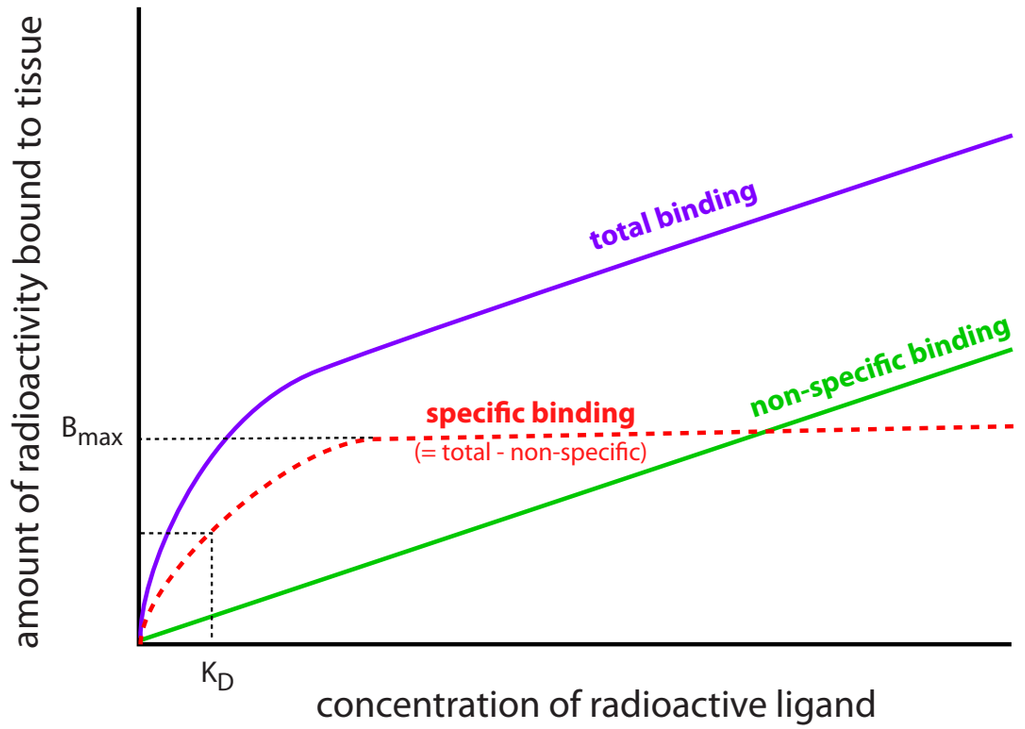
You do not need to know the details of how drug receptor interactions are studied, but you need to have some idea of the limitations of the methods used and how the results relate to whole animals.

Binding

The binding of drugs to receptors, and their displacement by other drugs, are usually measured using radioactive agonists or antagonists.

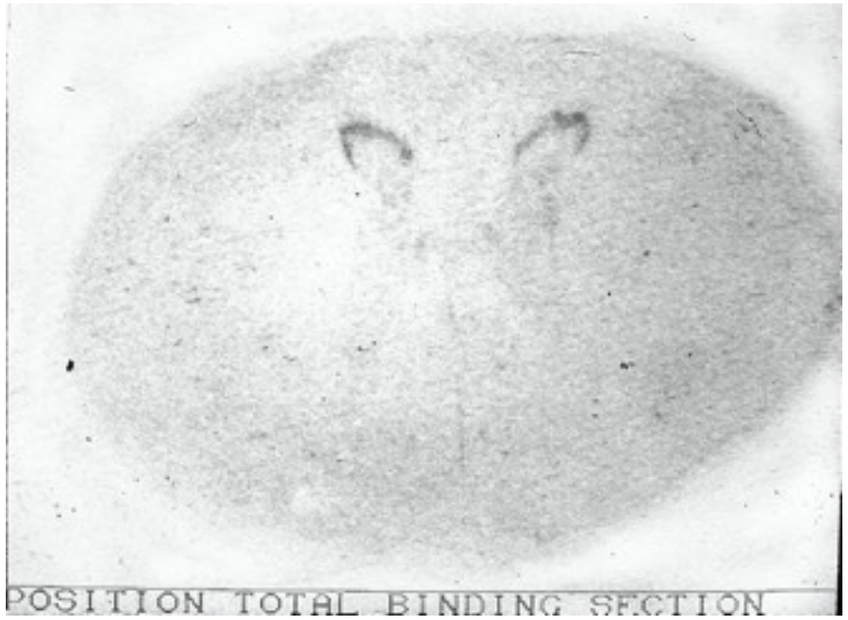
The tissue is homogenised in a test tube, washed and centrifuged so that only cell membranes (you hope) are left. The tissue is exposed to the radioactive drug and allowed to incubate so that the drug binds to the receptors, excess drug is washed off and the radioactivity measured. Most hot ligands are labelled with tritium, which is a β emitter: the homogenised tissue with drug bound to its receptors is put into a vial of fluid which scintillates when a β particle is emitted and the flashes are counted by a machine.A control group is subjected to the same procedure but the radioactive drug is displaced by a non-radioactive (cold) agonist or antagonist (as appropriate) before washing. Any radioactivity measured in this group is assumed

DIAGRAM 1.3.1 Binding to membrane receptors



Specific binding is to receptors, non-specific binding is usually drug dissolved in the lipid membranes.

IMAGE 1.1 Autoradiography



Alpha 2 adrenergic binding in the gray matter of a horse's spinal cord.

to be nonspecific binding to lipids etc, so the two radioactive measurements are subtracted to get the specific binding. The specific binding must be to receptors, ie proteins, so the protein concentration is measured so that the binding can be quantified.

These sort of experiments show the Bmax which gives an indication of the number of receptors in the tissue, and the dissociation constant, KD, which is the concentration of drug which occupies 50% of the receptors.

A variation on this technique is to use a slice of tissue on a microscope slide rather than homogenised tissue. This allows the site of the receptors to be pinned down.

Another variation which can be used in patients is positron emisson tomography where a drug containing a positron emitting isotope is given to the patient and radioactivity is visualised by various techniques. This is particularly useful for showing how disease affects receptor numbers.

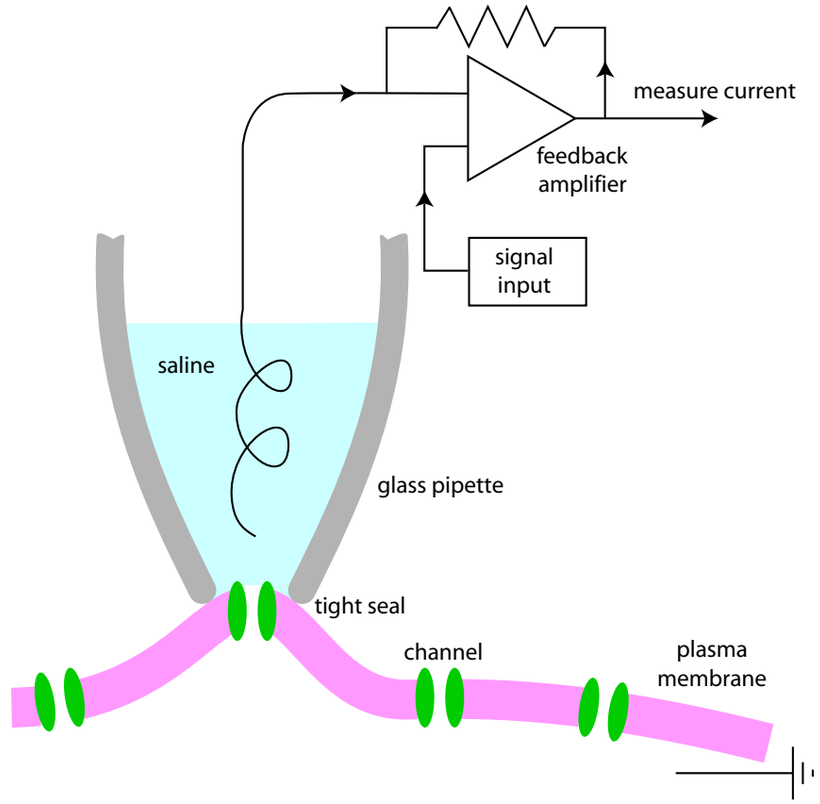
Patch clamping

Binding experiments do not tell us anything about receptor function: patch clamping in excitable tissue is a common way of assessing what happens when a drug binds to an ionotropic receptor or to a receptor coupled to an ion channel. A small patch of membrane containing the receptor and ion channel is sucked onto the end of a pipette and a constant voltage maintained across it. When the channel opens, ions go through, creating a small current (picoAmps). If you have the pipette connected to a very sensitive amplifier, you can measure these currents. Any sort of magnetic or electric field moving near your wires can produce very lifelike pictures.

Drugs can be applied to the whole cell, or put in the saline inside the pipette so that they only affect the channel being examined.

These experiments can give information on channel kinetics and receptor effector coupling, but are very prone to artefacts.

DIAGRAM 1.3.2 Patch clamping



Patch clamping can be used to measure currents through single ion channels. A fine glass pipette filled with saline is pushed against the cell membrane and held there by suction, which makes a tight seal. The feedback amplifier keeps the membrane potential constant and the current is measured when the channel opens.

Basic toxicology

Basic toxicology

☑ The dose makes the poison!

Definitions

Poison: any solid, liquid or gas that regardless of the route of exposure (oral, topical, inhaled etc) causes a harmful effect on the body.

Poisoning: occurs when the poison produces a clinical effect in the animal.

Toxin: generally used to describe poisons that come from biological sources. For example the tetanus bacteria produces a (bio)toxin that causes lockjaw in humans and animals.

Antitoxin: an antibody to the toxin of a microorganism (or zootoxin or phytotoxin) that specifically binds to the toxin and neutralises it; eg. Tetanus antitoxin is derived from injecting toxin into animals and collecting the antibodies for therapeutic use that is to bind the toxin in the sick animal.

Toxicity: refers to the amount of poison necessary to have harmful effects.

All substances are potentially toxic if given in sufficient quantities. The LD50 is an expression of the amount of compound that is necessary to cause death to half the animals exposed to the compound.

Toxic effect: any noxious effect on the body – reversible or irreversible; any chemically induced tumour-benign or malignant; any mutagenic or teratogenic effect or death as a result of contact with a substance via the respiratory tract, skin, eye, mouth, injection or any other route.

Toxic effects are undesirable alterations to the body's function (physiology) caused by a poison or toxin.

Antidote: a substance that specifically counters the action of a poison. (e.g. Vitamin K1 for anticoagulant poisons).

Toxicity Classes

Extremely toxic - only takes a small amount to kill, e.g. less than 1mg per kg of body weight

Highly toxic – from 1 to 50 mg per kg is deadly.

Moderately toxic – 50 to 500 mg per kg is deadly.

Slightly toxic – 500 mg to 5 grams per kg is deadly.

Practically nontoxic – 5 to 15 grams per kg is deadly.

Relatively harmless – more than 15 grams per kg is required to cause poisoning or death.

Exposure

Acute – the effects of a single dose or multiple doses that cause signs of poisoning during a 24-hour period.

Subacute – repeated exposure to a poison and effects that last for up to 30 days.

Chronic – refers to exposure to (a poison) or the effects of (poisoning) that occur over months.

Routes of Poisoning

Ingestion (by mouth)

Inhalation (gases, particles in the air)

Skin (topical)

Iatrogenic (given by someone - includes oral but also injectable methods such as intravenous or intramuscular.)

Species, breed, sex and age differences

Not all animals respond the same to a poison. Cats are more resistant to anticoagulant rodenticides than dogs.

Some breeds are more sensitive to a given poison than another. Examples include collie dogs poisoned by a normal dose of the parasiticide ivermectin that has no toxic effect on a Labrador; or Brahman cattle that are more sensitive to organophosphorus insecticides than Hereford or Friesian.

Some poisons are more toxic to one sex than the other sex. For example female dogs are more sensitive to monensin (a feed additive for growth promotion in cattle) than male dogs.

Age: young and old animals tend to be more sensitive to poisons than normal adults.

Healthy individuals are less sensitive to some poisons than sickly or debilitated animals.

What to do while the client is on the phone

1. Do "triage" assessment of the animal by asking the client questions

Assess if this animal going to die within the next few seconds unless drastic action is taken by the client at home?

- breathing okay?
- external bleeding? controlled?
- still in contact with the toxin?

Always remember that every minute a client spends doing something to the animal at home is a minute longer the animal is away from carefully monitored, critical veterinary care

2. Get a brief history (i.e. What's the problem?) and if toxicant is suspected to be involved, get the specifics.

- Have the client read the package of suspected toxicant to you.
- If there is no package but toxic materials are around, have the client put them in a plastic zip–lock type bag for you - warn the client about their own cutaneous (topical) exposure!
- If no toxic substances have been found but you still suspect a possible toxicity, tell the client this so they can be thinking of all the possible poisons that the animal may have accessed during their drive to your office or your drive to the farm.
- Note: just because the client thinks their animal has been poisoned, do not assume that is a correct diagnosis!!!
- Dogs with bloody diarrhoea from parvovirus are often presented with the owner convinced that someone poisoned their dog.
- Male cats toxic from an obstructed urethra will "go down" fairly quickly leading the owner to assume that the roaming tom cat has been poisoned.
- The presence of a few toxic plants in a pasture does not clinch a toxic diagnosis (almost every pasture has some toxic plants in it!).

3. If you suspect a cutaneous toxin is involved and the animal is conscious and somewhat stable, it may be worth it to have the client wash the animal thoroughly to prevent further absorption of the toxicant

• Lots of clean water is probably the best liquid to use (warm if possible).

• Tarry petroleum products seem to come off well with dishwashing soap; avoid contact with the eyes. don't use petrol, cleaning fluid, or electric dishwasher detergent to clean the animal (liquid, granular etc as they are caustic and will burn).

• Make sure the client wears gloves!!!

4. If toxicant was ingested do not routinely recommend the client induce vomiting!

• Caustic substances (strong alkali or acids) will burn coming back up as well as going down the oesophagus.

• Light petroleum products like petrol, cleaning fluids, etc. have such a light viscosity that they are easily aspirated! (bad news!)

• If the animal is unconscious or severely depressed the gag reflex may be ineffective.

• Induction of vomiting always poses a risk of aspiration pneumonia which has the potential to be more life threatening than the toxicant.

• Many emetic preparations available to the general public are ineffective in animals. The following have a variable effect:

- Soapy water or a crystal of washing soda (sodium carbonate) with water (approximately 3 tablespoons of dishwashing liquid (e.g. Sunlight) in 250 ml of water; give about 10 mL/kg (do not use products for electric dishwashers or washing machines))

- hydrogen peroxide (use 3% only at 1-3 ml/kg)

- Table salt, mustard, copper sulphate are not very effective due to difficulty owner will have getting sufficient amounts into the animal. Salt may cause hypernatraemia.

- Zinc sulphate capsules may be distributed by pest control operators to farmers living in areas with pesticide operations. Works reasonably well.

5. If client wants to dilute the toxic compound:

• consider the gain achieved by diluting the toxic substance compared to the time lost in getting the animal to the hospital while the owner is trying to get water into the animal - but if it is a caustic compound dilution is valuable.

• allow the animal to drink as much water or milk as it wants

• egg white can also be administered

• activated charcoal may be given if the client has it readily at hand (sometimes called "universal antidote")

6. Have the client bring (or have them gather together if you are making a house/farm call) the following:

• any suspected toxic materials or their containers

• any vomitus

If the client is bringing the animal in, have another family member hunt around for possible sources of toxicity; if on a farm call, have the client do a thorough search while you're on the way

What to do once the animal arrives at the clinic or you arrive at the farm

Use the same general guidelines as you would use for any clinical disease.

Signalment

• different species susceptibilities help rule in/rule out

- cats are generally much more susceptible to toxic agents than other species due to their poor ability to conjugate (metabolize) certain compounds

- horses seem to be more susceptible to plant toxins than cattle grazing on the same pasture

• age is very helpful in diagnosing some toxic agents

- white snakeroot (poisonous plant in USA) afflicts nursing calves while not affecting the mature cow to the same degree

- neonatal and young dogs and cats have livers that are less developed and hence less able to metabolise some toxic agents

- young animals are often more curious about potentially dangerous things; puppies chew on everything

- older animals in a group or a herd may be most afflicted by a toxic agent due to their reduced renal or hepatic function as a result of older age

History

Chronological order of events is very important

• if an animal becomes acutely ill in 3 hours, it is more likely to die quickly than the animal that has been gradually getting worse over the past 2 weeks

• very sudden onset of acute signs is generally more characteristic of toxicosis (or trauma) than infectious agents. Increased temperature does NOT rule out a toxicosis

• several animals acutely afflicted at once is suggestive of intoxication versus infectious disease in which several animals become sick over a span of days or weeks (although toxicity can also appear this way)

Environment where the animals are maintained

• grazing animals, as a rule, will not eat most toxic plants unless good forage is unavailable

• junk cars, poorly maintained trash heaps, barrels or bags of discarded fertilizer, herbicides are all toxicologic accidents waiting to happen

• does the dog or cat run free? (increased exposure)

• history of other pets in the area suddenly dying?

• have chemicals been applied recently to grass, grazing land, or areas through which water might run off and pass through grazing land

Food and water source (esp. for grazing animals)

• where is food stored? what is stored with it?

• what is composition of stored forage?

• observe water source (algae growth, contamination from upstream water, etc.)

• correlate any change in feed and problem onset?

Vaccination and veterinary care status (help arrange your differential list more accurately)

• possibility of drug–induced toxicosis

• rule out non–toxicologic problems by knowing vaccination status (e.g. bromethalin toxicity in dogs often resembles distemper)

• although there is a wide variability, the regularity of veterinary care may give you a feel for the type of livestock management of an operation or the care of the companion animal

Physical Exam

Repeat your triage to determine if, during the time the animal was being transported or you were driving to the farm, emergency procedures now need to be done

• check for patent airway, cardiovascular regularity, shock status, ease of breathing

• all the antidotes in the world won't be any good if one or more organ systems has shut down

Be aware that many of these toxic compounds can be very painful; be aware of this so as to prevent you or your staff from becoming injured (muzzle, restrain, etc.)

Be aware that a topical or cutaneous toxin can be absorbed into you as well as the animal; if the toxic material is still on the animal, wear gloves!

Remember that repeated assessment of the physical condition may be necessary if this is a rapidly progressing acute toxicity

• dyspnoea may develop in warfarin toxicity due to bleeding into the chest cavity

• seizures may develop in ethylene glycol due to acidosis and metabolic derangement

• fatal arrhythmias may occur with plants that are cardiotoxic

Your physical exam should be thorough and quick

• don't be too aggressive on the abdominal palpation if you suspect ingestion of a caustic substance

• the thoroughness of your physical will be dictated by the need to stabilize the animal; if toxic, but stable (CRT okay, no dyspnoea, etc.) be thorough (determines baseline)

Because of possible legal implications (e.g. intentional poisoning, insurance claims, etc.) make sure your records are as accurate and detailed as possible

Obtain samples to rule out toxicity

Remember that in most cases you can't wait for the results of the toxicity profile before treating; decisions will have to be made on the basis of the history and physical exam.

Preserve the vomitus or suspected toxic substance (including packages, labels, etc.) in clean plastic or glass containers.

Contact the Animal Disease Diagnostic Lab at MAF or Massey University (or a similar diagnostic laboratory in your area) for advice on what samples (blood, urine, etc.) to obtain and how best to ship them.

General rule: wrap the specimen in aluminium foil and then place in a sealed plastic bag.

Treatment

"Treat the animal, not the toxicant!"

The therapeutic goals, in order, are:

1. **emergency support** (shock, cardiac arrest, respiratory arrest) Stabilise
2. **maintain systems** (renal, respiratory, cardiovascular, etc.) Stabilise
3. **prevent further absorption** of the toxicant
4. **application of antidote**

"...the extent of potential poisons far exceeds the number of safe and effective antidotes available.."

"Although antidotal treatments are often emphasized in the management of toxicoses, veterinary patients will often benefit as much (if not more) from intensive supportive therapy."

"Many 'antidotes' are simply directed toward achieving stabilization of vital signs, decreasing exposure, and facilitating toxin removal."

David Dorman in Kirk's CVT XII p 211

5. **increase elimination** of the poison

Emergency Support

see also Cardiovascular System

Airway

Keep it open!

- chemical or irritant toxicants inhaled or ingested can cause laryngospasm and bronchospasms
- if vomiting is likely and the animal is weak, depressed, semi– or totally unconscious, tracheal intubation is indicated
- if intubation is indicated but the animal starts to vomit prior to placement of the tube, the chance for aspiration can be reduced by inverting the patient so the head is lower than the rest of the body. Suction is useful!

Breathing

Use mechanical ventilation if necessary

- some toxins paralyse the respiratory muscles or inhibit the respiratory centers in the medulla
- tetanic seizures may stop breathing due to the animal being unable to expand the chest during the seizure
- if deep anaesthesia is necessary to control convulsions, respiratory depression may occur

- if forced ventilation is needed, moistened room air is probably preferable to oxygen - the presence of high % of oxygen in the inspired gas can result in production of oxygen free radicals within tissue resulting in further tissue damage. Oxygen is contraindicated in paraquat toxicity for this reason

Circulation

Cardiovascular function can't be maintained unless the respiratory function is maintained!

Cardiac arrhythmias can result from dyspnoea or from direct effect of the toxin itself; can also result from gross disturbances in electrolytes

• severe acidosis (e.g. ethylene glycol, metaldehyde salicylates) can result in a severe loss of bicarbonate ion. Correction involves slow return to normal pH by controlled administration of sodium bicarbonate. Rapid administration of $NaHCO_3$ into systemic circulation can result in paradoxical cerebral acidosis. Severe acidosis can result initially in a compensatory tachypnoea; however as the acidosis increases the respiratory center can shut down (bad news!). Correction of systemic acidosis will usually clear up the electrolyte imbalances that may have caused arrhythmias

- direct cardiotoxic effect (e.g. cardiac glycosides like digoxin)
- sinus bradycardia: caused by organophosphate/carbamate insecticides, beta–blockers, digoxin: treat with atropine or glycopyrrolate
- second degree heart block (on/off AV block): caused by digoxin toxicity or foxglove: treat with atropine or dopamine
- atrial standstill (usually associated with hyperkalaemia): caused by decreased secretion of K from drugs like potassium–sparing diuretics or from potassium being shifted from intracellular stores into the blood: treat with normal saline solution or insulin/glucose combination to shift potassium from blood into cells.
- premature ventricular contractions (PVC's): caused by some cardiotoxic plant alkaloids or electrolyte disturbances: treat with lignocaine (dog); cats rarely require therapy but they can be given propranolol (lignocaine can result in seizures in cats at higher doses)

Treatment of shock

Important because of the need to keep cardiovascular and renal functions going (kidneys needed to remove many toxicants or their metabolites)

Fluid therapy, corticosteroids, analgesics (pain relievers) may be used (think about it first!)

Control of seizures

During tetanic seizures cyanosis may occur

Hyperthermia often occurs with persistent seizures; this combined by hypoxia can result in CNS damage

Acidosis results from release of lactic acid from muscles during seizures

Give diazepam iv (titrate to effect). If diazepam fails (or long term control needed) try phenobarbitone. If phenobarbitone fails, anaesthetise the animal with pentobarbitone (slowly to effect).

Place animals in a dark, quiet room (especially with strychnine toxicosis)

Prevent Further Absorption Of Toxicant

Remove cutaneous toxicant by washing.

Dilute ingested toxicant with milk or water.

• this is actually somewhat controversial in that studies have shown that large volumes of water given with the toxicant increase GI absorption of the toxicant and therefore increase toxicity

• dilution is still highly recommended in cases of ingested corrosive substances (acids, alkalies, etc.)

Induction of emesis

• of little value after 4 hours (has moved beyond duodenum); liquids may move faster, further reducing the amount of time emesis is effective (< 2 hrs); if compound is uncharged, it will be rapidly absorbed in the stomach and upper intestine (e.g. aspirin, ethylene glycol) NB giving some food (e.g. dog roll) may aid in the removal of an ingested poison

do not induce emesis in:

- rodents (incapable of vomiting), rabbits (stomach wall not strong enough to tolerate it), and horses (which can't vomit)
- hypoxic or dyspnoeic animals
- seizuring animals
- extremely weak, comatose, or lacking normal pharyngeal reflexes

- if vomiting has already occurred repeatedly
- if strong alkali, acid, or other corrosive ingested - oesophagus does not have protective mucus and is easily damaged by corrosive agents - first time down, the epithelial layer may be stripped away leaving the muscular layer; a 2nd exposure may cause rupture

• caution in using in animals that have ingested a CNS stimulant (vomiting can precipitate seizures)

• antiemetic drugs, either given as a toxicant or as a therapeutic agent to control seizures, may prevent emesis or reduce the effectiveness of emetics

- phenothiazine tranquilizers (acepromazine)
- marijuana
- barbiturates
- antihistamines
- codeine

Emetic drugs

Apomorphine stimulates the CRTZ to produce emesis, but it also inhibits the firing of the emetic centre. The idea is to stimulate the CRTZ (which has no real blood brain barrier) before the morphine has a chance to get through the blood brain barrier to the emetic centre. Because blood concentrations rise slowly when given PO, the emetic center will be inhibited (stop vomiting) before the CRTZ is sufficiently stimulated**.**

Drug of choice in dogs; doesn't work that well in cats (less sensitive to emetic effects)

Administration: crush 1 tablet in 1/2 mL of water and place, drop by drop, into the conjunctival sac until vomiting occurs; terminate by rinsing the sac with water OR put whole or partial tablet in eye and rinse out after the dog vomits.

IV administration is more reliable and has an immediate effect of short duration (1–2 mins); however, overdosing is difficult to treat. Overdose of apomorphine can result in respiratory and CNS depression as well as protracted vomiting. While respiratory and CNS depression are reversible with narcotic antagonists (naloxone) they will not reverse the protracted vomiting in the dog.

Sodium carbonate (washing soda used in washing machines when water is high in minerals to act as a clothes softener). Use a crystal/pinch or more on the back of the tongue to induce vomiting. Repeat 2 to 3 times at 15-20 minute intervals.

Zinc sulphate capsules may be available from some pesticide operators or councils in areas where pesticides are used.

Hydrogen peroxide 3%: 1–2 ml/kg; at 10 minutes intervals for 3 treatments, if animal has not vomited, try another emetic

Xylazine: effective in cats; cat dose 1.1 mg/kg IM or SQ; reverse with yohimbine

Gastric lavage

- if within 2 hours is fairly reliable
- need large diameter tubes and lots of water
- anaesthetise animal; place endotracheal tube (cuffed!) with end extended 5–7 cm beyond the end of the mouth
- lower head and thorax slightly
- measure stomach tube: nose to xiphoid; use tube same size as endotracheal tube
- place and verify location
- infuse warm water initially at low pressure to collect samples
- allow to drain via gravity
- use water or saline flushes until fluid is clear then follow with a charcoal slurry and a cathartic (sorbitol) unless contraindicated
- rumen lavage follows similar guidelines

Adsorbents

These are designed to adhere to toxicant preventing absorption. **Activated charcoal** is best (make sure it is activated; meaning it is of petroleum or vegetable origin, not mineral or animal origin) (See Kirk's CVT XII p. 215)

- - dose: 1–4 g/kg combined with saline or osmotic cathartic (such as sorbitol) and water (mix 1g of charcoal to 5ml of water)
- - charcoal tablets are 25% less adsorptive than powders
- - owners should be warned that stools will be quite black and animal will usually have diarrhoea with administration of charcoal and laxative (constipation may also occur with activated charcoal if inadequate liquid is given and a cathartic is not administered)
- - usually recommended that some charcoal be left in the GI tract and a cathartic (laxative) be given to remove adsorbed toxin and prevent constipation
- - activated charcoal does not adsorb acids, alkalies, petroleum, alcohol aand many heavy metals

- - contra-indicated if no bowel sounds, corrosive ingestion, abdominal trauma or obstruction of bowel

Ion exchange resins for instance cholestyramine resin (Questran). Cholestyramine binds with lipoproteins and bile acids thus preventing intestinal absorption that occurs via these systems. Cholestyramine can interrupt the enterohepatic recirculation of compounds excreted via the bile. Examples of compounds that the resin will bind with are phenobarbitone, propranolol, tetracycline, benzylpenicillin, digoxin, thyroxin, phenylbutazone, some pesticides, any highly lipophilic compound, heat stable *Escherichia coli* enterotoxin and warfarin. The recommended dosage for animals is 50-75 mg/kg PO. Fluid therapy may be required as hydration status is important when cholestyramine resin is used. Questran contains 4 grams of cholestyramine with aspartame and orange flavouring to be mixed with water, milk or fruit juice.

The potential side effects of cholestyramine are nausea, hypoproteinaemia, constipation, steatorrhoea and the loss of fat-soluble vitamins. In humans the reported side effects include irritation to the tongue and perianal area, muscle and joint pain, headache and dizziness.

Cathartics

Saline or osmotic cathartics are most commonly used. They are composed of poorly absorbable salt that osmotically draws water into the lumen of the gut, causes dissension, and stimulates movement

Sodium sulfate (Glauber's salt) is more effective than magnesium sulfate (Epsom salt); can get sufficient magnesium absorption to cause Mg++ toxicosis in renal compromised animals

Sorbitol mixed with active charcoal is sold as Carbosorb S; do not give repeated doses of Carbosorb S, if repeat dosing is required use only activated charcoal. Repeated doses of sorbitol may cause dehydration and electrolyte imbalances. Dose: Sorbital 70% 1-2 ml/kg

Oil cathartics (liquid paraffin, olive oil)

- liquid paraffin is not likely to be absorbed across normal mucosa
- vegetable oils (olive, etc.) are much more likely to be absorbed and could facilitate absorption of some toxicants, thus they are not recommended.

Application Of Specific Antidotes

There are few toxicants where an antidote is effective. Examples include: atropine (OPs and carbamates), acetyl cysteine (paracetamol), ethanol or 4-methylpyrazole (ethylene glycol)

Increase The Elimination Of Toxicants

- enhance ion trapping in the urine for those compounds that are excreted by the kidneys and can become ionized by altering the urine pH
- acid compounds (aspirin, some barbiturates) can be removed faster by alkalinizing the urine (sodium bicarbonate 1–2 mEq/kg) Use care!
- alkaline compounds (amphetamines, strychnine) can be removed by more rapidly by acidifying the urine (ammonium chloride)
- diuretics may be used for those compounds that are renally excreted
- must maintain hydration of the animal
- check renal function first as many toxins are nephrotoxic
- frusemide or mannitol can be used

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Clinical signs and poisons

Anaemia

blood loss anaemia

- aflatoxins – liver damage results in loss of clotting protein production; highly modified coumarin
- anticoagulant rodenticides – acute cases - blood loss
- moldy sweet clover
- pit viper venom – pooling of blood in thorax (cats) or liver (dogs) (not in NZ!)

haemolytic anaemia

- paracetamol
- red maple leaves – horses
- zinc (chronic or low dose tox)
- copper

microcytic, hypochromic

lead (chronic) – fragility of RBCs; not a feature of acute lead toxicity; increased (5–40 NRBCs/100 WBCs)

pancytopaenia

bracken fern – in cattle, due to bone marrow aplasia

phenylbutazone – in humans and dogs

regenerative

anticoagulant rodenticides – chronic

Breed predispositions

Collie – ivermectin

Doberman – anticoagulant rodenticides – if have Von Willebran's

Cardiovascular

arrhythmias

digoxin

bradycardia

ammonia (urea) toxicosis – parasympathetic signs

antiarrhythmic drugs (beta blockers, calcium channel blockers, lignocaine)

carbamate insecticides

organophosphate insecticides – cholinergic stimulation

yew plant

hypotension

acepromazine tranquillizers

antiarrhythmics – hypotension from negative inotropic effect plus inability of weakened heart to respond

pit viper venom – severe loss of fluid due to loss of capillary integrity; pooling of blood in liver or thorax

tachycardia, fibrillation

- decongestants – primarily a 1 stimulation but also b1
- sodium fluoroacetate (Compound 1080) rodenticide – herbivores show ventricular. fibrillation. and cardiac arrest
- thornapple (*Datura*) – atropine toxicity so blocks parasympathetic system; tachycardia
- ionophores (e.g. monensin in cattle)

Electrolyte imbalance

Often secondary to renal failure

hypercalcaemia

cholecalciferol rodenticides – more than 4.99 mmol/L

hyperphosphataemia

cholecalciferol rodenticides – inc. GI absorption, inc. renal reabsorption

hypocalcaemia

- ethylene glycol – oxalate precipitates out with calcium to form crystals
- oak – mechanism?
- rhubarb leaves – soluble oxalates precipitate with Ca^{++}

hypokalaemia

frusemide

Epistaxis

anticoagulant rodenticides

Failure to clot

anticoagulant rodenticides

mouldy sweet clover – usually cattle in winter

GI tract

bloat

(can also be secondary to overall body toxicosis)

blue–green algae – hepatic toxin

colic

(seen as a sign with many toxicants)

lead – colic precedes CNS signs; more common with lower level lead toxication

constipation or diarrhoea

- narcotic or opioid antidiarrhoeal compounds (Lomotil, diphenoxylate, loperamide)
- oak – faeces dry and dark brown; diarrhoea may follow constipation (many toxicants produce diarrhoea by irritation, motility changes, hypersecretion)
- see also haematemesis
- copper toxicosis (acute) – greenish tinged diarrhoea
- nitrates in cattle - diarrhoea

dry mouth

nightshade – usually associated with lethargy, respiratory depression, and mydriasis

dysphagia (see Nervous system)

haematemesis

- anticoagulant rodenticides – warfarin, bromadiolone, brodifacoum
- NSAIDs – from ulcer formation
- Zinc phosphide

haemorrhagic diarrhoea or melaena

aflatoxicosis subacute and chronic – aflatoxin is highly modified coumarin; haemorrhage

anticoagulant rodenticides

- arsenic (including herbicides MSMA, DSMA) – bloody, rice– water diarrhoea
- NSAIDs – from ulcer formation
- thallium – also cracking skin and oral ulcerations

megaesophagus

lead

salivation

(will occur to some degree in most animals with gastric or enteric irritation or vomiting)

- ammonia (urea) toxicosis – associated with belligerent behavior in cattle
- carbamate insecticides
- mercury
- metaldehyde (molluscicide) – hyperesthesia also present along with muscle tremors
- organophosphate insecticides
- pyrethrin insecticides
- rhododendron, azalea, mt. laurel – primarily ruminants
- slaframine (red clover) – few other signs; may be clinically normal otherwise
- trichothecene (T2, Fusarium) – stomatitis caused by oral ulceration and slough produces drooling

stomatitis

- mercury – loosening of teeth and salivation also
- gastric/duodenal ulcers
- NSAIDs – block prostaglandins that normally provide mucus, decrease HCl release, and maintain perfusion

vomiting

- things that directly irritate the gastric or enteric mucosa – plants, corrosives, NSAIDs
- things that stimulate the emetic centre or CRTZ – drugs, ethylene glycol

Hair/Fur

- fescue (ergot) – summer syndrome in cattle horses results in retention of winter coat
- mercury – hair loss starting at tail head
- molybdenum tox (copper deficiency) – depigmentation of hair or wool; curly hair
- selenium – long hair of horse tail and mane fall out first (bob tail disease)

Hepatic

acute hepatic failure

- Paracetamol – especially dogs
- aflatoxicosis
- blue-green algae – get lethal intrahepatic hemorrhage within 1 day (acute) from toxin absorbed from GI tract
- iron tablets
- phenols – directly hepatotoxic
- phenobarbital – much less than primidone but has been reported to cause

drug induced hepatopathy

- primidone + phenytoin (Dilantin) – hepatopathy
- thiabendazole anthelmintics mebendazole and oxibendazole icterus
- aflatoxin chronic and subacute – fatty changes in liver due to inability of body to properly metabolize fats
- copper tox (chronic) – hepatic damage due to accumulation of copper within the liver
- pyrrolizidine (grounsel, ragwort, Senecio) – chronic hepatotoxicity; liver enzymes increased
- zinc (chronic or low dose) – due to hemolytic anaemia
- zinc phosphide

hepatic tumours

aflatoxin (Aspergillus flavus) – modify DNA template; hepatoma and carcinoma in trout, rats, and swine

Hyperthermia

(other than associated with fever)

- bromethalin rodenticide – secondary to hyperactivity and seizures
- molluscicide (metaldehyde) – 40 C+ is common
- strychnine – secondary to seizures
- water hemlock – (seizures and hyperactivity)

Lab Tests

(special tests)

- blood lead levels
- cholinesterase – organophosphates, carbamate insecticides – less than 25% normal is diagnostic
- NRBCs – lead (PCV usually greater than 30%; 5–40 NRBCs/100 WBCs)

Methemoglobinaemia

- paracetamol
- copper toxicosis (chronic) – sudden release of copper from liver stores
- nitrate toxicosis
- pine oil – only large dosages

Musculo-skeletal

lameness

- anticoagulant rodenticides – bleeding into the joint
- black walnut – shavings; equine; due to laminitis
- fescue/ergot – vasoconstriction to hoof - ischaemia

necrosis and slough (fescue foot)

selenium – hoof deformity circular crack at the coronary band; progresses down and breaks off

muscle cramping

black widow venom – abdominal cramping to the point of producing severe pain (no visceral pain on palpation)

muscle tremors

(may be nervous system toxicant)

- ammonia (urea) toxicosis – ear twitching, rapid eye blinking, progress to tonic convulsions
- bromethalin rodenticide – severe; from CNS stimulation; usually high dose syndrome
- organophosphate insecticides (nicotinic signs) – progresses to neuromuscular junction paralysis; chlorpyrifos
- hemlock – nicotinic signs, then block and paralysis
- pyrethroid (fenvalerate, permethrin) – progresses to seizure activity
- strychnine – early phases; progresses quickly to sensory– stimulated seizures
- tobacco (nicotine) – muscle trembling
- white snakeroot (USA) – not lactating animals; trembling more prominent after exercise

reflexes

see nervous system

Necropsy

(only included if significant findings)

brain

bromethalin – presence of vacuoles in white matter, non– inflammatory spongy degeneration of brain, spinal cord,

Gut

oil/fuel ingestion – black tarry material in rumen

Lungs

paraquat – lungs are severely congested and fibrotic; look like liver

Nervous system

ataxia, incoordination, paralysis

- anticoagulant rodenticides – if they cause bleeding into spinal cord or cranium
- blue green algae (anatoxin a) – nicotinic cholinergic agonist produces neuromuscular block; including muscles of respiration
- botulism – flaccid paralysis (NMJ block) intact sensory
- bracken fern – equine signs; thiaminase results in neuropathy; get arched back, incoordination, tremors
- chlorinated hydrocarbon insecticides – spastic gait; progresses to seizures
- coral snake venom – flaccid paralysis by a curare–like effect on the motor end plates
- ethylene glycol – early phases (stage I); alcohol–like drunkenness; 1–3 hours after ingestion
- fungicides
- herbicides – atrazine and others
- horsetail or equisetum – same signs as brackenfern in horses (no signs in cattle)
- ivermectin – hind limb ataxia; progresses to coma
- karaka berries (Corynocarpus laevigatus) – weakness and hindlimb paralysis
- locoweed – due to selenium accumulation; produces blind staggers or polioencephalomalacia in cattle and sheep
- mercury (acute) – incoordination; abnormal posturing
- monensin (Rumensin) – weakness in hindquarters
- oil/fuel ingestion – incoordination; head shaking, mental confusion
- organophosphate insecticides (nicotinic signs) – progressive ataxia and paralysis; NMJ block
- organophosphate insecticides (delayed neuropathy syndrome) – 1–3 weeks after acute exposure
- pigweed – weakness, incoordination, trembling, and paralysis of rear legs (perirenal oedema)
- hemlock – nicotinic signs earlier - progress to paralysis
- rhubarb leaves – soluble oxalates - nephrotoxicity
- selenium – blind staggers; paralysis of tongue and pharynx
- tick paralysis – ascending afebrile motor paralysis with sensory still intact; normal anal tone
- tobacco – nicotinic tremors progressing to paralysis

- white snakeroot – progressive weakness in cattle; unable to stand; lactating animals less affected

behavior changes – aggressive, belligerent, etc.

- ammonia (urea) toxicosis – belligerent; bellowing; stampeding; rapid eye blinking; ear twitching; ruminants
- chlorinated hydrocarbon insecticides – belligerent behaviour in cattle
- lead – continuous barking, vocalizing, running in circles, biting indiscriminately (looks like distemper)
- locoweed (astragalus or oxytropics)

blindness

- anticoagulant rodenticides – cranial bleeding
- enrofloxacin (Baytril) in cats
- ivermectin – miosis or mydriasis can also occur
- lead – collapse of small arterioles and disruption of cerebral blood flow
- selenium – get lingual and pharyngeal paralysis also
- metaldehyde
- closantel

coma

(many toxicants produce coma in the terminal phases)

- alcohol (isopropyl)
- ethylene glycol – from e.g. itself and stage I metabolites producing CNS depression
- ivermectin
- water hemlock

deafness

- aminoglycoside antibiotics
- chlorhexidine

dysphagia

coral snake venom – flaccid paralysis of NMJ

selenium

hyperaesthesia

metaldehyde (molluscicide)

black widow venom – acute painful abdomen because of severe muscle cramping

hyperreflexia

bromethalin – primarily hind limb, other CNS signs

paralysis

(see Nervous system: ataxia above)

seizures and seizure–like syndromes (extensor rigidity, opisthotonus)

- ammonia (urea) – excitement then tonic convulsions
- bromethalin – from increased CSF pressure in CNS; associated with lower, chronic exposure
- chlorinated hydrocarbon insecticides – especially cattle; fasciculations and spastic gait precede seizures
- lead – reflects CNS irritation; convulsions; mistaken for distemper encephalitis
- organophosphate insecticides – CNS cholinergic effects
- pyrethroids (fenvalerate) and permethrin – preceded by excitation and tremors
- strychnine – sensory/sound stimulated; tetanic seizures; sawhorse stance
- sodium fluoroacetate (1080) rodenticide – frenzied running; violent 1 minute seizure; die during long seizure
- water hemlock – death from respiratory centre paralysis
- zinc phosphide
- throat paralysis
- white snakeroot – equine

Ocular System

blindness

see nervous system

lacrimation

anything that stimulates the parasympathetic nervous system (OPs, carbamates, etc.)

anything that is a direct ocular irritant (household products, irritant gasses like ammonia or sulphur)

miosis

- carbamate insecticides
- ivermectin – mydriasis can also occur; loss of menace reflex
- organophosphate insecticides

mydriasis

ammonia toxicosis – associated with hyperactivity, belligerent behavior

- ivermectin – absence of menace reflex / miotic
- thorn apple (Datura) – atropine toxicosis
- nightshade plants (Solanum species) – lethargy, dry mouth, GI irritation, respiratory depression

Respiratory System

bronchoconstriction

- organophosphate insecticides – dyspnoea from this and increased secretions
- smoke
- bradypnoea from respiratory centre depression
- opioids, narcotics, and dextromethorphan (OTC cough suppressant)
- organophosphate insecticides – CNS effect; dyspnoea also from paralysis of respiratory muscles (nicotinic signs)
- sulphur gas – concentrations higher than 200 ppm

dyspnoea or inability to ventilate from miscellaneous causes

- coral snake venom – paralysis of respiratory muscles results in death
- nitrogen dioxide – turns to nitric acid in contact with water in lungs; silo fillers disease; pulmonary oedema and pneumonia
- paraquat – lungs become fibrotic
- pine oil – chemical pneumonitis; passes across from blood to alveoli if absorbed systematically
- strychnine (or other tetanic seizure compounds) – inability to expand chest during tetanic seizure
- sulphur oxide (smog, acid raid) – chronic effects cause pulmonary fibrosis
- zinc phosphide

haemoptysis

anticoagulant rodenticides – if they cause bleeding into the alveoli or pulmonary air space

pulmonary oedema

ANTU (alpha naphthyl thiourea) rodenticide – increased vascular permeability

Tryptophan in pasture grasses or crops

tachypnoea

- carbon dioxide – direct respiratory centre stimulation until CO_2 gets high enough to depress CNS
- ethylene glycol – acidosis
- thorn apple (Datura) – atropine toxicosis; blockage of parasympathetic nervous system
- phenol – direct stimulation of the respiratory centres

Renal

acute renal failure

- arsenic (subacute) polyuria progressing to oliguria as a result of nephrosis; GI signs also seen
- ethylene glycol – metabolites are nephrotoxic
- cholecalciferol rodenticides – may or may not have mineralization; ischaemia from smooth muscle constriction
- Ochratoxin – porcine nephropathy syndrome; can affect calves but adult cattle resistant
- Raisins, sultanas, grapes – dogs
- Easter and Day lilies – cats
- Zinc phosphide

perirenal oedema

- pigweed (*Amaranthus*) – pigs and calves - renal failure
- ischaemic papillary necrosis
- NSAIDs – secondary to blockage of prostaglandins that normally dilate renal arterioles

Reproductive tract

abortion

- carbon monoxide – foetal haemoglobin is converted to carboxyhaemoglobin resulting in fetal death
- nicotine – pigs; usually nicotinic signs predominate
- fescue (ergot) – abortion or weak calves; get agalactia
- vitamin E / selenium – interference with oxidative processes in the foetus
- macrocarpa / cupressus - isocupressic acid
- pine trees: western, ponderosa
- subterranean clover (Trifolium subterraneum)
- lupins (Lupinus)

- hybrid Sudan grass (sorghum)
- corticosteroids
- nitrates
- halogenated dioxins
- vitamin A & D

male infertility

gossypol

masculinisation

- anabolic steroids
- halogenated dioxins

oestrogenic compounds

- mycotoxins-zearalenone and zearalenol
- Trifolium and Medicago (lucerne)
- soybean (Glycine max)
- DDT and DDE

prolonged gestation

fescue (ergot) – mares

reproductive failure

- chlorinated hydrocarbon insecticides – thin shells in raptors
- Ochratoxin – egg shells rubbery in poultry
- selenium – due to interference with oxidative processes in the foetus

teratogenesis

- tobacco (*Nicotiana*)
- poison hemlock (*Conium*)
- Sudan grass (*Sorghum*)
- laythyrism (*Lathyrus*)
- fescue (with ergot *Acremonium coenophialum*)
- mercury
- selenium
- halogenated dibenzodioxins or aromatics
- vitamin A
- corticosteroids
- griseofulvin
- thalidomide
- cocaine
- ethanol

vaginal prolapse

- zearalenone (F–2, Fusarium) – oestrogen effects; males get prepuce enlargement; onset of oestrus
- growth promotants-oestrogenic

Sudden death

- aflatoxicosis (acute) – hepatomegaly
- ammonia toxicosis – within hours
- anticoagulant rodenticides – if they bleed into pericardium and cause cardiac tamponade
- arsenic – signs within minutes, death within hours
- carbon monoxide – haemoglobin tied with CO molecule; skin is characteristic cherry red color
- water hemlock – death within 15 minutes to 1 hour possible; seizures precede
- yew – cardiac glycoside toxin

Skin

colour

- see also Methaemoglobinaemia
- carbon dioxide – cyanosis (increase in CO_2 in haeme)
- carbon monoxide – bright cherry red due to alteration of haeme pigment
- cyanide – bright red due to retention of oxygen on haeme molecule
- thallium – red skin

cracking

- arsenic – topical application (subacute) cracking with bleeding
- thallium rodenticide – oral ulcerations also

erythema

corrosives (acid, alkali, oxalates)

St. John's wort – photosensitization and "sunburn" in non–pigmented areas due to fluorescent pigment in plant

haematoma

any toxicant listed with anaemia; blood loss

pustules

mercury – also get ulcers and eczema

ulceration

corrosives (acid, alkali, oxalates)

mercury

sloughing

- brown recluse – necrotic centre of bite, erythema, white swelling in rings (bullseye)
- ergot (fescue) – ischaemic necrosis of ear tips, tail, hoof/claw, nose
- trichothecene (T–2, Fusarium) – contact epithelial necrosis
- white-tailed spider as with brown recluse

swelling

- anticoagulant rodenticides – bleeding into the fascial planes
- brown recluse (early stage)
- oil/fuel topical application

Urinary System

increased urination (volume or frequency)

- ethylene glycol – initially diuretic effect from e.g. excretion; PU/PD follows due to renal failure
- thornapple – atropine toxicosis; increased frequency of urination
- organophosphate insecticide – increased frequency
- sodium fluoroacetate (Compound 1080) rodenticide – straining to urinate

haemoglobinuria

- paracetamol – secondary from haemolysis
- copper toxicosis (chronic) – copper release from liver causes haemolysis
- red maple leaves – haemoglobinuria; equine
- zinc (subacute or chronic) – from haemolysis

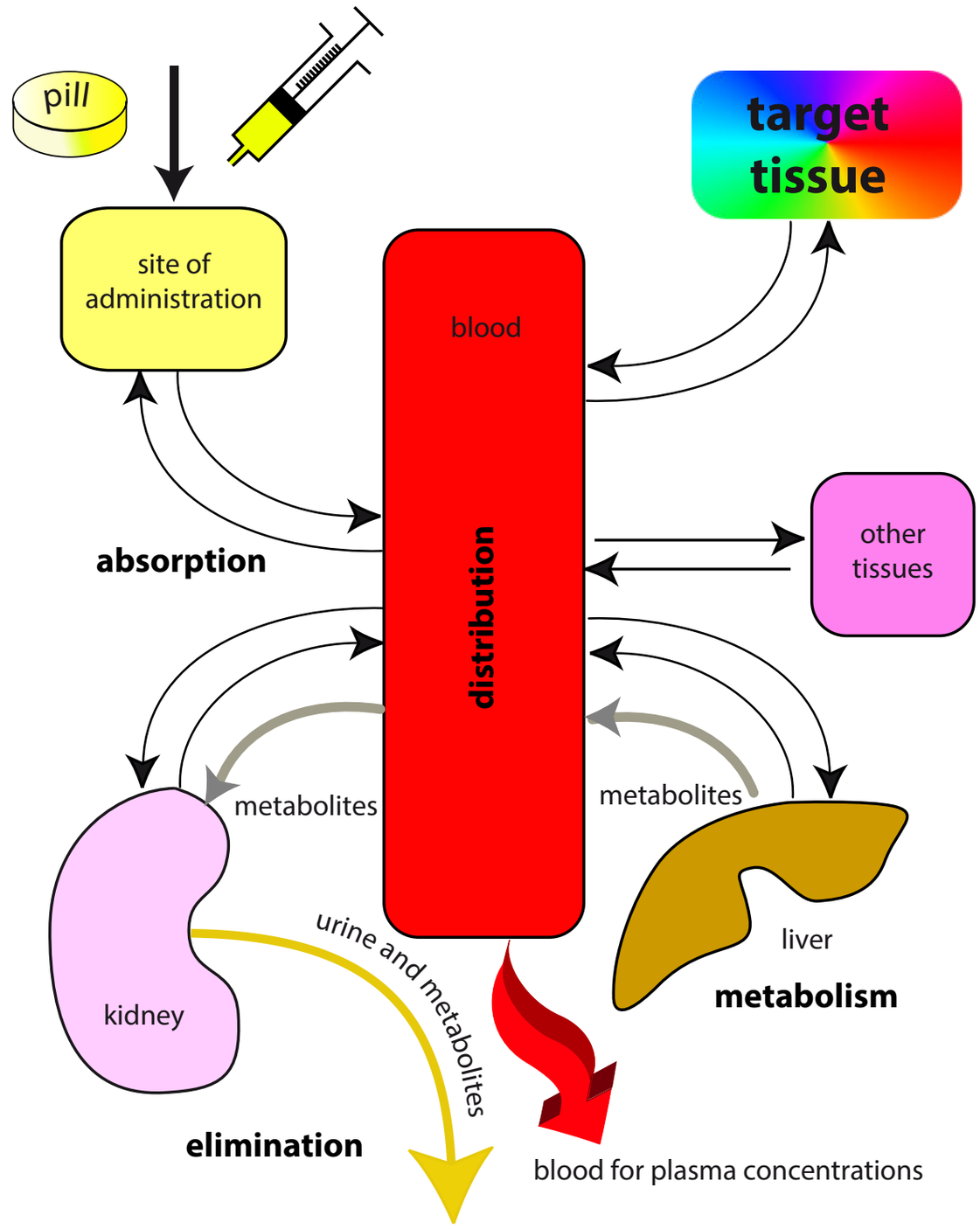
TABLE 1.4.1 Emergency poisons kit - view in portrait

Compound	Poison	Action/Dose/other
acetamide	1080	Dissolve 15g acetamide in 1L warm 5% glucose. Give 10mL/kg over 15min and reduce to 8mL/kg/hr until finished. Make up more and give at 5mL/kg/hr as needed. Heart rate may greatly increase.
activated charcoal	for most poisons except heavy metals, acids and alkalies	Adsorbs poisons. Make up a slurry of 1 gram per 5 ml of water. Add sorbitol or non oily laxative. Give 1-4 grams/kg Orally Dogs; Cattle 1kg/500kg
adrenaline (epinephrine)	anaphylactic shock	5 - 20μg/kg (1:1000 - 0.1 – 0.5 ml) SC if used IV then dilute 1 ml of 1:1000 with 9 mls of normal saline and use 0.5 to 5 ml depending on species and weight
mepyramine	for allergic reactions	1-2 mg/kg
apomorphine	emetic for dogs	Put 1 or part of 1 tablet subconjunctivally (eye) until vomiting occurs and then wash out the remainder of the tablet.
atropine	carbamate and organophosphorus poisoning	For bradycardia 0.01-0.02 mg/kg IV, IM or SC OP/Carbamate 0.05-0.25 mg/kg slowly IV and give 0.15 mg/kg SC may need to repeat if signs return
calcium EDTA or versenate	lead zinc poisoning	25 mg/kg SC q6h as a 10 mg/ml solution in saline for 5 days, then 5 days off, then 5 days more; or use d-penicillamine po.
dexamethasone	shock	4 mg/kg IV
diazepam	seizure control	0.5 mg/kg IV repeated up to 3 times
dimercaprol (BAL)	arsenic poisoning	5 mg/kg IM then 2.5 mg/kg q3-4 h for 2 days then q12h prn
Epsom salts magnesium sulphate	cathartic (strong laxative)	Speeds up elimination of the poison. Dog ½ - 1 g/kg; Cat max of 2-5 g; Large animal 100-200 g; sheep, goat or pig 25 –125 g.
ethanol (7%) made up in Hartmann's	ethylene glycol poisoning (antifreeze)	Dogs 600 mg/kg IV once followed by 100-200 mg/kg/hr IV for 48h
ethanol (20%)	ethylene glycol poisoning (antifreeze)	Dogs: 5.5 ml/kg IV q4h for 5 times then q6h for 4 more time Cats 5 ml/kg IV q6h for 5 time then q8hr for 4 more times
frusemide	diuretic and reduce calcium-cholecalciferol	2-4 mg/kg IV or SC every 6-8 hours
n-acetyl cysteine (Parvolex)	paracetamol, nitrite or selenium poisoning	140 mg/kg IV once; then 70 mg/kg q6h IV for 3 days or as required. Must use a 5% solution!
naloxone (Narcan)	opioid overdose	0.01-0.04 mg/kg IV, IM, SC repeated q1-2h as needed
pentobarbitone	seizure control	2-30 mg/kg IV to effect NB – slow onset
phenobarbitone	seizure control	Dogs 2-6 mg/kg IV to effect q6-12h Cats 1 mg/kg IV to effect q12h NB – very slow onset
pralidoxime (2-PAM)	op poisoning (dogs & cats)	10-40 mg/kg slowly IV then SC q 8-12h
sorbitol	laxative	70% solution at 1-2 ml/kg (mix with Activated charcoal)
xylazine	emetic for cat	0.2-0.4 mg/kg SC
vitamin K1 (Konakion)	anticoagulant poisoning	1-5 mg/kg/day SC, PO If given IV, administer slowly to avoid anaphylaxis

Chapter 2

Pharmaco-kinetics

This part covers movement of drugs in the animal and how the animal gets rid of them.



Pharmacokinetics

Pharmacokinetics

- ☑ There are usually four components:
- ☑ **absorption** from site of administration
- ☑ **distribution** around the body including to the target tissue
- ☑ **metabolism** to something which can be excreted more easily (although some drugs are excreted unchanged)
- ☑ **elimination** from the body, usually via the kidneys and urine

There are usually four components to pharmacokinetics (as opposed to pharmacodynamics)

1. **absorption** from site of administration
2. **distribution** around the body including to the target tissue
3. **metabolism** to something which can be excreted more easily (although some drugs are excreted unchanged)
4. **elimination** from the body, usually via the kidneys and urine

These processes differ between animals of different species, age, sex, health status and size, and within an individual from time to time.

Understanding pharmacokinetics is important because unless the drug reaches a sufficient concentration at the target cells it will not work. If the concentration at other sites is high enough, you will get side effects. The effect is usually proportional to plasma concentration rather than dose (absorption can be very variable).

It is useful to think of the body as a number of compartments with barriers between them that the drug has to cross to get from the site of administration to the target tissue and then out of the body.

Consider a cat that has been bitten on the tail by another cat. These puncture wounds are usually infected with *Pasteurella* spp. and an abscess will form rapidly unless the bacteria are killed with an antibiotic (usually penicillin). To kill the bacteria, there must be a sufficient concentration of penicillin in the fluid bathing them for a sufficient length of time. It is not usually possible to apply the penicillin directly to the bacteria; the cat is usually given a tablet or injection which means that the penicillin has to get from the cat's stomach or the injection site to the extracellular fluid around the bite in the tail and stay there for long enough to kill the bacteria. In the meantime, the cat's kidneys will be doing their best to get rid of the penicillin into the urine.

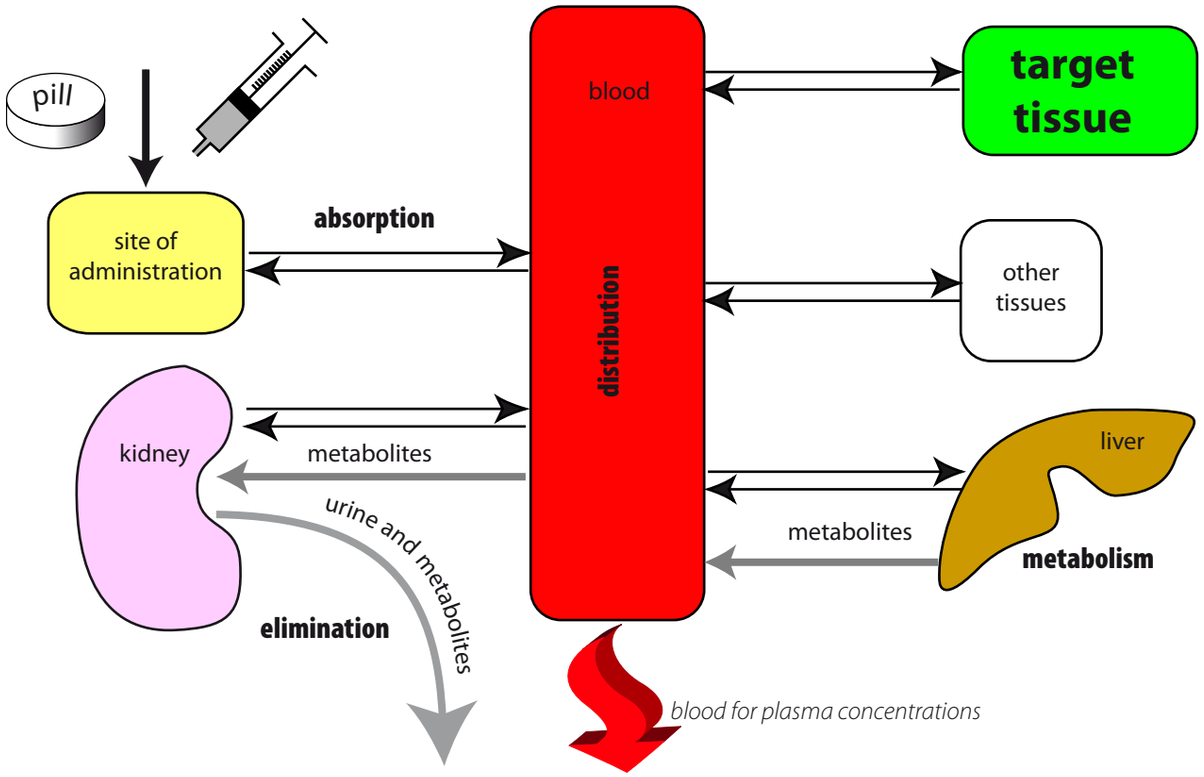
The penicillin thus has to be **absorbed** from the stomach or injection site, **distributed** to the tail (and other tissues) and **eliminated** by the kidneys (penicillin is not **metabolised** to any great extent). Penicillin is a very safe drug so the simplest way of ensuring that the bacteria are killed is to overdose the cat. With most drugs however, overdosing will cause serious problems with side effects: getting exactly the right concentration of drug in the target tissue requires a knowledge of pharmacokinetics. It is largely a matter of giving the right amount of drug by the right

route for that particular animal, and requires skill and judgement since no two animals are exactly the same.

Further reading

Journal of Veterinary Pharmacology and Therapeutics, 2004, (6). A special issue with review papers on various aspects of pharmacokinetics.

DIAGRAM 2.1.1 Pharmacokinetics



Drug concentrations are usually measured in plasma (because it is easier) rather than the target tissue, which would be more useful. The liver is not the only organ which metabolises drugs, but it is probably most important for most drugs.

MOVIE 2.1 Pharmacokinetics 2

Another way of looking at pharmacokinetics.

Absorption

Absorption

- ☑ most drugs must be absorbed to act.
- ☑ iv administration bypasses drug absorption
- ☑ absorption depends on lipid solubility and ionisation
- ☑ drugs are often formulated to provide delayed absorption
- ☑ bioavailability gives an indication of the extent of absorption

This is the process that involves the drug moving from its site of administration into the blood. A major factor here is the route of administration. Once the drug is administered, it must dissolve in the body fluids to be absorbed. This step is manipulated by altering the formulation of the drug.

Administration

Possible routes of administration:

- oral (po = per os)
- intramuscular (im)
- subcutaneous (sc (SQ in USA))
- topical
  - epithelial surfaces
  - mammary gland
  - nasal mucosa
  - cornea
  - intact skin (pour on, ointments)
- inhalation
- intraperitoneal (ip)
- spinal
  - epidural
  - intrathecal (it)
- rectal
- intratracheal
- (sublingual - not usually practical in animals)

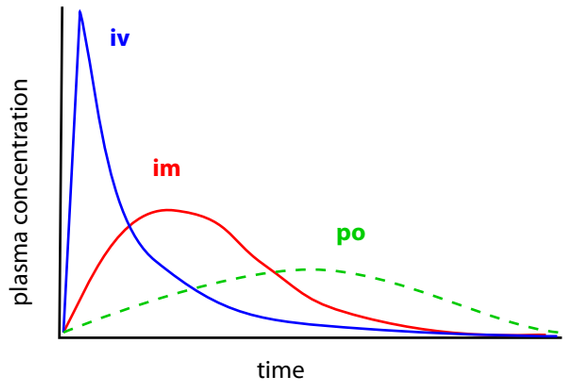
Intravenous (iv) administration bypasses the absorption process but other routes give rise to variation.

Effects Of Route Of Administration On Absorption

As a very rough rule, iv injection has a peak plasma concentration in seconds (at the end of injection), im in 15 mins, sc / po in 30 mins - 1 hour. This will depend on many factors. Peak effect will usually occur several minutes after peak plasma concentration, depending on the drug and the site of action. There are many exceptions to all this!

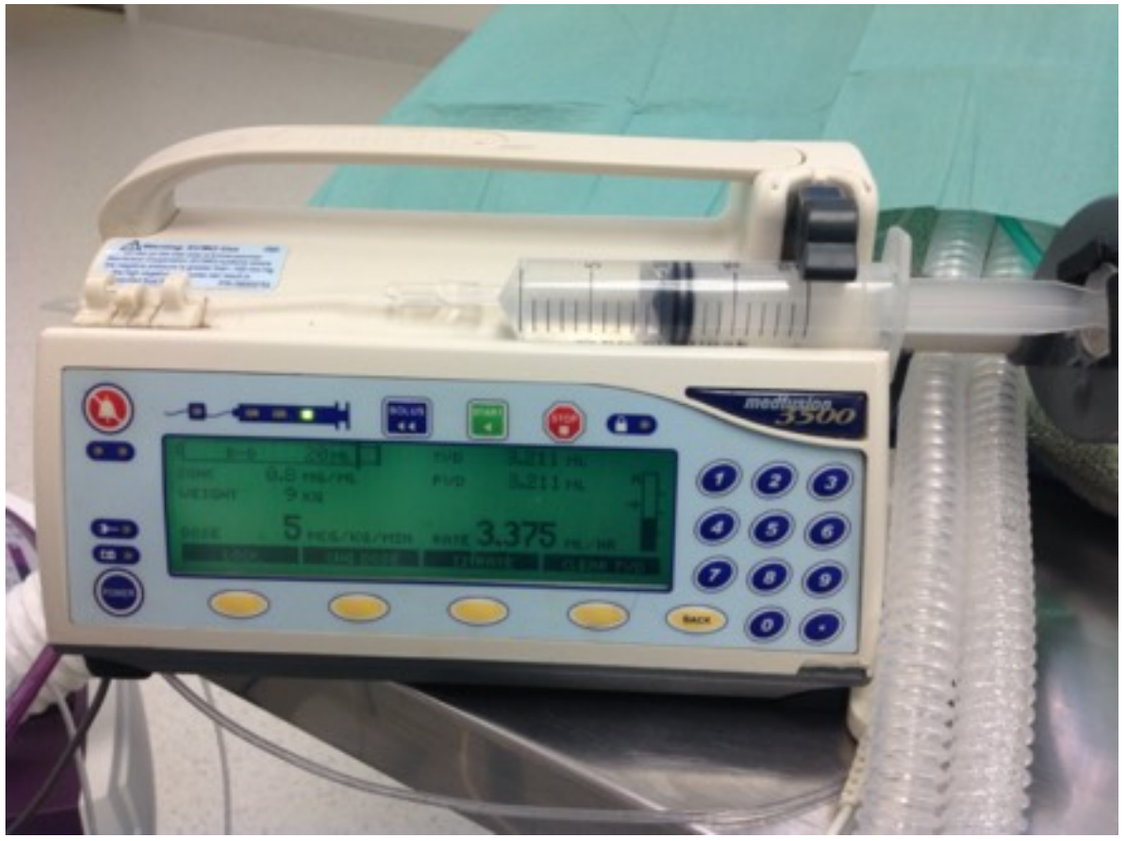
Since it is usually desirable for drugs to be present at their site of action for a specified period, it is either necessary to repeat the dose often or give a large dose in such a way that the absorption is slow and the drug is being continuously released into the plasma. This can be done by using different routes of administration, by altering the formulation of the drug or by using a device which releases the drug slowly.

DIAGRAM 2.2.1 Concentration - time curves



Plasma concentration time curves after administration of the same dose of drug by different routes

IMAGE 2.1 Syringe pump



An iv infusion device and be used to control iv "absorption" where this is critical.

Intravenous

The "absorption" phase is the time it takes to inject the drug. Usually iv injections are made reasonably quickly (30s - 1min) so that the plasma concentration reaches an almost instantaneous peak and rapidly declines as the drug is distributed away to other tissues. However, intravenous injections can be made with an infusion pump so that the rate of "absorption" can be directly controlled. This is usually only necessary during anaesthesia or intensive care where potentially dangerous drugs are given to sick animals, or where the dose has to be titrated directly to the effect. For instance, if an animal's blood pressure is critical, a drug which increases blood pressure, such as adrenaline, can be infused to reach the target blood pressure. Vasodilators are sometimes used in the same way.

MOVIE 2.2 Intravenous injection

iv injection for induction of anaesthesia in a greyhound.

IMAGE 2.2 iv catheter

An iv catheter being placed in the medial saphenous vein of a cat.

Intravenous injections are usually only used where the drug has to act rapidly (anaesthetics and sedatives), which have to be given in large volumes (fluids) or which are irritant (parenteral nutrition solutions).

Any superficial vein can be used: in dogs and cats the cephalic vein is usually used, although the lateral (dogs) or medial (cats) saphenous vein is also used. In large animals, the jugular vein is usually used. In pigs and rabbits, the marginal ear vein is used.

Catheters can be placed into veins so that an iv injection can be made quickly and reliably. If the vein is collapsed, usually because of shock, it may be necessary to cut down onto it. A catheter is always placed in this sort of situation.

Oral

The surface area of gut available for absorption of the drug is the most important factor effecting the rate of absorption. Disease processes such as gastroenteritis, neoplastic infiltration or villus atrophy may significantly change the available absorptive surface area. This should be taken into account before the administration of an oral medication.

Dilution of the drug by administration with feed or with fluid would retard the rate of drug absorption since the drug diffuses down a concentration gradient. Some foods contain substances which bind to the drug, preventing absorption.

The concentration gradient is the main factor affecting the rate of drug absorption (rather than purely the drug concentration in the gut). Therefore, the drug concentration in the blood or extravascular fluid is also an important determinant of the rate of drug absorption. Factors which affect the drug concentration in the blood or extravascular fluid include the rate of distribution and the rate of elimination of the drug. More importantly, in the local environment of the absorptive process, the rate of blood flow and / or lymph flow determines to a large extent the steepness of the concentration gradient. Blood flow and lymph flow are dependent upon the timing of the drug administration with respect to meals, exercise and other variants of cardiac output.

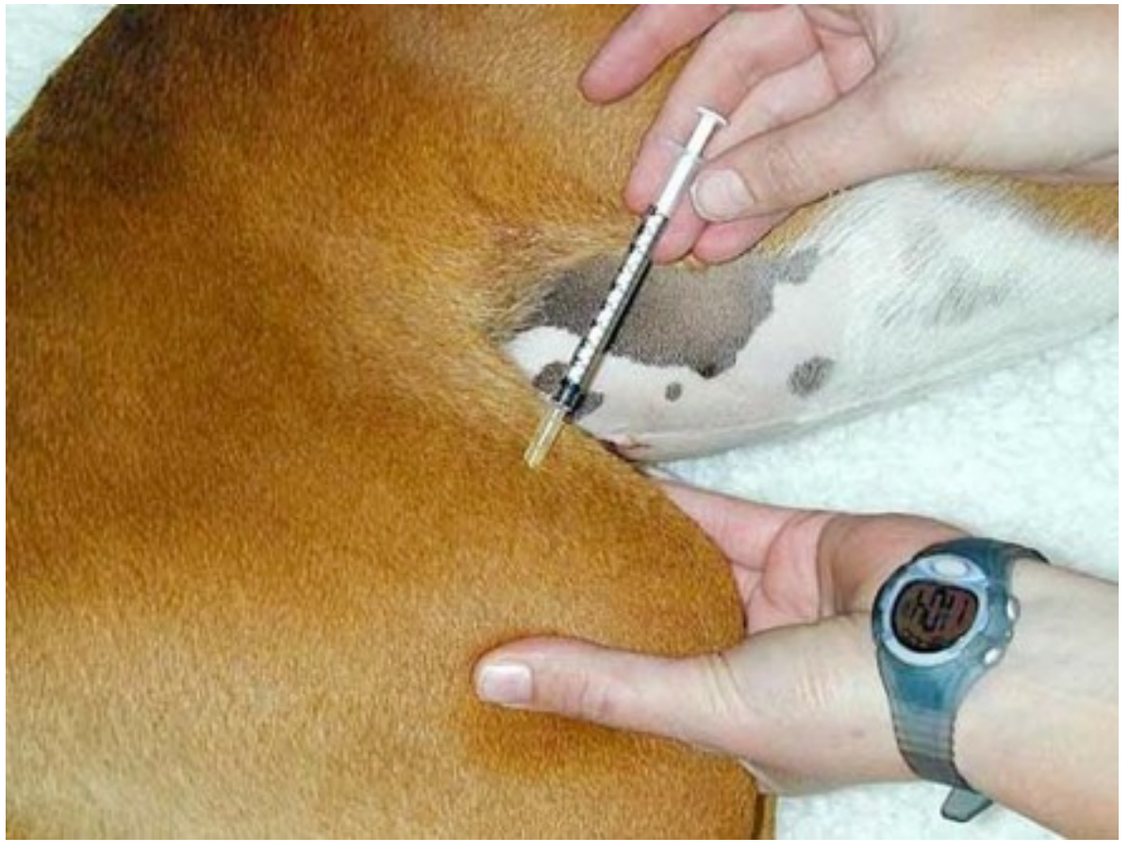
Drug absorption can also be altered by alterations in the permeability of the gut wall. Diseases such as infiltrative neoplasia, inflammatory bowel disease and mucosal injuries by viruses, bacteria, parasites and caustic chemicals can all increase the rate of absorption of drugs. In addition increases in the permeability of the gut wall can result in the absorption of drugs not normally absorbed from the gut. Obviously, if the animal vomits its medication up, the drug will not be absorbed. Gastroenteritis usually results in a faster than normal passage of gut contents, the drug may not be there long enough to be fully absorbed. Therefore care needs to be taken in consideration of administration of all drugs to animals with gastrointestinal disease.

Intramuscular

Surface area can be altered by injecting a given dose in aliquots to multiple sites, thus increasing the rate of absorption.

The concentration of drug in the injection will also determine the steepness of the diffusion gradient for drug absorption. The concentration of the drug in the injection might be altered after injection due to a formulation which is not isosmolar. Drug concentration in the tissue fluid will also effect the diffusion gradient. Both the rates of lymph and blood flow vary from muscle to muscle and also vary dependent upon on exercise, cardiac output and catacholamine release.

FIGURE 2.1 Intramuscular injection in a dog



The quadriceps is the largest and safest site for im injection in dogs.

The pH in the muscle may vary from one muscle to another as a function of exercise and tissue perfusion. Therefore difference in the rate of absorption of an intramuscular injection will vary dependent upon the formulation used and the injection site. The cranial third of the neck is the preferred site in food animals (both for better absorption and reduced residues in edible meat), the quadriceps or deltoid muscles in small animals (although im injections are not often used in small animals because they are painful).

There are only a few examples where the permeability of blood vessels in the area of an injection might significantly alter the expected rate of drug absorption. In particular, it is important to ensure that an injection is not made into an inflamed area where blood vessel permeability might be expected to have changed. The proximity of the injection to impermeable boundaries such as fascial planes and fat is an important determinant of the rate of drug absorption after intramuscular administration and is to some extent controllable by appropriate choice of injection site.

If an "intramuscular" injection actually goes into fat (easy with pigs) or between fascial planes (easy with cats), absorption will be variable but probably much slower than expected. If it goes into a vein, absorption will be much faster than expected, resulting in a relative overdose of organs with a high blood flow, and probably side effects.

Subcutaneous

The rate of absorption is likely to be similar / slower than an intramuscular injection but much more variable because of differences in the rates of blood and lymph flow to the skin due to species, gender, age, environmental temperature and body temperature. Care needs to be taken that the drug is not given into fat but is truly subcutaneous, since fat is poorly perfused. The usual site is over the ribs, or in the scruff in small animals.

Intramammary

In cows with mastitis, the usual route of drug administration is intramammary. The drugs either directly affect bacteria in the milk or cross into macrophages and mucosal cells where the bacteria are hiding. Significant systemic absorption can occur; with dry cow therapy, nearly all the drug is absorbed systemically and eliminated. Great care is needed to ensure that dirt on the end of the teat is not injected as well as the drug.

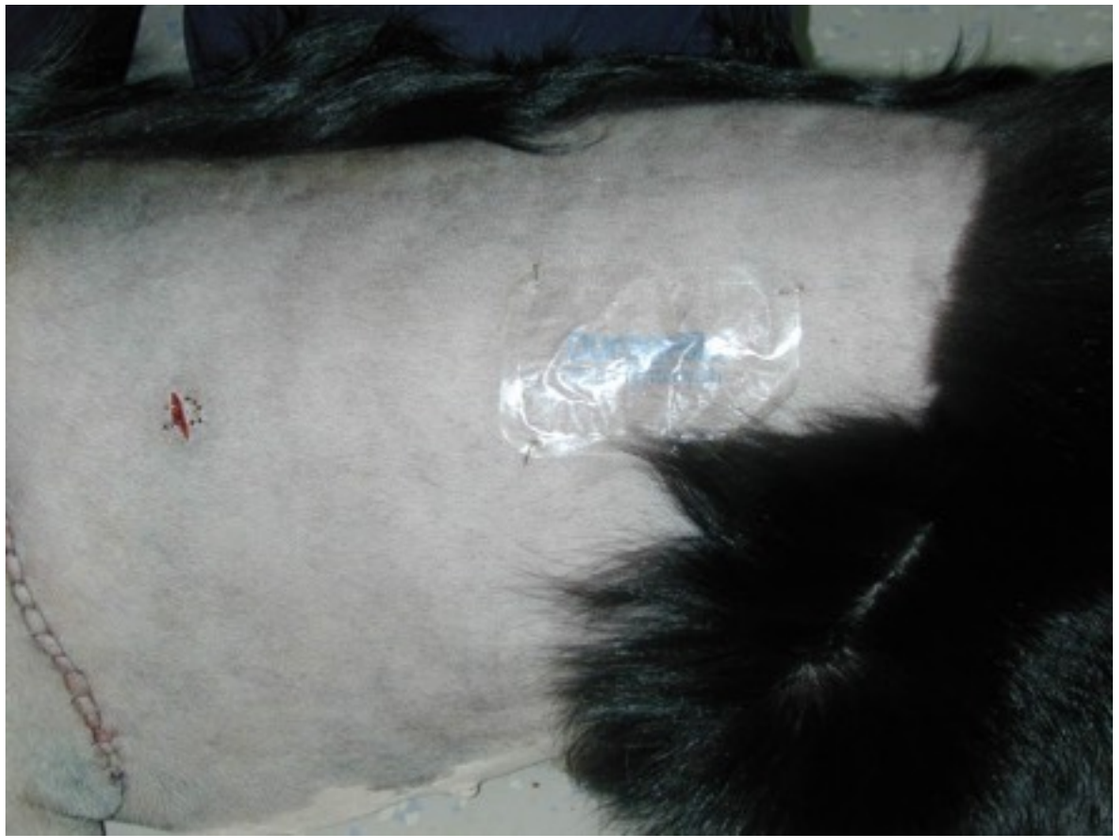
Other Routes of Administration

Topical

Transdermal patches containing drugs can be applied to hairless skin. The drug is absorbed either by simple diffusion (which is slow), by solvent carrier assisted diffusion (which can be faster) or by voltage assisted diffusion. Transdermal patches containing fenatanyl have potential for the administration of analgesia to animals both for chronic pain and for acute pain post-operatively. They are often used in people and have been used clinically in dogs, horses and pigs. There are species differences in absorption, but they usually take 24 hours to reach analgesic concentrations in the brain, which limits their usefulness.

Other topically administered drugs may be absorbed transdermally also. Sometimes this absorption is by design, eg, pour on anthelmintics, and sometimes an accident, resulting usually from a breakdown of the cutaneous barrier. Breakdowns of the cutaneous barrier occur with disease processes such as inflammation and where wounds exist. Drugs used in this way include nitroglycerine (see cardiovascular notes) and many anthelmintics for large animals. Care is necessary as in some

IMAGE 2.3 Topical administration



A fentanyl patch applied to a dog for analgesia after thoracotomy.

circumstances the skin can act as a reservoir of drug. It is worth bearing in mind that any drug designed to cross an animal's skin will also cross human skin.

Drugs applied topically to the eye or subconjunctivally in the treatment of ocular disease are frequently absorbed systemically. There have been cases of iatrogenic Cushing's syndrome being caused by steroid administration in topical preparations to the eye of the dog.

Drugs applied to the nasal mucosa can be rapidly absorbed. This route is undergoing investigation in people for the administration of peptides, which would be broken down in the gut if given orally. Many new drugs are peptides, so this route may become more important in future.

Rectal

The administration of drugs by rectal suppository is not often used in veterinary medicine. Very little work has been done studying the pharmacokinetics of rectal suppositories in domestic animals. However, this route of administration may be appropriate for administering drugs to animals with upper gastrointestinal disease or with protracted vomiting.

In large animal practice drugs are sometimes administered in pessary form into the lumen of the uterus. Many drugs administered in this fashion are absorbed systemically - may be important with respect to drug withholding times for slaughter.

Inhalation

Some soluble drugs can be applied by nebulisation and inhalation of the resulting aerosol. These drugs are used mainly for local treatment of respiratory tract disease. Doses need to be calculated carefully because systemic absorption does occur through the mucosa. Drug classes which can be applied in this fashion include mucolytics, antibiotics and β adrenergic agonists. In emergencies, adrenaline is sometimes given intra-tracheally and is absored rapidly across the mucosa.

Volatile anaesthetics are administered by inhalation and absorbed very rapidly across the alveolar membranes (see anaesthesia notes).

Intraperitoneal

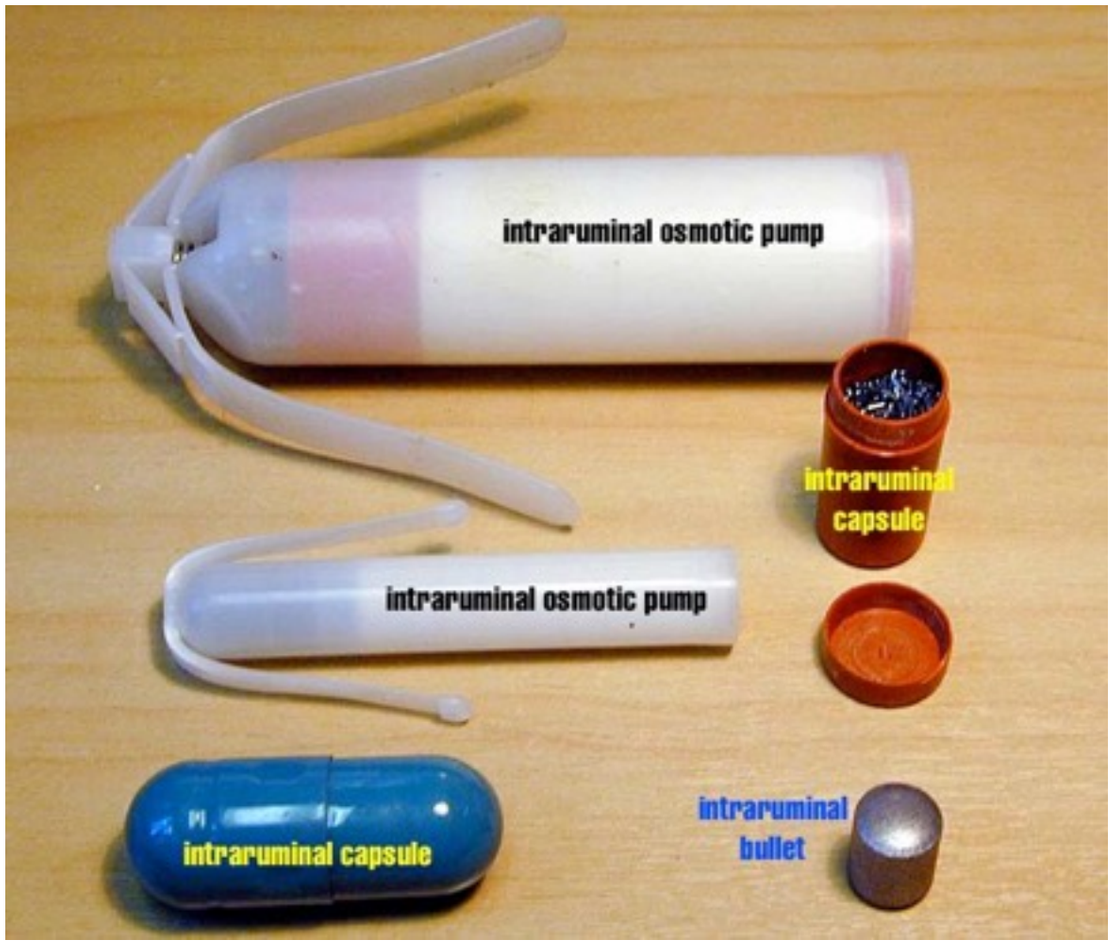
The intraperitoneal (ip) route used to be used commonly. Now it is only used in laboratory animals with no or very small veins. Everything else should have drugs given iv.

Dissolution

The solubility of the drug is important in determining the rate of drug absorption. Solubility is a function of the molecular structure of the drug and the fluid surrounding it. Solubility can be altered by forming salts of the drug; eg, morphine chloride is more soluble than morphine sulphate and both are much more soluble than morphine base. For weak acids or weak bases the solubility of the drug varies with the drug's pKa and the environmental pH of the medium in which the drug is dissolved. This pH varies from site to site along the gastrointestinal tract and in similar sites between species (the rumen has a pH of about 8.5; the monogastric's stomach about 1.5). Exercise and inflammation can alter pH at injection sites.

The solubility of drugs might vary from one proprietary preparation to another since the formulations may have different excipients or a different pH. Many drugs are prepared as relatively insoluble salts to ensure a slow absorption and a prolonged effect. Some are suspensions of finely divided particles; these give a sustained release but will block arterioles if injected iv (eg lente insulin).

FIGURE 2.2 Devices to slow dissolution



Formulation of the drug is very important for oral preparations. Some tablets are coated to protect them from acid in the stomach; they then dissolve in the intestine where the pH is completely different. The particle size will affect the rate of dissolution (bigger is slower), the excipient (often lactose) will affect how quickly the tablet breaks up. An extreme example is trace element supplements for ruminants, where the excipient is sometimes glass!

Some drugs are practically insoluble in water and are dissolved in lipid emulsions or other vehicles for injection. Some of these vehicles can be dangerous in some species, eg, polyethoxylated castor oil will cause massive histamine release in dogs (the same thing can happen in other species, but the risk is acceptably low). Oily injection diluents can act as depots from which the drug is slowly leached. The lipid solubility of the drug and the nature of the oil determine the absorption. Waxes are often used for situations such as dry cow intramammary preparations where a slow release of drug is required (typically 30 days). Where extremely slow absorption is required (100 days), such as growth promoting hormone implants, silicone rubber is used. A variety of plastics are used for intravaginal delivery of hormones in cattle and sheep, these implants usually have a string attached and are pulled out when they have finished delivering the drug.

Mechanical devices such as osmotic pumps are occasionally used. These are capsules containing a compartment with a hypertonic solution and a semipermeable membrane open to the ECF. As fluid diffuses across the membrane the hypertonic compartment expands, pushing the drug out of the other end of the device. These give accurate drug delivery which can act over several months but are expensive. Similar pumps are used for slow delivery in the rumen of oral drugs such as anthelmintics and trace elements.

Implanting devices to release a drug a a precise rate in the right place is likely to increase in the future; pumps with electric motors are increasingly being used in people for insulin administration and have been tried in cattle for hormone manipulation.

Drugs for intravenous injection bypass the dissolution process so they must already be dissolved in water, or in a form which will quickly dissolve once injected. Relatively fat soluble drugs are usually in the form of an emulsion, so the drug is at

least miscible with the plasma. Emulsifiers used like this can often cause side effects.

Drugs which are not in solution or in an emulsion of some sort should not be given iv.

Passage Across Membranes

For a drug to get from the site of administration to the blood, it has to cross cell membranes. (It also has to cross membranes to get from the blood to other tissues). Thus a drug given orally must cross into a mucosal epithelial cell, out the other side of the cell, across any connective tissue and through an endothelial cell or through a fenestration in an endothelial cell. There are two main ways that drugs can cross cell membranes:

- diffusion through the lipid bilayer
- transport by a carrier molecule

Rate of diffusion through membranes is largely determined by a drug's lipid solubility (molecular weight becomes important for large molecules). Lipid solubility is often expressed as oil - water partition coefficient because it is usually measured by shaking some drug up in a bottle with some water and some oil (often olive oil) and then measuring the concentration of drug in the water and the oil, and expressing this as a ratio.

MOVIE 2.3 Passage across membranes

Ionisation

An important complicating factor here is pH. Most drugs are either weak acids or weak bases and the degree of ionisation will depend on pH. The ionised form of the drug is usually insoluble in lipid so it will not cross membranes. The lipid solubility of the unionised form is a property of the drug but is usually much greater than that of the ionised form. The dissociation constant, pKa is an important concept. It is given by the Henderson - Hasselbalch equation: ie, the pKa is the pH at which the drug is 50% ionised. A weak acid usually has a low pKa eg aspirin - 3.5, a weak base usually has a high pKa eg pethidine 8.6. This has practical applications if the pH on each side of a membrane is different.

EQUATION 2.2.1 Henderson - Hasselbalch equation

$$\text{for a weak base: } pK_a = pH \log_{10} \frac{[BH^+]}{[B]}$$

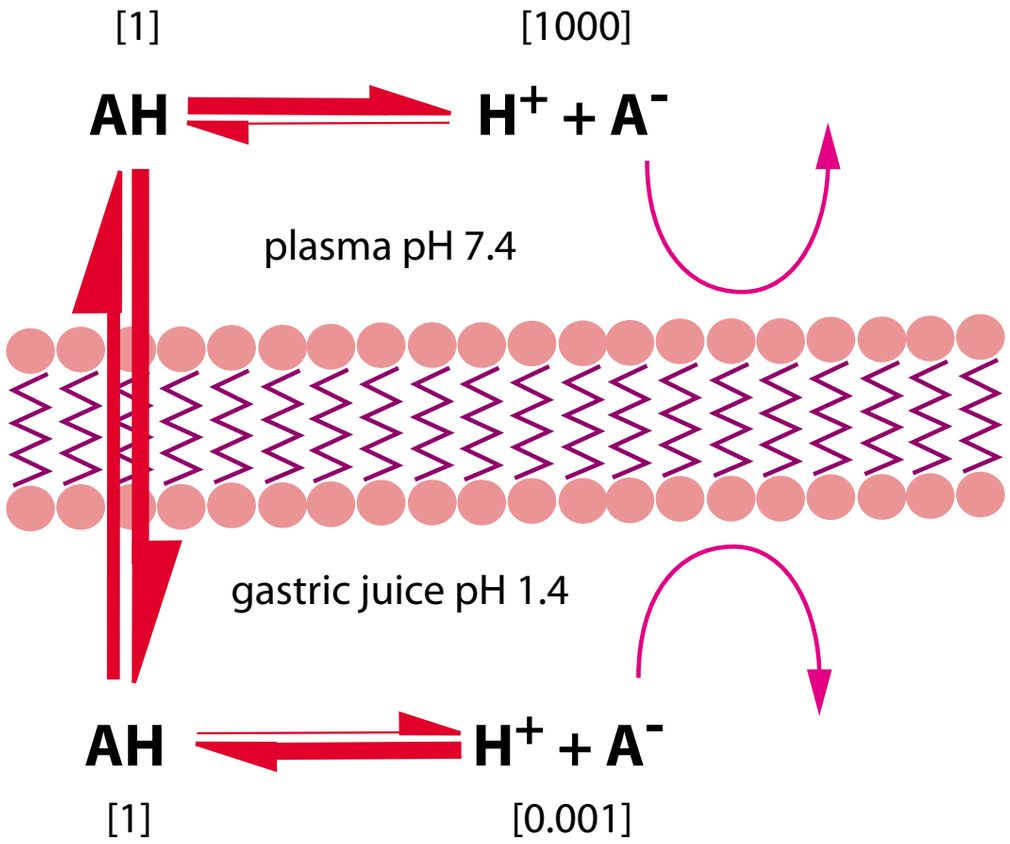
$$\text{for a weak acid: } pK_a = pH \log_{10} \frac{[AH]}{[A^+]}$$

If a drug is to stay in solution in the bottle, the pH is sometimes manipulated. Thiopentone (an anaesthetic) is a weak acid so will be ionised, and thus water soluble, in an alkaline solution. A 2.5% solution of thiopentone usually has sodium carbonate added so that the pH is about 9. This is corrosive to tissue unless it is immediately diluted in blood, ie, given iv!

Ion trapping and pH partition

Inside a body compartment, the ionisation of a drug is determined by the pH and pKa. Where the pH varies across a membrane, eg plasma pH 7.4 and gastric contents pH 2, the degree of ionisation will be different. Since only the unionised form can cross the membrane, it will diffuse down the concentration gradient to the other side of the membrane where most of it will become ionised and thus trapped. Thus a weak acid (such as aspirin) will move out of the gastric juice and into the

DIAGRAM 2.2.2 Ion trapping



Ion trapping of a weak acid (pKa 4.4 to make the arithmetic simple) encourages movement across the gastric lining. This can be important with aspirin like drugs

plasma.mA weak acid will accumulate in a compartment with high pH, a weak base will accumulate in a compartment with low pH.

This can be useful to increase the concentration of drugs in various sites, eg milk (pH 6.8, but rises with inflammation), inflammatory exudate (pH variable but acid), urine pH can be altered as required to encourage elimination of acidic or alkaline drugs.

Carrier mediated transport

Many cells have carrier proteins which normally facilitate the transport of endogenous substances such as sugars, aminoacids, metal ions and neurotransmitters. Drugs which are analogues of these substances are often transported by the carriers. This process can be passive or require energy (active transport). It often involves exchange with other ions such as Na^+. These processes are important for transport in the kidney (particularly to pump weak acids and bases into the proximal convoluted tubule) and blood brain barrier as well as absorption across the gut mucosa. These carrier processes are saturable, ie, once all the molecules are busy carrying drug, adding extra drug does not increase the rate of carriage. This can be exploited: when penicillin first came out and was very expensive, the weak acid transporter in the proximal convoluted tubule which excretes was usually blocked by probenecid to prolong the action of penicillin.

These carrier molecules can also pump drugs out of cells, preventing them moving across the cell to get where they are supposed to go to produce a response. Glycoprotein P plays a major part in the blood brain barrier (as well as in drug resistant tumour cells and bacteria).

Effect of Alterations in Absorption Rate

A decrease in the absorption rate of a drug results in several changes to the plasma concentration time profile. These changes are of major clinical importance.

It is obvious from the graph that a decrease in the absorption rate results in a delay and a decrease (because the animal carries on eliminating it) to the maximum plasma concentration reached (lower Cmax and Tmax). In some cases this may be beneficial by reducing unwanted side effects (e.g.phenobarbitone), but in other cases it may prevent attainment of effective plasma drug concentrations (e.g. benethamine salts of penicillin).

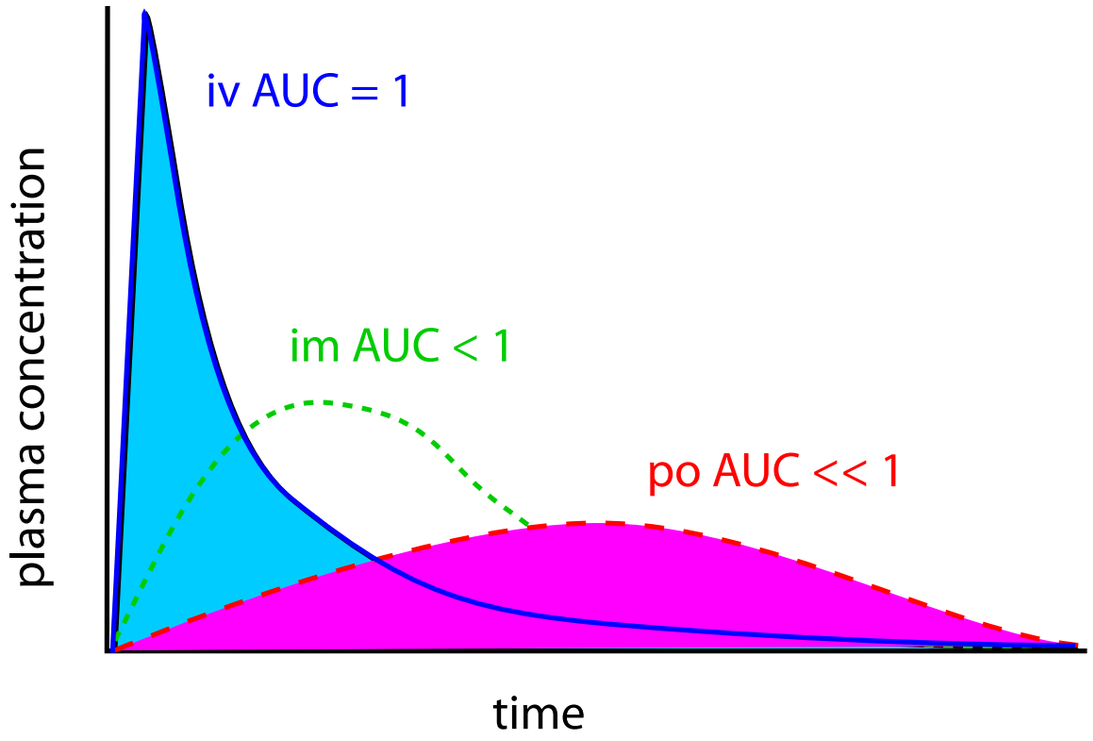
A more important effect of decreasing absorption rate is a prolonged time before the onset of drug action. In clinically acute situations this might be quite important and therefore in these situations a route of administration such as intravenous, where absorption rate changes cannot occur, would be more appropriate.

Depressed absorption rate may alter the duration of drug action by either shortening or lengthening it, depending on the particular drug's elimination kinetics and its minimum effective concentration.

Bioavailability

The bioavailability of a drug is the fraction of the dose given which finds it way into the systemic circulation. It should be noted that this is not necessarily equal to the fraction of the dose which is absorbed, since a drug might be absorbed, for example across the gastrointestinal lumen, but removed from the portal blood by the liver

DIAGRAM 2.2.3 Bioavailability



Bioavailability of different routes is compared to iv = 100%.

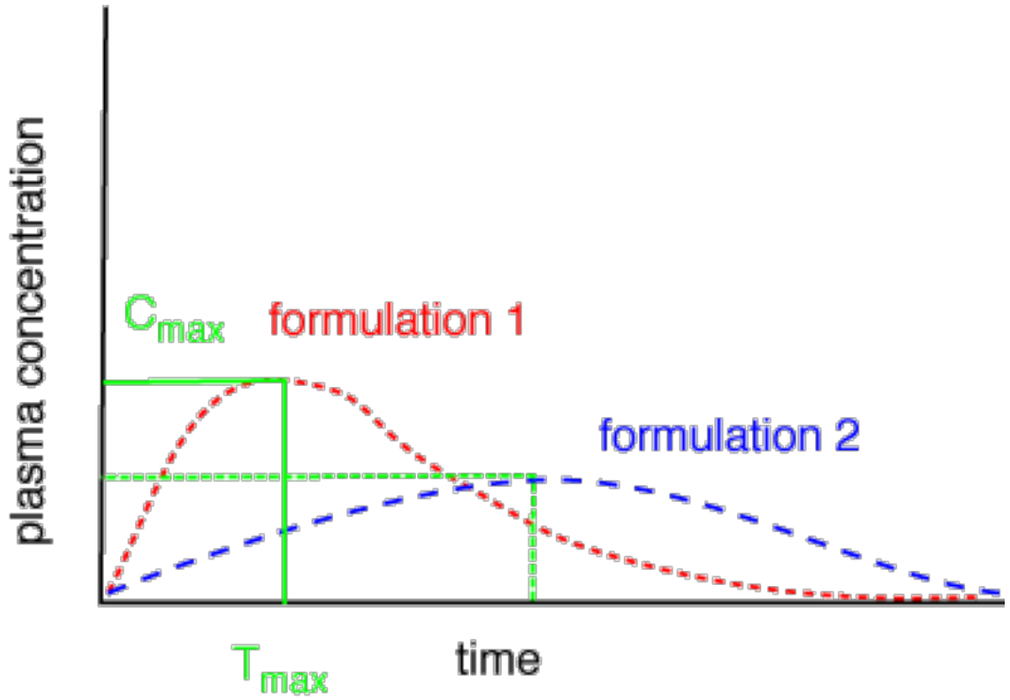
by metabolism before reaching the systemic circulation. Similarly, for topically applied drugs the skin is an organ of drug metabolism and might biotransform a drug already absorbed before it reaches the circulation. The same of course is true for drugs administered by any route other than a simple intravenous injection.

The bioavailability is calculated from the area under the plasma concentration / time curve and expressed as a proportion of the area under the iv curve, ie, if the area under the po curve is 20% of the area under the iv curve, the bioavailability is 0.2 or 20%.

Bioequivalence

Different formulations of the same drug are said to be bioeqivalent when they are absorbed to a similar extent and at a similar rate, ie, the Cmax, Tmax and AUC are similar. This technique is used when generic versions of drugs just out of patent are being licensed, to avoid having to carry out expensive efficacy and safety trials. Beware - some definitions of bioeqivalence only cover the extent of absorption and not the rate. For an antibiotic, for instance, if Cmax does not rise above the MIC, it is unlikely to work. There is also a difference between "being similar" and "not being significantly different from". In the past, this sort of thing was only a concern to the licensing authorities, but under the new deregulated system you might have to make assumptions about bioequivalence yourself.

DIAGRAM 2.2.4 Effects of alterations in absorption rate



Formulation 1 and formulation 2 are likely to have different effects in the animal.

Distribution

Distribution

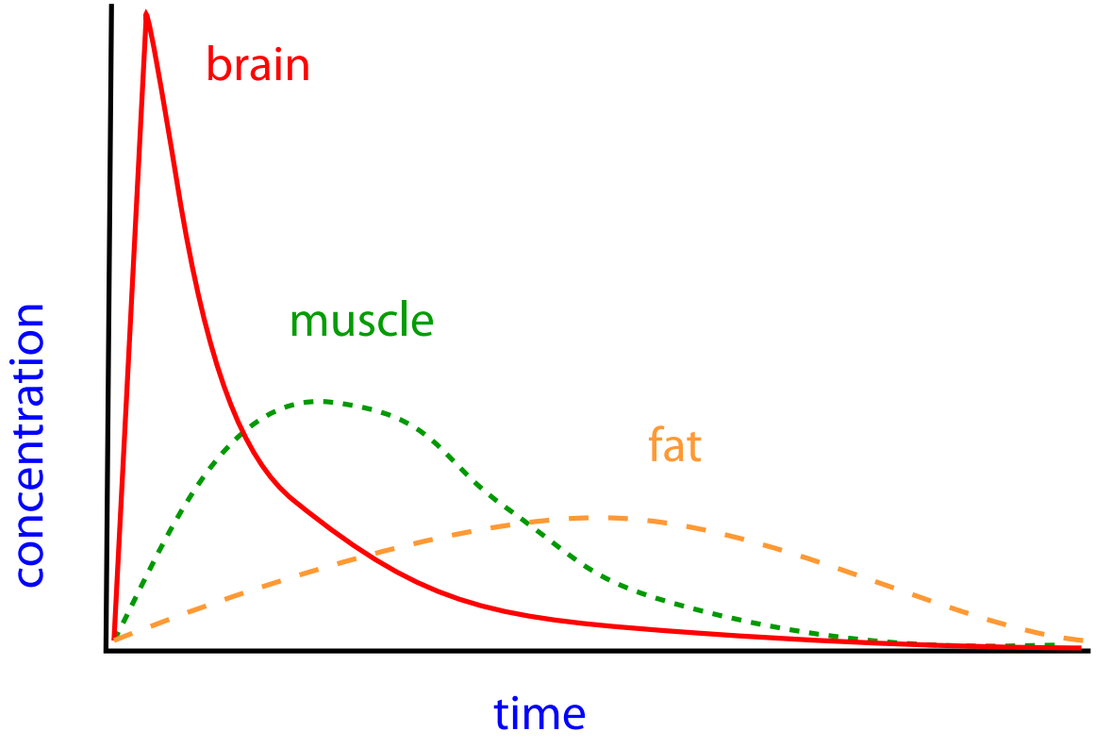
- ☑ drugs are usually distributed from the site of administration to the site of action via the blood.
- ☑ many drugs bind to plasma proteins and are unavailable for action or metabolism.
- ☑ drugs are not usually evenly distributed throughout the body.
- ☑ every drug has a volume of distribution which can be useful to know when calculating doses

Most drugs, apart from those appplied to the site of action, are distributed around the body by the blood. Tissues with high blood flow, such as the brain, will have more drug distributed to them initially than tissues with low blood flow such as fat. Disease can alter this, eg in heart disease, the blood flow to all tissues is reduced; inflammation usually increases the bood flow to the affected tissue.

Blood brain barrier

The brain is protected from many drugs by the blood brain barrier. This is both a physical barrier - there are tight junctions between the brain capillary endothelial cells so that a drug must be lipid soluble enough to cross the cells, and a physiological barrier - the endothelial cells contain P glycoprotein pumps whcih pump drugs out of the cells back into the blood. Occasionally these Pglycoprotein pumps are missing in some individuals which can let drugs get access tot he brain and cause unexpected side effects, eg, ivermectin gets into the brains of many collies and causes anaesthesia.

DIAGRAM 2.3.1 Distribution to different tissues



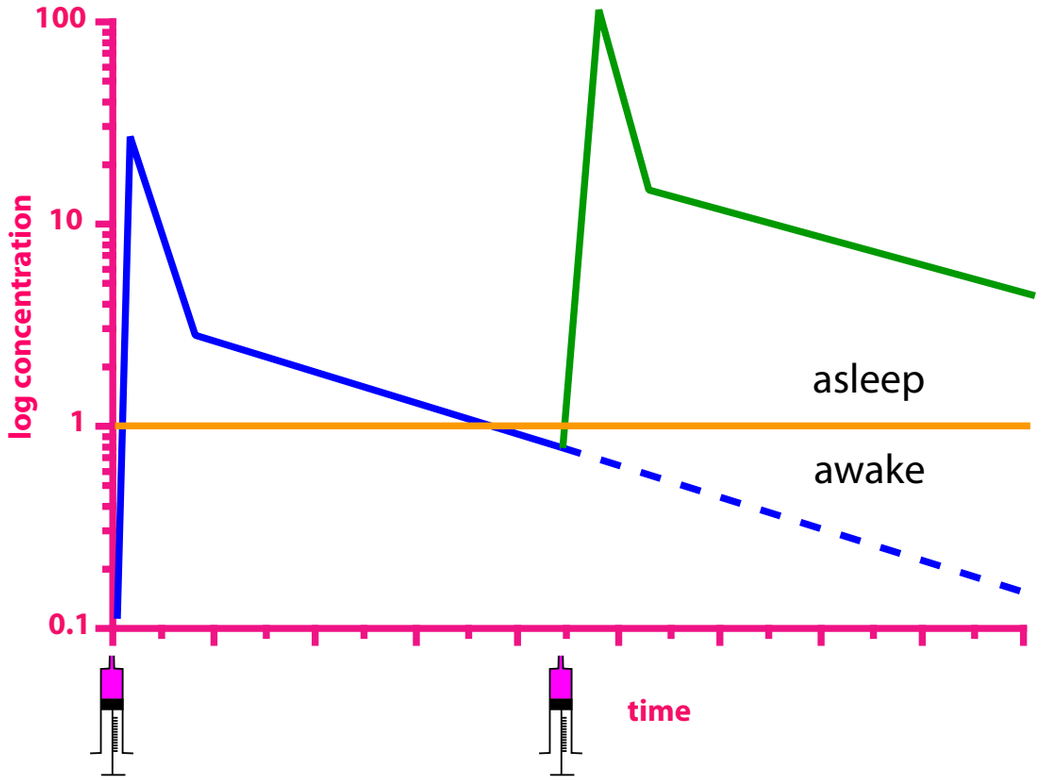
Distribution to different tissues depends on blood flow, among other things

The blood placenta barrier is similar, and it is safe to assume that any drug which gets into the brain will also get into the foetus.

This means that drugs which must get into the brain to work, such as anaesthetics, are small, highly fat soluble molecules. Similarly, large, polar molecules do not usually get into the brain and can be chosen as a way of avoiding CNS side effects. However, in inflammation (meningitis) the blood brain barrier breaks down and these drugs can get in.

The blood brain barrier can be bypassed by giving drugs intrathecally or intracisternally, but it is very rarely necessary to do this. It is also highly dangerous.

DIAGRAM 2.3.2 Effects of distribution on plasma concentrations



A drop in plasma concentration of a drug when it distributes to the tissues can have clinical effects, for instance when using thiopentone for induction of anaesthesia. A single dose gives a rapid wakening, but a top up dose can lst a long time!

Protein binding

Once many drugs get into the plasma, they bind to plasma proteins, especially albumin. Plasma albumin is particularly important in binding acidic drugs; basic drugs may be bound by β globulin and acid glycoprotein. Binding depends on:

- drug concentration
- affinity for the binding sites
- protein concentration

There is usually a much larger number of binding sites than molecules of drug to bind to them, but this can change if there is a low concentration of albumin (liver disease) or if many of the binding sites are already occupied by another highly protein bound drug. This is clinically important since it is the free (unbound) proportion of the drug which can move into the target tissue and is thus active. If you give a drug which is normally 98% protein bound leaving 2% to produce the expected effects, if the binding sites are not available the amount of free drug may be dramatically different from expected and the effects may be much greater. This can cause embarassment if the owner is watching. However, most modern drugs are so potent (ie, work at very low concentration) that displacement is rare. Old drugs such as sulphonamides and phenylbutazone can occupy clinically significant numbers of binding sites.

Protein bound drug is also unavailable for metabolism (but if the free drug is metabolised, some bound drug will quickly take its place, so this is not a limit on metabolism).

Compartments

Highly lipid soluble drugs will be partitioned into fat. Thus nearly all the administered dose of thipentone (fat : water partion coefficient 10:1) would be dissolved in fat at equilibrium. Fortunately, fat has such a poor blood supply that equilibrium never occurs, but fat can still be a significant reservoir for thiopentone. This then slowly leaches out and has a prolonged effect in much the same way as a depot injection dissolved in oil.

Ion trapping can also occur in tissues, eg, non-steroidal anti-inflammatory drugs tend to be trapped in inflamed tissue.

The body can be regarded as a number of fluid compartments:

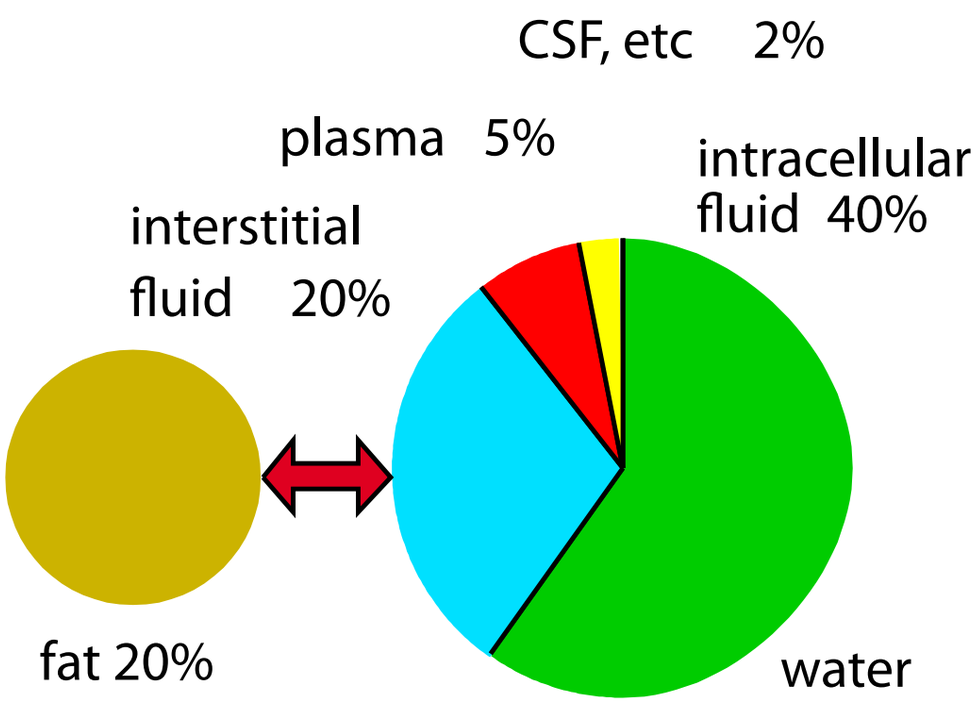
- plasma 5% body weight

- extracellular fluid 20%
- intracellular fluid 40%
- CSF etc 2%
- fat 20% (variable!!!)

Volume of distribution

Some idea of where drugs go can be obtained from the apparent volume of distribution (Vd). This is defined as the volume of fluid required to contain the amount of drug in the body at the same concentration as that present in the plasma. Thus if the volume of distribution is the same as the plasma volume (c 0.05 L/kg), the drug is probably staying in the circulation, eg large protein bound molecules like heparin. If it is much greater than the volume of the total body water, or even of the body, the drug is being distributed to a reservoir somewhere, usually fat, eg morphine (c 5 L/kg).

DIAGRAM 2.3.3 Fluid compartments

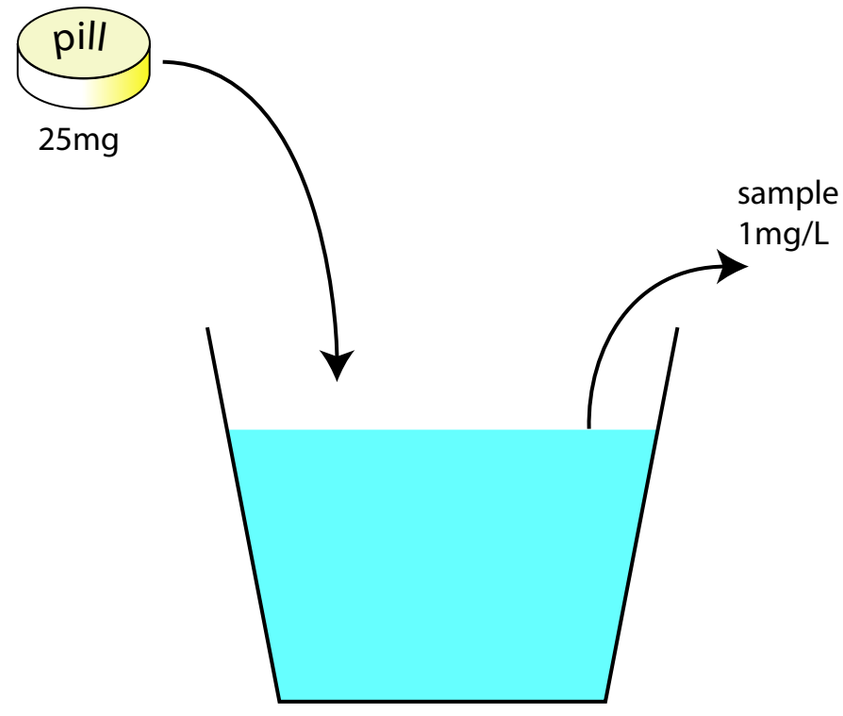


It is important to know which fluid compartments drugs might distribute into.

Drugs with a large volume of distribution usually cross the blood brain barrier, which may be desirable, and also the placenta, which is usually not.

The volume of distribution is sometimes used to calculate the dose required to reach a target plasma concentration.

DIAGRAM 2.3.4 Volume of distribution



Volume of distribution: the Vd can be calculated if the amount put in (the dose) and the concentration are known. nb - animals are more complicated than a bucket of water!

Metabolism

Metabolism

- ☑ most drugs are metabolised in two phases - they have a “reactive handle” attached by a cytochrome P450 enzyme which is then conjugated with a water soluble molecule - usually glucuronide.
- ☑ •some drugs will induce increased production of P450 which will increase the rate of metabolism.
- ☑ produgs have to be metabolised to produce their action.
- ☑ liver disease usually slows metabolism

The main route that the body uses to get rid of drugs is metabolism in the liver followed by elimination in the kidney. Lipophilic drugs are easily reabsorbed in the kidney, so drugs are usually metabolised to a more polar metabolite before elimination, although some drugs are eliminated unchanged, eg penicillin, which is a weak acid.

Most metabolism takes place in the liver, but other organs such as the lungs and kidneys, and even the skin, can be important. Metabolism usually inactivates a drug; exceptions to this are prodrugs; these are inactive and have to be converted to the active metabolite to have an effect, for instance, the sedative chloral hydrate has to be converted to trichloroethanol before any effects are seen. Some active drugs also have active metabolites, eg, the sedative diazepam.

Modern drugs are sometimes given as lipid soluble prodrugs, then converted to the active drug at the site of action, and hopefully trapped there. Most angiotensin converting enzyme inhibitors given to dogs with heart failure are prodrugs.

Metabolism usually occurs in two phases:

Phase 1

- oxidative reactions
  - hydroxylation
  - dealkylation
  - deamination
- reductive reactions (rare)
  - hydrolytic reactions

Phase 2

- conjugation with
  - glucuronide (**not cats**)
  - sulphate (not pigs)
  - methyl
  - acetyl (not dogs and cats)
  - glycine
  - glutamine (mainly man)
  - ornithine (birds only)

Phase 1

These reactions generally produce a more reactive molecule which can then conjugate with a polar molecule in phase 2. Occasionally these reactive intermediates are toxic (eg, paracetamol).

Most phase 1 reactions take place in hepatocytes (so lipid soluble drugs have better access) catalysed by enzymes attached to the smooth endoplastic reticulum (microsomal enzymes). The most important of these is the cytochrome P450 system of enzymes (mixed function oxidase system). Cytochrome P450 enzymes (CYP) usually carry out the first step of phase 1 which is then finished off by other enzymes. At least 50 different CYPs have been cloned in people and this work is starting to be carried out in dogs. They are grouped into different families depending on their homology, ie, CYP1, CYP2 etc. These are further divided into CYP2A, CYP2B etc, and then into CYP2A1, CYP2A2 etc. CYP3A4 and CYP2D6 are commonest in people. They are reasonably non-specific in what they will metabolise, but there are exceptions to this.

For many drugs in people, the specific enzyme in the P450 family which metabolises that drug is known. This can be useful to know if you also know that the person is deficient in that enzyme, which is fairly common. This also happens in dogs (and probably other species). For instance, celecoxib, an aspirin type drug, is metabolised in dogs by CYP2D15 (thought to correspond to CYP2D6 in people). However, only 45% of dogs possess this enzyme and they metabolise celecoxib much faster than the rest.

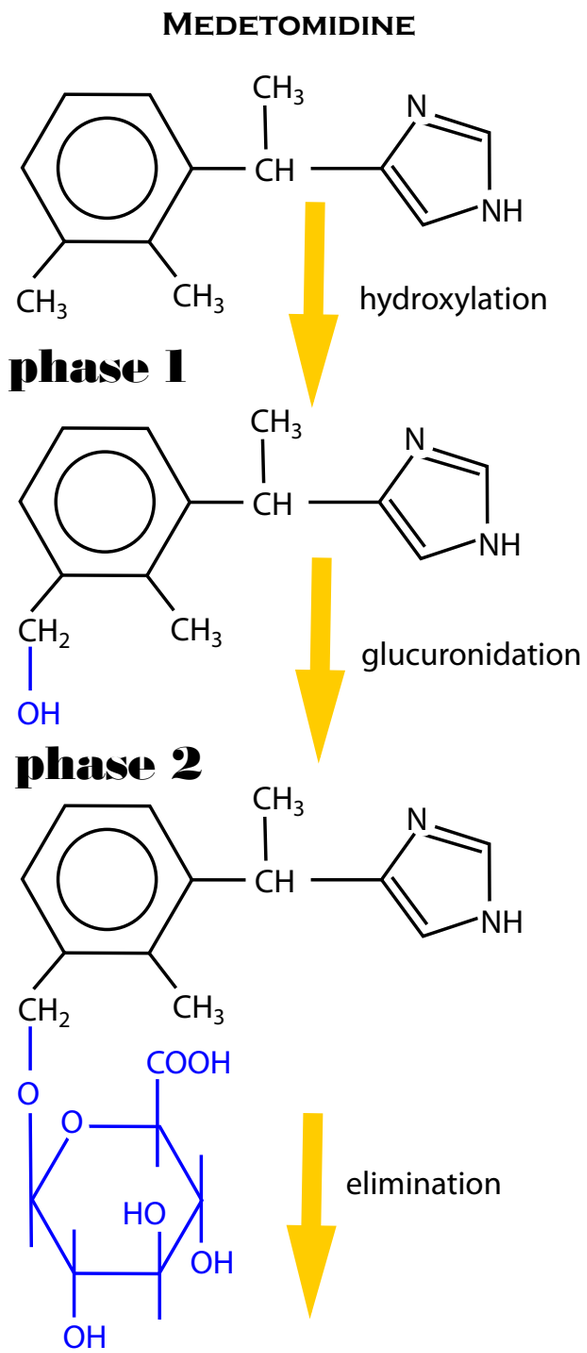
Cytochrome P450s are also present in the intestinal mucosa, and can metabolise some drugs before they reach the systemic circulation.

Phase 2

These reactions occur when a molecule has a suitable reactive group for the attachment of a substituent group. Although the reactive group is usually put there by phase 1 reactions, some drugs can be conjugated without going through phase 1. These reactions also take place mostly in the liver.

Glucuronidation, the commonest reaction, is catalysed by glucuronyl transferase (except in cats which do not possess this enzyme); acetylation by acetyl coenzyme A and methylation by S adenosyl methionine.

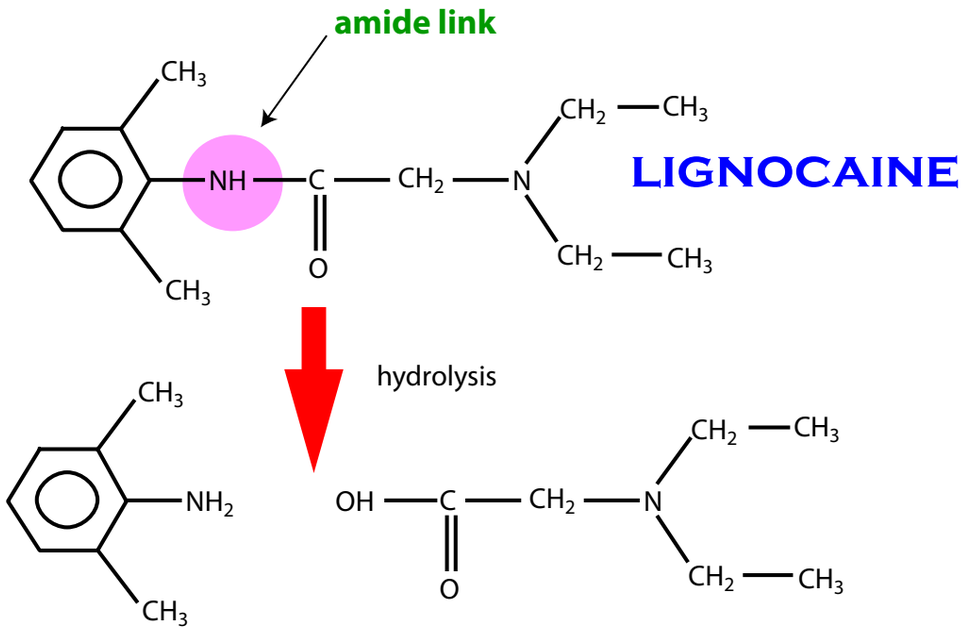
DIAGRAM 2.4.1 Metabolism of medetomidine



Main metabolic pathways of medetomidine, an α2 agonist sedative and analgesic, in most species. Several other pathways are possible.

There are major species differences in phase two reactions - see list above. There are probably also major individual differences (there certainly are in people).

DIAGRAM 2.4.2 Lignocaine metabolism



The hydrolysis of lignocaine - a very rapid phase 1 reaction.

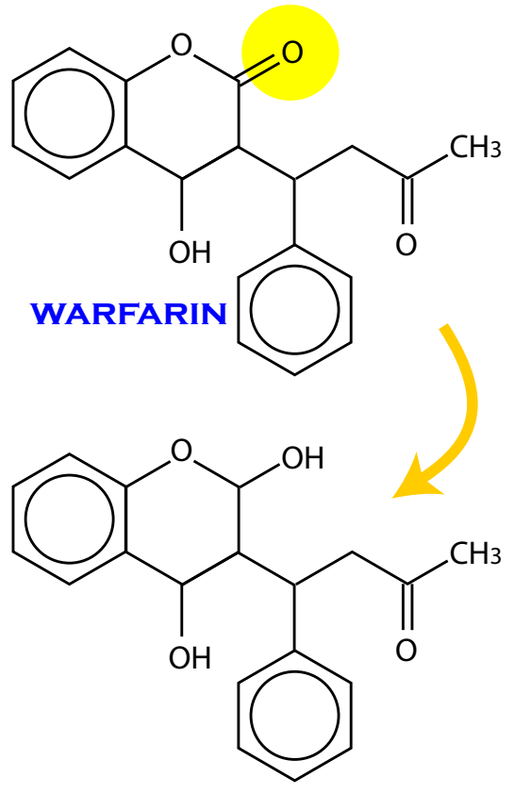
Phase 2 reactions can be reversed. Etorphine is conjugated with glucuronide in most species and a significant amount is excreted in the bile where it is exposed to the gut bacteria. These bacteria can lop off the glucuronide, allowing etorphine to be reabsorbed (and thus produce a second set of effects - in the case of etorphine this is sedation). This process is called enterohepatic recirculation.

Drugs are usually metabolised by several different pathways so the end result is a range of different metabolites.

Newborn animals do not possess many of the enzymes required for drug metabolism. This can be important, eg during caesarian section, anaesthetics will cross the placenta as well as the blood brain barrier; since the newborn animals have no enzymes to metabolise the anaesthetics, they may suffer from prolonged sedation which will not increase their chances of survival. (The answer is to use drugs which are eliminated without metabolism, such as inhalation anaesthetics.)

Older children usually metabolise drugs faster than adults, this has not been shown in animals (but no-one has looked).

DIAGRAM 2.4.3 Warfarin metabolism



Phase 1 reduction of warfarin. A rare but important reaction.

Old animals and particularly animals with liver disease also tend to metabolise drugs slowly. Some individuals also lack the necessary enzymes - but this is usually discovered after the drug has been given!

Enzyme Induction

The rate at which metabolism proceeds can be altered by drugs. Some drugs, such as phenobarbitone, cause a greatly increased synthesis of cytochrome P450 and glucuronyl transferase which means that the phenobarbitone (and other drugs) will be metabolised much more quickly (up to five times faster). This process is known as induction. It is of great clinical importance: many dogs are given phenobarbitone chronically for epilepsy, if they are then given some other drug the duration of action of the other drug may be much shorter than expected. Brassicas (rape, kale etc) also contain compounds which induce P450 enzymes. Grapefruit juice is a potent inhibitor of CYP3A enzymes in people, but it is not often drunk by animals! Ketoconazole, usually used as an antifungal drug, also inhibits CYP3A4, and is sometimes used to prolong the effects of expensive drugs in dogs. Macrolide

antibiotics such as erythromycin and clarithromycin also inhibit CYP3A4 in people. Fluoxetine (an antidepressant) inhibits CYP2D6.

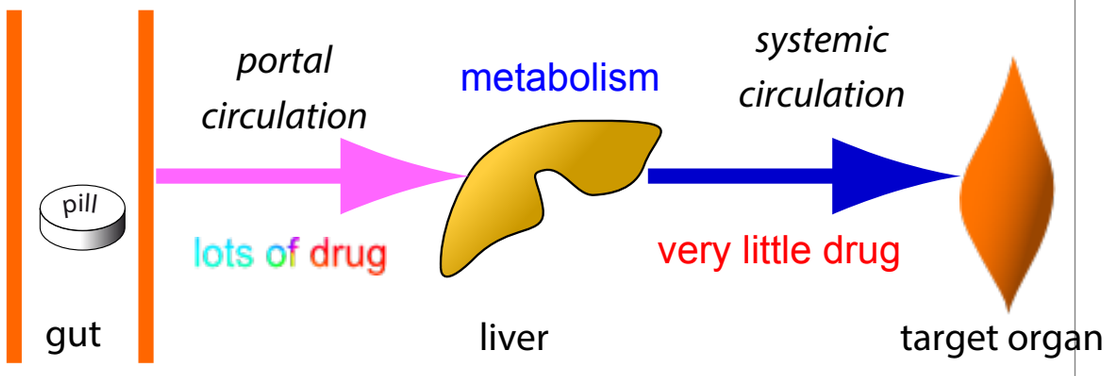
The rate of drug metabolism is also altered by changes in liver blood flow. These can occur in heart disease or shock, or can be caused by drugs.

First Pass Metabolism

Some drugs are metabolised so rapidly by the liver that they cannot be given orally. They are taken up by the portal system and most or all of the drug is metabolised by one passage through the liver so that very little or no drug appears in the systemic circulation. This is known as first pass metabolism. It is important for drugs like lignocaine (all removed) and morphine (about 80% removed).

Although most drug metabolism takes place in the liver, other organs (eg, skin, kidneys) are clinically important for some drugs. Intestinal lining cells may also be important in first pass metabolism.

DIAGRAM 2.4.4 First pass metabolism



First pass metabolism can remove all or most of the drug before it reaches the systemic circulation.

Elimination

Elimination

- ☑ the plasma concentration of most drugs falls exponentially
- ☑ a drug's half life is the time for the drug concentration to fall by (to) half
- ☑ nearly all the drug is gone after 5 half lives (but this may not be enough to avoid residues)
- ☑ with repeated dosing, a steady state is reached after about 5 half lives
- ☑ some drugs show a biexponential decay corresponding to distribution and elimination

Most drugs and their metabolites are excreted in the kidney. Biliary excretion is also important for some drugs.

Most drugs (except those that are highly protein bound) are freely filtered in the glomerulus. There are also transporter systems in the proximal tubules which actively excrete some drugs (especially weak acids), even when they are protein bound. Competition can occur for these carriers and one drug can have a major effect on the excretion of another, eg probenecid has been used to block the excretion of penicillin.

Polar drugs and metabolites do not cross the tubule walls easily and are therefore concentrated in the urine as the water is reaborbed. pH and thus ionisation is important here - basic drugs are more rapidly excreted in an acid urine because they will be more highly ionised and thus not reaborbed. With acidic drugs the opposite is true. Since the urine pH can be altered with drugs, the concentration of some drugs in the urine can be altered. This can be important in treating urinary tract infections.

Some drugs such as frusemide, penicillins and digoxin are excreted unchanged by the kidney - they are polar enough without metabolism.

If the kidney is not working properly (common in old age) then drug excretion will be reduced.

Conjugates (usually glucuronides) can be subject to enterohepatic recirculation.

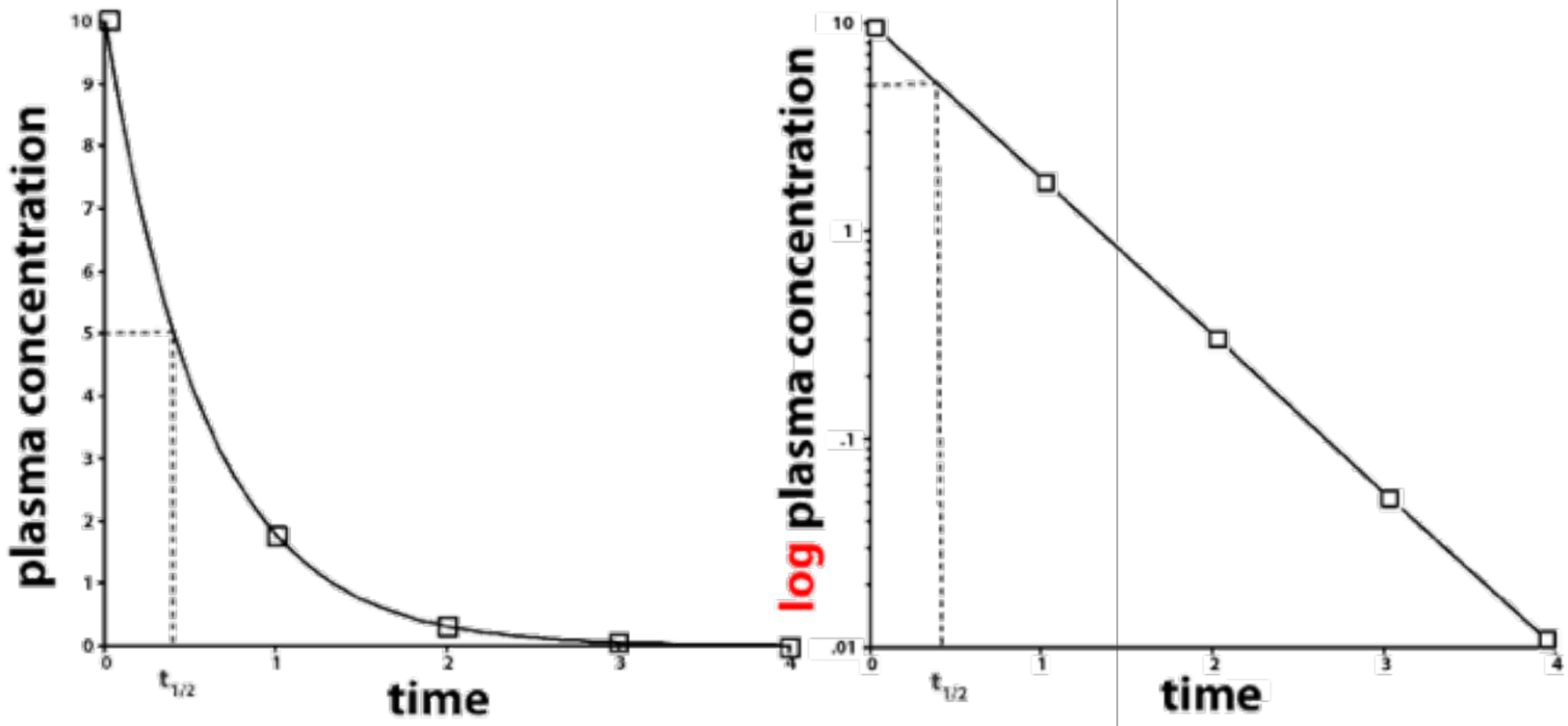
Clearance

Clearance (CL) is a measure of how quickly a drug is eliminated from the body. It is defined as the volume of plasma cleared of drug per unit time. It is sometimes divided into renal clearance, hepatic clearance etc but total clearance is probably a more useful concept.

Mathematical models

It is useful to be able to predict what a drug will do before you give it to an animal. If you have a computer with suitable software and are that way inclined you can have hours of fun fitting curves and deriving equations for plasma concentration / time curves of drugs which may help you to do this. There are a few clinically important concepts, however, which allow prediction of how long a drug is likely to stay in the plasma and thus how long it is likely to act.

DIAGRAM 2.5.1 First order elimination



a: plasma concentration / time curve, linear scale; b: plasma concentration / time curve, semilogrithmic scale. The slope of the line in b is the elimination rate constant. The time taken for the concentration to fall to half its original level is the half life (t1/2).

There are several different ways of doing this, all of which can be taken to absurd levels of complexity. In stochastic models, drug molecules are assumed to move randomly as each is absorbed, distributed, metabolised and eliminated. Each molecule hangs around in the body for a finite length of time, thus the mean residence time (MRT) gives an idea of the time course of absorbtion and elimination. This approach requires few assumptions but the MRT is of limited usefulness.

Another approach is compartmental modelling. This requires more assumptions to be made, but if the assumptions are correct, the data is more useful. In the simplest model the animal consists of a single (purely theoretical) compartment in which drugs are quickly and evenly mixed. The volume of this compartment is the volume of distribution of the drug (Vd). The concentration of drug will fall as it is eliminated by metabolism and excretion. With most drugs, rate of elimination is directly proportional to concentration (first order kinetics). Some drugs rely on a saturable metabolic or excretion system; once this is saturated, adding more drug will make no difference, the system proceeds as fast as it can which is a fixed rate (zero order kinetics). Not many veterinary drugs do this at normal doses, phenlybutazone in the horse at some dose rates, paracetamol in the cat and phenytoin in the dog are the only obvious examples.

When a drug exhibits first order kinetics, its plasma concentration will decay exponentially. If a graph of plasma concentration is plotted on a logarithmic scale against time, the decay shows a straight line. The slope of the line is the elimination rate constant (kel).

A more useful concept than kel is the half life (t1/2) which is inversely related to the elimination rate constant:

t1/2 = ln 2 / kel

or

t1/2 = 0.693 / kel

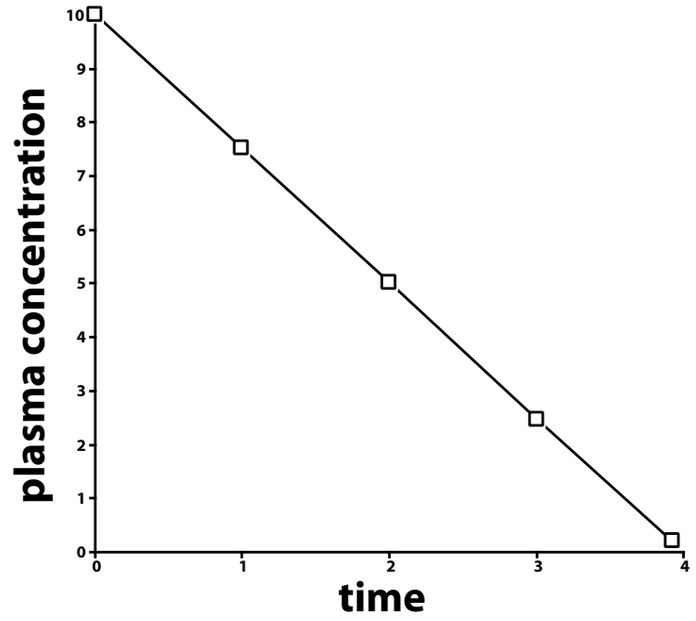
The half life is the time taken for the drug concentration to be reduced to half the original concentration. This gives some idea of how long the drug remains in the plasma and thus its duration of action. (Drugs eliminated by zero order processes do not have fixed half lives.)

Thus:

after	1 half life	50% of drug remains,
after	2	25%
	3	12.5%
	4	6.25%
	5	3.125%
	6	1.56%
	10	0.098%, ie 99.9% has been eliminated.

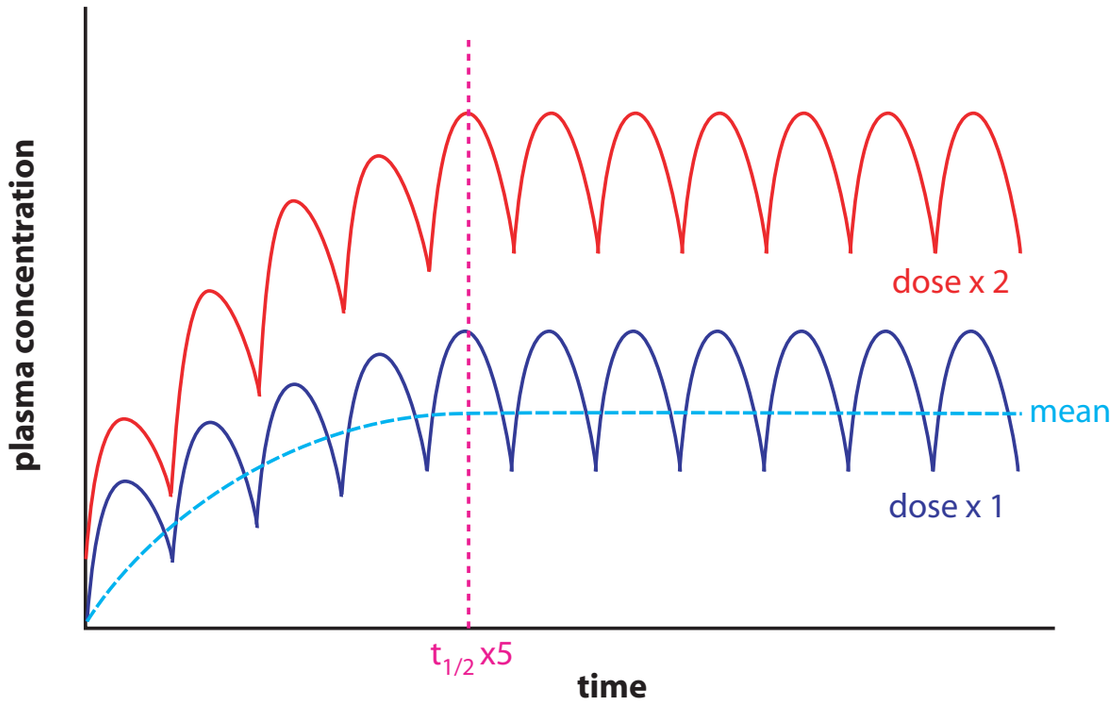
For practical purposes in clinical veterinary practice, a rule of thumb is that 5 half lives must pass before effectively all of the drug is eliminated (but this may not be

DIAGRAM 2.5.3 Zero order kinetics



This usually happens where elimination is by a saturable process, eg, a carrier molecule.

DIAGRAM 2.5.2 Repeated dosing



Concentration time curves for repeat dosing (wavy line) or infusion (mean). A steady state is reached after about five half lives no matter what the dose.

enough to avoid residues, see below). Similarly five half lives must pass before a change in dose results in a new steady state plasma concentration. It can be seen therefore that the time one must wait before attaining a new therapeutic plasma concentration or before attaining complete elimination of a drug is a function solely of the half life of that drug. The dose rate and the dose interval do not effect the length of time necessary to wait for attaining a new steady state plasma concentration or complete elimination.

Two Compartment Models

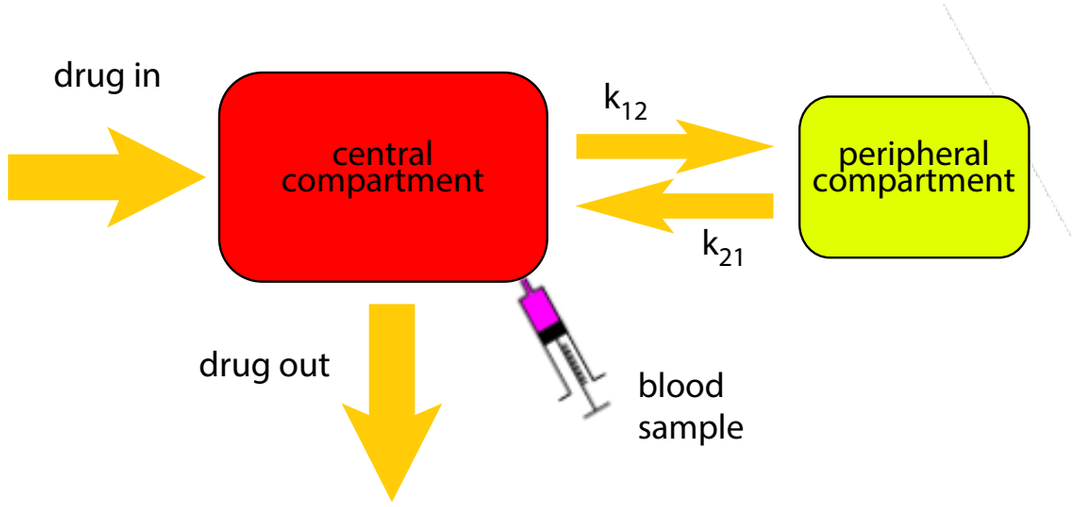
Many drugs' concentration/time curves are fitted to a two compartment model. Again, these compartments are purely theoretical, although they are sometimes called the central and peripheral compartments. In a two compartment model, the "curve" is fitted to two straight lines, corresponding to distribution from one compartment to the other, and elimination from the second compartment. These straight lines have slopes of α and β, and intercepts in the Y axis of A and B. These values are used in equations predicting plasma concentrations at any given time. The two lines each have a different half life, the distribution half life ($t_{1/2\alpha}$) and the elimination half life ($t_{1/2\beta}$).

A word of caution

Multiple compartment models are possible. The body is obviously not a single homoeogeneous compartment: the line produced by a semilogarithmic plasma concentration / time plot is usually a curve and can be fitted by a series of straight lines representing different compartments. It is important to keep a sense of reality: this curve is a series of points with a line interpolated, even the points are an average of several animals or several experiments in one animal (and may be of dubious accuracy depending on the measurement method used). The graph above is a typical plasma concentration time curve obtained experimentally. It is obvious that a number of different curves could be fitted to these data. In this case, the computer decided that a two compartment model gave the best fit, and the parameters were worked out on that basis.

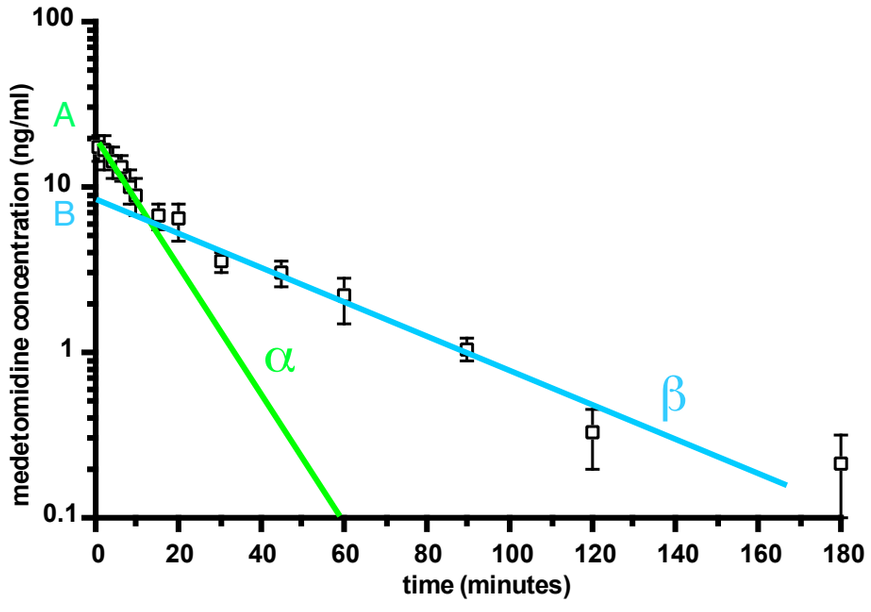
If the object of a knowledge of pharmacokinetics is to predict what is going to happen in another animal, all the (large) variables must also be taken into account. Clinical pharmacology is still an art rather than a science.

DIAGRAM 2.5.5 Two compartment model



A two compartment open model which describes the behaviour of most drugs in the body.

DIAGRAM 2.5.4 Data fitted to a two compartment model



Medetomidine plasma concentration time curve in sheep with a two compartment model fitted.

Practical applications

Working Out How Much Drug To Give And When

If you know the target plasma concentration and the volume of distribution you can work out what the dose should be by multiplying the two (assuming 100% bioavailability). Obviously this does not take into consideration the elimination of the drug, so you need to know what the upper and lower limits on plasma concentration are to work out the dose schedule. You also need to know the half life of the drug. In clinical practice, these figures are not often known, and even if they are, you have to make the large assumption that the individual animal you are treating is the same as the animals in the literature. Disease will alter pharmacokinetics!

Very toxic drugs, eg anticancer drugs, are often given on body surface area rather than weight. This is because body surface area corresponds better with metabolic activity than weight. Small animals need relatively more than big animals. Body surface area (m2) is given by:

bsa = k x W0.67 x 10-4

where W is weight in g, k = 10.1 in dogs and 10 in cats.

Therapeutic Drug Monitoring

Therapeutic drug monitoring is appropriate as a clinical tool only under certain, well defined conditions:

- when the drug of interest has a narrow safety index (i.e. therapeutic plasma concentrations are very close to toxic plasma concentrations), e.g. gentamicin, digoxin
- when the therapeutic effect of the drug of interest is difficult or impractical to monitor, or would require an extended period of individual trial and dose adjustment, e.g. phenobarbitone for epilepsy
- when the drug's half-life or clearance is likely to change as a result of its use, or the co-admistration of other drugs, e.g. phenobarbitone, phenytoin
- when the drug's distribution or elimination cannot be predicted
- (i)because of pre-existing or on-going disease, e.g. liver or kidney disease, or

- (ii)because of 'unusual' physiology, such as in neonates or in pregnant animals
- when there has been a failure of the drug to induce the expected therapeutic results
- when there is the suspicion that the drug is not being administered as directed, i.e. breakdown of client compliance.

The usefulness of therapeutic drug monitoring in any of these situations is based on the assumption that the therapeutic efficacy or toxicity of a drug is a direct function of its plasma concentration. This assumption is fundamental, since it is the plasma drug concentration which is measured, but it does not hold true for all drugs, eg NSAIDs. The target plasma concentrations must be obtained from the literature (beware - human figures are often used and assumed to be valid for other species); a further assumption is that these are appropriate for the individual patient being treated. In the end you have to use your clinical skill and judgement!

Abbreviations

These are included for reference only - do not try to memorise them!

α = slope of the component of the plasma concentration / time curve attributable to distribution. Used for predicting Ct
A = the intercept of this line on the Y axis. Used for predicting Ct
AUC = area under the plasma concentration / time curve
AUC_{o-inf} = area under the plasma concentration / time curve extrapolated to infinity
AUC_{o-12} = area under the plasma concentration / time curve for the first 12 hours
AUMC = area under the moment curve. A theoretical concept used for deriving the MRT.
β = slope of the component of the plasma concentration / time curve attributable to elimination. Used for predicting Ct
B = the intercept of this line on the Y axis. Used for predicting Ct
bsa = body surface area. Corresponds more closely to metabolic rate than weight, especially important with drugs with a low therapeutic ratio. Used for extrapolating doses from big animals to small ones and vice versa.
C = **Cp** = plasma concentration of drug. Units usually μg/mL (M rarely used).
Css = **Cpss** = plasma concentration at a steady state, ie, the amount of drug going in is the same as the amount of drug going out.
CL = clearance = the volume of blood cleared of drug per unit time. Units usually mL/min/kg
CLsystemic = **CLtotal** = the sum of CLhepatic, CLrenal, etc
Cmax = maximum plasma concentration reached after a dose of drug.
D = **Q** = dose or quantity, ie, amount of drug given.
F = bioavailability (fraction of dose reaching the systemic circulation).
k_a = absorption rate constant
k_{el} = elimination rate constant - slope of the plasma concentration / time curve in a single compartment model. Used in deriving the half life and other parameters.
Ln = natural logarithm
λz = slope of the terminal elimination phase in a multicompartment model (corresponding to kel in a single compartment model)
MRT = mean residence time = AUMCo-inf / AUCo-inf Gives some indication of how long a drug persists in the body. nb - covers absorption as well as distribution and elimination.
Q = amount of drug
$t_{1/2}$ = half life = the time it takes for drug concentration to fall by half.
$t_{1/2\alpha}$ = half life of the distribution phase
$t_{1/2\beta}$ = half life of the elimination phase
Vd = volume of distribution = the volume the drug would occupy if it was evenly distributed at the concentration found in the plasma. Gives some idea of where the drug goes.
Vd_c = volume of distribution of the central compartment
Vd_{ss} = volume of distribution at a steady state
$Vd_{\lambda z}$ = **Vd_β** = **Vd_{area}** = volume of distribution during the terminal elimination phase.

Drug residues

Drug residues

- ☑ no observable effect levels (NOELs) are worked out in lab animals
- ☑ human acceptable daily intakes (ADIs) are calculated from NOELs and what the average Kiwi eats
- ☑ maximum residue levels (MRL, MPL, tolerance, etc) are calculated from these
- ☑ withholding times are calculated to allow most animals to eliminate the drug to below the MRL
- ☑ vets **must** set withholding times for drugs used in food animals

Definitions

maximum residue level (MRL) = maximum permitted level = maximum permitted tolerance = tolerance level = the maximum amount of drug allowed in food. **nb. MRLs are different in different countries**. At the moment, NZ uses different MRLs for domestic and export food, although this should change.

withholding time = withdrawal period = the minimum length of time between the last dose of drug and slaughter / milking. **Also different in different countries, and for different formulations of the same drug**.

acceptable daily intake (ADI) = the maximum amount of drug the average person could eat for the rest of their life without causing any effects

After a drug has been administered and reached peak concentration, the amount of drug in the body usually declines exponentially.This means that most of the drug is removed fairly quickly, but the last bit takes a long time. (If the decline was truly exponential, the concentration would never reach zero.) Since most large animals will eventually be eaten, there is a danger of consumers ingesting some drug in their meat or milk.

International and domestic markets have a right to expect that the food animal products they are buying are safe, wholesome, and true to label. However, residue testing is being used more today to control access to markets than it is for food safety. Europe has led the way in this but the rest of the world is following. The general public has a grossly distorted perception of the relative risks that residues pose to their health.

What constitutes a food animal varies from country to country. Because the French eat horses, horses are classified internationally as a food species and are subject to the full range of regulation. (The same does not apply to Koreans and dogs - yet!)

One way of removing the problem of residues would be to test every animal slaughtered and the milk from every cow (at every milking) for all the possible drugs each animal may have had. This is obviously not possible, although that does not stop some people advocating this approach.

New Zealand relies on an “integrated quality assurance approach” (to use MAF speak). This includes having a registration process for veterinary medicines and agrichemicals which is geared towards international market requirements, well informed users (ie, vets and farmers), and some law on which to base enforcement activities. Rather than being a screen, residue testing in New Zealand is regarded as an audit of both the effectiveness of the controls put in place, and of farmer compliance with the relevant conditions of use. This system relies heavily on vets using drugs responsibly and making sure that farmers do the same.

Different foods are treated differently for historical reasons. Milk residues are usually dealt with by the dairy industry, Milk residues are usually dealt with by the dairy industry, most of the rest is covered by the Food Safety Authority, which is officially part of MAF but comes under the Minister of Health. This is still in the process of being sorted out.

Residues may also come from other sources, eg pesticides, environmental contamination (particularly heavy metals) and plant and fungal toxins. Problems can arise when a fungal toxin in pasture is the same thing as a drug produced by fungal cultures in a lab.

Maximum residue levels

Current analytical techniques (usually HPLC MS) are so sensitive that it is possible to detect some residue of a drug even years after its administration if you look hard enough. This means that there must be an allowable level of drug in food which is considered “safe”. Since safety is rather subjective, it is not surprising that different countries choose different levels (and call them different things). Eventually, everyone may follow the World Health Organisation’s Codex Alimentarius, but at the moment Europe and the USA have different but parallel systems to the WHO: Australia and NZ have a half way house where some levels are different again. The WHO and EU call the “safe” amounts of drug in food the maximum residue level (MRL). You must know about these, since exports from NZ must conform to Codex, or failing that, EU MRLs. These are also accepted for imported food. Food for the domestic market is currently subject to different MRLs. There are moves afoot to sort out this situation, but don’t hold your breath.

How Are MRLs Calculated?

First the acceptable daily intake (ADI) value for each chemical is established. The ADI is calculated from chronic toxicology studies on at least two species of laboratory animals. These animals are given different doses of the drug and the highest dose which produces no effect is called the no observed effect level (NOEL). For antibiotics, the effects examined are changes in the gut flora, either the normal flora or axenic mice with human gut flora added.

For most chemicals the ADI is based on the amount the average human could consume for their entire life and still show no observable effect. This involves using the animal NOELs and multiplying by various fudge factors (usually 100) to increase safety. Drugs which are potentially carcinogenic cannot have an ADI since it is assumed that one molecule could be enough to start a tumour. This raises problems when those drugs are also naturally present in man and animals, eg oestrogen. Different countries deal differently with such drugs: they are banned in Europe, given very low MRLs in the USA, and generally ignored in NZ in the hope that they will go away.

The first principle of establishing MRL values is that they should be set low enough for each food type so that the ADI will never be exceeded by anyone eating a diet made up of foods which could conceivably contain these residues. The Ministry of Health (noe the NZ Food Safety Authority) has tables showing the “average” diet of different ethnic groups in NZ. The second principle currently applied is that they should be further restricted to that level which is required if they are used in accordance with 'good agricultural practice'. This term is not defined.

MRLs used in NZ

European MRLs (and a brief explanation of how they were decided).

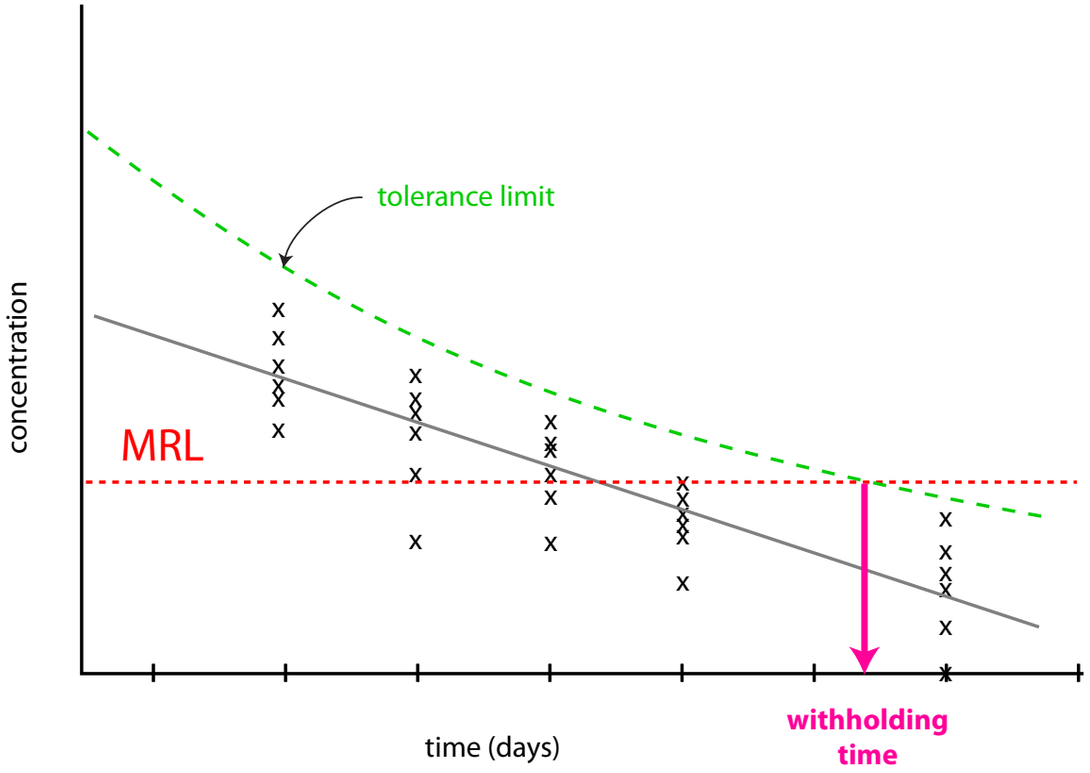
Australian MRLs

American are more difficult to find (and they don’t call them MRLs).

Withholding times

Once the MRL for the active ingredient has been established (and officially approved), drug companies carry out pharmacokinetic tests with their product to see how long it takes for tissue levels to decline to the MRL. Another fudge factor is added on to allow for individual variation (and sometimes for the effects of disease) and that time becomes the withholding time. Since the pharmacokinetics of a drug will be different in different species, this process must be repeated for each species. This is expensive. nb, the withholding time calculated by a drug company is only valid for their formulation of the drug, a product containing the same active ingredient from a different company may require a different withholding time.

DIAGRAM 2.6.1 Withholding time calculation



Each cross usually represents an animal killed for a meat sample, so the actual data points are usually few! The tolerance limit is the 95% CI of the 95th percentile under most countries' rules.

If you use the drug according to the instructions on the bottle and stick to the withholding time given, the chances of a residue above the MRL are very small (although not zero). If you vary the dose or route of administration, or give the drug to an animal for which it is not licensed, then you have to work out a new withholding period. There are several options.

If you have the full pharmacokinetic data and are into stats / suffer from masochistic tendencies you can use the same procedure as the drug companies (outlined here. The procedure is similar (but not the same) in this FDA document. Of course, the EU does it slightly differently.

If you have data on the half life of the drug in milk or meat, and you double the dose, you can establish a new withholding time by adding on a half life. **Beware - this does not work for slow release formulations!**

TABLE 2.6.1 NZ default withholding times

Animal	Meat	Milk	Eggs
ruminants	91	35	
pigs	63		
horses	180		
birds	63		10
camelids	63		
rabbits and hares	63		

These have no basis in science or law, but they are widely used in NZ.

If the drug is licensed overseas (EU or USA) for the use you intend, then you could use the overseas withholding periods. Beware - the MRLs may not be the same. You must also compare like with like - eg penicillin injections from different companies may have different formulations which affect their pharmacokinetics and thus withholding times. Information for products in the USA can be obtained from http://www.farad.org/ Europe does not yet have much useful information on line, but the British data is published by NOAH in two annual publications: "Withdrawal Periods for Veterinary Products" and "Compendium of data sheets for veterinary products". It is also contained in the Veterinary Formulary.

You can use a "standard" withholding time. This is a (long) time calculated to avoid residues for most drugs. In the UK the figures are 28 days for meat, 7 days for milk and eggs and 500°days for fish. The NZFSA has a set of very conservative default times for animals which have been in clinical trials (table). These have been advocated for drugs where the withholding time has not been established, but there is no legal or scientific basis for this recommendation.

It is always wise to err on the side of caution, but bear in mind this will probably involve increased costs for the farmer.

The bottom line is that unless you know what you are doing, or there is absolutely no chance of the animal getting into the food chain, it is better to stick to the instructions on the bottle.

Problems arise with horses, which are classified as food animals (even in NZ) because of the barbaric habits of the French. It is illegal not to give an animal's owner information which will prevent residues in the meat, even though the average girl with a sick pony is unlikely to take kindly to being told not to eat her pet for the next four weeks. One way around the problem is to write "this horse must not be sold for human consumption for x weeks" in very small print at the bottom of the invoice.

Further reading

Riviere et al., (1998) Primer on estimating withdrawal times after extralabel drug use. JAVMA, 213, 966 - 968

Enforcement

How are excess residues prevented?

- Focus your farmers on the importance of withholding times
- Follow label instructions closely
- If you deviate at all then increase the withholding time
- Make sure treated animals are readily identifiable
- Leave a written record of all treatments and the withholding time

National Residue Monitoring and Surveillance (NRMS) programme

MAF is responsible for running New Zealand's National Residue Monitoring and Surveillance programme (NRMS) for meat and offal, and undertakes most of the enforcement activities. The analytical testing alone costs in the region of 2 million dollars a year with 117 chemicals specifically looked for, and approximately 70,000 analyses completed.

The NRMS programme consists of three different parts.

1. The random monitoring programme is designed to provide domestic and international assurances as to the overall effectiveness of New Zealand's residue controls in preventing consumers from being exposed to toxicologically significant amounts of residues. All animals sampled are randomly selected and this prograннne is essentially an audit of the effectiveness of the control measures the country has in place to prevent residues in excess of defined limits finding their way into the human food chain.

2. The surveillance targeted sampling programme targets suppliers and animals which for some reason have been identified as posing more of a risk. Previously identified non-complying farmers, sheep smelling of dip, and cattle with mastitic udders or injection site lesions are examples of reasons why certain animals or lines will be specifically targeted for more intensive sampling and analytical testing.

3. Surveys aimed at identifying potential problems are a way the MAF and the industry can be more proactive, and allow for early identification of possible future problems so that effective control measures can be implemented in advance. They also provide valuable data on which the Ministry can base a case against overseas markets trying to impose more testing on us.

Consequences of residues- NZ

- Condemnations
- Suspect listing
- Increased costs
- Black listing by processors
- Possible prosecution

If the NRMS programme detects residues above MRLs in any samples analysed then; firstly, a trace back is undertaken to ascertain which control system has failed to deliver. Secondly appropriate actions are taken to ensure the problem doesn't reoccur, and thirdly the number of analyses increases dramatically so we are able to provide additional assurances both domestically and internationally that any problem has indeed been rectified.

Where the supplier is found to be at fault, either through not complying with label directions or withholding periods, or through having inadequate management systems, then extra conditions of supply are placed on this farmer. These involve compulsory notification of the Inspector in Charge prior to sending any stock for slaughter so that the stock can be subjected to more intensive inspection and sampling, automatic condemnation of all offal, and/or retention of carcases until tested clear. Repeat offenders, or those blatantly disregarding the controls, can face prosecution and or movement control notices being served on them.

Where the product or its label directions are found to be a contributing cause, a formal request is put to the Animal Remedies Board for a prioritised review of the withholding period and label of the product.

Where there has been a failure in buyer / seller communication responsibility is put on the buyer to set up systems which prevent a reoccurrence. It is up to the buyer to initiate his/her own actions against the seller. Similarly, if a farmer claims his or her veterinarian failed to inform him or her of the relevant withholding period associated with the sale or administration of a prescription animal remedy (PAR) this is a civil matter between the farmer and this professional.

Consequences - overseas

- Consignment rejections
- Reduced credibility
- Increased costs
- Market access restrictions
- Consumer backlash

The reaction of the importing country depends to some extent on the chemical residue found and the type of product it is found in. At the very least an explanation is requested on how product containing residues above their specifications is being certified to their market. Most regard the presence of excess residues in exported produce as evidence of lack of effective control by the exporting country's controlling authority. Accordingly, they reject the consignment and demand assurances and evidence of what will be done to prevent a reoccurrence. In the interim, trade restrictions and increased rates of testing at port of entry may be imposed. In some situations market access for that product type will be blocked.

However, these are the government to government interactions. Increasingly, the real risk associated with residue detections is associated with the media coverage and the inevitable consumer backlash this causes.

Overview of the law

NZ law on residues is rather confusing since so many different acts of parliament and regulations made under those acts are involved. These are starting to be consolidated under the Animal Products Act, but there is still some way to go. The recently established NZ Food Safety Authority oversees all this, as well as the licensing of veterinary medicines (although there are different departments involved in each). See the Law chapter of this study guide for the latest details.

Agricultural Compounds and Veterinary Medicines Act (1997)

It is an offence for vets to fail to provide a client with information to prevent the occurrence of residues ($15,000 fine).

New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards (2010) made under the Food Act (1981)

This is the list of MRLs for veterinary medicines and agricultural chemicals. It is updated regularly. Note that these MRLs are often different from those used in Europe and America (and the Codex). In these cases, it is effectively the overseas MRL which is used in NZ!

Dairy Industry Act (1952) and Dairy Industry Regulations (1990 / 290)

These mainly relate to quality and hygiene, but are written vaguely enough to cover drug residues as well. Dairy products must not be sold or exported if they are likely to endanger public health. Milk purchasers may take samples for analysis. Milk and dairy products must be fit for human consumptionion.

Animal Products Act 1999

This is supposed to replace the previous acts and regulations with mandatory food standards.

It is an offence to submit animals for slaughter with residues present greater than the MRLs or inside the withholding period.

The Director General of MAF may decree that animals treated with some groups of drugs must be permanently identified (currently hormonal growth promoters and Johne's vaccine) (it is also an offence to use officially sanctioned ear tags for anything else). It is illegal to use a drug to promote growth unless it is licensed for that.

Anyone selling a treated animal must tell the buyer.

MAF can control movement of animals.

Overseas information

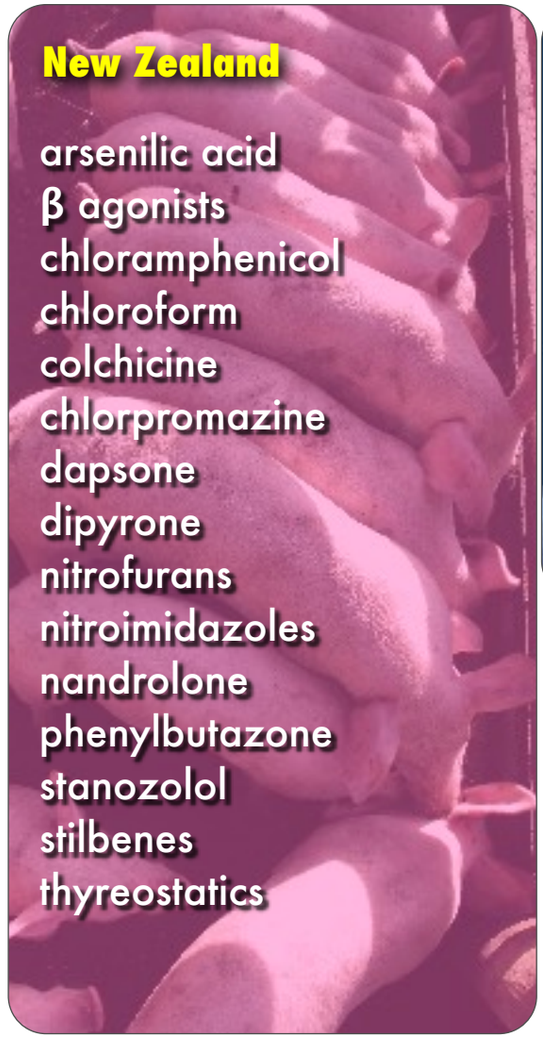
The FDA (USA) publish MRLs and other useful information and the EMEA (Europe) publish MRLs and toxicity data. The urls keep changing, so check the pharmacology website for the latest link.

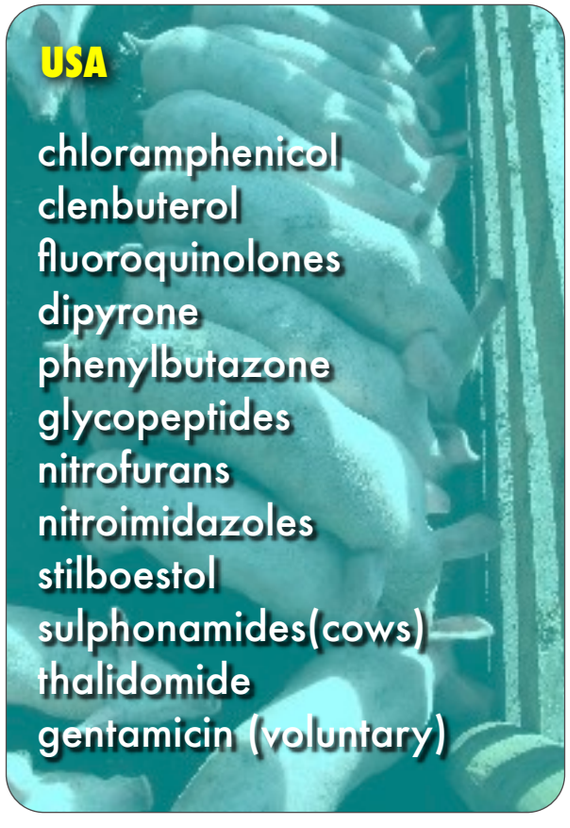
When looking at overseas information, remember that MRLs may be different from here, and that different formulations of the same drug may have different withholding times.

Banned drugs in food animals

Some drugs have been banned in food animals because of the risk of residues.

The method of "banning" varies from place to place: in NZ it is not illegal to give the drugs in the table but it is illegal for the farmer to move the animals or present them for slaughter when they contain the drugs. This gives rise to anomalies: clenbuterol is licensed for delaying parturition in cows, but as a β agonist is banned in food animals. These lists are constantly getting longer!!! Check the latest.





CHAPTER 3

Peripheral nervous system

This part covers the peripheral (mainly autonomic) nervous system and the organs innervated by it.

*Deadly nightshade (*Atropa belladona*), the source of atropine.*

Parasympathetic system

commonly used drugs

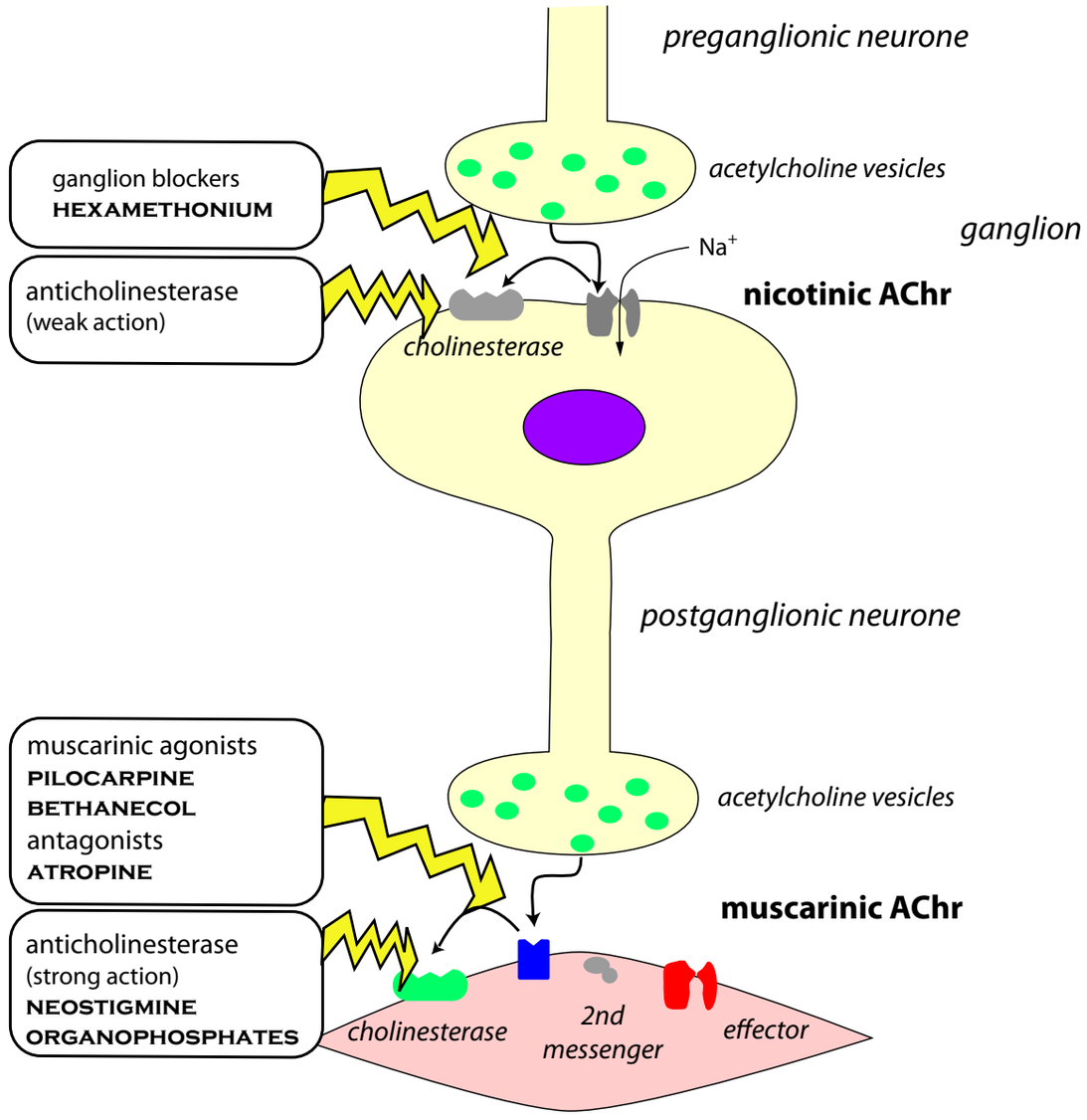
atropine

Parasympathetic system

- ☑ acetylcholine is released at nerve endings to act at muscarinic ACh receptors
- ☑ there are several subtypes of muscarinic receptors
- ☑ atropine is widely used as a non specific antagonist
- ☑ muscarinic agonists are not widely used because of side effects
- ☑ all autonomic nervous system drugs have widespread side effects

Only one important group of drugs acting on the parasympathetic system is used in veterinary practice - the muscarinic antagonists. However, there are many acetylcholine analogues found in plants which can act as agonists or antagonists and poisoning is relatively common. Many obscure snake and spider toxins have interest-

DIAGRAM 3.1.1 Parasympathetic drugs



Summary of sites of action of drugs in the parasympathetic nervous system.

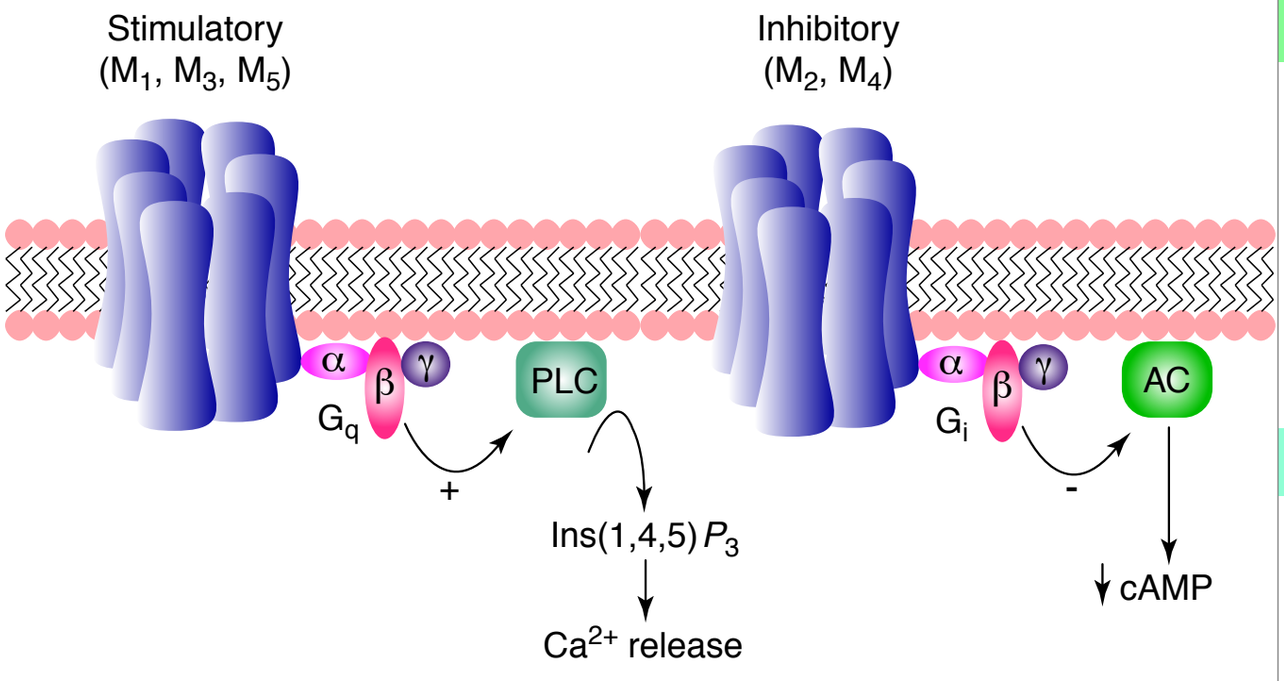
TABLE 3.1.1 Muscarinic subtype affinities

Antagonist	Receptor subtype [a]				
	M_1	M_2	M_3	M_4	M_5
Atropine	**9.0**	**8.8**	**9.3**	**8.9**	**9.2**
Darifenacin	7.8	7.0	8.8	7.7	8.0
Himbacine	6.8	7.7	6.9	7.5	6.1
Methoctramine	7.5	8.7	7.0	7.6	7.0
Tripitramine	8.9	9.9	7.8	8.5	7.0
Oxybutynin	**8.2**	**7.5**	**8.3**	**8.1**	**7.7**
Pirenzepine	**8.2**	**6.5**	**6.9**	**7.4**	**7.2**
S-Secoverine	8.0	7.9	7.7	7.7	6.5
Tolterodine	**8.4**	**8.1**	**8.2**	**7.9**	**8.4**
Zamifenacin	7.7	7.7	8.2	7.0	7.6

[a]Values are apparent affinity constants (log K_i) [8] derived from radioligand binding studies.

Antagonist affinities for muscarinic receptor subtypes in recombinant human receptors

DIAGRAM 3.1.2 Muscarinic receptor subtypes



Second messenger systems used with muscarinic receptor subtypes.

ing effects on cholinergic transmission. Clostridial toxins block the release of acetylcholine.

Nicotinic receptors

Nicotinic receptors are ionotropic receptors composed of five subunits. There are lots of different possible subunits, the receptors are classified on their type of α subunit. For practical purposes, ganglionic receptors are different from receptors in the neuromuscular junction (see later) - and CNS receptors are different again. Drugs are usually specific for the ganglia or the neuromuscular junction. Agonists are not used (animals do not generally smoke tobacco). Channel blockers such as hexamethonium were used in the past to lower blood pressure under anaesthesiaby blocking sympathetic ganglia (but had major parasympathetic ganglion blocking effects).

Anticholinesterases

Occasionally used to reverse neuromuscular blockers (see NMJ below) but are non specific. Organophosphates (insecticides and acaricides, eg couamphos) are potent anticholinesterases and will produce side effects in mammals (including people) by increasing cholinergic transmission. Organophosphate insecticides are obsolescent and are usually ecountered as poisons. Since most of the dangerous effects are muscarinic, antimuscarinic drugs are usually given.

Muscarinic receptors

There are five muscarinic receptor subtypes. M1 & M5 receptors occur in neurones of the autonomic and central nervous systems. M1 receptors are involved in CNS excitation and memory, and in gastric acid secretion and gut motility. M2 receptors are found in the heart, where they slow depolarisation in the SA and AV nodes. There are also presynaptic M2 receptors in the brain, which reduce acetyl choline release. M3 & M4 receptors are found in smooth muscle and secretory glands where they increase secretion, contract smooth muscle and cause vasodilatation by increasing nitric oxide production.

Muscarinic Agonists

Not often used except pilocarpine in the eye and bethanecol in the bladder (see below). Muscarine itself comes from the fungus fly agaric (Amanita muscaria) which sometimes causes poisoning in animals.

Muscarinic Antagonists

Very (too?) widely used in veterinary practice to reduce secretions before anaesthesia (dubious value) and to treat bradycardia (they usually have to be given iv to be effective at this). **Atropine** (originally derived from deadly nightshade, *Atropa belladonna*) is the only drug commonly used; **hyoscine** (scopolamine USAN) is similar but crosses the blood brain barrier more easily. It produces hallucinations and sedation in people: this is not obvious in animals. Many toxic plants contain atropine or hyoscine and poisoning is fairly common. **Glycopyrrolate** (glycopyrronium INN) is a quaternary ammonium compound which does not cross the blood brain barrier at all: it is longer acting and is more specific for the heart. Its only drawback is price.

Atropine blocks all muscarinic receptors, but specific drugs are being developed. **Pirenzepine** is a relatively specific antagonist for M1 receptors and is used in the gut to reduce acid secretion.

Atropine effects

- dry secretions, reduce salivation (effects last hours)
- slow gut (effects last hours)
- tachycardia (effects last minutes)
- dilate pupil (effects last hours)
- blurred vision (cycloplegia) (effects last days)
- difficulty with urination (effects last hours)

Atropine indications

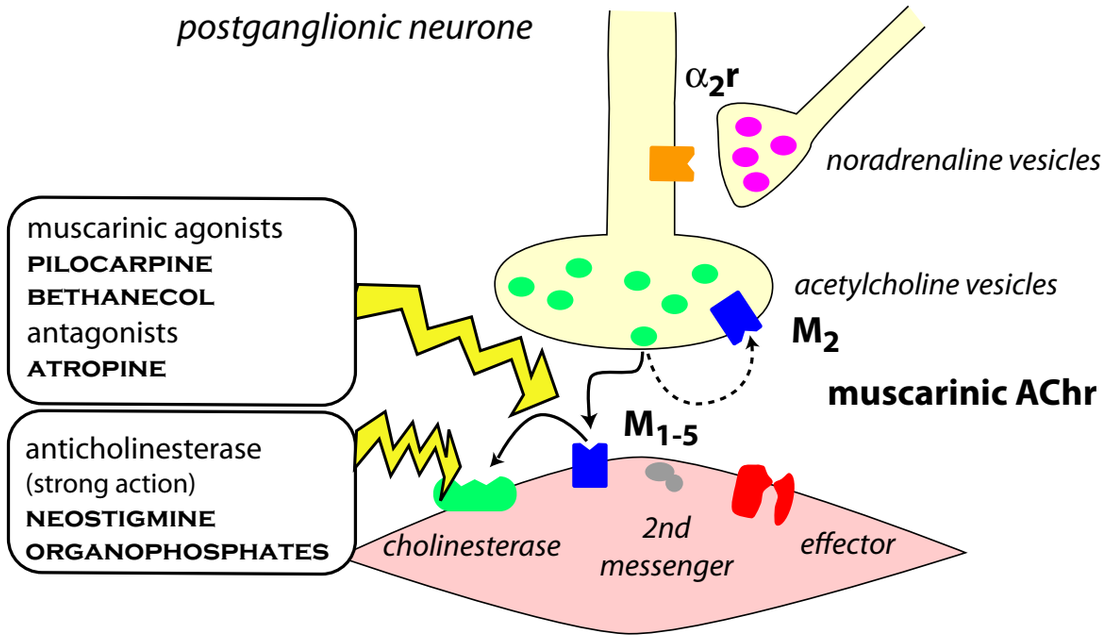
- anaesthetic premedication
- in cats (and pigs?)
- in conjunction with irritant anaesthetics like ether
- treating gut spasm
- treating bradycardia
- organophosphate poisoning

Atropine contra-indications

- glaucoma
- tachycardia
- Atropine precautions
- cardiac disease - tachycardia reduces blood flow to the myocardium
- horses - cycloplegia often causes panic
- ruminants - blocks parotid secretions but not submandibular - very sticky saliva

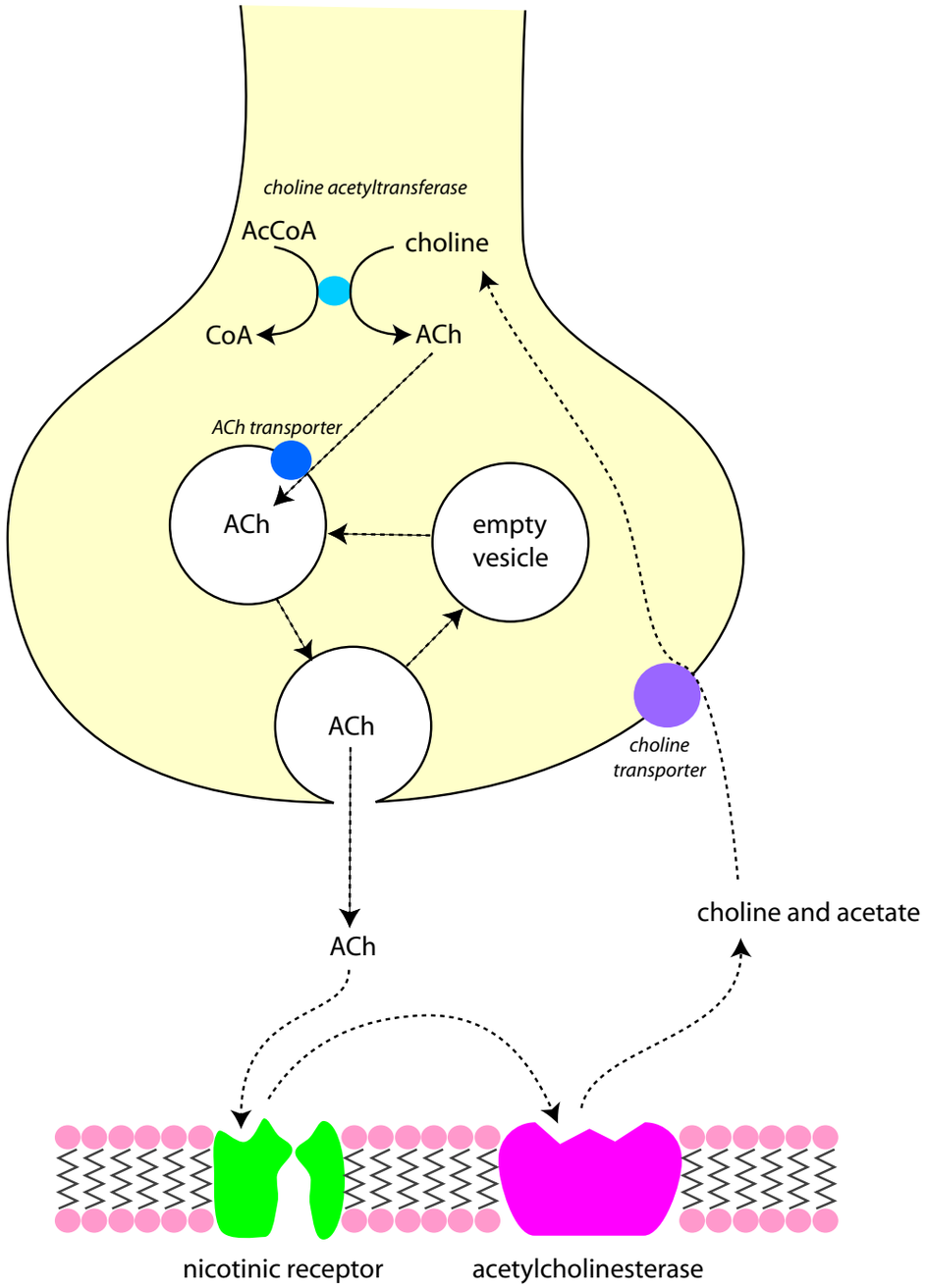
Rabbits possess an enzyme which breaks atropine down rapidly - it is too short acting to be of much use in this species.

DIAGRAM 3.1.3 Parasympathetic postganglionic neurone



Receptors and drugs at the postganglionic neurone in the parasympathetic system. The neurone on the right is an inhibitory input from the sympathetic system.

DIAGRAM 3.1.4 Autonomic ganglionic transmission



Acetylcholine synthesis and breakdown at the parasympathetic ganglion. The process is the same in the postsynaptic neurone, but the receptors would be muscarinic.

Sympathetic system

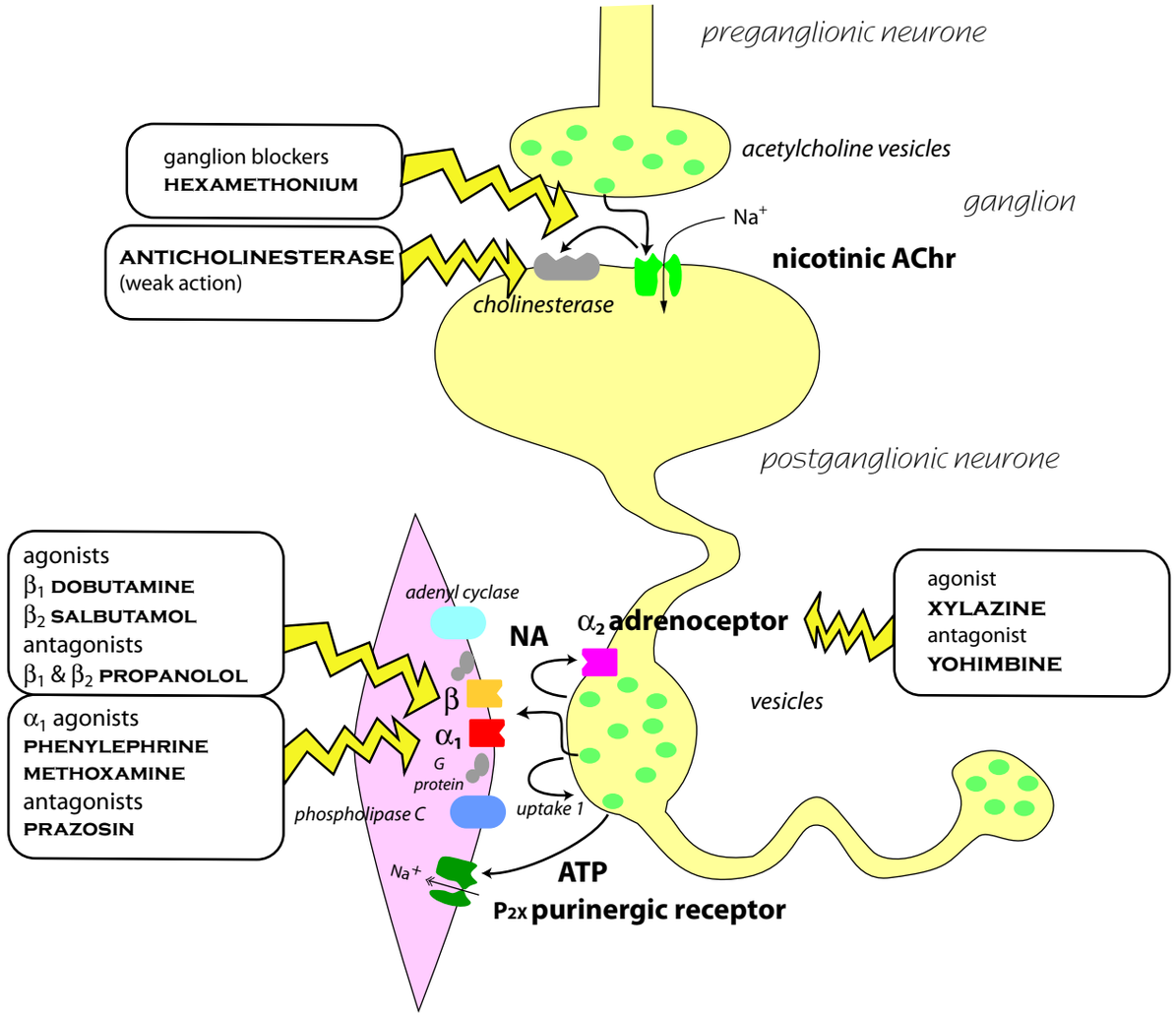
commonly used drugs

adrenaline

Sympathetic system

- ☑ noradrenaline is synthetised from tyrosine and stored in vesicles
- ☑ its release requires calcium
- ☑ it binds to adrenergic receptors - subtypes of these are present throughout the body
- ☑ its action is terminated by reuptake
- ☑ all these processes can be affected by drugs
- ☑ ATP co-transmission is important for the fast component of sympathetic stimulation

DIAGRAM 3.2.1 Sympathetic drugs



Sites of action of drugs in the sypathetic nervous system.

Physiology

Ganglionic transmission is the same as the parasympathetic system and is affected by the same drugs.

When a post ganglionic sympathetic neurone fires, noradrenaline is released. It acts at α1 or β1 receptors (excitatory) on the postsynaptic membrane or on α2 receptors (inhibitory) on the presynaptic membrane. (Note that CNS α2 receptors are different - most of them are postsynaptic). Adrenaline will act as an agonist at all these receptors and also β2 receptors.

The effect produced depends on the receptor activated and the tissue. Different tissues have different receptor distributions and there are several subtypes of each receptor (eg, α2A, α2B, α2C, α2D)which also have different distributions. More specific drugs for these subtypes are being developed.

Peripheral α2 receptors are interesting in that they are located on the presynaptic neurone. Activation of these receptors causes inhibition of the presynaptic neurone and reduces the likelyhood of noradrenaline being released, thus forming a negative feedback system.

After the noradrenaline has bound to the receptor and the second messenger system has been activated, the noradrenaline dissociates from the receptor again and most is taken back up into the presynaptic neurone (uptake 1) and recycled. Some is broken down by monoamine oxidase (MAO) and catechol O methyl transferase (COMT) to inactive metabolites. Drugs which block uptake 1 (eg, **amitriptylline**) and MAO inhibitors are important in human medicine (as antidepressants etc.) but are not often used in animals.

These receptors are widely distributed throughout the body. Most drugs are specific for one receptor rather than one tissue (although some will not cross the blood brain barrier) so the range of side effects is wide. For instance, α2 agonists such as xylazine are widely used in veterinary practice for their CNS effects as sedatives and analgesics.

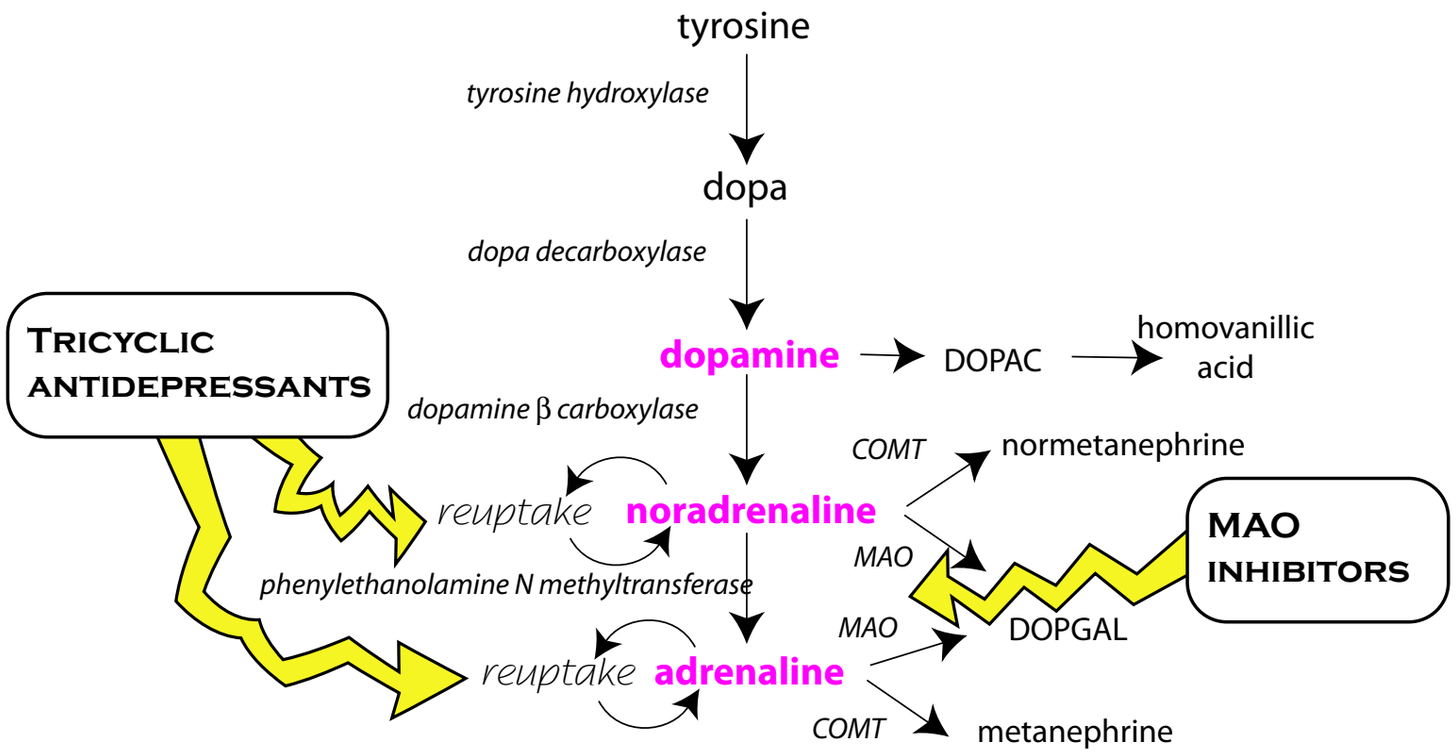
Some drugs act indirectly as sympathomimetics. Most get into the presynaptic cell by uptake 1 then displace noradrenaline from its vesicles with the end result that more noradrenaline is released. Peripherally acting drugs are used as vasoconstrictors (**methoxamine**), centrally acting drugs are widely abused (**amphetamines**, **cocaine**) and should not be used in veterinary practice.

The individual drugs are covered in the notes on the main system they affect (mainly cardiovascular system).

TABLE 3.2.1 Adrenergic receptors and drugs

Receptor	Transmitter	Useful Effects	Agonist	Antagonist
α_1	adrenaline noradrenaline	vasoconstriction mydriasis	phenylephrine	prazosin
α_2	adrenaline noradrenaline	sedation analgesia (vasodilatation)	xylazine detomidine medetomidine	atipamezole yohimbine
β_1	adrenaline (noradrenaline)	+ve inotropy tachycardia	dobutamine dopamine	atenolol metoprolol
β_2	adrenaline	bronchodilatation vasodilatation (skeletal muscles) uterine relaxation	salbutamol clenbuterol	propranolol (non selective)
(β_3	adrenaline noradrenaline	lipolysis)		

DIAGRAM 3.2.2 Synthesis and metabolism of catecholamines.



MAO = monoamine oxidase, COMT = catechol O methyltransferase. Reuptake and MAO can be inhibited by drugs.

NANC transmission

commonly used drugs

antihistamines - lots

Autacoids

- ☑ a large and important group of neuromodulators / inflammatory mediators
- ☑ rarely act alone and interactions are not well understood
- ☑ most drugs which alter smooth muscle funtion or inflammation interact with autacoids
- ☑ important as CNS neuromodulators
- ☑ histamine blockers and NSAIDs are widely used in animals

Not all autonomic transmission involves acetylcholine or noradrenaline: some autonomic neurones do not use these transmitters at all (NANC - non - adrenergic non - cholinergic transmission), while most autonomic neurones use other transmitters in addition to acetylcholine or noradrenaline (co-transmission). There is a wide spectrum of putative alternative transmitters from substances which are probably always released (such as ATP with noradrenaline) to local mediators of inflammation. The end result is usually to fine tune the effects of autonomic activity for that particular tissue.

Co - transmission

Adenosine triphosphate (ATP) is a major component of the vesicles containing noradrenaline which are released on sympathetic activiation. It is thought to be responsible for the fast component of sympathetic responses, with noradrenaline having similar but slower effects.

Neuropeptide Y, acting at NPY receptors, is probably usually released with noradrenaline too.

Other co-transmitters include: vasoactive intestinal peptide, gonadotrophin releasing hormone, 5 HT, GABA, and dopamine. Many more substances are also implicated.

Other transmitters

The major NANC transmitter is thought to be nitric oxide (NO), although a number of peptides are also produced. Nitric oxide is a potent smooth muscle relaxant. Organic nitrates (converted to NO) have been used as vasodilators for many years (see cardiovascular notes), but there is intensive research at the moment into the wider use of drugs to manipulate NO transmission, such as drugs to regulate NO synthase. However, NO is so widely used throughout the body that a general interference with its production results in far too many side effects. Some local applications have been tried, such as inhaled NO to relax bronchial smooth muscle in intensive care situations and correct ventilation / perfusion mismatching.

The peptides are slower acting and modulate transmission rather than acting as transmitters. They are not well understood but are another potentially important area for drug action.

These transmitters are thought to be important for local regulation of smooth muscle function such as vasoconstriction to control blood flow. Possible important ap-

TABLE 3.3.1 The oxides of nitrogen.

Oxide	Structure	Physiology	Effects
nitric oxide	NO	autacoid	neuronal excitation, smooth muscle relaxation
nitrous oxide	N2O	anaesthetic	analgesia
nitrogen dioxide	NO2	environmental contaminant	lung damage

plications could be anti - inflammatory drugs, and matching blood flow to ventilation in the lungs during anaesthesia.

Autacoids

There is a big overlap between local neuromodulators / transmitters and inflammatory mediators (see anti-inflammatory notes). The physiology is not well understood at present but there is a lot of work being done on this area.

Autacoids are a large (and rapidly growing) important group of neuromodulators / inflammatory mediators. They rarely act alone; most drugs which alter smooth muscle function or inflammation interact with autacoids. They are also important as CNS neuromodulators.

5 Hydroxytryptamine

5HT (serotonin) is used to regulate smooth muscle, particularly in the gut and cardiovascular system, and as a neurotransmitter in the CNS. It also regulates platelet aggregation.

Its pharmacology is complicated by the fact that there are at least 15 different 5HT receptor subtypes, and many drugs which act at some of these but are not specific. There also seem to be species differences. Synthesis, storage, release and uptake are similar to noradrenaline (at least in the CNS); somatostatin, substance P and vasoactive intestinal peptide are probably co-transmitters.

Drugs used clinically for their effect on 5HT receptors include ondansetron, a 5HT3 antagonist used as an antiemetic; metaclopramide, a 5HT4 antagonist used as a gut prokinetic (see gut notes) and many antidepressants, such as fluoxetine (Prozac) used to modify behaviour (see CNS notes). Very many other drugs affect 5HT receptors as a side effect.

Purines

The nomenclature is illogical and confusing and hopefully will be changed soon. This note is meant for guidance; do not try to learn it. Adenosine, ADP and ATP can all act as neurotransmitters / modulators, as well as having their better known metabolic effects.

Adenosine acts on a series of G protein coupled receptors: on A1 receptors to reduce adenylyl cyclase activity, on A2a and A2b receptors to increase adenylyl cyclase activity, and on A3 receptors to reduce adenylyl cyclase activity. Other receptor subtypes have been found in dogs' hearts. Xanthines (A1 and A2 antagonists) are the only drugs of veterinary relevance at the moment, although adenosine itself is sometimes used as an antiarrhythmic and vasodilator (A1). A2 receptors may be involved in pain and anxiety; there will probably be specific agonists and antagonists soon.

ADP and ATP act on P2 receptors. ATP released with noradrenaline from sympathatic varicosities acts on P2X ionotropic receptors, of which there are at least 7 subtypes. These receptors are also widely distributed in the CNS as well as on smooth muscle. The other P2 receptors are coupled to G proteins: P2Y receptor activation leads to increased phospholipase C and reduced adenylyl cyclase activity: there are probably many subtypes of this receptor as the range of effects is very large. ATP acting at P2U receptors mediates some aspects of inflammation. P2T receptors occur on platelets; ADP is an agonist, causing aggregation, ATP is an antagonist. ATP can also produce a non selective increase in cell permeability by acting at P2Z receptors. There are several other receptors which are probably also P2 receptor subtypes. Confusing, isn't it?

Peptides

Peptide neuromodulators are very widely distributed, and usually have a wide range of effects. Many of these effects involve amplifying or damping down inflammation. For instance, substance P, a tachykinin, is released from both ends of primary afferent C fibre nociceptors. At the central end, it enhances the transmission of pain signals, at the peripheral end, it causes vasodilatation and helps to initiate

and maintain an inflammatory reaction. It also causes pruritus, probably by both a central and peripheral effect. The related neurokinins A & B are neuromodulators in the CNS.

Peptides are not usually given as drugs because they are poorly absorbed or rapidly broken down (nasal administration may avoid some of these problems). Many conventional small molecule drugs act at receptors for endogenous peptides. The opioids such as morphine, mimic the effects of endomorphins and β endorphin, and produce good analgesia (see CNS notes).

Histamine

Histamine is probably more important as an inflammatory mediator than a neuromodulator although it plays an important role in the gut in the control of acid secretion (see gut notes) and in the CNS in the control of sleep.

Histamine release, usually as part of an allergic reaction, in the skin causes vasodilatation and pruritus, in the circulation causes massive hypotension (anaphylaxis). H1 antagonists are used clinically to prevent these. Histamine is also involved as a neuromodulator in vomiting, and several H1 and H2 antagonists are used as antiemetics (see gut notes).

Most H1 antagonists cause sedation (although not always by H1 antagonism - see CNS notes). However, tripelennamine, a non-specific antagonist, causes excitation, particularly in ruminants. It is sometimes misused in an attempt to get a downer cow up.

Eicosanoids

20 carbon phospholipid derivatives, which include prostaglandins, thromboxanes, leukotrienes and lipoxins, are mainly important as inflammatory mediators, but again act as neuromodulators in the CNS and periphery. Prostaglandins are probably the main mediators of inflammation in animals, or at any rate, the most easily inhibited by drugs. Non-steroidal anti-inflammatory drugs such as aspirin and corticosteroids such as prednisolone are very widely used to stop the production of prostaglandins (see CNS and inflammation notes). Prostaglandins are also involved in luteolysis and parturition, gastric acid secretion and emergency vasodilatation in the kidney. In people at any rate, they are also important in asthma.

Others

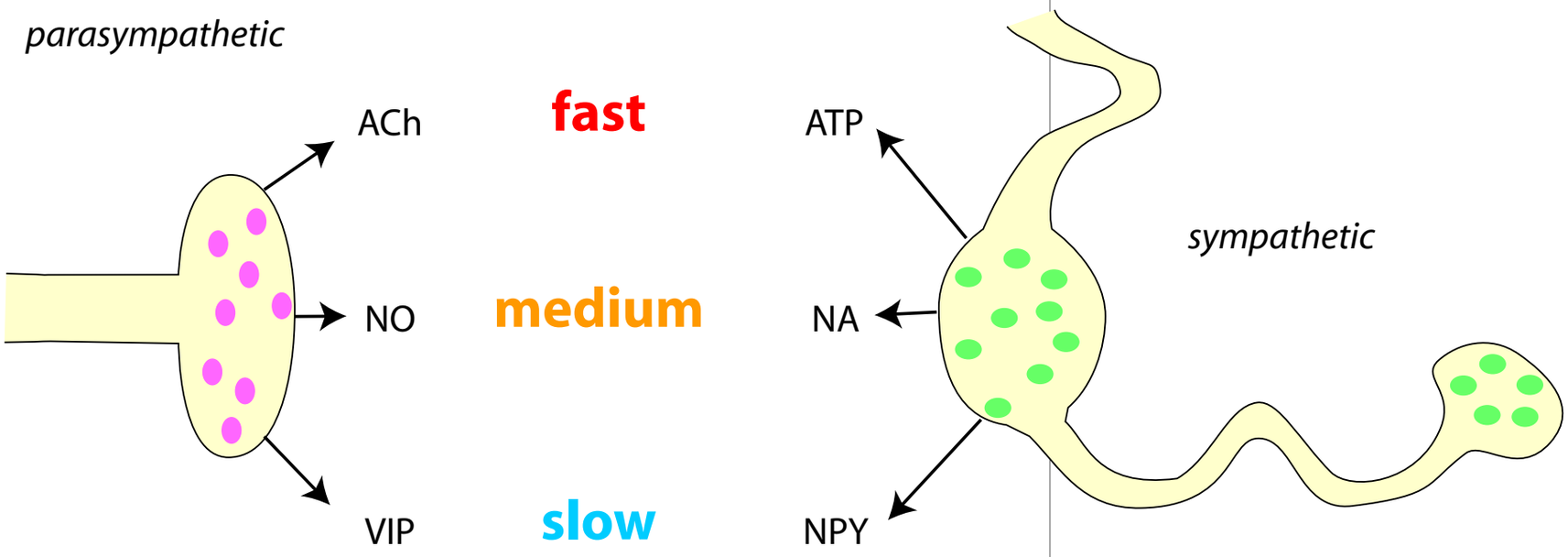
Bradykinin is involved in vasodilatation, contraction of smooth muscle, fluid secretion and pain; but probably only in inflammation. The pain it produces is markedly potentiated by prostaglandins. Experimental receptor anatonists exist and have been tried as analgesics. Bradykinin is broken down by angiotensin converting enzyme. Inhibitors of this enzyme are used for heart failure without side effects attributable to bradykinin (with the possible exception of mild coughing).

A large variety of cytokines are released in inflammation to increase or reduce it. They include interleukins, tumour necrosis factor, interferons, growth factors and many more. Some non-specific inhibitors of these are starting to emerge, including some old drugs which are used in veterinary practice.

TABLE 3.3.2 histamine receptors and drugs

receptor	distribution	antagonist
H1	skin, smooth muscle, chemoreceptor trigger zone	promethazine, chlorpheniramine, mepyramine, terfenadine, astemizole, cetirizine tripelennamine
H2	gastric parietal cells, chemoreceptor trigger zone	cimetidine, ranitidine, tripelennamine
H3	presynaptic neurones in CNS (& periphery?)	tripelennamine

DIAGRAM 3.3.1 Co-transmission



VIP = vasoactive intestinal peptide, NPY = neuropeptide Y. There are lots more possible modulators!!!

The eye

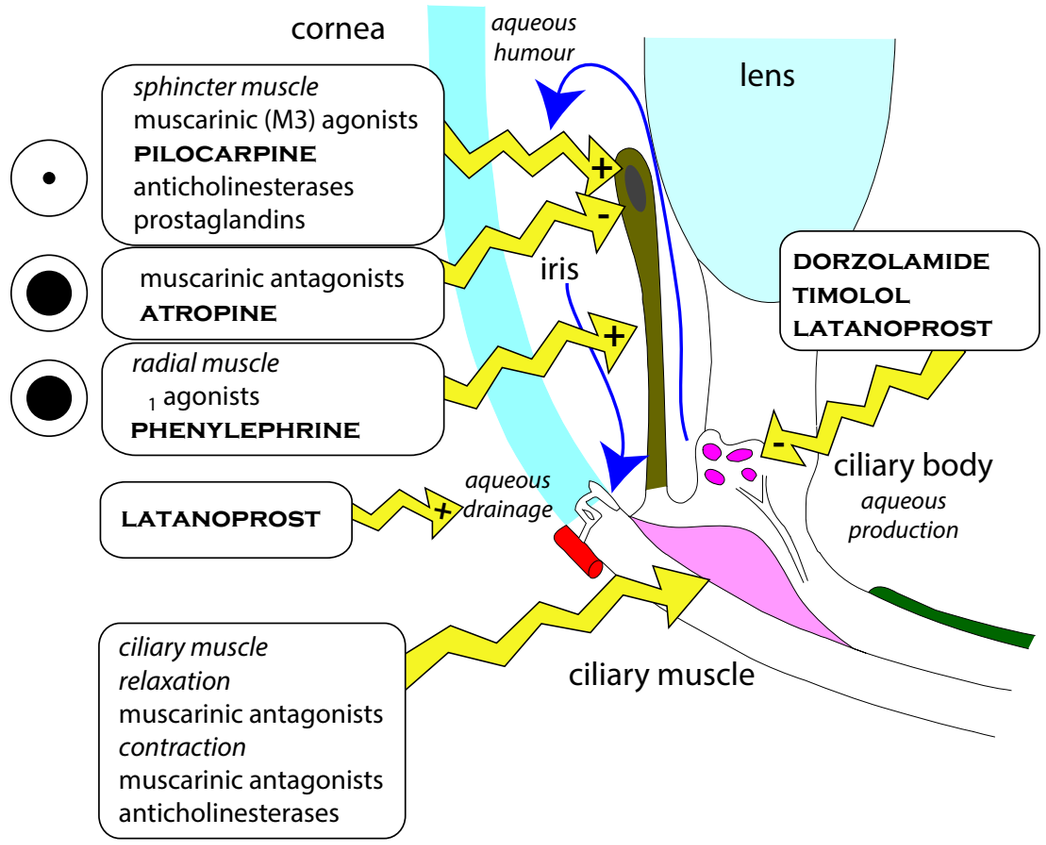
commonly used drugs

corneal examination - fluoroscein
local anaesthesia - proxymetacaine
mydriasis - atropine
miosis - pilocarpine
antibiotics - cloxacillin (large animals), gentamicin (small animals, horses)
anti-inflammatories - hydrocortisone

eye

- ☑ local anaesthetics are useful for examination and removal of foreign bodies
- ☑ antibiotics are instilled onto the cornea to treat bacterial / chlamidial infections
- ☑ glaucoma is usually treated with topical carbonic anhydrase inhibitors or prostaglandin analogues
- ☑ great care is required with steroids

DIAGRAM 3.4.1 Drugs affecting the eye.



Most drugs given for ocular problems are instilled onto the cornea as drops or ointment (although if high doses are given they can be absorbed and produce systemic effects). Occasionally subconjunctival injections are made - usually to provide a depot of drug, particularly in large animals. Systemic administration of drugs is only used in serious cases. Smart delivery systems such as drug impreganated contact lenses (in people) and various plastic implants (in animals) are starting to be used.

Common Problems

Foreign bodies often get into animals' eyes and cause some degree of inflammation. This is painful, so local anaesthetics are usually necessary to allow a proper examination (and possibly removal). Corneal damage can be detected by applying fluorescein drops to the eye; ulcers will stain green. Green appearing at the nose will also show that the nasolachrymal ducts are patent. Corneal infection is relatively common in all species and is treated with antibiotics. Mydriatics (drugs which dilate the pupil) are used to allow examination of the retina and to stop the iris forming adhesions after anterior chamber infection. Glaucoma is rarely diagnosed in dogs until it has progressed to the stage where drugs are not very effective, but a variety of drugs are used to reduce the formation of aqueous humour and increase drainage. Keratoconjunctivitis sicca usually responds to cyclosporin (see immunosuppressive drugs notes). Corticosteroids have to be used with great care in the eye because they stop corneal ulcers healing; these can become infected and perforate the anterior chamber. Steroids are usually only used in chronic inflammation to prevent the growth of blood vessels across the cornea.

Local Anaesthetics

The local anaesthetic most commonly used in other situations, lignocaine, is not usually used in the eye as it is an acid solution and stings on application (although it blocks senation after the initial stinging). Proxymetacaine is used for examination of the eye; it has a rapid onset and a short duration of action (15mins). Amethocaine (tetracaine USAN) has a longer duration of action.

Antibiotics

(See antibiotic notes for full details)

Penetration of the eye after topical administration varies but since many infections are superficial this does not usually matter. Systemic therapy is not usually used (but note that some antibiotics are absorbed systemically after application to the eye). Cloxacillin is commonly used for pinkeye in cattle and sheep - duration of action up to 48 hours which is usually enough to clear the problem. Gentamicin is sometimes used for chronic ulcers, tobramycin is used where gentamicin resistance is a problem. Framycetin has poor penetration but is used for superficial infections while oxytetracycline is sometimes used for chlamydial infection in cats.

Chloramphenicol penetrates the eye best but is no longer used much in NZ (illegal in food animals).

Drugs used in glaucoma

Glaucoma is common in dogs. It is an increased intraocular pressure caused in dogs by reduced drainage of aqueous fluid. (In man, it is often caused by increased production of aqueous - beware the confusion when reading human textbooks.) Increased intraocular pressure will damage the retina leading to blindness; the immediate treatment aims to reduce the intraocular pressure, longer term treatment in dogs is usually to increase aqueous drainage. Surgery is sometimes used in the longer term.

Diuretics

For emergency reduction of intraocular pressure, osmotic diuretics such as mannitol (iv) or glycerine (po) are usually used.

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors such as acetazolamide have a direct effect on the ciliary body to reduce aqueous formation (and are also diuretics). Topical CAIs such as dorzolamide and brinzolamide are more commonly used as theya re more efective with fewer side effects.

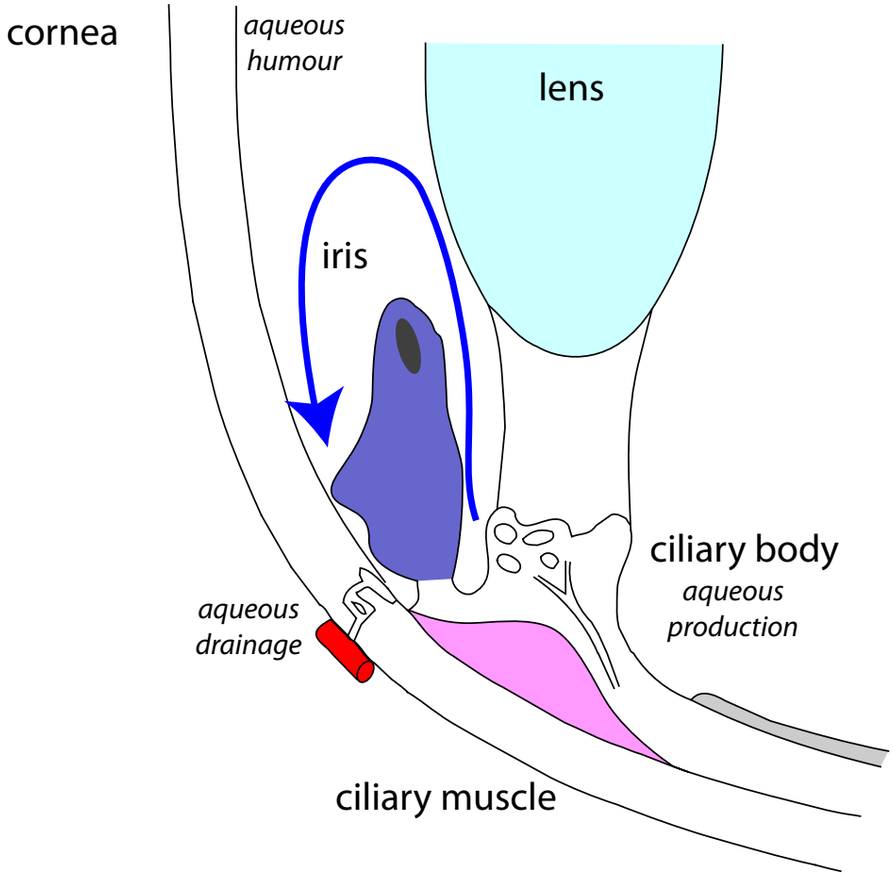
Prostaglandin Analogues

The PGAs latanoprost, bimatoprost, and travoprost are the most effective glaucoma medications in humans and dogs. They act at FP receptors. Cats rely on EP receptors to lower intraocular pressure in response to PGs, so these do not work in cats. Given topically.Contra-indicated in lens luxation, care in uveitis.

Miotics

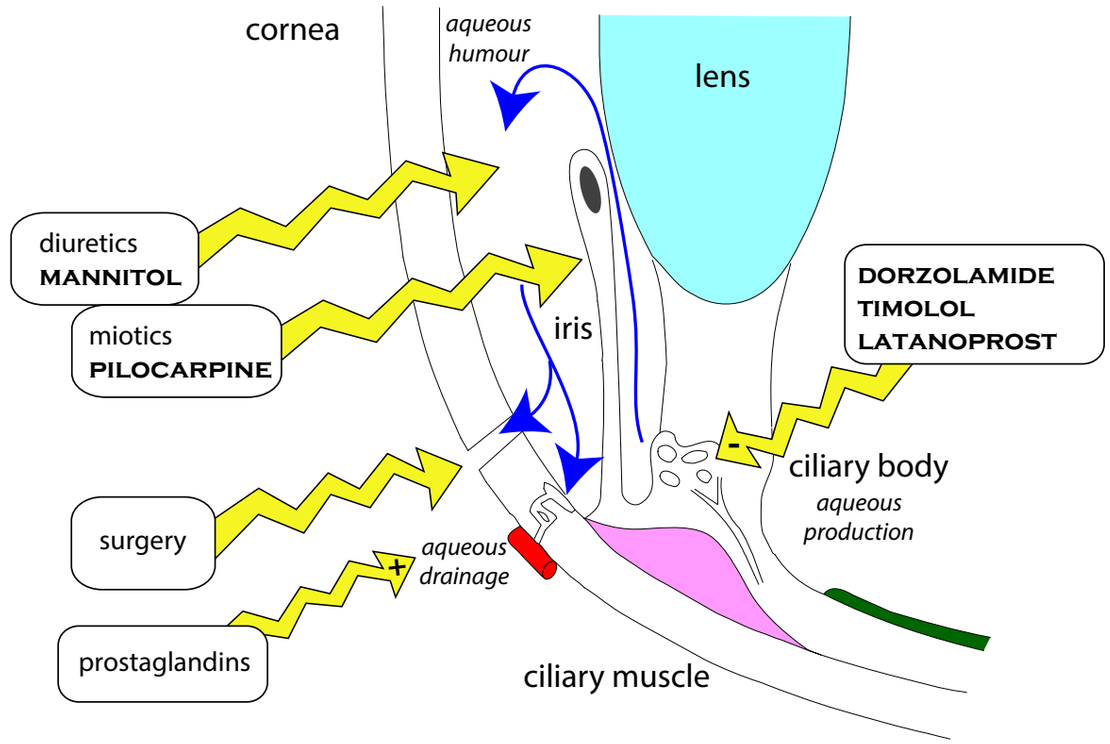
Miotics are used to lift the iris away from the trabecular meshwork and allow the aqueous fluid access to drain away. Pilocarpine, a cholinergic agonist, which acts rapidly and lasts about six hours is sometimes used. Occasionally, physostigmine, a longer acting anticholinesterase is used, although it may cause retinal problems in long term use.

DIAGRAM 3.4.2 Glaucoma



Glaucoma in dogs develops when aqueous outflow is blocked. In this case the iris has collapsed over the canals of Schlemm.

DIAGRAM 3.4.3 Glaucoma treatment



Options for treating glaucoma. Diuretics are used in the short term, lifting the iris off the trabecular mesh in the longer term. Reduction of aqueous production does not work reliably in dogs

Miotics are contraindicated in anterior uveitis / anterior lens luxation.

β Blockers

In man, timolol is commonly used to reduce aqueous formation from the ciliary body. Although it is a β blocker, it may produce its effects on the eye by a different mechanism. It is less effective in dogs and cats than people. Other β blockers are not so effective in any species.

Other Drugs

The α2 agonist brimonidine is also used in people.

Surgery is sometimes used to treat glaucoma - a hole is made at the edge of the cornea and the aqueous humour drains out under the cornea.

Drugs used in keratoconjunctivitis sicca

This is a condition where tear secretion is reduced - usually autoimmune and often caused by sulphonamides. The cornea dries out and usually gets badly damaged. There are two main treatments: immunosupressants and artificial tears to provide lubrication, although surgery (transplantation of the parotid duct) is popular in some places.

Cyclosporin eye drops are the usual immunosuppressive treatment. Tear production usually returns in 1 - 8 weeks after immunosupression with cyclosporin.

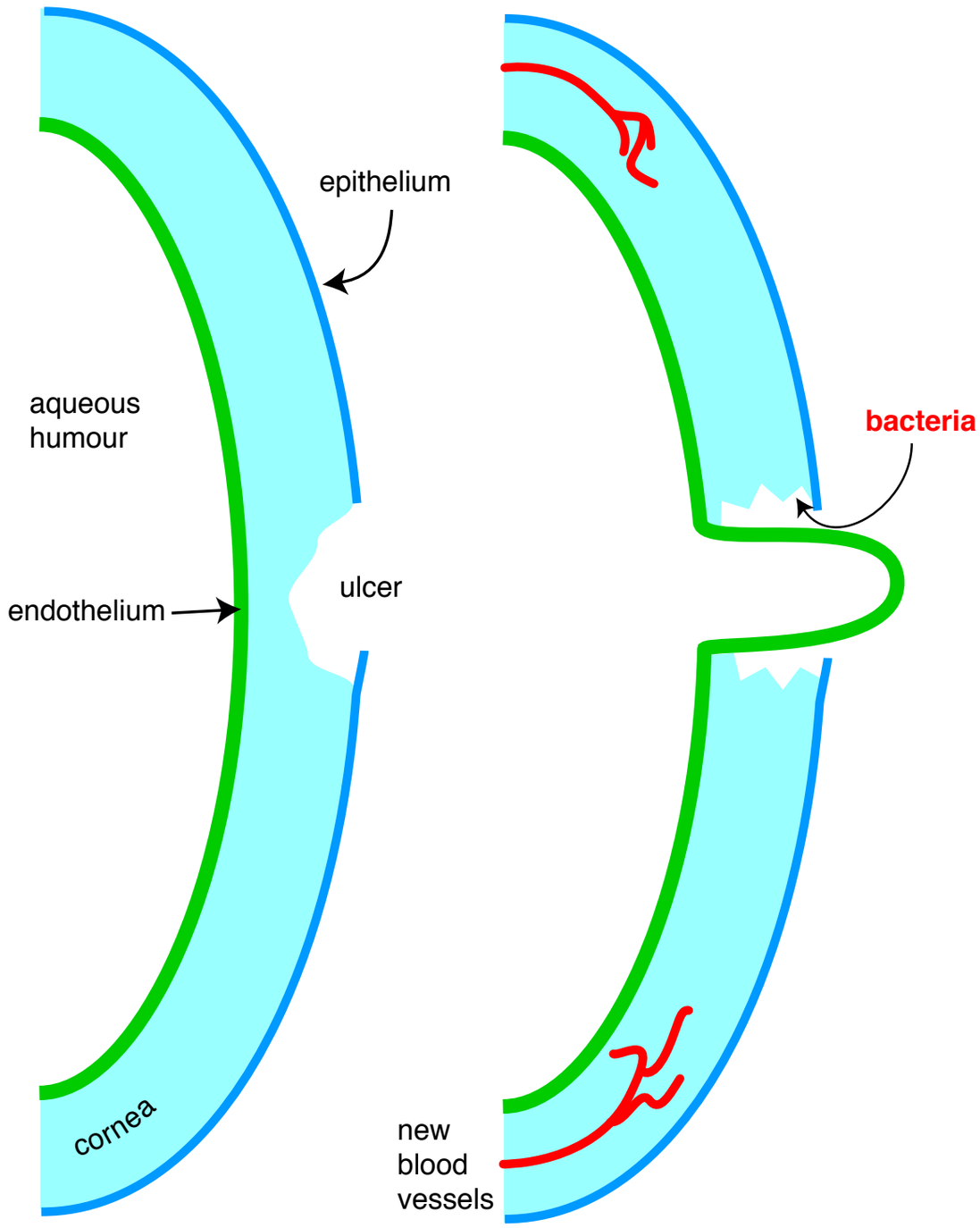
Hypromellose eye drops are the most commonly used artificial tears - they are not very practical as they have to be applied every 1 - 2 hours.

Anti-inflammatory drugs

Corticosteroids (usually hydrocortisone) are normally only used to stop blood vessel growth, pigment deposition and scarring in the cornea. They are contra-indicated in corneal ulceration as they can slow healing of the ulcer and may make the ulcer deeper. If the ulcer penetrates the full thickness of the cornea, the anterior chamber will burst resulting in blindness. Topical application gives higher concentrations at the cornea than systemic administration.

NSAIDs are used to reduce the inflammation of surgery, particularly cataract removal. Sometimes used as anti-inflammatories in corneal ulceration. Diclofenac and flurbiprofen have been the traditional drugs.

DIAGRAM 3.4.4 Corneal ulceration



If the ulcer penetrates the full thickness of the cornea, the vulnerable endothelium will "cone" out. If this ruptures, the lens and iris are usually displaced into the hole and the animal is unlikely to see out of that eye again.

The bladder

commonly used drugs

cystitis - amoxycillin

incontinence - phenylpropanolamine ± oestrogen

bladder

- ☑ cystitis is common and is treated with antibiotics
- ☑ incontinence is common after spaying in bitches - α1 agonists ± oestogens
- ☑ urine pH is sometimes manipulated to increse the effects of drugs or dissolve stones
- ☑ drugs which affect motility have lots of side effects
- ☑ drugs do not always work

Common Problems

- cystitis
  - antibacterials
  - (urinary antiseptics)
- urolithiasis
  - antibacterials and surgery
  - dietary control
  - urinary acidifiers / alkalinisers
  - diuretics
  - specific drugs to stop production of calculus substrate
- sphinter mechanism incontinence
  - α1 agonists
  - oestrogens
- urinary retention
  - cholinergic agonists or antagonists
  - central muscle relaxants

Several of these problems can occur together, eg bacterial cystitis may lead to urolithiasis under some circumstances which then leads on to incontinence.

Drugs used for cystitis

Antibacterials

Cystitis may be caused by a wide range of bacteria (coliforms are common in most species) and a broad spectrum antibiotic which is actively excreted unchanged by the kidneys, such as **ampicillin** or **amoxycillin**, is often used (for more details see antibiotic notes). The effectiveness of some antibacterials is altered by the urinary pH, so this is sometimes manipulated during antibiotic treatment.

Urinary Acidifiers

Ammonium chloride and **sodium acid phosphate** are sometimes used to make the urine more acid, particularly when treating cystitis. Some antibiotics such as penicillin, tetracyclines and nitrofurantoin are more active at lower pH (5.5).

Urinary Alkalinisers

Erythromycin, **streptomycin** and **co-trimazine** are more effective at higher pH (8): **sodium bicarbonate** and **sodium acid citrate** are used (rarely) to make the urine more alkaline.

Urinary Antiseptics

Hexamine (methenamine USAN) used to be used to kill bacteria in the bladder and may make a comeback with the emergence of antibiotic resistant bacteria. Bacteria break it down to formalin, which then kills them. Relatively innocuous but not very effective.

Drugs for incontinence & retention

For the bladder to fill normally, the muscle of the bladder wall must be relaxed and the sphincter contracted; this is reversed for micturition. Incontinence can arise from excessive tone in the bladder wall during filling (cystitis, nerve deficits from spinal injury, idiopathic detrusor instability) or from lack of tone in the bladder wall (nerve deficits from spinal injury) or sphincter (usually bitches spayed before their first oestrus).

Otherwise obscure drugs are often chosen for use in the bladder in the hope that they will not cross the blood brain barrier and thus give rise to central effects. They are not always sucessful at this and will usually give rise to the full range of peripheral side effects as well.

Anticholinergics

Propantheline is used in detrusor instability (increased contraction of the body of the bladder - rare in animals but common in women) to relax bladder and allow filling. More specific drugs such as tolterodine are used in people. Anticholinergics are contra - indicated in urinary obstruction and glaucoma.

Alpha Adrenergic Agonists And Sex Hormones

Urinary incontinence in spayed bitches is a common problem. **Oestrogens** upregulate α1 adrenergic receptors in the internal sphincter, a lack of oestrogen reduces the number of α1 receptors and thus the ability to contract the sphincter. Therefore oestrogens given with α1 agonists produce the greatest effect. Since oestrogens cause a wide rqange of side effects in dogs and α1 agonists cause vasoconstriction, low doses of both drugs will reduce the side effects. Oestrogen treatments take several weeks to work but α1 agonists can work almost immediately. Probably the best treatment strategy is to try α1 agonists first, increase the dose if there is no response and then add in low dose oestrogens if there is still no response or side effects are seen.

Side effects of oestrogens incude bone marrow depression (potentially fatal), attraction for male dogs, pyometra (if any endometrium is left) and mammary carcinomata.

Contraindications for oestrogens include pregnancy and oestrogen dependant tumours (unlikely in a spayed bitch): for α1 agonists heart disease.

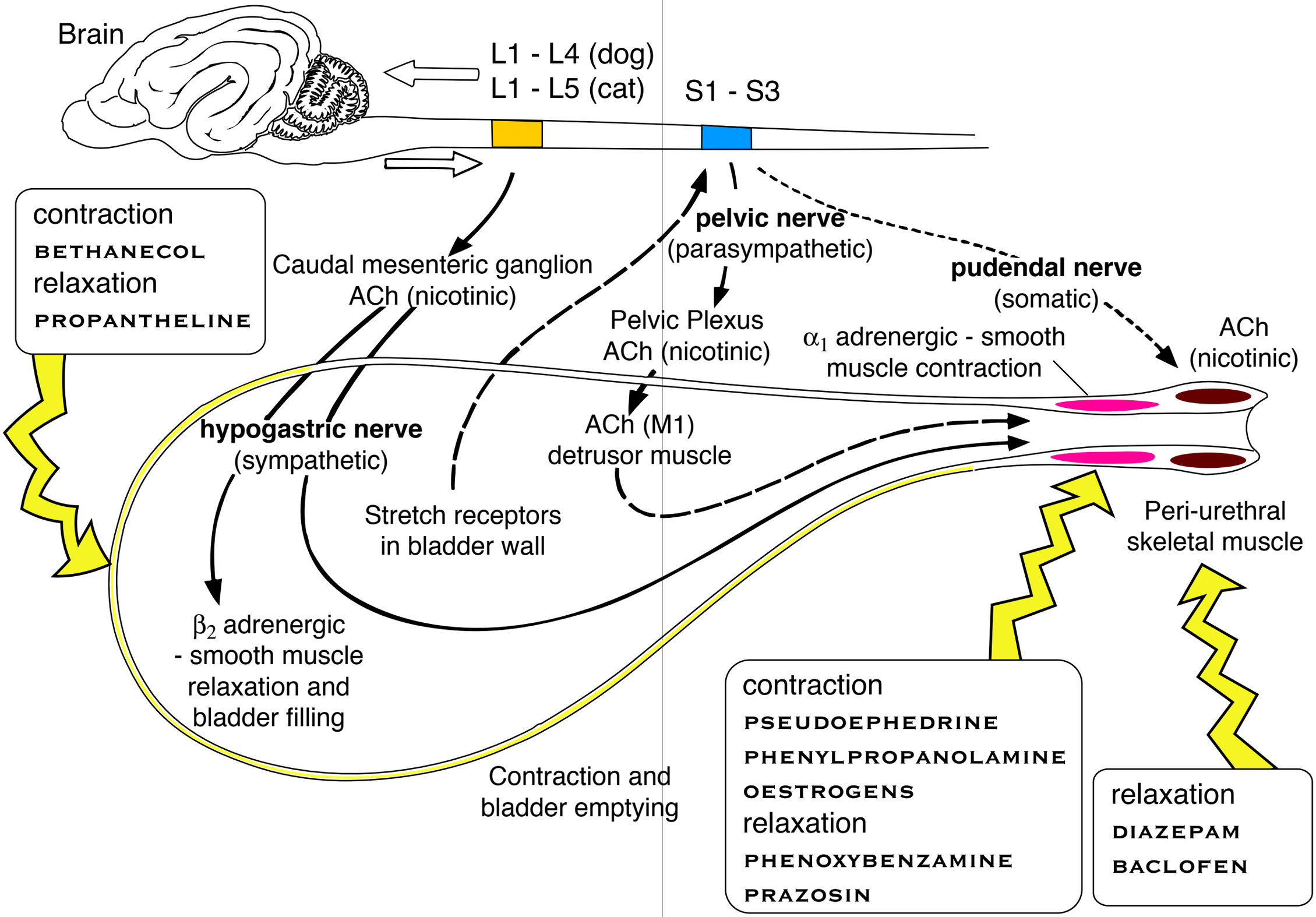
All oestrogens can be absorbed across intact skin, so handle with care and warn the owner, particularly women and children.

Phenylpropanolamine is the most widely used α1 agonist. It is considered safe in dogs but increases the risk of stroke in women (it causes vasocontriction and increased blood pressure). Ephedrine should not be used as it crosses blood brain barrier to cause stimulation. It is a drug of abuse in people. Pseudoephedrine is widely available as a cold cure: it does not cross the blood brain barrier in any great amount and causes less CNS stimulation than ephedrine. Pseudoephedrine is used as a precursor in the illegal manufacture of methamphetamine, so if you prescribe a lot of it, you may attract attention from the police or MoH. All α1 agonists will cause vasoconstriction - check the animal's cardiovascular system before use.

Stilboestrol was the most widely used oestrogen but is now unavailable in NZ because of worries that it is carcinogenic (however, all oestrogens are carcinogenic). One of the main reasons for spaying bitches is to prevent them developing mammary tumours, oestrogen replacement is likely to negate this. Oestrogens may also make bitches attractive to male dogs and cause life - threatening bone marrow depression.

Oestradiol benzoate injection is licensed for use in dogs but is not really practical. Oestrogen tablets are widely available for human use but one preparation ("Premarin") is widely used because it is a mixture of oestrogen metabolites and not very potent, and it comes in tablets small enough for dogs. Use the lowest dose that works. Oestrogens are rapidly metabolised in the liver; ethinyloestrenol is commonly used in women because it is rapidly absorbed and metabolised to oestradiol. It is mainly used as a contraceptive pill: you will have to be prepared to explain to the bitch's owner why you charged lots of money to spay the bitch and are now putting her on contraceptives. Oestriol, a natural oestrogen normally used for HRT in

DIAGRAM 3.5.1 Bladder drugs



Sites of action of drugs in the bladder. Do not give them all at once!

women, has recently come on the market in NZ for dogs. It is claimed not to cause as much bone marrow suppression as oestradiol, probably because it is a much weaker oestrogen.

Testosterone is sometimes useful in castrated males - mechanism unknown

Cholinergics

Bethanecol is sometimes used to contract the detrusor muscle in urinary retention caused by bladder paralysis after spinal injury. It is now difficult to obtain and tends not to work very well in some cases.

Alpha Adrenergic Antagonists

Used when urinary retention is caused by excessive sphincter tone, phenoxybenzamine (non specific α antagonist) is often given with diazepam to relax the external spincter. Care is required in animals with heart disease. Phenoxybenzamine binds irreversibly to the receptors so tends to last for the lifetime of the receptors (3 - 4 days). More specific drugs such as prazosin tend to be used in people.

Drugs for urolithiasis

Calculi (stones) nearly always damage the bladder causing cystitis and bacteria are often a problem so antibacterials are usually given. Stuvite calculi may dissolve in acid urine, urate calculi may dissolve in alkaline urine. Allopurinol is sometimes used to reduce the formation of urates. Prescription diets are usually used to prevent recurrence.

Urolithiasis can be excruciatingly painful in people - animals should be given the benefit of the doubt (and NSAIDs).

Further reading

Moreau, P.M. and Lappin, M.R. (1989) Pharmacologic management of urinary incontinence. in *Kirk's Current Veterinary Therapy X*, Small Animal Practice, Saunders

The uterus

commonly used drugs

relaxation - clenbuterol

contraction - oxytocin

uterus

- ☑ clenbuterol is used to relax the uterus to postpone calving for 6 - 12 hours
- ☑ oxytocin is used to promote uterine involution after parturition and induce farrowing in sows with uterine atony

The uterine muscle contracts rhythmically. This contraction originates in the muscle rather than being under direct nervous control, and is greatly influenced by circulating hormones.

The effects of drugs on uterine tone depends on the species and stage of pregnancy (although they are rarely used except at parturition). Drugs which affect uterine tone as a side effect can cause abortion.

Relaxants

Clenbuterol (β2 adrenergic agonist) is used to delay parturition in cows for about 12 hours (very variable) to allow calving to take place at a convenient time of day. It can also be used to relax the uterus for caesarian sections, foetus manipulation in dystocia, embryo transplant etc.

In growing cattle, clenbuterol will encourage the production of lean meat and lipolysis (sometimes referred to as a partitioning agent), probably by an effect at β3 receptors. Although this use is illegal in most places, clenbuterol is widely abused for this reason in some countries under the name of "angel dust". It is also abused by human athletes, particularly cyclists for some reason.

Isoxuprine (also thought to be a β2 adrenergic agonist) will relax the uterus and is available for use in cattle.

Other smooth muscle relaxants sometimes used in women include nifedipine (calcium blocker) and glyceryl trinitrate (both covered in cardiovascular notes).

Constrictors

Drugs which contract the uterus are sometimes used after parturition. Oxytocin is a peptide produced by the hypothalamus: uterine contraction will depend on the species and the state of pregnancy (although it is usually used in large animals at the time of parturition when the uterus is most sensitive to its action). Low doses cause regular coordinated contractions, high doses cause spasm. Also causes milk let down. It is used to promote uterine involution and reduce bleeding from the uterine lining and to induce parturition in sows with uterine atony.

Prostaglandin F2α has been used to cause abortion in bitches (and women). It is a very potent bronchoconstrictor in most species, including people, and must be handled with great care. It can also be absorbed across the skin and cause bronchoconstriction in people.

ANS toxicities

commonly used drugs

symptomatic treatment

ANS toxicities

- ☑ cyanobacteria
- ☑ organophosphates
- ☑ carbamates
- ☑ levamisole

Toxicants affecting the autonomic nervous system (and in some cases, voluntary nerves as well). This is not an exhaustive list.

Toxicants With Cholinergic Effects

- Tertiary amines (no charge, penetrate BBB and CNS)
- -atropine
- -hyoscine
- Quaternary Amines (charged, do not penetrate BBB)
- -atropine methyl nitrate
- -hyoscine methyl bromide
- -propantheline (Pro-Banthine)
- -glycopyrrolate (Robinul-V)
- Plants
- - belladonna (Atropa belladonna)
- - henbane (Hyoscyamus niger)
- - thornapple (Datura)
- - mushrooms (Amanita panterinae and A. muscaria)
- Solanaceae that usually have primarily atropine-like effects
- - ground cherry (Physalis)
- - matrimony Vine (Lycium halimifolium)
- - jessamine (ripe berry) (Cestrum spp.)
- - angel's Trumpet (Datura)
- - potato, green (Solanum tuberosum)
- -Other Solanaceae that Sometimes Have Mainly Atropine Effects
- -Black nightshade (S. nigrum)
- -Tomato leaves, green fruit (Lycopersicon)
- -Jerusalem cherry (S. pseudocapsicum)

-Note: Unlike the effects of atropine the clinical effects of the solanaceous alkaloids (solanine, solanidine, etc.) which predominate in many of the Solanaceae are largely due to gastrointestinal irritation and cholinesterase inhibition

Toxicants With Muscarinic Effects But No Nicotinic Effects

- -muscarine
- -pilocarpine

- -arecoline
- -methacholine
- -carbachol
- -bethanechol
- -muscarinic/histaminic mushrooms
- -Amanita muscaria - only a minority of member of this species
- -mouldy red clover (slaframine) (Trifolium pratense infected with Rhizoctonia leguminicola)
- Inhibitors of Cholinesterase
- -organophosphorus insecticides (e.g. coumaphos, diazinon, propetamphos)
- -carbamate insecticides (e.g. methiocarb, propoxur)
- -blue-green algae (Anabaena flos-aquae) [Anatoxin- a(s)] and other cyanobacteria
- solanaceous alkaloid (solanine and solanidine) containing plants
- -black nightshade (Solanum nigrum)
- -silverleaf nightshade (S. carolinense)
- -horse nettle, bull nettle (S. carolinense)
- -European bittersweet, climbing bittersweet (S. dulcimara)
- -tomato (green or vine) (Lycopersicon)
- -groundcherry (Physalis)
- -jessamine (unripe berry) (Cestrum)
- -matrimony vine (Lycium)

Toxicants With Nicotinic Effects

- -nicotine sulfate (blackleaf)
- -tobacco (Nicotiana)
- -Indian tobacco (Lobelia)
- -cardinal flower (Lobelia)
- -giant lobelia (Lobelia)
- -poison hemlock (Conium maculatum).
- -lupin (Lupinus)
- -mescal bean (Sophora spp.)
- -kentucky coffee tree (Gymnocladus dioica)
- -goldenchain (Laburnum anagyroides)
- -levamisole
- -blue-green algae (Anabaena) (anatoxin-a)

Blue-green Algae - Cyanobacteria

- Anabaena spp (lakes and rivers both islands)
- Microcystis spp (Anacystis spp)
- Nodularia spp (Nodularin poisoning of stock in Canterbury)
- Oscillatoria spp

Sources

Fresh Water bodies (lakes, rivers) with the right environmental conditions (warmth, nutrients).

Cyanotoxins

Hepatotoxic – cyclic peptides (Microcystins and nodularin)

Neurotoxic – alkaloids (anatoxin-a, saxitoxins) (cause of deaths in NZ dogs)

Lipopolysaccharides (LPS)

Principle toxic effects

Anatoxin-a

- nicotinic depolarising alkaloid
- neuromuscular blocker
- Potent and fast acting

  Anatoxin-a(s) 10X more potent than Anatoxin–a (not reported in NZ)

- acetylcholinesterase inhibitor (s for salivation)

Microcystin

- hepatic necrosis and gastroenteritis

Clinical signs of poisoning

Hepatotoxic algae

- signs begin within 1- 4 hours after exposure. Death in 24 hours to 5 days.
- Lethargy, vomiting, diarrhoea, depression, weakness, pallor shock, and death from hepatic failure.

Neurotoxic algae Anatoxin-a and Anatoxin-a(s)

- signs occur abruptly within 60 minutes of exposure and death may occur within 30 minutes of the appearance of clinical signs.

- Clinical signs include muscle rigidity, twitching of limbs, tremors, seizures, coma, paralysis, respiratory paralysis, cyanosis, hypersalivation, and death.
- Anatoxin-a(s) causes an acute onset of salivation, lacrimation, urination, defaecation (SLUD), convulsions, respiratory arrest and death within an hour.

Diagnosis

Send water samples to testing laboratory for identification. Test stomach samples for evidence of toxin.

Clinical Pathology of hepatotoxic exposure causes marked elevations of hepatic enzyme activity, which may decrease over time.

Treatment

- Decontaminate (oral and dermal)
- Symptomatic care
- Atropine for anatoxin-a(s)

See February 2006 VetScript for recent poisonings in the Hutt River XIX (1)6-8.

Organophosphates

Sources

- Various Insecticides/Pesticides:
- Dips
- Pour-ons
- Flea Collars
- Sprays
- Anthelmintics

Mechanism of action

- Inhibition of acetylcholinesterase in the Nervous System
- Muscles (neuromuscular)
- Glands
- Erythrocytes (RBC)
- May inhibit “pseudo” cholinesterase found in serum, plasma, liver,

Clinical signs

(over stimulation of the parasympathetic nervous system)

Muscarinic receptors (acetylcholine) in the smooth muscle

S - Salivation

L - Lacrimation

U - Urination

D - Defaecation

D - Dyspnoea

E - Emesis

and sweating, brady or tachycardia (adrenalin release), pinpoint pupils and nasal discharge.

Nicotinic signs due to acetylcholine at the motor nerve endings and autonomic ganglia tremors, weakness/paralysis

Central Nervous Signs

nervousness, apprehension, ataxia, convulsions, coma; Small animals-occasionally seizure, are hyperactive and hyperreflexive

Large animals-rarely seizure, may be hyperactive

OPIDN (organophosphate-induced delayed neuropathy): e.g. leptofos, fenitrothion, trichlorfon and others

Diagnosis

History, Access, Garlic odour, Measure acetylcholinesterase activity of heparinised or EDTA whole blood: less than 50% of normal is suspicious, less than 25% is fairly diagnostic (also tests on brain cholinesterase activity after death)

Test dose of Atropine (if normal atropinisation occurs-Not OP or carbamate)

Treatment - OPs

- Decontaminate - Activated charcoal
- Atropine sulphate (0.1-0.2mg/kg) - Give 1/4 dose IV rest SQ (repeat as needed q4-8hr) (Horses: use with extreme care: monitor GI sounds. Stop if sounds of GI motility decrease.)
- Respiration maintained

- Bradycardia monitored
- CNS signs controlled with diazepam (not barbiturates)
- Pralidoxime (2-PAM, Protopam chloride) Must be given early (within 8-12 hours) to be of use for most OPs - 20 mg/kg IV or IM or SQ give q12h until nicotinic signs resolve

Supportive treatment

Intermediate Syndrome

NOTE: A recently recognised condition in cats and dogs due to exposure to lipophilic organophosphorus insecticides. This syndrome may occur from a single exposure or repetitive exposures to organophosphate or carbamate compounds.

It may or may not include acute classical signs. One example is dermal exposure of cats to chlorpyrifos, which lacks the SLUDDE effects, instead causing weakness, anorexia, diarrhoea, muscle weakness and tremors, abnormal behaviour, depression and death.

Acetylcholinesterase activity is usually severely suppressed in poisoned animals.

Treatment: Atropine is not effective. Generally animals respond to 2-PAM treatment several days after exposure. Care should be taken with cats as some anecdotal reports of death are associated with 2-PAM treatment but dramatic improvement in affected animals has also been reported.

Carbamates

Sources

Carbaryl-insecticide spray

Mesurol, methiocarb Methiocarb, 4-methylthio-3, 5 xylyl-N-methylcarbamate. This is commonly used in New Zealand as a molluscicide and is marketed as a blue pellet (Mesurol Bayer NZ Ltd). Dogs and cats can be easily poisoned by this material as with metaldehyde.

Propoxur, 2-(1-Methylethoxy)phenol methylcarbamate

An insecticide licensed in New Zealand to control ectoparasites in dogs and cats.

Mechanism Of Action

Cholinesterase inhibition as with organophosphate compounds.

Toxicity

Animals which show signs of carbamate toxicity may recover completely in a few hours, while with the OPs recovery may not occur or take considerably longer.

The LD50 of methiocarb for a dog is about 25 mg/kg of methiocarb. A 20 kg dog would have to eat approximately 25 grams of Mesurol containing 2% (20 g/kg) methiocarb to receive a fatal dose.

Clinical Signs

Similar to OP toxicity

Treatment

See OP above

The use of oxime compounds (2 PAM) for the reactivation of acetylcholine esterase in carbamate toxicity is contraindicated. The latter compounds do not react with the carbamyl moiety of the inhibited enzyme but only bind to acetyl cholinesterase at the ionic site, thus also rendering functional enzyme molecules temporarily inactive.

Usually the acute signs of methiocarb intoxication last for only a few hours, but the patient may need several days to recover completely.

Controversy exists over the use of 2-PAM with carbamates. When you do not know whether the compound is OP or carbamate use 2-PAM.

Don’t use 2-PAM if carbamates are the known cause of the poisoning.

Levamisole

Levamisole is used extensively as an anthelmintic against a range of nematode parasites. It is toxic to a range of domestic species, including cattle, sheep, goats, pigs, and horses as well as kiwi.

Mechanism of action and Toxicity

Levamisole causes depolarization of nerve cell membranes

Acts like a nicotinic ganglionic stimulant

May have both nicotinic and muscarinic effects at cholinergic receptors

First it causes stimulation, then blocks ganglionic and skeletal muscle transmission. 2-3 times the therapeutic dose may cause toxicity

Clinical Signs

Within 15 minutes of dosing a full range of nicotinic effects including:

In cattle, sheep, goat, pigs and horses the main signs are hypersalivation

cattle muzzle foaming may occur for a few hours, at normal dose rates;

head shaking, lip licking, vomiting in pigs, muscle tremors, ataxia, anxiety, hyperaesthesia, irritability, clonic convulsions, CNS depression rapid respiration, frequent urination and defecation

in fatal cases, respiratory collapse and death;

in non-fatal cases in sheep and goats the clinical signs will peak by about 30 minutes and recovery may occur within 1-6 hours.

In pigs, a subcutaneous overdose may lead to respiratory failure and death within 5-60 minutes.

In dogs, following the repeat dosing with levamisole, an haemolytic anaemia occurred.

Post-mortem Examination

main organ changes include:

splenic congestion, pulmonary congestion, marked subepicardial haemorrhage, intense enteritis, acute liver degeneration with marked subcapsular haemorrhage and liver necrosis.

haemorrhage of the thalamus.

Detectable residues of levamisole are not found after 24 hours in fat, blood or muscle. The liver is free of detectable residues within 72 hours.

Treatment

In dogs, emesis is recommended within an hour of ingestion, followed by the use of activated charcoal and a saline cathartic;

symptomatic and supportive therapy if significant signs develop

convulsions may be controlled with diazepam or a barbiturate.

Autonomic toxicology cases

Case 1

Eight yearling dairy beef steers, weighing 250 kg were accidently drenched with a formulation containing trichloronat, an organophosphorus insecticide.

What are the clinical signs in cattle of organophosphorus toxicity?

Describe the mechanism of toxicity due to organophosphorus compounds.

What treatment should be administered to affected cattle?

The farmer did not realise the mistake at the time of drenching, thus no treatment was initiated. Two steers died initially. The farmer calls you now because of the ataxia and knuckling over of the steers. Is this related to the trichloronat drenching? Explain.

Case 2

A small block farmer calls you about a number of sick and dying lambs. You get a vague history over the phone about sudden death. You rush out to the farm and examine the flock. There are 30 lambs from 1-2 weeks of age. Ten or fifteen lambs started showing signs of respiratory distress and dying acutely about an hour ago. You look at the lambs and suspect toxicity due to the sudden onset. At a distance you observe that the lambs have a variety of clinical signs from depression to anxiety, hypersalivation, muscle tremors, head shaking, convulsions, tachypnoea, dyspnoea, frequent urination and defaecation to collapse and prostration. You question the farmer about the handling of the lambs. The lambs were drenched this morning with levamisole. The farmer gave these lambs 5-6 mls of Nilverm Gold[?], which has 40 g/L of levamisole HCl (recommended dose is 8mg/kg).

a. Do you think levamisole is the cause of the sudden onset of disease? How would you determine if it was? Explain/discuss.

b. What toxicities might cause similar signs?

c. What do you expect 1-2 week old lambs to weigh?

d. What treatment is recommended?

e. What's the prognosis doctor?

Case 3

An owner calls you concerning her missing dog. She arrived home after work, it is dark and her dog is not there to greet her. She finds her dog got into a shed with slug and snail bait. It is apparent that the dog has eaten all or part of a box of Mesurol[?], methiocarb. She has the following questions:

1. The owner wants to know what the poison will do to her dog so it might help her find it. What do you advise the owner? (Clinical signs, mechanism of action, etc)

2. How would you treat a dog showing clinical signs of methiocarb toxicity? AND How does this differ from the treatment of organophosphate toxicity?

3. Assuming the bait contained 20g/kg of active ingredient methiocarb and the LD50 is about 25 mg/kg for a dog, how much bait would a 20 kg dog have to eat to get the LD50 dose?

The lungs

commonly used drugs

oxygen

frusemide

oxytetracycline

codeine

bromhexine

lungs

- ☑ pulmonary oedema is a life threatening condition - treat with oxygen and frusemide iv
- ☑ expectorants are sometimes useful
- ☑ opioids will stop coughing but should not be used with productive coughs
- ☑ bronchodilators may be useful in some circumstances

Problems

- infection (pneumonia, bronchitis, tracheitis)
- bacteria antibiotics
- viruses symptomatic treatment, NSAIDs
- both anti-inflammatories ± antibiotics
- pulmonary oedema
- oxygen, diuretics
- coughing
- antitussives, expectorants

Pneumonia and pulmonary oedema can be rapidly fatal and must be treated rapidly.

Coughing is usually caused by infection, but may also be the first sign of pulmonary oedema or bronchoconstriction. It is usually the first thing that the animal's owner notices, and the reason the vet is called in.

Acute pulmonary oedema

Pulmonary oedema constitutes an acute life-threatening condition that requires prompt and diligent attention. Treatment usually requires:

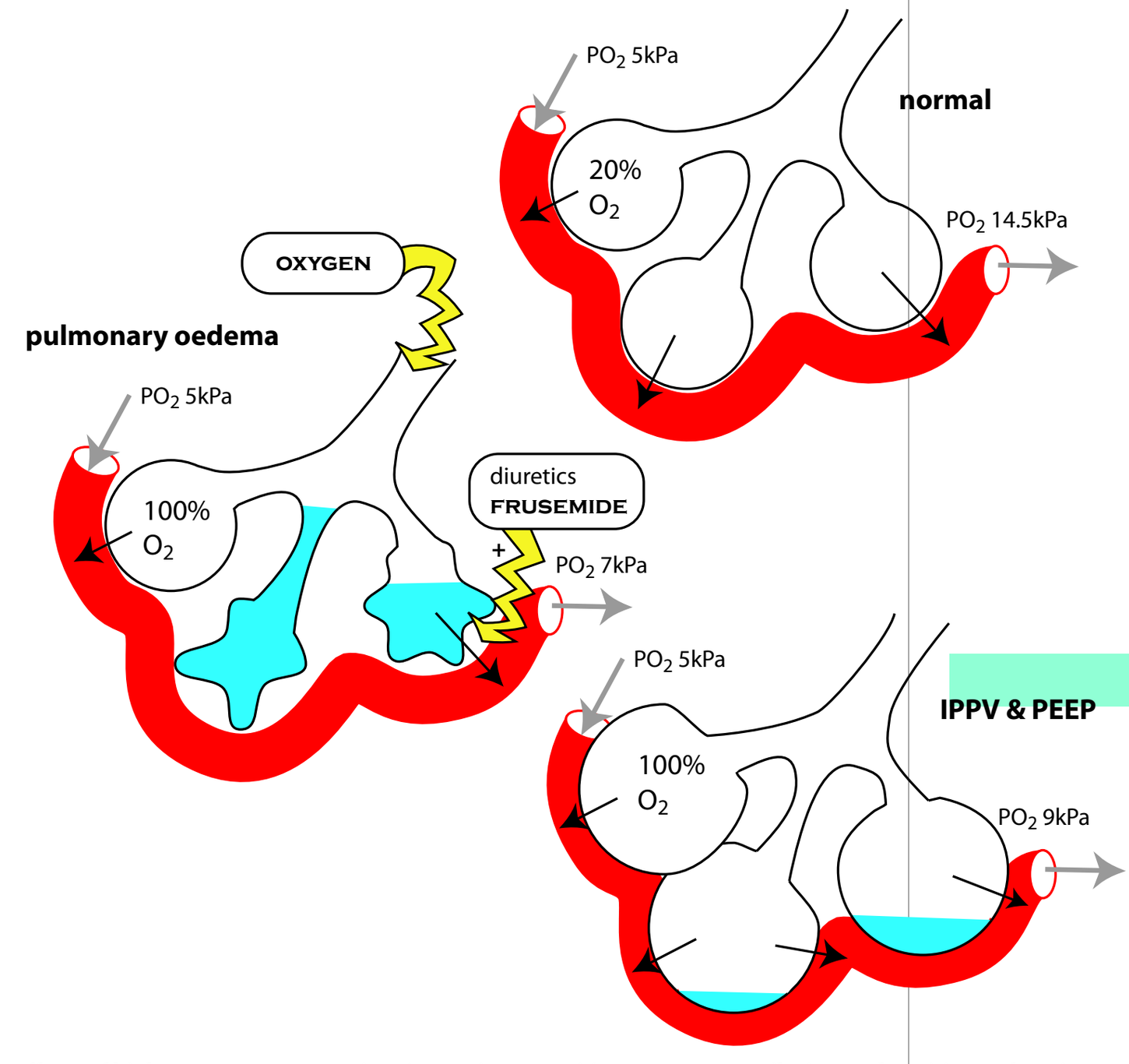
- oxygen therapy - possibly with a respirator ± positive end-expiratory pressure (5-20 cm H20)
- diuretics preferably a loop diuretic such as frusemide at high dose rates iv

Oxygen

When alveolar ventilation is critically compromised, for whatever reason, the primary goal is to provide an adequate supply of oxygen. Oxygen can be delivered by means of a mask, endotracheal tube, nasal catheter, respirator, or an oxygen cage. The route which causes least excitement is best as oxygen requirement is then least. Use of oxygen cages is fraught with potential problems, such as hyperthermia and hypercapnoea. Other routes of oxygen administration should be used if practical. Nasopharyngeal tubes are well tolerated by most animals.

There are theoretical advantages to using a mixture of 95% oxygen and 5% carbon dioxide. Oxygen tends to increase the viscosity of respiratory secretions and the addition of carbon dioxide promotes hyperaemia of the respiratory tract and an increase in the volume and fluidity of secretions and may provide a physiological stimulation of the respiratory centres, although if there is any interference with respiration, the $PaCO_2$ is likely to be elevated anyway. 95% oxygen and 5% carbon di-

DIAGRAM 3.8.1 Pulmonary oedema



Effects of high oxygen concentration, intermittent positive pressure ventilation and positive end expiratory pressure on pulmonary oedema.

oxide is not usually available in practice.

If 100% oxygen is administered alone for more than five hours, damage to pulmonary endothelial cells, pulmonary oedema and generalized atelectasis (chronic oxygen toxicity) will occur. A concentration of 50% oxygen in the inspired air is regarded as optimal and can be breathed indefinitely. If an animal requires a higher fraction of inspired oxygen, then breaks of air breathing must be inserted. Flow rates of 2-5 l/min for small animals, and 12 l/min for large animals are used (depending on the breathing system used).

In people, hyperbaric (ie high pressure) oxygen is sometimes used, but requires specialised equipment and carries increased risks of oxygen toxicity. (Oxygen at more than 2.8 bar can cause acute toxicity - twitching to convulsions. Chronic toxicity is a function of both time and pressure - the higher the pressure, the less time it takes to develop.)

Remember that oxygen strongly supports combustion - smoking around an animal on oxygen can provide amusement for your colleagues!

Other Drugs Sometimes Used

- inotropic agents -when pulmonary oedema is caused or aggravated by left ventricular failure
- bronchodilators β2 agonists and aminophylline
- morphine (small doses) decreases respiratory rate, diminishes anxiety, and dilates splanchnic vessels
- plasma expanders to correct hypo-albuminaemia (gelatin)

Have been advocated but of dubious benefit:

- antibiotics - sometimes misused to prevent secondary bacterial infection.
- corticosteroids and dimethyl sulphoxide -may limit transcapillary effusion in the presence of pulmonary insult
- ethanol nebulization (or other nonionic surfactants such as propylene glycol and glycerol) limits foaming within the

bronchial tree and promotes effective alveolar ventilation and gaseous exchange.

Infections

Pneumonia

Pneumonia can be a life - threatening disease. It is usually treated with antibiotics and oxygen with frusemide if necessary. The causative bacteria are different for different species - see antibiotic notes for more information. Oxygen may be required as well.

Other Infections

Most other conditions are not life threatening, but correct treatment will ease an animal's discomfort. Treatment depends on the cause of the problem:

- Support intrinsic pulmonary defence systems (e.g. adequate nutrition, hydration, minimal stress, immunopotentiators, interferon, hyper-immune serum) and avoid impairing the clearance and inactivating mechanisms (e.g., starvation, dehydration, chilling, acidosis, uraemia, endotoxaemia, corticosteroids, immunosuppressant drugs, poor lung perfusion, low oxygen tension, viral and secondary bacterial infections).
- Promote tracheobronchial secretions to protect dry, inflamed mucosae or to facilitate clearance of mucus and purulent exudate (mucokinetic or expectorant agents following rehydration).
- Increase the beat frequency of airway cilia to promote airway clearance (cilia augmentors)
- Suppress excessive unproductive coughing, which is exhausting and disseminates infection (antitussive agents).
- Enhance alveolar ventilation and ensure adequate oxygen delivery (bronchodilators, oxygen therapy, and respiratory analeptic's) (only if specifically indicated).
- Shrink swollen and hyperemic mucosae in the respiratory tract (decongestants, antihistamines, and corticosteroids).
- Minimize the destructive effects of acute inflammation within the lungs or respiratory tract (non-steroidal anti-inflammatory drugs or corticosteroids -but only in extreme situations) .
- Treat specifically identified infections with antibacterial, antifungal, antiviral, or antiparasitic drugs to which the pathogens are sensitive.

Coughing

A wide variety of drugs are used to treat conditions characterised by coughing. A recent meta-analysis of these drugs in people concluded that there is no evidence that they do any good (BMJ 2002, 324, 329). They are still widely used in all species, however.

Expectorants / Mucokinetic Agents

Healthy cilia, adequate volumes of respiratory tract secretions, and a functional cough are all necessary to effectively clear airway mucus; however, many diseases, eg, tracheobronchitis, bronchopneumonia, and chronic obstructive pulmonary disease, disturb these functions and promote retention and drying of mucus. Many drugs can alter the consistency and rheological behaviour of airway mucus, but often only at higher than recommended doses. The clinical usefulness of mucokinetic agents remains dubious mainly because there are no reliable methods to quantify and evaluate their effects. Nevertheless, expectorants are almost always included as ingredients in cough medicines and are frequently used to treat respiratory disorders in large animals.

Tracheobronchial secretions can be modified and mobilized by increasing the sol (colloid solution) layer, the hydration of mucus, and the motility of cilia, and by decreasing the amount and viscosity of mucus. These effects can be achieved by direct local action on the tracheobronchial epithelial cells and the submucosal tubuloacinar glands, or by reflex action mediated by autonomic (especially vagal) pathways. Expectorant or mucokinetic agents are administered orally, parenterally, or by inhalation (vaporization or nebulization).

Mucokinetic Diluents

These substances dilute airway mucus after aerosol or systemic administration. Dehydration is common in animals with lung disease because of diminished water intake and excessive insensible water loss associated with pyrexia and hyperpnoea. In this state, it is difficult to evacuate airway secretions. Thus, rehydration is essential for effective expectorant therapy. Water and saline solutions are the practical mucokinetic diluents used to liquefy hyper viscous mucus; oral rehydration, administration of parenteral fluids, and inhalation of water vapour (vaporization or "steaming") or saline aerosols (nebulization) are the approaches used. Diluents also serve as convenient carrier vehicles in aerosol therapy. Several surface active agents, with a mode of action closely related to that of diluents, are also used to facilitate hydration, emulsification, and liquefaction of adhesive bronchial secretions. Commonly used surface active agents are propylene glycol (2-5%), sodium

bicarbonate (2-5%), and glycerine (5%). These agents may be administered by mucosae or, at lower concentrations, instilled directly into the respiratory tract.

Bronchomucotropic Expectorants

These drugs increase the volume and fluidity of secretions from the airway mucosa by mechanisms that are not completely understood. They probably stimulate the gastro-pulmonary vagal reflex, the vagal centre, terminal cholinergic fibres, or the submucosal glands directly. Many of the traditional expectorants are volatile oils or their derivatives, and resin containing balsams. These agents probably stimulate the tracheobronchial glands directly and produce an associated active hyperemia in the respiratory tree. The most frequently encountered compounds found in various cough remedies include oil of eucalyptus, oil of pine, camphor, menthol, benzoin, and terpin hydrate. These compounds may be dosed po but are usually employed in vaporizers for inhalation. Essential oils are potentially toxic. They tend to produce gastrointestinal and urinary tract irritation.

Secretory Expectorants

Several inorganic and organic salts (saline expectorants) seem to stimulate the gastro pulmonary vagal reflex with subsequent activation of the submucosal bronchial glands. With iodide salts, direct stimulation occurs because iodides concentrate in the glands. The most frequently used saline expectorants are iodides, ethylenediamine dihydroiodide, ammonium chloride and carbonate, and sodium and potassium nitrate. The main adverse effects to be avoided with saline expectorants are iodinism with prolonged use of the iodides, and acute hyperammonaemia with ammonium salts in animals with hepatic insufficiency.

A number of substances of plant origin that produce nausea and emesis at higher doses are occasionally used at lower levels to stimulate the vagus to produce reflex secretion by the tracheobronchial glands. These agents are found mostly in proprietary cough mixtures. Examples are ipecac, squill, balsam of tolu, and cocillana.

Glyceryl guaiacolate (guaiphenesin), a derivative of guaiacol obtained from creosote, is a common secretory expectorant in cough medications (for people). It is active as a centrally acting muscle relaxant and sedative when administered iv (during anaesthesia). Carbon dioxide and certain sulphonamides also act as secretory expectorants.

Mucolytic Expectorants

Mucolytics are substances that interfere with the structural integrity (and thus alter the viscosity) of the constituents in mucoid or purulent airway secretions, which favors airway clearance by cilia. Depolymerization of glycoprotein molecules or hydrolysis of protein or nucleoprotein strands are the usual mechanisms involved.

Acetylcysteine and carbocysteine are mucolytic agents that are administered as aerosols or intratracheally. Side effects include bronchospasm, ciliary inhibition, severe coughing, and its propensity to inactivate antibiotics, particularly penicillins.

Bromhexine is a similar drug which also results in an increase in immunoglobulin levels in airway secretions. It may be administered either po or parenterally and has been used as ancillary therapy in the management of bronchopneumonia in horses, cattle, and pigs, as well as for the treatment of amniotic fluid aspiration in newborn calves and piglets.

Dembrixine enhances serous glandular secretions and diminishes the viscosity of tracheobronchial mucus.

Several types of enzymes have been administered by inhalation or instillation into the bronchi to dissolve components of mucopurulent bronchial secretions. Included among these preparations are deoxyribonuclease, streptokinase, streptodornase, and trypsin. The response to these medications remains equivocal, and side effects, including airway irritation, are not uncommon.

In general, there is little place in respiratory therapy for mucolytic expectorants, since their effects do not assist clearance of the respiratory secretions except when the mucociliary escalator is intact and functioning. Most disease which results in inspissation of respiratory secretions coincidentally compromises the airway clearing mechanisms. Therefore, mucolytic expectorants result in a gravitational pooling of respiratory secretions within the small airways, beyond the reach of effective coughing.

Cilia Augmentors

These are substances that increase, directly or indirectly, the beat frequency of airway cilia. The precise mechanisms involved remain unclear.

Expectorants

Potassium iodide and ammonium chloride are probably the most effective.

Adrenergic agents

Adrenergic β2 agonists are the most effective cilia augmentors. Examples include salbutamol, terbutaline, fenoterol, and clenbuterol.

Methylxanthines

Theophylline and aminophylline, in addition to their ability to relax smooth muscle of airways also increase the beat frequency of cilia.

Cholinergic agents

Neostigmine directly stimulates ciliary activity and bronchial secretions, but its airway-constricting effects preclude itstherapeutic use for this purpose.

Antitussives

These reduce coughing, and are indicated only when coughing is painful, unproductive, distressing, exhausting, or likely to exacerbate lung damage. They should not be used in the presence of productive coughs since this would allow the collection of fluids. They should never be employed symptomatically in the absence of a diagnosis since indiscriminate inhibition of the coughing reflex could have disastrous consequences. This group of drugs acts by interfering with the cough reflex, either at the sensory receptors in the pharynx or larynx or by inhibition of the cough centre in the medulla.

Demulcents, such as glycerine, syrup, or honey, which coat and soothe inflamed mucosae are used in man (rarely of much use in animals).

Local anesthetics (e.g. lignocaine) that block sensory impulses from the pharynx and larynx can reduce irritation and coughing. Benzonatate acts both peripherally and centrally.

Since one of the primary stimuli for coughing is bronchoconstriction, bronchodilators are frequently the most useful drugs in control of coughing (see below).

Opiates and several of their derivatives are inhibitors of the medullary cough centre at subanalgesic doses and are used specifically as antitussives, particularly codeine (short acting) and butorphanol (long acting). Theobromine has recently been shown to be more effective than codein as an antitussive. Other drugs usually seen in “cold cures” include: dextromethorphan , pholcodine, benzonatate, and noscapine (tends to result in histamine release in dogs).

Antitussives tend to produce sedative effects, respiratory depression, occasional vomiting, and constipation with continued use.

Other drugs

Bronchodilators

Bronchoconstriction produced by chemical mediators in hypersensitivity and inflammatory reactions is often a significant part of respiratory disease. Minor reductions in airway diameter have a marked effect on expiratory effort and frequently result in coughing. To correct or prevent this, various bronchodilators are commonly used in cough mixtures, and to treat asthma, acute bronchitis and pulmonary oedema.

Adrenergic Agents

Selective β2 activity produces bronchodilation without significant cardiostimulatory effects. Longer-acting drugs like salbutamol (albuterol USAN), fenoterol, hexoprenaline, clenbuterol and others are often used. Terbutaline is now difficult to obtain in NZ and its prodrug, bambuterol, is used instead. Common side effects observed with selective adrenergic drugs include nervousness, sweating, muscle tremors, weakness, and vomiting with high doses.

Adrenaline, ephedrine, and pseudoephedrine also possess a agonist properties that are beneficial because the induced vasoconstriction in the bronchi reduces mucosal swelling.

Methylxanthines

Drugs such as caffeine, theophylline, and theobromine inhibit phosphodiesterase and thereby to relax contracted bronchial smooth muscle cells. β agonists and the methylxanthines work on sequential steps on the same path and it is rational to use bronchodilators from both classes when dealing with a refractory case. The methylxanthines also possess other effects that promote bronchodilation, possibly through adenosine receptor blockade.

Theophylline and several of its derivatives are the most useful bronchodilators. Theophylline itself can be administered po only, whereas theophylline esters are also suitable for injection.

Anticholinergic Agents

These decrease vagal tone in bronchiolar smooth muscle, and may be useful in certain cases of bronchoconstriction. Atropine has been used for many years for the palliative relief of chronic obstructive pulmonary disease (heaves) in horses. Atropine and other anticholinergic drugs, such as glycopyrrolate, ipratropium, and deptropine, augment the bronchodilator effects of the adrenergic agents. The reduction in tracheobronchial secretions with an increase in mucus viscosity is a disadvantage when they are used to treat bronchoconstrictive states. Ipratropium delivered by aerosol is said not to have these side effects.

Glucocorticoids

Glucocorticoids may be very beneficial in asthma. They inhibit phospholipase-A2 in cell membranes and prevent the formation of prostaglandins and leukotrienes, both of which are powerful endogenous bronchoconstrictive substances. The corticosteroids also counteract the effect of histamine and other inflammagens, and enhance the bronchodilator effects of sympathomimetics. Glucocorticoids act to permit β adrenergic induced bronchodilation. Though they should not be used as bronchodilators themselves, the corticosteroids may produce successful responses in chronic refractory allergic respiratory conditions or in lifethreatening bronchoconstrictive episodes.

Decongestants

Adrenergic α1 agonists produce vasoconstriction in mucous membranes, which reduces swelling and oedema. These drugs are used topically as nasal decongestants in allergic and viral rhinitis, and systemically as respiratory tract decongestants. The use of decongestants in veterinary medicine is not common. Examples include pseudoephedrine, phenylephrine, phenylpropanolamine, and naphazoline. Note that pseudoephedrine may cause excitation in dogs at dose rates only marginally higher than therapeutic doses.

Antihistamines And Other Antiallergic Drugs

H1 receptor antagonists are commonly included in cough mixtures and cold remedies, and have been employed in the treatment of acute respiratory infections. The role of histamine in hypersensitivity reactions and as an inflammagen is well known, but the routine use of antihistamines for the treatment of disorders of the respiratory system, other than allergic manifestations, is dubious. Some antihistamines exert some central action on the cough centre and may reduce bronchospasm; examples include promethazine and diphenhydramine.

Sodium cromoglycate is used to control asthmatic attacks in man and to prevent attacks of chronic obstructive pulmonary disease in the horse. It acts by preventing antigen-induced release of histamine and other mediators from sensitized mast cells. Because it is available only as an aerosol of fine particles to be administered by inhalation, it is not often used in veterinary medicine. However, when it is administered to horses using a special nebulizer, clinically normal horses will be protected for 3 -20 days.

Theophylline is effective as an antihistamine because it inhibits the degranulation of pulmonary mast cells.

Leukotrienes C4, D4, and E4 are involved in airway inflammation, the experimental antagonists zafirlukast and montelukast may be clinically useful in the future.

Respiratory Stimulants

Respiratory analeptics (or medullary stimulants), such as doxapram, are occasionally used to stimulate the respiratory centres in the medulla. Their use is mostly limited to cases of drug-induced medullary depression and apnoea in the neonate. They increase cerebral oxygen consumption and are contraindicated in respiratory obstruction.

Further Reading

Jenkins,W. Clinical pharmacology of drugs used to manage respiratory disorders.in Pharmacological bases of Veterinary Therapeutics (1992) Proceedings 198, Postgrad Committee, University of Sydney

Cases to think about

1. You have just bought a new respiratory drug. The drug insert states that "this drug has been shown to decrease the activity of the mucociliary apparatus." What is the mucociliary apparatus and of what clinical significance is this to the dog with a productive cough?

2. Your colleague sends you to find some medication for an animal's cough. When you ask him what type of cough the animal has, he says, "A cough is pretty much a cough." What do you reply?

3. An animal is presented with a high fever, clinically dehydrated, and a dry non-productive cough. Before Dr. Wise does anything for the cough itself, he hooks the animal to an iv line and corrects the dehydration. How might this affect the nature of the cough and affect the subsequent therapy for a cough?

4. Morphine, when used as an analgesic can depress the respiratory centres in the medulla. Would this have an effect on an animal's cough? What about the animal's laryngeal gag reflex?

5. Your senior partner tells you to bring him the bottle of aminophylline injectable while getting ready to use acetylcysteine. Why?

6. How is it that neutrophils, macrophages, and other "protective" white cells actually can interfere with one of the normal defence mechanism?

7. A dog is presented with congestive left sided heart failure. Why would an expectorant be contraindicated for this dog's cardiac cough?

8. One of your classmates, who skipped the whirlwind pharmacology lecture on respiratory pharmacology, is amazed that when you went down to the pharmacy to get a drug for an animal with a dry cough, you came back with a muscle relaxant instead. What is the drug and what are you doing with it?

9. An animal is presented with a productive cough due to a low grade bacterial bronchitis. The animal appears to be in pretty good condition. The senior veterinarian tells you to administer a low enough dose of butorphanol to decrease the severity of coughing while not eliminating the cough totally so at least the animal can rest. A couple of minutes later another vet in the practice tells you to administer a full dose of butorphanol plus a saline expectorant so the animal will cough up all the "crud in the lungs" quicker. Whose therapy is better and why?

10. Decongestants work very well to slow down nasal discharge and respiratory tract secretions. So why don't we use them on these dogs with pulmonary oedema from left sided congestive heart failure?

11. A client comes into you one day and tells you that Fifi is "coughing and then gagging up small amounts of white frothy mucus". You determine that Fifi probably has a tracheobronchitis type of problem. Why does this disease tend to perpetuate itself for long periods of time? What drug would you use for it?

12. Your senior partner is in a rush today. And you're working together (oh joy...). Your partner sends you to the pharmacy to bring back an antitussive that acts on the medulla and has mild sedative activity. What do you bring?

13. Mrs. Grumbles calls and says that Prince is sleeping an awful lot but is coughing much less since you put him on that drug yesterday. She wants to know if Prince is feeling worse since he sleeps so much. What is a possible explanation?

14. The veterinary sales rep shoves a flyer under your nose touting XXX's new drug, “Greezed Leigtning”. The rep explains that this drug works well on respiratory disease because it, “cranks open them bronchioles by tickling them Alfer and Beter receptors”. Well, what do you think? Has the rep brought you a drug you can use?

15. There are two bronchodilators sitting on the shelf in the pharmacy. One is terbutaline and the other is isoprenaline. Which would you chose to use for bronchodilation? What disadvantage does the drug you didn’t chose have that made you chose against it?

16. Your clinic is presented with a cat in acute respiratory distress. The owners correlated the respiratory attack with the powdered carpet cleaner they put on the carpet where the cat usually lies. The cat is diagnosed as experiencing an allergic type of pulmonary reaction with bronchospasms producing the dyspnoea. The cat is admitted to the hospital for treatment and boarding until the owners can remove the powder from the carpet in the cat's environment. While the cat is in the hospital why are you not going to treat this condition with antihistamine drugs?

Respiratory toxicities

commonly used drugs

nitrate/nitrite - methylene blue

others - supportive treatment

Respiratory toxicities

- ☑ nitrate/nitrite - ruminants
- ☑ paraquat - any species
- ☑ selenium - grazing animals

Toxicants Affecting the Respiratory System

- Metals
- -Selenium and Selenium Containing Plants (Acute)
- Inorganic compounds
- -Nitrogen oxides
- -Ammonia
- -HCI
- -HF
- -Zinc Phosphide
- Organic compounds
- -Overheated Teflon Cookware (in Birds)
- -Paraquat
- -Kerosene, Gasoline and Other Petroleum Distillates
- -Iodine Compounds, Such as Ethylene, Diamine Dihydroiodide (EDDI)
- -Pennyroyal Oil (Ketone pulegone) (Insecticide)
- -Smoke and Heat Inhalation
- -Organophosphorus or Carbamate Insecticides
- -Freon (Fluorocarbons, Chlorofluorocarbons)
- -Formaldehyde
- -Fumonisins
- -Para-aminopropiophenone (PAPP)
- Plants
- -Rapeseed or Forage (Brassica)
- -Goats Rue (Galega officinalis)
- -3-nitro containing Locoweed (Astragalus and Oxytropis) (Some species of these plants cause emphysema in sheep)
- -3-Substituted Furans (Atypical Bovine Pulmonary Emphysema-tryptophan)
- -Purple Mint (Perilla frutescens)

- -maize (Zea mays)
- -Lush Pastures
- -Mouldy Sweet Potatoes (Ipomea batatas and Fusarium solani)
- Toxicants Causing Asphyxia
- -Nitrogen
- -Nitrous Oxides
- -Nitrogen Oxides
- -CO2
- -Helium
- -Hydrogen
- -Aliphatic Hydrocarbons (also explosive!)
- -Methane
- -Ethane
- -Hydrogen Sulfide
- Toxicant Inhibits Cytochromes
- -Cyanide

Cyanide

Plant sources: Poa aquatica, Sorghum species (Sudax and Sudan grass) prussic acid

Highest in plants after dry periods followed by rain and growth or after herbicide application.

Wilted frosted plants

Poison baits containing cyanide (very toxic) Feratox is marketed to kill possums.

Cyanogenic glycosides are exposed to enzymes in the rumen that release hydrocyanic acid.

Bitter almond smell to rumen contents

Cherry red blood in the acutely poisoned animal

Mechanism of action

The lethal effect of cyanide is due to the inactivation of the cytochrome oxidase system which is essential for tissue respiration. Cyanide forms a stable complex with Fe+3 which prevents electron transport and cellular respiration. The oxygen exchange between tissues and blood is stopped, so that initially the blood appears bright red because oxygen is retained in the blood. The blood becomes dark due to the inhibition of respiration. Anoxia occurs in all tissues, but death occurs primarily from tissue anoxia within the brain.

Clinical signs

(if seen before they die)

dyspnoea, anxiety, restlessness, recumbency, terminal clonic convulsions (+ opisthotonus)

Diagnosis

Samples: rumen contents-air tight container due to volatility.

GI irritation occurs, cherry red blood.

Treatment

Try acidifying the rumen with vinegar in cold water to slow the conversion to HCN.

Hydroxocobalamin binds cyanide strongly to form cyanocobalamin (vitamin B12) and, compared to nitrite, it does not interfere with tissue oxygenation. However, hydroxocobalamin as a cyanide antidote requires a large dose to be effective. To

TABLE 3.9.1 Cynaide treatments

	sodium nitrite	**sodium thiosulphate**
Cattle	3 g (10mLof 20% IV)	15 g in 200 mL IV (or 50 mL of 20% IV)
Beasley suggests:	10-20 mg/kg (20%)	500mg/kg
Sheep	1g (or 10 ml of 10% IV)	2.5g / 50 mL IV
Dog (repeat with half dose if necessary)	25 mg/kg IV 1% solution	1.25 g/kg 25% solution

detoxify 65 mg KCN requires 1406 mg hydroxocobalamin. One Feratox pellet contains 100 mg of KCN, which would require at least 2163 mg hydroxocobalamin per pellet ingested.

Alternatively, amyl nitrite, an antidote used in human cases of cyanide poisoning, is inhaled to treat cyanide toxicity. Artificial respiration with amyl nitrite ampoules broken into an Ambu bag may be life-saving in dogs severely poisoned with cyanide.

Nitrate/nitrite Toxicity

Sources

Pasture grasses, certain crops and weeds

maize*, Johnson grass*, sorghum*, regrowth brassicas*, beets,* sudan grass*, ryegrasses, green oats, fescue, wheat, lucerne, clover, pigweed, dock, nightshades, and soybeans (list is not exhaustive).

Dog rolls which were improperly cooked

Nitrogenous fertilizers with right climatic conditions

Nitrates in water

Fertiliser (particularly for small animals)

Remains toxic in plants when air dried (stems more toxic)

Herbicides (2,4 D) may increase nitrate concentration

ADME

Passively absorbed in the GIT, in ruminants peak concentration in 5-6 hours post ingestion.

Nitrate converted to nitrite in the rumen. Some evidence for hepatic reduction, but too slow to be of concern.

nitrate / nitrite toxicity

- ☑ Usually a ruminant toxicity requiring nitrate conversion to nitrite
- ☑ Herbicides may increase chance of poisoning
- ☑ Methaemoglobinaemia
- ☑ Clinical signs 1) Respiratory; 2) Gastrointestinal; 3) Circulatory-vasodilation
- ☑ Methylene blue (not an approved animal remedy)
- ☑ Preventable if careful management is applied.

Excreted by the kidneys, but some is recycled back to the GIT by salivary secretion and GIT secretions.

Mechanism Of Action

- Nitrite oxidizes haemoglobin to methaemoglobin.
- 30-40% methaemoglobin = mild signs
- 75-90% methaemoglobin = severe clinical signs and death
- Young (neonates and the foetus) are more susceptible than adults.
- Production of methaemoglobin overwhelms the enzyme methaemoglobin reductase.

Clinical Signs

- Combination of GI, respiratory, CNS signs and vasodilation
- Acute Syndrome- onset 1-4 hours after ingestion
- GI irritation (vomiting, salivation, diarrhoea)

- Dyspnoea
- Tremors, Ataxia, cerebral anoxia, muscle tremors
- Rapid weak heart beat
- Terminal convulsions
- Death in 6-24 hours (increases when animals are stressed)
- Also sudden death!
- Vasodilation may reduce blood pressure
- Chronic Syndrome
- Abortion
- Poor growth and feed efficiency
- decreased milk production
- Infertility
- Goiter-primarily in sheep (interferes with iodine)
- Increased susceptibility to infection.

Toxicity

Toxic above 1% (10,000ppm) in plants (dry wt basis) or 1500 (ppm) .15% in water.

Dry periods followed by rain, overcast skies (preventing photosynthetic activity) increase likelihood of toxicity.

Diagnosis

- Brown blood (not always present after death)
- Diphenylamine test or laboratory quantitative analysis on aqueous humor up to 60 hr post mortem. (serum ante mortem)
- Tissues or stomach contents: Seal for analysis in air tight containers and remove as much air as possible.
- Freeze blood or store in phosphate buffer.
- Dry plant material to minimise loss of nitrate, about 2 kg
- Root crops send about three plants.
- Diphenylamine Test for nitrates or use nitrite screening test.
- Do a field test on forage, if positive send into MAF for a quantitative analysis.

Treatment

Do not stress, try to minimise excitement and movement.

Methylene blue (you will have to make it up yourself) (or can use ascorbic acid in cats, methylene blue is relatively ineffective in horses-Robinson, CT in Equine Med)

4 mg/kg Dog 15 mg/kg cattle in a 1% solution

May need to repeat; however, overtreatment may worsen the methaemoglobin.

Treat animals that are too toxic to be moved. (move others to safe pasture or lot)

Feed safe hay or feed which will increase the carbohydrate availability.

Para-aminopropiophenone (PAPP)

Para-aminopropiophenone (PAPP) has been trialed in the United States, Australia and New Zealand as an alternative pesticide to control mammalian predators. It has been tested in Australia to control feral cats and in New Zealand as a possible means of controlling possums and stoats. At this writing it is not a licensed pesticide in New Zealand, but registration is being investigated.

A complicating factor in its use is many animals appear to have a rapid vomiting response when PAPP is given as a bait Australian experience also suggests that possums are far less susceptible to PAPP than wild cats, but it has shown potential in stoat control.

The toxic effects of PAPP are related to the rapid formation of methaemoglobin in some species leading to death from anoxia. Carnivore species appear to be more susceptible to PAPP than birds.

Paraquat

Paraquat (1,1-dimethyl-4,4-bipyridylium dichloride) is a herbicide that is widely used for agriculture and horticulture (in New Zealand and other countries). Several trade names for paraquat are Gramoxone and Pathclear. Diquat is sold under the trade name Reglone. It is generally considered a “low hazard” herbicide when used properly. There is no antidote for poisoning, although antioxidants (eg. Vitamin E, Selenium and others) are beneficial in experimentally induced paraquat poisoning.

Products

10-20% sprays: Gramoxone, Pathclear

Kills plants by contact with leaves.

Rapidly absorbs to clay and becomes non-toxic.

Absorption, Distribution, Metabolism And Excretion

• Paraquat is poorly absorbed topically, but can be toxic if sufficient exposure occurs.

• Only about 20% of an oral dose is absorbed.

• absorbed paraquat is selectively taken up and concentrated by pulmonary alveolar cells (Type II, the Clara cell and possibly Type I) to ten times the levels in other tissues.

• It is excreted mostly unchanged in urine in 24-48 hours.

Mechanism Of Toxicity

Paraquat accumulates in the lung tissue where free radicals are formed, lipid peroxidation is induced and nicotinamide adenine dinucleotide phosphate (NADPH) is depleted. This produces diffuse alveolitis (lung inflammation) followed by extensive pulmonary fibrosis.

The process is as follows: paraquat (PQ) readily accepts an electron to become a free radical, but it is reoxidised by losing the electron and a superoxide free radical is now formed. This superoxide radical is unstable and spontaneously breaks down to the reactive, singlet oxygen. The singlet oxygen reacts with lipid membranes which results in the destruction of lung cells.

Toxicity

As little as 4mg/kg can be fatal for a person. The toxic dose for a dog is 25-50 mg/kg.

Clinical Signs

Biphasic course of poisoning includes a transient renal and hepatic insufficiency with pulmonary oedema, followed by a latent period, then pulmonary fibrosis.

300 ppm can cause pulmonary fibrosis; 50 mg/kg can result in acute intoxication

Cattle and horses grazing sprayed pasture show few problems. Horses have been reported to develop buccal irritation followed by severe ulceration and sloughing of the mucosa.

Respiratory signs appear 2 to 7 days post exposure if a sufficient dose is received.

Moist rales, cyanosis, dyspnoea, tachypnoea, gasping and death within eight days.

Pathology

Lungs are dark, heavy and rubbery with congestion and some hemorrhagic areas from ecchymotic to consolidated size. Deaths after 7 days post exposure show fibrosis.

Pathology consistent with loss of Type I and II pneumocytes, necrosis of bronchiolar epithelium and alveolar collapse. Fibrosis replaces damaged cells.

May see renal changes of tubular necrosis and centri-lobular necrosis of liver.

Diagnosis

Important to determine ASAP. History of exposure. Early on no characteristic signs. Must check urine within 24 hours to find paraquat.

Treatment

Difficult with generally a poor prognosis, however:

paraquat

- ☑ Biphasic poisoning (renal and hepatic, pulmonary)
- ☑ Free radicals cause lipid peroxidation especially in the lungs
- ☑ Decontaminate with activated charcoal or Fuller's earth (clay)
- ☑ Do not use oxygen therapy
- ☑ Forced diuresis and antioxidant therapy (e.g. Vit E)

Remove compound with adsorbants like activated charcoal, bentonite or Fuller's earth followed by a cathartic, forced diuresis to increase urinary excretion, symptomatic treatment of dehydration and other signs (do not use oxygen, may exacerbate injury), antioxidants such as selenium, vitamin E, butylhydroxyltoluene (BHT) or superoxide dismutase (SOD) to prevent free radical injury. Perhaps DMSO may be of value. The treatment of paraquat poisoning is controversial.

Do not use oxygen therapy in early stages of poisoning! Oxygen will enhance the oxygen radical injury to the lung tissue.

Selenium

In New Zealand soils are usually low in Se.

In USA, Australia, Israel, Ireland some areas have very high Se soil levels. (alkali disease)

Sources

Multiple methods of supplementing Se

Selenates are relatively soluble, while selenite and selenium are not.

Selenium Plants

Some plant species accumulate Se even from low Se soils. These species can be toxic if grazed. Obligate and Faculative accumulates.

All plants will take up Se from high Se soils and may achieve toxic concentrations.

Therapeutic Uses

Therapeutic doses of Se dose (miscalculation leading to toxicity)

In drenches as NaSelenite (Se+4) or selenate (Se+6)

Intraruminal bullets

Injectable forms

Se prills for topdressing 1% NaSelenate

Dermatological shampoos with Se for dogs and cats

Toxic Dose

- 1-5 mg/kg orally is acutely toxic
- 0.2 mg/kg parenterally is acutely toxic
- 0.7 mg/kg parenterally is LD50 for sheep.

ADME

Rapidly absorbed from GI tract if soluble

widely distributed crosses placenta

excreted in urine, faeces, sweat, milk, breath

T1/2 is 15 to 24 hours

Toxicity usually occurs due to double dosing, increased frequency between doses and failure to adequately mix the drench.

Mechanism Of Action

• The biological role of selenium-present as selenocysteine at four sites of glutathione peroxidase enzyme.

• Uses glutathione (GSH) to reduce peroxides in cells. Probably due to GSH depletion and resulting lipid peroxidation.

• Toxicity may be reduced by increased levels of Vitamin E and Copper or Iron.

Clinical Signs

Acute/Subacute poisoning

ruminants/horses: 1-2 hours onset.

• dyspnoea, cyanosis, respiratory failure, nasal discharge, colic, diarrhoea, tympany.

• polyuria, rapid weak pulse, lethargy, anorexia

• hair loss, hoof separation

• posterior paralysis, incoordination

pigs-anaemia, hairloss, joint erosions, blindness, ataxia

poultry-decreased weight gain, egg production, reproductive performance. Deformed embryos.

Death may occur within 24 hours or as late as several weeks.

Chronic Se poisoning/Alkali Disease

• Primarily in cattle and horses grazing plants on high Se soil (not likely in NZ).

• Hair loss, particularly mane, tail or switch (cattle).

• Horn and hoof deformation

• Dull coat, emaciation, depraved appetite.

Lesions include: cardiomyopathy, hepatic cirrhosis, kidney necrosis, generalised haemorrhages and congestion of various organs.

Diagnosis

Submit liver and kidney samples. In live animals may check glutathione peroxidase levels; however, selenium analysis is more valuable. Glutathione peroxidase levels lag at least 9 days behind changes in selenium levels-not useful in establishing a selenium toxicity.

Postmortem

Acutely-congestion of organs, gastroenteritis, renal necrosis and haemorrhages, hydrothorax, pulmonary oedema, and pale cardiac muscle.

Subacute lesions in swine include focal symmetrical poliomyelomalacia, which is usually found in the cervical and thoracic spinal cord.

Chronic selenium intake may cause transverse lines of abnormal growth on the hooves, cardiomyopathy and chronic hepatic fibrosis or cirrhosis.

Treatment For Chronic Cases

- If possible, dilute feed with low Se feed
- Increase protein content in diet
- Pretreatment with Cu is protective

Acute Treatment

- Expensive may wish to euthanise seriously poisoned animals.
- Symptomatic
- Acetyl cysteine (Parvolex®) 140 mg/kg IV loading doses then 70 mg/kg IV q. 6 hours repeatedly (New Ethicals price 10 mls at 200 mg/ml $125 per 10 mls)

Differential Diagnosis

- Acute Salmonellosis
- Coccidiosis
- Arsenic Psg.
- Nitrate Psg.
- OP
- 1080 psg.

selenium

- ☑ Parenteral is more toxic than oral
- ☑ Glutathione depletion leads to lipid peroxidation
- ☑ Antioxidants may help (e.g. Vitamin E, but particularly N-acetylcysteine)
- ☑ Copper and Iron decrease toxicity (adequate amounts in the diet)
- ☑ Respiratory and neurological effects, Salivation

Polytetrafluoroethylene (TEFLON) in Birds

Polytetra fluorethylene is a synthetic polymer used to make Teflon and Silverstone non-stick cookware. Overheating of the empty pan (>280˚C) on the stove causes pyrolysis which releases several toxic products. If pet birds are kept in the household they may be acutely and severely poisoned. The exposure can be rapidly fatal. Acute pneumonia with clinical signs of pulmonary distress, noisy respiration and dyspnoea usually occur. Affected birds may exhibit rocking movements, eyelid blinking, and birds may have agonal convulsions before death. Humans exposed to overheated cookware may have transient flu-like symptoms.

Toxic breakdown products include carbonyl fluoride, perfluoroisobutylene, hexafluorocyclo-butylene, carbon tetrafluoride, hydrofluoric acid and monomeric tetrafluoroethylene.

Treatment consists of removing the bird(s) from exposure to fumes and symptomatic care.

Atypical Interstitial Pneumonia

(Tryptophan poisoning or Acute Bovine Pulmonary Emphysema and Oedema): This condition has been diagnosed in the Central Waikato region of New Zealand on several occasions. Isolated cases have been reported in other areas of NZ.

Sources

Lush pasture or turnips or high tryptophan levels in feed

Mechanism Of Toxicity

• Rumen bacteria convert L-tryptophan from the feed to 3 methylindole. Peak levels in 4-5 days; drop off 6-7 days

• 3-methylindole is absorbed into the blood and metabolically activated by the mixed function oxidase system in pulmonary epithelial cells to a pneumotoxic product which damages lung cells.

Clinical Signs

- Sudden tachypnoea
- Expiratory dyspnoea
- Cattle have similar signs as when bloated, i.e. heads extended, nostrils dilated, open mouth and head extended.
- Inspiratory and Expiratory sounds SOFT
- Survivors have harsh respiratory sounds
- Subcutaneous emphysema may occur
- Most die in 2 days after onset of signs
- May die acutely
- Mortality in four outbreaks 50-80%

Post mortem

- Lungs bilaterally rubbery, wet, heavy; White foam in large airways
- Pulmonary tissue does not collapse
- Blood-tinged, slightly viscous fluid in alveolar and interstitial spaces
- Emphysematous distention of interlobular septa
- Petechiae and ecchymoses in laryngeal, tracheal and bronchial mucosa

Diagnosis

History of exposure to:

turnip tops or other lush feed such as lucerne, kale or rapidly growing pasture (reports on ryegrass/clover) is supportive. (Only Adult cows affected).

Analysis of tryptophan levels in the feed. (2-4 g/kg of Dry Matter are considered high).

Histological lesions of interstitial pneumonia with supporting history and/or analysis.

Treatment

- Remove animals from source of tryptophan or give alternate feed, if <5 days on feed.
- If animals have been grazing for > 6-9 days, removing animals is not likely to prevent new cases.
- For severe cases: 0.4-1.0 mg/kg furosemide IV or IM q 12 hr (restrict drinking water)
- Flunixin meglumine IV at onset of illness, helps to alleviate the signs and lung pathology in experimentally induced toxicity. May be less (or not) effective in animals with fully developed disease. (Antiprostaglandin therapy)

L-tryptophan Toxicity

- Lush pasture or turnips may contain high amounts of tryptophan
- High levels of L-tryptophan 2-4 g/kg of dry matter
- Pneumotoxic metabolite causes lung injury
- Treat with diuretics and nonsteroidals e.g. flunixin

Phosphide (Zn, Al or Mg)

licensed pesticides/insecticides

Mechanism Of Action

Zinc phosphide bait is hydrolysed in the stomach to phosphine gas

Mechanism thought to be blocked cytochrome oxidase i.e. blocks energy production in mitochondria

Reactive oxygen species = peroxidation 20-40 mg/kg is usually lethal for many animals

Veterinarians are at risk of phosphine gas poisoning from postmortem exposure

Clinical Signs

- Rapid onset (15 minutes to 4 hours)
- Ingestion on an empty stomach will delay signs
- No specific signs
- Anorexia and depression early
- Rapid, deep respirations (wheezy)
- Vomit
- Horses: colic
- Ruminants: tympany and bloat
- Ataxia, weakness recumbency hypoxia and struggling
- Possible convulsions and hyperaesthesia

Post mortem

- No specific clinical pathology
- No specific postmortem changes:
- Liver and kidney congestion
- Yellow mottling of liver
- Gastritis, enteritis
- Pulmonary congestion
- Diagnostic testing - put samples in airtight containers on ice

Treatment

Time is critical

Early decontamination very helpful

Central acting emetic like apomorphine used

Increase gastric pH to slow conversion to gas

Activated charcoal and laxatives

Symptomatic care as no antidotes existCases

Case 1

A farmer is grazing dairy heifers on green oats in June. The farmer discovers one dead this morning and several others in sternal recumbancy. You arrive within the hour and examine the heifers. Clinical signs of the recumbant heifers include: dyspnoea, rapid heart rate and "muddy" mucous membranes. You observe that several other heifers in the group have a range of clinical signs from evidence of abdominal pain and diarrhoea, to ataxia, dyspnoea and hyperpnoea with cyanosis.

1. What do you suspect is the cause of these clinical signs?

2. What treatment is required?

3. What advice should you give to the farmer regarding the feeding of this group of dairy heifers and preventing more clinical cases?

4. Describe a test that you can perform on the farm to help confirm your diagnosis.

Case 2

Selenium is a nutritional requirement of all animals. Levels in various New Zealand soils are generally low, resulting in low levels in plants growing on these soils. Deficiencies in livestock result in white muscle disease, unthriftiness and other disorders. As a consequence, many forms of selenium supplementation have been considered, e.g. fertilisation of pasture, drenching, bolus and injectable. This raises a concern that overdosing of selenium may occur, particularly now that farmers/stockmen will have greater accessibility to over-the-counter products containing selenium. As a veterinarian it is important to be aware of the features of selenium toxicity.

A good client and breeder of valuable purebred sheep calls. This morning he drenched 100 lambs with a Selenium 100 (sodium selenate), at the manufacturer's recommended dose of 1-2 mg per lamb. Now, about two hours after the treatment, several lambs are showing signs of distress.

1. What clinical signs would you expect to see in lambs with acute selenium intoxication?

2. The affected animals are valuable ram lambs which the client would like to treat. Assuming that this is an acute selenium overdose, what recommendations/advice would you give the client regarding treatment?

3. The client has not supplemented these lambs with any other form of selenium. What is/are possible explanations for signs of toxicity in the affected lambs?

4. What would you advise the client concerning the rest of the lambs (which are not showing signs of toxicity)?

5. If a horse was acutely poisoned with selenium supplementation, what clinical signs would you expect? What clinical signs with chronic overdosing?

TABLE 3.9.2 Respiratory toxicities

Toxicant	Blood Colour	Mechanism	Treatment	Physical Characteristic
Nitrate (nitrite)	Brown	Methaemoglobin	Methylene Blue	
Sodium Chlorate	Brown	Methaemoglobin	Methylene Blue	
Silo Gases (nitrogen dioxide; nitric oxide)	Slight Brown	Irritates deep portions of lungs; slight methaemglobin	Methylene Blue; Ca Gluconate	Heavier than air
Cyanide	Cherry Red	Blocks Cytochrome oxidases	Nitrite-thiosulphate	
Carbon Dioxide	Dark	Displaces oxygen	Oxygen; fresh air	Heavier than air
Carbon Monoxide	Bright Red	Reduces ability of haemoglobin to carry O2	Fresh air; oxygen + 5% CO2; thionine solution	Lighter than air

The gut

commonly used drugs

diarrhoea - saline solutions

ulcers - ranitidine, omeprazole

vomiting & ileus - metaclopramide

colitis - sulphasalazine

gut

- ☑ diarrhoea - fluids po if possible, iv if not
- ☑ do not give antibiotics unless bacteria are invading mucosa - they often cause diarrhoea
- ☑ vomiting - iv fluids, antiemetics only for persistent vomiting
- ☑ ulcers - H2 antagonists, proton pump inhibitors or sucralfate - not antacids or NSAIDs
- ☑ increased motility - metaclopramide, erythromycin
- ☑ colitis - sulphasalazine

Common problems

- vomiting
- fluids, antiemetics,
- but treatment depends on cause
- diarrhoea
- fluids, motility reducers,
- (antibiotics),(anti-inflammatories)
- (parasiticides) depending on cause
- ulcers
- proton pump inhibitors, coating agents,
- H2 antagonists
- ileus
- prokinetic drugs
- colic
- analgesics, fluids, antispasmodics
- constipation
- irritants by enema
- bloat
- non-ionic surfactants, ionophores

All these problems are usually signs of underlying disease, so treating them will not necessarily cure the animal. Failure to treat vomiting and diarrhoea can rapidly lead to shock.Diarrhoea

Fluids

An animal with diarrhoea loses water and ions. These are replaced using fluids, either intravenously or by mouth.

Fluids are covered in more detail in the cardiovascular pharmacology notes (next year). As a general rule, it is a good idea to replace what has been lost with something similar. Thus the major component of vomit, diarrhoea and fluids is water. Various ions are important, and sometimes proteins (mainly for their osmotic effects).

In vomiting, lots of H+ and Cl- are lost and a metabolic alkalosis develops. The kidney tries to compensate for H+ losses by excreting K+ so a hypokalaemia can develop. If the vomiting is severe, the animal will not be able to keep water down; excessive loss in vomit and a lack of intake mean it will dehydrate rapidly. Thus a

vomiting animal needs water (water normally follows Na+ around the body), H+, Cl- and possibly K+.

In diarrhoea, lots of K+ and HCO3- are lost as well as water and Na+.

In some gut disease (usually more chronic) plasma proteins and red blood cells are lost.

It is best to get the animal to drink the fluids, but this is not possible in many cases, and they have to be given iv. The usual object of treatment is to get the animal's kidneys working - they are much better at calculating the animal's requirements than most vets!

Oral rehydration solutions

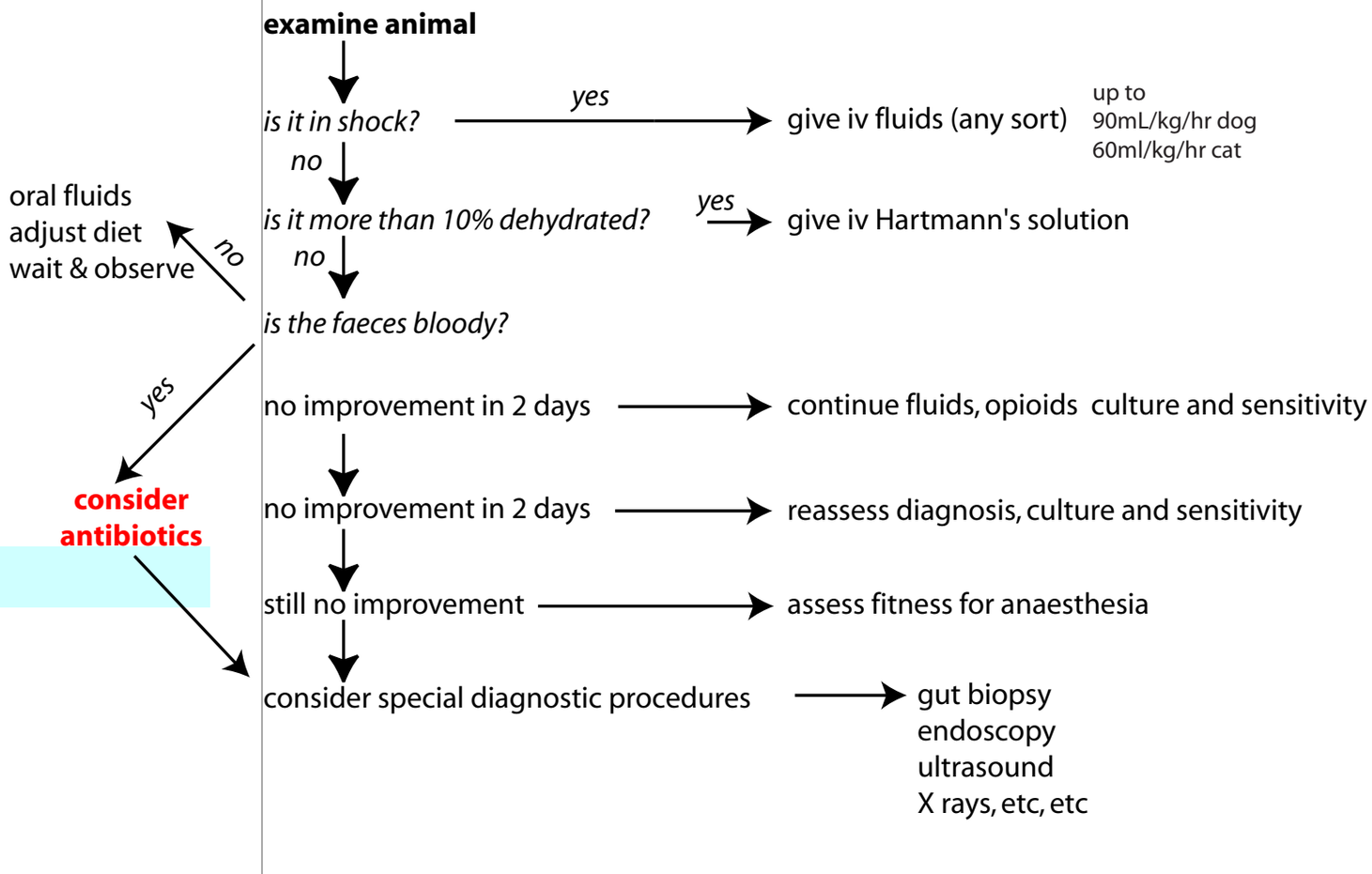
Very important in large animal medicine and to a lesser extent in small animals. They are used in cases of minor fluid deficits or to supply maintenance fluid requirements but economics often dictates their use even in more severe dehydration. Most solutions contain glucose (or sucrose) and amino acids (usually glycine) to take advantage of the cotransport pathways for the absorption of electrolytes and organic molecules, in addition to water and electrolytes. During acute diarrhoea (especially secretary diarrhoea but including rotaviral diarrhoea) such sodium-coupled organic solute absorption remains largely intact. It is very important that solutions are approximately isosmolar (300-350 mOsm) otherwise iatrogenic osmotic diarrhoea occurs. The desire to provide more organic substrate (and hence greater fluid and electrolyte absorption) but not exceed osmolality limits, has led to the recent usage of ORS containing synthetic glucose polymers or glucose and amino acid polymers derived from foods. Cooked cereal powders (especially rice) have proved suitable for this purpose.

Intravenous fluids

Compound sodium lactate solution (Hartmann's, Lactated Ringer's solution) is the fluid of choice for the replacement of fluid deficits caused by vomiting and/or diarrhoea. It has sufficient lactate (a bicarbonate precursor) to prevent the "dilutional acidosis" caused by the dilution of serum bicarbonate by intravenous fluid. It does not have enough alkalizing power to neutralize large quantities of circulating acids, but by improving circulating volume it reduces tissue ischaemia and anaerobic metabolism. As a result, production of lactic acid is reduced and the liver metabolizes circulating lactic acid correcting the lactic acidosis resulting from the hypovolaemia. Hartmann's contains calcium which can result in incompatibilities when drugs are added to the fluids. Although Hartmann's contains small amounts of potassium (4 mEq/L), additional potassium is usually required for the replacement of the major losses of potassium that occur with vomiting or diarrhoea. For this reason, the fluid is usually spiked with an additional 10-20 mEq of KCl per litre. Hartmann's contains too much sodium for long term maintenance of animals without major on-going losses of sodium in vomiting or diarrhoea. In this situation, it should not be used for longer than 3 days before a lower sodium "maintenance" fluid is substituted (eg dextrose saline or Hartmann's diluted 50:50 with 5% dextrose).

0.9% sodium chloride is a high sodium, mildly acidifying fluid. Its primary use is in dogs and cats is the treatment of alkalosis resulting from vomiting due to obstruc-

DIAGRAM 3.10.1 Diarrhoea protocol



One approach to treating diarrhoea.

tions of the pylorus or upper duodenum. It is also often used in the treatment of calf scours (along with bicarbonate) and upper gastrointestinal complaints in cattle because it used to be cheaper than Hartmann's. It does not contain calcium so most drugs can be added to the fluid without risk of incompatibility (eg sodium bicarbonate) . The fluid does not contain potassium and 15-25 mEq/L should be added prior to use in most gastrointestinal complaints.

Sodium bicarbonate is often added to sodium chloride if a potent alkalizing fluid is required to treat severe acidosis (eg pH below 7.2) . The amount of bicarbonate to add to the saline can be calculated from blood gas results. If these are not available a rule of thumb is 1-2 mEq of sodium bicarbonate per kg bodyweight.

Fluid therapy is covered more fully under the cardiovascular system.Vomiting

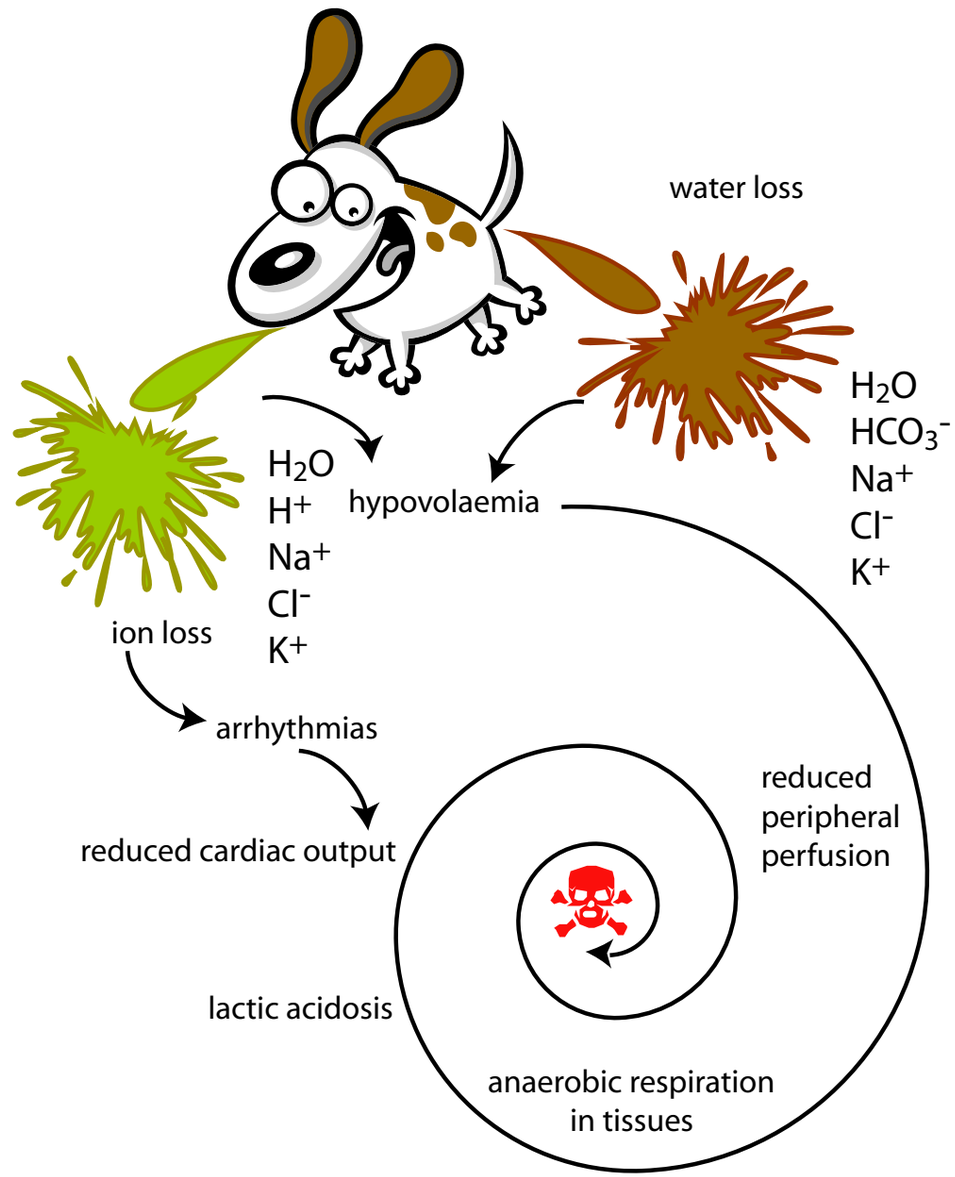
The physiology of vomiting is complicated with a large number of pathways and neurotransmitters involved (see diagram). A wide variety of stimuli can provoke vomiting by neural or humoral mechanisms which are coordinated by the vomiting centre in the medulla. Antiemetics vary in their site or sites of action and this influences their effectiveness in different clinical situations. Most of the older dugs have been used empirically for a long time and have actions at several possible sites. Blocking several sites may provide a synergistic antiemetic effect, but there are species differences and our knowledge of what happens in dogs and cats is limited.

Antiemetics are indicated for the control of intractable vomiting causing distress to the animal or its owner. They are not necessary when the vomiting is intermittent and fluid and electrolyte balance can easily be corrected. Antiemetics are symptomatic treatments, and the underlying cause of the vomiting should be treated.

Phenothiazines

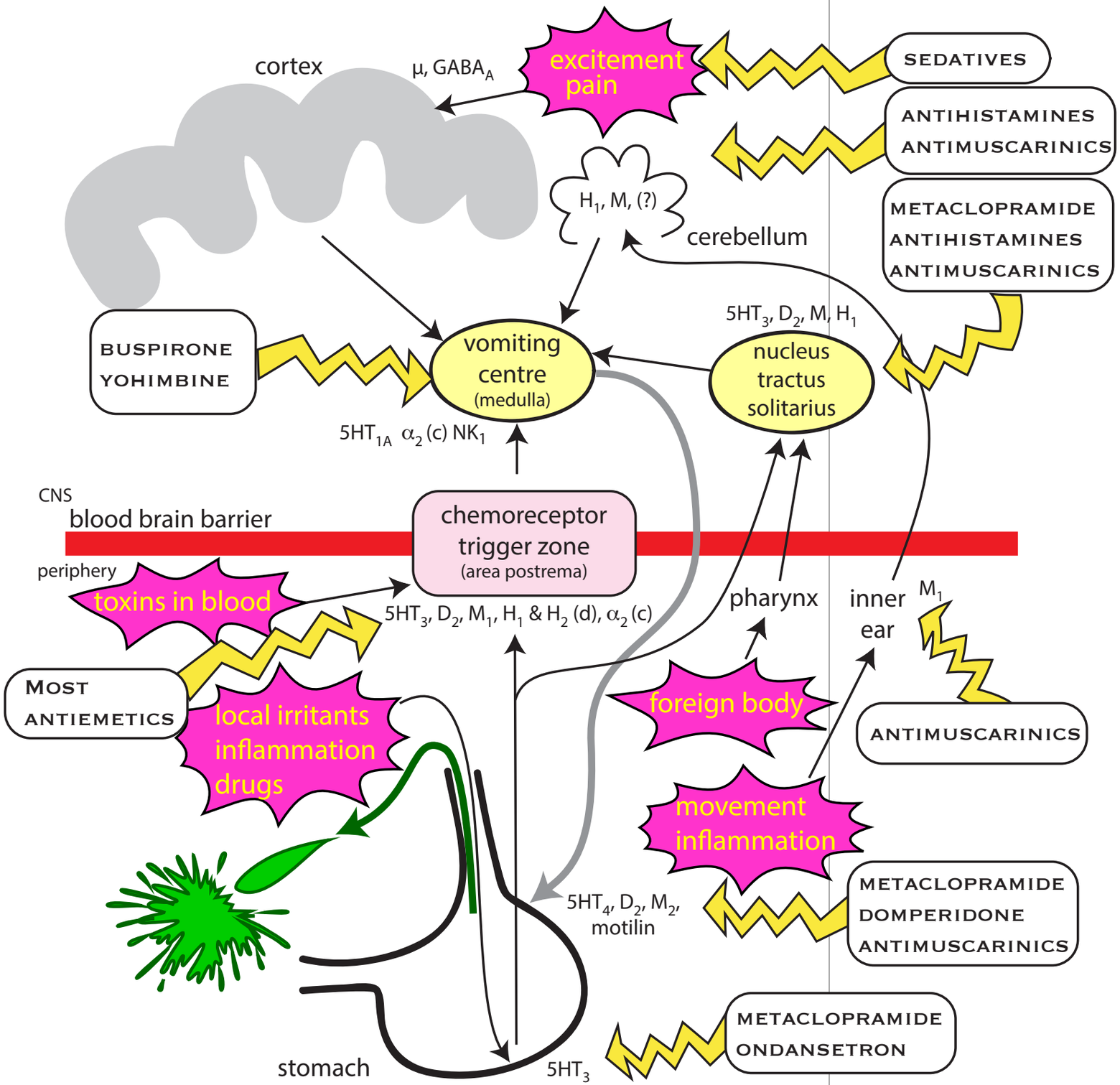
Some of the most generally effective antiemetics are phenothiazines such as prochlorperazine which act as dopamine D2 antagonists in the vomiting centre and the chemoreceptor trigger zone, although they also have weak anticholinergic activity and a variety of other effects. Because of their inhibition of all the CNS centres involved in vomiting the phenothiazines are effective antiemetics for most causes of vomiting. Their antiemetic effects occur at drug concentrations much lower than necessary to produce sedation, but sedation is often seen in practice, probably because of changes in the volume of distribution in dehydrated animals. They must be used with caution in dehydrated patients because they are α1 adrenergic receptor blockers, and can cause or aggravate hypotension. In general, the antiemetic properties (and side effects) of phenothiazines are dose related. If control of vomiting is not achieved at low doses, the dose can be judiciously increased until a beneficial effect is observed or significant side effects (usually hypotension) are seen. Acepromazine is much less effective than prochlorperazine.

DIAGRAM 3.10.2 Vomiting and diarrhoea



If untreated, vomiting and diarrhoea can quickly lead to shock and even death.

DIAGRAM 3.10.3 Vomiting



Vomiting and antiemetic drugs. There are some species differences.

Antihistamines

Antihistamines, such as diphenhydramine, cyclizine and meclozine primarily inhibit vomiting by blocking H1 receptors in the vestibular apparatus and, to a lesser extent, the chemoreceptor trigger zone. They can be very effective in people, but less so in animals. They are mainly used in the treatment of vomiting from motion sickness in dogs. Cats are more resistant to their effects.

Dopamine Antagonists

Metoclopramide (when used as an antiemetic) and droperidol primarily act as D2 antagonists at the chemoreceptor trigger zone and inhibit vomiting due to blood borne emetic agents such as bacterial or uraemic toxins. Metaclopramide also promotes gastric emptying (see below), probably by acting as a 5HT4 agonist, which adds to its antiemetic effect. In slightly higher doses it is also a 5HT3 antagonist, which also potentiates the antiemetic effects. Droperidol is a very potent D2 antagonist at much lower doses than required to produce sedation , but can produce a variety of side effects. Vomiting due to delayed gastric emptying may respond to these or to prokinetic drugs such as cisapride (a 5HT4 agonist). They may have some sedative effect. Domperidone (D2 antagonist) is used in people, but rarely in animals. It does not cross the blood brain barrier (although it has an effect on the CTZ) so the CNS side effects of the other D2 antagonists are not seen.

Neurokinin1 Antagonists

Maropitant seems to work well in most causes of vomiting except motion sickness. Similar drugs are used in people.

Anticholinergic Drugs

These are rarely effective as antiemetics in dogs and cats (although they are sold for children) unless vomiting is initiated by contraction or spasm of smooth muscle in the gastrointestinal tract, when they will occasionally be able to relieve the spasm and reduce the stimulus to vomit. Anticholinergic drugs do not prevent the vomiting caused by stimulation of peripheral receptors or by inflammation. Since these drugs reduce gastrointestinal motility, they may actually be contraindicated in vomiting because they may exacerbate the hypomotility of the gastric body. Hyoscine is occasionally helpful in motion sickness in dogs and cats.

5HT3 Blockers

Ondansetron and tropisetron are used in people, particularly for vomiting associated with cancer chemotherapy. Destruction of gut epithelium by the anticancer drugs causes the release of 5HT from chromaffin cells in the afferent pathways; 5HT3 receptor antagonists block these pathways. These drugs have not been used much in animals because of expense, although they have been shown to be effective in dogs and cats.

Other Antiemetics

If vomiting is caused by excitement, sedatives such as diazepam can be effective, although acepromazine may be better as it is a D2 antagonist as well. Cannabinoids have an antiemetic effect: in the UK, nabilone, a Δ9 tetrahydrocannabinol analogue, is sometimes used in people. It is very expensive. α2 antagonists (yohimbine, atipamezole) may be useful in the cat although they are not often used as antiemetics. Buspirone, an anxiolytic, may also be useful in cats as a 5HT1A agonist in the vomiting centre.

Corticosteroids are sometimes used in people, particularly in combinations to treat cancer chemotherapy induced emesis. Thier mechanism of action is unknown, and in view of their side effects, they are probably best avoided in animals.

Emetics

It is occasionally necessary to make an animal vomit, usually as part of decontamination in suspected poisoning cases. Emetics should not be used unless the animal is fully conscious and there is no risk of it inhaling vomit.

Apomorphine, a dopamine agonist with a similar structure to morphine, is the most reliable emetic. The most convenient way of using it is to put a tablet under the eyelid and when the animal starts vomiting to remove the tablet. Injections can cause prolonged vomiting and should be avoided. Morphine itself usually causes vomiting in dogs, except when they are in pain. This is probably a balance between its antiemetic effects on the cortex (either direct or indirect) and its emetic efects on the CTZ. Xylazine will cause vomiting in about 25% of dogs and 30 - 50% of cats if given iv at 200µg/kg. Saturated salt solutions, sodium carbonate solutions (or a single crystal placed in the pharynx) and mustard solutions given orally can also be used in an emergency but are not recommended. Ipecacuanha is a general sales medicine used in children which is also effective in animals, particularly in cats. However, overdose can cause serious side effects, including death. It is becoming difficult to obtain as it is abused by anorexics.

Ulcers

Gastric acid makes ulcers worse and stops them healing; inhibitors of gastric acid secretion encourage their resolution. Many cases of ulcers in dogs are caused by non-steroidal anti-inflammatory drugs, although there are many possible causes. Helicobacter pylori infection is recognised as very important in people and possibly some other species, but its role in the dog is unclear. Drugs used to inhibit acid secretion are often classified into three groups: receptor antagonists that block the interaction of secretagogues with their receptors (eg. anticholinergics, H2-receptor antagonists); drugs that act on cellular metabolism to inhibit hydrogen ion secretion (eg. prostaglandins) ; and proton pump inhibitors such as omeprazole which inhibit the H+/K+ ATPase in the apical parietal cell membrane.

Altering gastric pH will also alter the absorption of many drugs, so H2antagonists and proton pump inhibitors can cause many interactions.

H2-Receptor Antagonists

Cimetidine inhibits histamine-stimulated gastric acid secretion in dogs and cats. Ranitidine is more potent and longer acting, but both work well clinically. Famotidine is a newer H2-receptor antagonist that has been promoted as being more effective than both cimetidine and ranitidine: studies in dogs have suggested that it is of similar clinical efficacy to ranitidine. H2-receptor antagonists cause minimal side effects even at high doses. There is evidence that, at least in people, tolerance to H2 blockers can develop.

Proton Pump Inhibitors

Omeprazole irreversibly inhibits the proton pump (H+/K+ ATPase) at the apical border of parietal cells, reducing hydrogen ion secretion. As this is the final stage of the process, omeprazole inhibits acid secretion no matter what secretagogues are present. It is very potent in dogs. A single daily dose can result in virtually no acid secretion. The drug does not affect other gastrointestinal secretion in dogs. Omeprazole is a weak base that is lipophilic at pH 7.4. Once the drug enters parietal cell canaliculi into which hydrogen ions are being secreted it becomes trapped in its active (protonated) form within the cell. When not in an acidic environment, the drug does not accumulate and remains inactive, so once it has increased pH, it has no more effect. Omeprazole is useful in diseases requiring profound inhibition of acid secretion. For instance, in humans and dogs it has been shown to be superior to H2 blockers for the treatment of severe reflux oesophagitis and the occasional indolent gastroduodenal ulceration. There is a delay in onset of action of 3 - 5 days while the drug accumulates and a similar delay in offset after stopping administration. The drug is safe in dogs and probably in cats, although there has as yet been little clinical experience in cats. Omeprazole inhibits microsomal enzymes to a similar extent to cimetidine. Therefore, when using omeprazole in multi-drug therapeutic protocols, the potential for drug interactions must be carefully evaluated.

Prostaglandins

Prostaglandin E analogues inhibit gastric acid secretion, they also have a variety of other beneficial effects (such as improved blood flow and trophic effects) that have proven valuable in managing mucosal lesions. Misoprostol is an analog of prostaglandin El which is the drug of choice for NSAID-induced ulceration and may have a role in the treatment of stress erosions or ulcers, although it is expensive. Side effects can include diarrhoea, abdominal discomfort and abortion if pregnant.

Antacids

Gastric acid can be briefly neutralised with antacids. These drugs must be given at least six times daily to have any benefit in the treatment of gastric ulcers, which makes them impractical in small animal medicine. Less frequent dosing may actually result in greater than normal rates of acid secretion (acid rebound), potentially making ulcers worse. Common antacids include aluminum, calcium, and magnesium hydroxides or silicates. Aluminum or magnesium containing antacids are probably the most effective. Aluminium-containing antacids tend to promote constipation whereas magnesium-containing antacids encourage looser stools. Aluminum reduces gastric motility and delays gastric emptying. Mixtures of magnesium and aluminium salts are most commonly used.

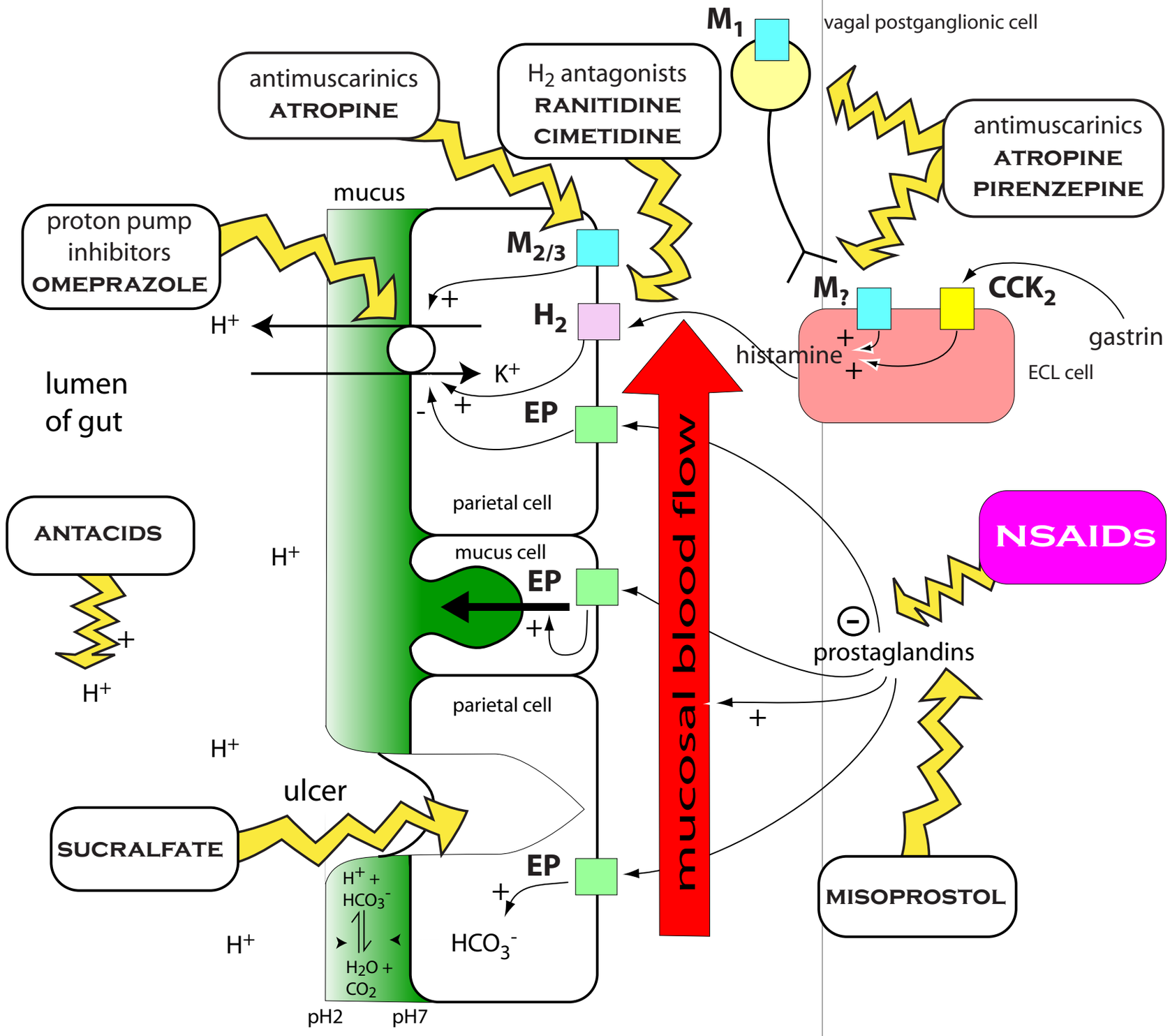
Aluminium hydroxide reduces phosphorus absorption and can be useful in chronic renal disease.

Mucosal Protectants

Mucosal protectants coat the ulcer and protect it from acid and proteolytic enzymes, allowing it to heal.

Sucralfate is the aluminum salt of a polysulphated derivative of sucrose which is used to treat gastric and particularly duodenal ulcers. Uncontrolled trials in dogs and cats with vomiting have suggested a beneficial effect. In an acidic environment, the molecule dissociates into aluminum and sucrose sulphate. The negatively charged sulphate groups bind to the positively charged exposed proteins of disrupted epithelial surfaces, providing a sticky protective barrier against the action of acid and pepsin. Sucralfate inhibits pepsin activity and stimulates bicarbon-

Diagram 3.10.4 Gastric ulceration



*Sites of action of drugs used to treat ulcers. Note that NSAIDs **cause** ulcers.*

ate and mucus secretion by surface mucosal cells and also appears to reduce parietal cell responsiveness to secretagogues. It also stimulates the release of prostaglandins. Sucralfate is not absorbed from the gastrointestinal tract and has no toxic side effects. Great care is required when using it with other drugs because it reduces the absorption of many drugs including tetracyclines, fluoroquinolones and cimetidine. The effectiveness of sucralfate is inhibited (but not completely eliminated) in an alkaline environment. It is common practice to give sucralfate 1-2 hours prior to the use of antacids or drugs that inhibit gastric acid secretion.

Colloidal bismuth subcitrate and bismuth subsalicylate are useful for the treatment of acute gastritis. Both drugs have been shown experimentally to reduce stress ulceration in rats but bismuth subcitrate has become the compound of choice for upper gastrointestinal lesions whereas bismuth subsalicylate is predominantly used for acute diarrhoeal diseases. Their beneficial effects in gastrointestinal disease have been attributed to their cytoprotective and demulcent properties but bismuth compounds also have antibacterial activity against helicobacter-like organisms (and possibly other bacteria). Bismuth products are very safe when used for short courses at standard doses. Careful dosing is required with bismuth subsalicylate because the salicylate is released by gastric acid and absorbed in the stomach and duodenum. This can cause overdose, particularly in cats. Bismuth subsalicylate is available in various proprietary mixtures; bismuth subcitrate has been used in dogs.

There is little evidence that non-specific gastric protectants, such as kaolin and pectin, hasten the recovery of acute ulcers. Any beneficial effect they might have is less likely to be from the coating of ulcers than the adsorption of bacterial toxins. Although traditionally used for diarrhoea, they do not shorten the course of this disease either.

Atropine and most other commonly used antimuscarinics act on all types of muscarinic receptor resulting in inhibition of acid secretion in people. Pirenzepine (a selective M1 receptor antagonist) inhibits gastric acid secretion without the effects on gastric motility mediated by drugs acting on M2 receptors. None of them appear to be very effective at inhibition of acid secretion in animals, and they also reduce gastric motility, which is undesirable. They are rarely used in veterinary practice.

Gut motility

Drugs that enhance gastrointestinal motility are valuable in the treatment of delayed gastric emptying, adynamic ileus and other motility disorders in dogs and cats. Drugs which reduce motility are often used to treat diarrhoea. Their use should be reserved for persistent diarrhoea.

Prokinetic Drugs

Metoclopramide has both antiemetic and prokinetic properties. Although it is a dopaminergic D2 antagonist, its effects on motility are probably caused by its 5HT4 agonist activity which, among other effects, increases acetylcholine release. Cisapride acts in the same way to stimulate lower oesophageal sphincter tone, gastric emptying and small bowel peristaltic activity, and may be more effective. Cisapride has been withdrawn in the USA because it sometimes causes fatal arrhythmias in people; although it is currently available in New Zealand, this may not last. However, there is a variety of new 5HT4 agonists, such as prucalopride, going through clinical trials in people overseas, which may be useful in animals in the future. They appear effective in experimental dogs. 5HT4 agonists increase colonic motility in dogs and cats and are useful for megacolon in cats.

The antibiotic erythromycin can be a valuable prokinetic in dogs and cats when used in low doses. It mimics the effects of the hormone motilin in cats and has a similar but indirect effect in the dog. The dose required is much smaller than the antibacterial dose. Similar macrolides with no antibiotic activity are in development.

Ranitidine, although usually used as an anti-ulcer drug, also has a prokinetic effect, probably by acting as an anticholinesterase and possibly as a M3 cholinergic agonist.

Opioid antagonists which do not cross the blood brain barrier are entering clinical trials in people as prokinetics. They may be useful in dogs and cats in future.

Motility Reducing Drugs (spasmolytics)

Intestinal transit time is largely determined by the ratio between peristalsis (the driving force for moving intestinal contents aborally) and segmentation contractions which narrow the bowel lumen and increase the resistance to flow, which helps to mix the contents. Theoretically, therefore, motility modifiers could reduce diarrhoea by decreasing peristaltic contractions or by increasing segmentation contractions. In real life, reducing peristaltic activity by drugs such as anticholinergics is of little value for the treatment of diarrhoea. Increased peristaltic activity is usually not the primary reason for the rapid transit of bowel content during acute diarrhoea. Antimuscarinics reduce, but do not abolish, peristalsis and they also reduce segmentation contractions. As long as some peristaltic activity is present, no matter how weak, it can propel liquid contents through a flaccid tube and diarrhoea will occur. Because of their questionable effectiveness and potential to produce adverse effects, such as adynamic ileus, antimuscarinics should not be used for the treatment of diarrhoea. The only role for antimuscarinics is the treatment of abdominal pain resulting from bowel spasm. Hyoscine combined with dipyrone (Buscopan) is commonly used for this purpose in horses and, to a lesser extent, dogs. It may be better to use a pure NSAID.

Increasing the resistance to flow of ingesta through the intestine by administering drugs that promote segmental contractions is a more sensible method of prolonging intestinal transit time. In contrast to antimuscarinics, there is good evidence that drugs which work in this way, such as the opioids, effectively slow intestinal transit and reduce diarrhoea without predisposing to adynamic ileus. Opioids acting at μ receptors increase the amplitude of rhythmic segmentation and decrease the propulsive contractions. The net effect is to markedly inhibit the flow of intestinal contents, delay gastric emptying, and increase tone in the ileocolic valve and anal sphincter. There are also many δ receptors throughout the gut. δ agonists help to reduce secretion in people, and possibly dogs and cats. There are interactions between the receptors, and most of the commonly used drugs have some effect at δ receptors, although their main effect is probably at μ receptors.

Effective opioids include morphine and its crude extracts such as paregoric, pethidine, diphenoxylate and loperamide. Pethidine also has a short anticholinergic type spasmolytic effect. Diphenoxylate and loperamide are the most commonly used for the treatment of diarrhoea because they do not cross the blood brain barrier to any great extent and so are difficult for drug addicts to abuse. Some opioids, in particular loperamide and to a lesser extent diphenoxylate, also increase fluid and water absorption. Loperamide has a faster onset of action than diphenoxylate and fewer side effects. Atropine is added in small quantities to diphenoxylate to minimize its abuse in humans as the sensation of a dry mouth is unpleasant. The amount of atropine has no effect on the gastrointestinal tract.

Cannabis derivatives, acting at the CB1 receptor, have the same effects as opioids - agonists slow the gut, antagonists speed it up. These drugs are not currently approved in New Zealand.

The major disadvantage to using opioids is their central nervous system depression if used in inappropriately high doses. They are also contraindicated in diarrhoea resulting from infection with invasive bacteria. In these cases, diarrhoea performs an important protective role that helps get rid of the organism. Slowing intestinal transit may prolong the residence time of the bacteria in the bowel, leading to greater opportunity for growth, invasion of the mucosa, and the absorption of toxic products.

Infections

Antibiotics

Antibiotics are nearly always contraindicated in gut disease, but are often used in veterinary practice. They have a number of predictable adverse effects on the gastrointestinal tract and if injudiciously used will complicate recovery from diarrhoea. Of particular concern is the adverse effects on the normal flora that can predispose the patient to diarrhoea, infection with virulent pathogens and to sepsis. Additional adverse effects of antibiotics include various side effects such as anorexia, vomiting, and iatrogenic diarrhoea that can confuse the clinical picture and delay recovery. Gastrointestinal upset is most commonly seen in dogs and cats as a result of treatment with neomycin, tetracycline, erythromycin, metronidazole, penicillins, clindamycin, or chloramphenicol. In horses, tetracyclines are the usual culprit. The diarrhoea resulting from tetracyclines results from changes in the intestinal microflora (often overgrowth of clostridia) and possibly from an irritative effect and may well be fatal in horses and guinea pigs.

Oral aminoglycosides, in particular, should not be administered to animals with diarrhoea unless a susceptible enteric pathogen is strongly suspected. Even then, parenteral therapy is preferred because the aim is to kill the enteric pathogen as it enters the lamina propria. Neomycin can cause a malabsorption syndrome resulting from direct precipitation of micellar fatty acids and monoglycerides or from alteration of microbial flora. Neomycin also appears to interfere with pancreatic lipase activity and decrease bile acid resorption. In addition, aminoglycosides have well recognized renal toxicity, vestibular toxicity, and ototoxicity. The renal toxicity of aminoglycosides is enhanced by youth, dehydration, overdosage, and concurrent administration of certain drugs such as some cephalosporins and nonsteroidal anti-inflammatory drugs. These predisposing conditions occur frequently in diarrhoeal diseases. Oral aminoglycosides are often administered in quantities that far exceed the recommended parenteral doses. In normal animals the aminoglycoside is not absorbed, and no systemic toxicity results. In animals with a disrupted intestinal mucosal barrier, however, the absorption of oral aminoglycosides can be increased. In particular, toxic systemic levels can result if repeated oral administration is continued in an animal with decreased glomerular filtration from renal disease or dehydration. Oral aminoglycoside preparations should never be given to dehydrated patients with evidence of a disrupted mucosal barrier.

Antibiotics are only justified for diarrhoea if:

bacteria have invaded the intestinal mucosa, from whence they could be a potential cause of bacteraemia or septicemia. Evidence of mucosal invasion includes haemorrhagic diarrhoea (dysentery) and evidence of sepsis such as fever, depression, degenerative left-shifted leucograms, or positive blood cultures. The presence of occasional streaks of fresh blood on the stool is not an indication for antibiotic therapy.

a known pathogen is cultured from the faeces of the patient, or if firm evidence of a bacterial aetiology is obtained by faecal smears (eg high numbers of clostridial spores), quantitative culture of duodenal fluid (bacterial overgrowth) or intestinal biopsy (eg enteroadherent bacteria). Even in the face of a positive faecal culture, if the animal is not showing evidence of sepsis, antibiotic therapy may not result in more rapid recovery than the provision of supportive care alone. Animals have a large variety of natural defences against bacterial pathogens, not the least of which is floral resistance. Thus, most bacterial enteritis conditions will resolve without antibiotics. In people, antibiotics have been shown to prolong diarrhoea, probably by killing the wrong bacteria.

Factors that influence the decision whether to treat with antibiotics-include the type of bacteria cultured, the nature of the clinical signs, and the likelihood of a public health risk from the particular bacteria cultured. Salmonellae and campylobacter are potentially zoonotic, but in people they are not usually treated with antibiotics because this tends to prolong the carrier state without noticably shortening the clinical course of the disease.

Routine usage of antibiotics in non-haemorrhagic diarrhoea is not warranted, in view of the rarity with which enteric pathogens are cultured, the self-limiting nature of many bacterial infections, and the potential adverse effects of antibiotic therapy. Antibiotics of any form are seldom required for longer than five days in the treatment of acute diarrhoea.

The antibiotic should be chosen after consideration of the spectrum of activity and the concentration of the antibiotic achieved in the bowel lumen, two factors which are prime determinants of the disruptive nature of the antibiotics on normal flora. Ampicillin, and, to a lesser extent, amoxicillin are broad spectrum antibiotics that are highly disruptive of normal flora. These antibiotics should thus be avoided for the treatment of gram negative bacterial pathogens. On occasion, it may be advantageous to use ampicillin or amoxicillin precisely because of their effectiveness against anaerobic flora in the intestinal lumen. For instance, these drugs are indicated in the treatment of patients with clostridial overgrowths, such as are seen in intestinal obstruction.

Potentiated sulphonamides are good choices for the treatment of enteropathogens. These drugs have broad spectrum activity against invading aerobic and anaerobic bacteria but minimally disrupt intestinal flora.

Fluoroquinolones are also very effective drugs for the treatment of enteropathogens. However, they are the drugs of last resort for treating life threatening Gram negative infections in man , and should never be used to treat diarrhoea in animals.

Gentamicin is useful for gram negative septicaemia in both large and small animal medicine.

Metronidazole is an antimicrobial drug with a very broad spectrum of activity against anaerobic bacteria and protozoa. The primary role of metronidazole is in the treatment of inflammatory bowel disease, anaerobic small intestinal bacterial overgrowth, and peritonitis secondary to bowel perforation. Metronidazole has been superseded by albendazole and fenbendazole as the drug of choice for the treatment of giardiasis in dogs.

Tylosin is an antibacterial agent similar to erythromycin and has been successfully used for idiopathic intractable diarrhoea in small animals and for enteropathogens in large animals. Erythromycin is primarily indicated for the treatment of Campylobacter.

Probiotics And Prebiotics

Probiotics are defined as live microbial feed supplements which beneficially affect the host animal by improving its microbial balance. While appealing in concept, there is as yet little objective evidence to establish a role for probiotics in the treatment of diarrhoea. Nevertheless, the field of probiotics is an active area of research and recent developments using bacteria that are part of the dominant anaerobic flora of the host, such as Bifidobacterium species, show considerably more promise than Lactobacillus species. Similarly, "prebiotics" (drugs or nutrients - eg fibre - that encourage the growth of normal flora) show considerable promise.

Anthelmintics

A variety of anthelmentics are used for the treatment of parasitic problems affecting the gastrointestinal tract. In small animals, most parasitic problems can be safely treated with pyrantel with the exception of whipworm infection and protozoal diseases such as giardiasis. To treat whipworm, oxantel ("plus") preparations are necessary or fenbendazole. Piperazine remains useful for the treatment of ascarids. Giardiasis can be treated with metronidazole, or preferably, albendazole or fenbendazole. See your parasitology notes for more info.

Anti-inflammatory drugs

Because of the high prevalence of immune-mediated disorders of the gastrointestinal tract in small animals, anti-inflammatory drugs such as corticosteroids, azathioprine, chlorambucil etc are commonly required to treat chronic GI complaints in dogs and cats. In large animal medicine, NSAIDs such as flunixin, are frequently used to control abdominal pain and to combat endotoxaemia. Most antiinflammatory drugs are not used specifically for treating gut inflammation. The only exception is sulphasalazine.

Sulphasalazine is a combination of 5-aminosalicylic acid and sulphapyridine, joined through an azo bond. Sulphasalazine is the drug of choice for the pharmacological therapy of chronic colitis in the dog and perhaps the cat. After administra-

tion, about 75% of the sulphasalazine reaches the colon, where bacteria break the azo bond and release the component parts of the drug. Because sulphasalazine needs bacterial metabolism to release its active moiety, the drug is effective only against large bowel inflammation. The majority of the activity of sulphasalazine resides with the 5-aminosalicylate. Other non-steroidal antl'inflammatory drugs such as aspirin are ineffective in treating colonic inflammation and may actually worsen the disease.

The most common side effects of sulphasalazine in dogs are anorexia and vomiting. Keratoconjunctivitis can occur as a result of sulphasalazine therapy. Dogs maintained on long term sulphasalazine therapy should have periodic Schirmer's tear testing to identify KCS early. The relatively high incidence of side effects with sulphasalazine has led to the development of analogues of sulphasalazine that contain 5 aminosalicylate but not sulphapyridine (eg mesalazine, olsalazine). These drugs appear to be effective and safe in dogs.

Laxatives

Laxatives increase frequency of defaecation or soften the faeces making it easier to pass. The first considerations in the treatment of constipation are correction of any fluid and electrolyte imbalance and attention to the primary cause if one can be identified. Chronic use of laxatives requires great care: many of these drugs alter water and ion secretion and can cause problems in long term use, including flatulence and pain as well as ion imbalance.

A lubricating warm water enema with manual fragmentation and removal of the hardened stool (under anaesthesia) is valuable in severely constipated animals. A suitable enema solution is warm water mixed with generous quantities of methylcellulose lubricant. Phosphate enemas are contraindicated in small animals because of the likelihood of absorption and subsequent intoxication.

Animals with less severe constipation can be treated by regular warm water lubricating enemas containing soaps such as docusate sodium (dioctyl sodium sulphosuccinate). Lubricant laxatives such as white soft paraffin and liquid paraffin are commonly used in cats and large animals, respectively, although both work in small animals. Syringe administration of liquid paraffin should be avoided in cats and dogs because of the risk of aspiration.

Beware - the nomenclature of the paraffin series is complicated. They are all mixtures of hydrocarbons with the general formula C_nH_{2n+2} The lightest is paraffin oil (= kerosene), then liquid paraffin (= mineral oil) followed by white soft paraffin (= petrolatum, Vaseline) and paraffin wax (= paraffin). Confusion can arise because liquid paraffin has in the past been called paraffin oil in the US although its official name there is mineral oil. If you give an animal kerosene in mistake for liquid paraffin you will kill it.

Bulk-forming laxatives are not absorbed from the gut but absorb water and form an emollient gel. The increased volume promotes peristalsis and the stool is kept moist. A variety of natural products such as psyllium, sterculia, bran and prunes are effective; methylcellulose has also been used. Bacteria in the colon may also break these down to products which exert an osmotic effect, adding to the laxative effect.

Osmotic laxatives are designed to pass through the animal and draw water into the lumen of the gut on the way. It is important that animals are allowed free access to water. Osmotic laxatives should not be given to dehydrated animals. The non-absorbable disaccharide, lactulose, is useful in some cats. Magnesium sulphate (Epsom salts) is an effective laxative in large animals, but is not usually used in dogs and cats.

Irritant laxatives, such as anthraquinones (from rhubarb) and extracts of senna, are not used much these days, but are effective. Several vegatable oils also have this effect. They are effectively converted to soaps by intestinal lipases. Castor oil is the most irritant, olive oil the blandest. Bisacodyl is another irritant laxative which seems to have a relatively specific effect on the large bowel. It inhibits glucose absorption, but its exact mecanism of action is unknown. It is also available mixed with soaps as an enema.

Fat pills

Weight reduction drugs are a huge area of research in human pharmacology and it was only a matter of time before reject human drugs appeared for animals. In the USA, dirlotapide is being marketed to slim down fat dogs (or to appease the consciences of their fat owners?). It blocks the uptake of lipids in the gut and induces a sense of fullness. It remains to be seen if these drugs are a fad or the future of small animal medicine.

Liver disease

Acute liver disease can be caused by a wide variety of viruses, bacteria and parasites, depending on species. Chronic liver disease can be caused by poisons (including drugs), metabolic disease or parasites.

Treatment involves removing the cause and managing the hepatic insufficiency. Remember that drug metabolism may be grossly abnormal. Antibiotics used for bacterial infection include ampicillin, co-amoxyclav and cephalosporins. Corticosteroids are sometimes used but great care is required. Ursodeoxycholic acid is sometimes used in chronic liver disease in small animals. It increases excretion of bile acids. Bedlington terriers and Westies are susceptible to copper toxicosis and are treated with penicillamine to chelate copper.

Hepatic encephalopathy is usually caused by a shunt in the liver and is treated surgically, but sometimes medical treatment to reduce ammonia uptake from bacterial protein metabolism is required. The laxative lactulose is often used. Occasionaly antibiotics which are not absorbed from the gut such as neomycin are effective.

Bloat

Definition

Bloat = an overdistention of the rumenoreticulum by gases of fermentation, with or without foam or separated gas. May occur in sheep as well as cattle.

The three main types of bloat based on aetiology

- Frothy (primary) - due to protein breakdown in the rumen. The most important in NZ.
- Free gas - gas and low pH
- Eructation dysfunction - extra ruminal causes

Aetiology

Animal factors

• Diet-A major factor that determines bloat is the composition of the rumen contents (the ruminant's diet) and the rumen microflora. Plant proteins are the primary foaming agent. The rapidity of plant breakdown is a factor in bloat. Adaptation to diet is important, abrupt changes may lead to bloat.

• Genetic make up- the predisposition of animals is a known factor. Animals have different specific salivary proteins. Sialoprotein stabilizes the leaf protein, there is less sialoprotein in saliva of susceptible than bloat-resistant cattle.

• Rate of saliva production-High vs Low production. Pilocarpine (stimulates salivary secretions) has been used to determine the susceptibility of ruminants to bloat. Animals given pilocarpine that have a higher rate of salivary secretions are less susceptible to bloat.

Plant factors

• The greater the amount of leafy (legumes) soluble proteins in pasture or hay the greater the risk of bloat.

• Tannin-like compounds in plants protect from bloat. Some plants have more of these protective compounds.

• The more muco-polysaccharides secreted by encapsulated bacteria (slime producing bacteria) the greater the chance of bloat.

• Increased viscosity due to saponins, pectins, hemicellulose and protein. Optimal pH is 6 for maximum stabilization.

Environmental factors

• Climatic conditions affect the bloat potential of a given pasture. Wet, fast growth, high daily temperatures and cool nights (minimum night time temperatures below 10˚C).

Pathophysiology

The rate of digestion and protein content of the diet are important factors. Legume hay or pasture bloat is different than bloat in grain-fed cattle. Proteins increase surface tension of rumen fluid, increased surface tension allows stable foam production because gas bubbles can not rise or coalesce due to fluid viscosity and entrapment among fine particles at the fluid surface.

The organization of water (H-O-H, dipole) in the rumen normally requires energy to maintain a surface charge. Proteins lower the energy needed to maintain the surface tension and aid in the entrapment of gas (and thus gas bubbles form).

Fermentation in cattle produces >25 L gas (methane)/hour, therefore the ruminant needs to eructate to prevent gaseous distention. Free gaseous distension of the cardia portion of rumen stimulates eructation but frothy (entrapped gas) bloat does not.

Frothy ingesta at neural receptors prevents the reflex relaxation of the cardia during the secondary contraction of the forestomach that ordinarily lead to eructation. Fluid or solid tactile stimulus of cardia decreases eructation. Distention also stimulates the high stretch receptors which in turn inhibit or decrease motility. Therefore frothy bloat decreases motility and eructation.

Clinical signs

Distention of left paralumbar fossa; may be difficult to see in sheep due to wool length. Bloat starts within an hour after ingestion of bloat-producing legumes or hay, but typically becomes a problem on the second or third day. Variable!

Dyspnoea, mouth breathing, protrusion of the tongue and extension of the head. Cardiovascular function is impaired by the pressure on the thorax. Death is due to asphyxiation.

Prevention

Prevention of bloat relies on the ability of the farmer to predict when forages may pose a risk (tricky!). Types of forage, climatic conditions and animal susceptibility must be considered. Generally, the farmer does not know for certain that a pasture is dangerous until bloat occurs. Then, once prophylactic drugs are used, it is difficult to know when it is safe to stop. Most anti-bloat medications need to be administered one to two weeks prior to the danger period.

Treatment

Mild bloat probably requires passing a stomach tube and the use of one of the following remedies such as oil or detergent.

Acute and severe bloat requires life-saving "heroics" remembering that frothy bloat will not be easily reduced by passing a stomach tube due to the entrapment of gas. Rumenotomy is often a necessity in a life or death situation.

Drugs

Synthetic Non-Ionic Surfactants

There are many commercial solutions containing ethoxylated alcohols (poloxamers, polyethylene - polypropylene glycols of various molecular weights) which reduce or prevent the build up of stable foam and gas in the rumen by decreasing surface tension.

Ethoxylated alcohols such as poloxalene are surfactants which have a faster action and require smaller doses than oils. They have a duration of action of about 10-18 hours. They are sometimes used in medicated blocks or added to the water supply. They should be administered several weeks prior to the "bloat season". These are the most popular drugs used both in the treatment and prevention of bloat because they are stable and easy to use. Always add the detergent to water.

These compounds are very safe, and are often also used as emulsifiers in injectable formulations of drugs.

Silicones such as dimethicone are sometimes used. They are more expensive and are always given orally.

Ionic Surfactants

Ionic detergents such as docusate (dioctyl sodium sulphosuccinate) were often included with oils to improve their destabilization of foam but have been replaced by non-ionic detergents. They are not used often because of their toxicity - they effectively make the lipds of cell membranes more water soluble - water rushes into the cells and they die. They are especially toxic for calves less than 12 months old, and are not recommended. Failure to rinse buckets adequately before feeding calves can result in toxicity.

Clinical signs of toxicity include central nervous system signs and diarrhoea. The detergent will dissolve (and thus denude) gut mucosa. The oesophageal groove in calves diverts liquids to abomasum. Even in adult dairy cows, the therapeutic/toxic dose is quite close so take care. These products can cause toxicity in adult ruminants if given directly into the abomasum.

When used for prevention, surfactants are given every 12 hours or as per manufacturer's recommendation.

Oils

Oils act as “wetting agent”, i.e. they decrease surface tension and destabilize the foam in the rumen. Any edible oil will do, peanut, sunflower, soyabean (Some oils such as turpentine and soya flavour the milk and butter which may result in penalties to the dairy farmer). Do not use fish oils - they stabilise the foam.

Liquid paraffin is also used as an oral treatment or sprayed on pastures (sometimes added to water in drinking troughs). The duration of action is several hours given a twice daily dose of 60-120 mls for prevention. For long term treatment, liquid paraffin will interfere with carotene absorption and will reduce the carotene and tocopherol content of the butter. Oils are better suited to prevention than to treatment.

Emergency Treatments

Alcohol such as whisky or vodka (diluted) might work, but only if nothing else is at hand. Milk or cream may work. Stab release of the pressure in the rumen using a knife or a trochar/cannula is very unlikely to work in frothy bloat - a full rumenotomy is required.

Altering Microflora

Altering ruminal flora can be used as a method to prevent bloat. This is obviously too slow for treatment. The object is to decrease butyric acid, decrease lactic acid and increase propionic acid, therefore rumen pH increases and less methane gas is produced, there are fewer capsulated bacteria and protozoa (they are thought to produce foaming mucopolysaccharides) and there is less tendency to bloat (of frothy type).

Antibiotics

Monensin is a monocarboxillic acid, polyether ionophorous antibiotic widely used to prevent bloat (and promote growth). It is most commonly used as Rumensin anti-bloat Capsule (Elanco) This is a controlled release intraruminal capsule which is effective for approximately 100 days. A plastic ring prevents regurgitation during the 100 days, but usually within 12 months the capsule will be regurgitated.

Monensin forms a neutral lipophilic complex with cations and transport these into and through biological membranes (ie, it acts as an ionophore), impairing physiologically normal transmembrane ion gradients. Therefore, Na+ can freely move into cell which results in osmotic injury, and thus reduces the number of protozoa and encapsulated bacteria in the rumen. Changes in the rumen flora result in decreased butyric acid, decreased lactic acid and increased propionic acid production. Monensin is also used as a growth promoter in cattle overseas because of an increase in propionic acid and a decrease in lactic acid production (and decrease in bloat).

Monensin is toxic in most monogastric species: LD50 Cattle about 20 mg/kg, LD50 Horse 2 mg/kg monensin kills horses (nb. it is also the standard coccidiostat in broiler chicken rations - do not let horses get anywhere near these). LD50 Dog 2 mg/kg but dogs are unlikely to eat it. The toxicity is potentiated by macrolide antibiotics. Accidents or poor care of mixing machines may result in toxic residues ending up in dog or horse products or cattle feeds at unacceptable levels.

Copper sulphate is sometimes used in sheep for its antibacterial action.

Other Types Of Bloat

Free gas bloat

This usually occurs in grain fed animals - stomach tube to release gas, or **in dire emergency only**, use trochar and canulla. The animal will probably have to be treated for acidosis (iv sodium bicarbonate - see fluids notes). Cattle fed on grain are usually also fed a variety of antibiotics to alter rumen flora and reduce lactic acid production - see antibiotics notes.

Abomasal Bloat in Lambs

Feeding systems that provide milk replacer to lambs ad lib, i.e. large quantities, infrequently or hand reared lambs. Particularly lambs fed unrefrigerated milk re-

placer that has been kept at 15˚C or higher twice a day (Refrigerated replacer is not as likely to cause bloating)

It is thought to be caused by sudden overfilling of the abomasum followed by proliferation of organisms which release abundant quantities of gas. Sarcina ventriculi is suspected of causing abomasal bloat in lambs. Severe distention causes compression of the thoracic and abdominal viscera and blood vessels. Lambs become distended within 1 hour of feeding and die shortly after distention is clinically obvious. At necropsy, the abomasum is grossly distended with gas, fluid and milk replacer that is usually not clotted. Mucosa is hyperemic.

There is no specific treatment known to effectively correct this condition. Symptomatic and supportive care is recommended. Recommend preventative measures to avoid future occurences. Prevention - include 0.1% formalin (37% formaldehyde) to 20% solids in milk.

Gut toxicology

Poisons affecting the gut

- ☑ arsenic
- ☑ copper
- ☑ phosphorus
- ☑ zinc

Poisons affecting the gut

- Radiation
- Metals, Other Elements, and Inorganic Compounds
- -Arsenic
- -Antimony
- -Boric acid
- -Chromates
- -Elemental and Inorganic Salts of Mercury (See Toxicants with Mixed Effects on the CNS)
- -Lead (Initial) (See Toxicants with Mixed Effects on the CNS)
- -Thallium (Acute)
- -Cadmium (Acute) (See Toxicants Affecting the Kidneys)
- -Copper (Acute) (See Toxicants Causing Hemolysis)
- -Phosphorus (Initial) (See Toxicants Affecting the Liver)
- -Zinc (See Toxicants Affecting the Kidneys)
- -Zinc Phosphide (Initial)
- -Fertilizer
- Organic Compounds
- -Nonsteroidal Anti-inflammatory Drugs
- -Cardioglycosides
- -Fluoroacetate (Initial (Canidae)
- -Cholinesterase Inhibitors
- -Rotenone
- -Carbon Tetrachloride
- -Chlorophenoxy Herbicides
- -Blister Beetles (Epicauta)
- -5-flurouracil (Effudex) Topical Creme (When Ingested)
- -ANTU

Plants Affecting the Gastrointestinal Tract

- 1. “Toxalbumins”
- -Rosary Pea, Precatory Bean (Abrus)
- -Castor Bean
- -Black Locust (Robinia)
- -American Mistletoe (Phoradendron)
- -European Mistletoe (Viscum)
- 2. Irritant Oils
- -Buttercup (Ranunculus)
- -Marsh Marigold (Caltha)
- 3. Saponin Containing Plants
- -Pokeweed (Phytolacca)
- -Bouncing Bet (Saponaria)
- -English Ivy (Hedera)
- -Corn Cockle (Agrostemma)
- -Rattlebox esbania)
- -Buckeye or Horsechestnut (Aesculus)
- 4. Gallotannis
- -Oak (Quercus spp.)
- 5. Purgative Glycosides
- -Christmas Rose (Helleborus niger)
- 6. Irritating Resins
- -Euphorbia Family
- -Mayapple (Podophyllum)
- -Milkweeds (Asclepias)
- -Manchineel Tree (Hippomane)
- 7. Isothiocyanates
- -Brassica (Mustards and Related Plants)
- 8.Carboxyatractyloside
- -Cocklebur (Xanthium strumarium)
- 9. Cardioglycoside and Andromedotoxin Plants
- 10. Miscellaneous Plants
- -Holly Berries (Ilex)
- -Hydrangea (Hydrangea)
- -Daffodil, Jonquil (Narcissus)
- -Elderberry (Leaves and stems) (Sambucus)
- -Privet (Ligustrum vulgaris)
- -Autumn Crocus (Colchicum autumnalis)
- -Daphne
- -Hyacinth Bulbs (Hyacinthus)
- -Lambsquarter (Chenopodium)
- -death cap (Amanita phalloides)
- -Pepper Plant (Capsicum)
- -Jerusalem Cherry (Solanum pseudocapsicum)
- -Other Solanaceous Plants
- -Bitterweed (Hymenoxus odorata)-Sneezeweed (Helenium amarum)
- -Nicotinic Plants
- -Cycad Palms
- Trichothecenes
- -Deoxynivalenol (Vomitoxin)
- -T-2 Toxin, HT-2 Toxin
- -Diacetoxyscirpenol (DAS)
- -Others
- Other Mycotoxins, Bacterial Toxins, and Zootoxins
- -Cyclopiazonic Acid (Mycotoxin)
- -Bacterial Toxins (Food Poisoning; MostGarbage Poisonings; Most Carrion Toxicoses)
- -Endotoxins and Enterotoxins
- -Staphylococcal Enterotoxins

- -Clostridial Enterotoxins
- -Antibiotic Induced Colitis
- -Scombroid Fishes (slightly deteriorated tuna, bonito, mackerel) (Histidine Histamine)

Arsenic

Sources

- Thermal areas
- Tanalised wood and processing sites
- Sheep dips (old)/Wool sheds
- Peltex arsenic hide tanning
- Herbicides

Toxicity

Trivalent more toxic than pentavalent e.g. arsenic trioxide is 3-10 times less toxic than sodium arsenite

Mechanism of Action

Targets organs/tissues rich in oxidative enzymes

Clinical Signs

Acute/Peracute 3-4 hours to death

Acute abdominal distress (pain)

Thirst

Salivation (vomiting in nonruminants)

Hypotension

Subacute 2-7 days to death

Depression, dehydration

Hypothermia

Anorexia

Arsenic

☑ Thermal areas, Tanalised wood, herbicides, past dips

☑ • Two distinct toxicities: Pigs- arsenilic acid as a feed additive; Other species- various forms of arsenic

☑ • Affinity for oxidative enzymes (multiple tissues)

☑ •Clinical Signs: Thirst, Abdominal pain, salivation, vomit, diarrhoea, Hypotension

☑ Rose coloured skin (non-pigmented animals), dermal necrosis

☑ • PM-red mucosa that peels away

☑ • Diagnosis- liver and kidney

☑ • Treatment-chelation BAL, supportive therapy/ fluids

Chronic exposure: (rare due to rapid excretion)

Dogs-severe necrosis and sloughing of skin from contact with tanalised wood

Systemically-anorexia, listlessness, soft faeces, rough haircoat, ulcerated mucous membranes

Post Mortem

Liver may be pale and have fatty degeneration

Gastrointestinal tract may be friable, sloughing of epithelium

Kidneys-all parts of the nephron are affected

Cutaneous-dry leathery, peeling skin

Diagnosis

History, clinical signs

Liver, kidney, urine, stomach contents

Hair, hoof and skin (remains in these tissues long after death)

Treatment

Generally a poor prognosis.

Early decontamination

Sodium thiosulphate or

British Antilewisite (BAL/dimercaprol) or Thiotic (better efficacy than BAL) or

Other chelators like mesodimercaptosuccinic acid (DMSA) are effective but not available except from chemical suppliers.

Boric Acid

Sources

Ant bait

Mechanism of Action

Unknown - suspected to be cytotoxic

Concentrates in the kidney and lesser degree in brain and liver

Toxicity

2-5g/kg LD50 in rats

dogs require a higher dose for toxicity - variable depending on the dose ingested

Young and old animals are more susceptible

Clinical Signs

Acute toxicity – boric acid is not caustic

Hypersalivation

Vomiting

Retching

Depression

Anorexia

Diarrhoea, Abdominal pain

High Doses cause the following Clinical Signs:

Weakness

Ataxia

Tremors

Focal, generalised seizures

Oliguria or anuria

Depression

Coma, Death

Other effects: metabolic acidosis, renal tubular nephrosis

Post mortem

Gastrointestinal tract inflammation/congestion, oedema and mucosal exfoliation

Brain – congestion and oedema

Renal changes variable

Diagnosis

Usually with history and clinical signs

Treatment

Emesis, if appropriate

no activated charcoal as poor binding

Symptomic care, which may include the following:

Isotonic IV fluids

GIT protectorants

Antiemetics if protracted vomiting

Acute renal failure 2 times maintenance dose of 0.9% saline diuresis

Sodium bicarbonate for metabolic acidosis

Diazepam for seizures

Prognosis is good unless a large amount has been ingested.

Copper

Affects all species, but particularly sheep, calves, and Bedlington Terriers.

Sources

• Salt licks-frequently used as mineral/salt supplements, they may contain up to 5% soluble copper.

Copper

- ☑ Sheep are more susceptible
- ☑ GIT irritation-necrosis of mucosa
- ☑ Liver injury-massive release of copper
- ☑ Haemolytic crisis
- ☑ Use liver enzymes (AST) in sheep to predict crisis
- ☑ Clinical Signs:
- ☑ Acute: Thirst, Abdominal pain, GI haemorrhage, irritation, Increased temperature, pulse and respiration
- ☑ Chronic: Haemolytic crisis, Haemoglobinuria, Pale or muddy mucous membranes
- ☑ PM Metallic sheen to kidneys
- ☑ Diagnosis- kidney (liver unless haemolytic crisis)
- ☑ Treatment-Chelation for affected animals (penicillamine)
- ☑ Herd prevention: Ammonium molybdate

GI hemorrhage and pain,

increase in temperature, heart and respiratory rate;

thirst, Shock and collapse;

green vomiting;

Blue-green diarrhoea; death in 1-2 days

Subacute poisoning in lambs

(generally due to overdose by injectable products)

Thirst

Abdominal pain and anorexia

Depression, weakness and recumbent

Sudden death or death within 7 days of treatment

(due to oral ingestion)

GI haemorrhage

Ascites

Pulmonary oedema

liver damage

No icterus or haemolysis

Chronic Cu (Mo deficiency)

Gradual accumulation of Cu without signs

Sudden stress that triggers haemolytic crisis.

Acute deaths or clinical signs of:

Anorexia

Thirst

Haemoglobinuria/anaemia (wool staining)

reluctance to move (port wine colored urine)

Mucous membranes muddy later jaundiced

Death in 1-3 days, may appear to recover, but die within a week.

Clinical Pathology

Look at liver enzymes-AST

Diagnosis with analysis for copper in the liver and kidney. (Note: in chronic excess intake of copper the liver levels decline rapidly after haemolysis and may be within the normal range.)

Treatment

• Difficult to treat poisoned animals-recognize a problem exists and suggest preventative therapy for other animals in flock or herd.

• Aim is to decrease Copper intake/absorption.

• Can use chelation but could be very expensive with extended treatment

D-penamine (D-penicillamine)

750 mg per sheep (15 kg sheep)

NB: has toxic side-effects, see Plumb's Vet. Drug Handbook before using.

Triethylene tetramine 2HCl (Trien) new drug used in Wilson's Disease (genetic copper storage disease) has been shown to be effective. (difficult to obtain)

• Fluid Therapy to decrease haemoglobinuric nephrosis

• Orally treat rest of flock:

100 mg NH3molybdate and 1 gm (anhydrous)Na2SO4 in 10 ml of water daily to reduce Cu, must remove source of Cu toxicity. Stress of drenching may precipitate haemolytic crisis. Alternatively gypsum (anhydrous CaSO4) is effective.

Phosphorus

- ☑ Source: Pesticide
- ☑ Mechanism of action is unknown
- ☑ White phosphorus: Garlic like odour, Fluorescence, Mixed with oil or grease for stability
- ☑ Gastrointestinal signs, Delayed hepatic failure, bleeding tendencies, jaundice, Hypoglycaemia, Elevated liver enzymes
- ☑ Renal disease – BUN, urinalysis +
- ☑ Treatment: Decontaminate with copper sulphate
- ☑ No oils!
- ☑ Symptomatic care: Vitamin K, fluids, Nutritional (diet especially for liver and renal failure)

Severe abdominal pain, tendency to bleeding with hypo-prothrombinemia

Ruminants may show a delayed photosensitivity similar to FE

Clinical Pathology

Hypoglycaemia, Elevated liver enzymes

Oliguria and rise in BUN, albuminuria, haematuria and amino acids

Phosphorus of blood normal (generally)

Post mortem

Fatty degeneration and swollen liver and icterus (jaundice)

gastrointestinal irritation, necrosis and haemorrhage

hepatic fatty change and /or periportal necrosis

renal tubular necrosis and casts may occur

Diagnosis

Early on by chemically demonstrating elemental phosphorus. Difficult to determine over time as it is oxidised to phosphates. Should freeze contents from stomach or faeces for chemical determination.

Treatment

No antidote.

Dogs and cats use a 1% Copper sulphate as a lavage (preferable to emesis) to aid elimination and form insoluble copper phosphide.

Activated charcoal and saline cathartics are recommended.

Do not give oils!

For hepatic and renal failure, cystine and a high carbohydrate diet, low protein are recommended as are high doses of B-vitamins and ascorbic acid. Fluids to increase urine output-continue to monitor function. Vitamin K, fluids and dopamine for haemorrhage, hypotension and poor perfusion, respectively.

Give supportive treatment. Very grave prognosis.

Zinc

Zinc

- ☑ Source: therapy and prophylaxis for facial eczema
- ☑ Zinc salt solution precipitate proteins - causes gastroenteritis
- ☑ Excreted via bile and pancreas
- ☑ Acute Toxicity: violent GI signs: abdominal pain, vomiting (monogastrics), GI bleeding, diarrhoea, polydipsia, renal failure
- ☑ • Haemolytic crisis may occur
- ☑ • Degenerative liver (hepatocellular necrosis)
- ☑ • PM-pancreatitis or oedematous abomasitis (± greenish)
- ☑ Symptomatic treatment, decontaminate, chelate
- ☑ Zinc does not accumulate in the body;tissue residues may be present for 2 weeks
- ☑ Don’t slaughter for at least 2-3 weeks.

In general for acute toxicity:

Violent GI signs:

abdominal pain

Vomition (monogastrics)

GI bleeding

Diarrhoea

Ruminants subacute/chronic:

anorexia, depression, polydipsia, polyphagia,

decreased milk yield, chemosis, exopthalmia,

convulsions and death.

Monogastrics-subacute or chronic:

Anorexia,

Haemolysis and haemoglobinuria,

weakness, icterus

PU/PD,

oral ulcers associated with acute renal failure,

Convulsions and or death.

Small Animals that ingest zinc oxide ointments tend to vomit.

Laboratory Diagnosis

Regenerative anemia (haemolytic)

Incr SAP

Bilirubinemia

Decr PO_4

Isostenuria

Uremia

Bile casts in bile canaliculi

Pathological Diagnosis

Tissue zinc can be determined from:

Liver, kidney

Stomach contents or feed

Pancreas swollen/oedematous/gelatinous in appearance

Treatment

difficult

Remove from further absorption

surgical

emetics or gastric lavage

cathartics

adsorbants (not activated charcoal)

Na bicarbonate + egg white + tannic acid is said to chelate zinc.

Systemic vs chelation therapy (May be economically driven).

Ca EDTA

Penicillamine

Zinc does not accumulate in the body; however, tissue residues may be present for 2 weeks. Animals with overdoses of zinc or zinc toxicity must be held from slaughter at least 2-3 weeks. (7 weeks for some products)

Poisons affecting the liver

- Hepatotoxic Chemicals and Drugs
- -iron dextran and other iron compounds
- -phosphorus
- -carbon tetrachloride
- -coal tar, pitch, clay pigeons, phenolics
- -paracetamol (acetaminophen)
- -tannic acid
- -copper
- -carbon disulfide
- -halogenated hydrocarbons including halogenated dioxins
- -vitamin a
- -carbamate fungicides
- Mycotoxins Affecting the Liver
- -aflatoxins
- -sterigmatocystin
- -rubratoxins a and b
- -sporidesmin (facial eczema)
- -penicillic acid
- -cyclopiazonic acid
- -F. moniliforme contaminated corn in the horse
- Poisonous Plants Affecting the Liver
- -Cocklebur (Xanthium)
- -Pyrrolizidine Alkaloid Containing Plants, Ragwort (Senecio)
- -Groundsel (Senecio)
- -Rattlebox (Crotalaria)
- -Fiddleneck (Amsinckia)
- -Viper's Bugloss (Echium)
- -Heliotrope (Heliotropium)
- -Comfrey (Symphytum)
- -Trichodesma
- -Hound's Tongue (Cynoglossum)
- -Blue-Green Algae (Microcystis, Nodularia spumigena)
- -Lantana (Lantana).
- -Sneezeweed (Helenium spp.)
- -Bitterweed (Hymenoxys spp.)
- -Kochia scoparia
- -Alsike Clover (Trifolium)
- -Birdsfoot Trefoil (Lotus)
- -Cycad Palm (Cycas and Zamia spp.)
- -Mushrooms (Amanita phalloides)
- -Gossypol (Cottonseed meal)
- -Rapeseed (Brassica)
- Hepatogenous Photosensitizers
- -Horsebrush (Tetradymia glabrata or T. canscens especially when sensitized with black sage Artimesia salina)
- -Panic Grasses (Panicum spp.)
- -Puncture Vine (Tribulus terrestris)
- -Sacahuiste, Bunchgrass (Nolina texana)
- -Agave (Agave lecheguilla)
- -Sporidesmin (Mycotoxin)
- -Pyrrolizidine Alkaloid Plants
- -Lantana (Lantana)
- -Moldy post-frost Florida Bermuda Grass (Cynodon)
- -Blue-green Algae (Microcystis spp.)
- -Rape (Brassica)
- -Kochia (Kochia scolparia)
- -Alsike Clover (Trifolium hybridum)
- -Congenital Liver Anomale-Southdown sheep

- -Ngaio (NZ Native) (Myoporum laetum)

Facial Eczema

(Sporidesmin toxicity)

In New Zealand facial eczema is by far the most important mycotoxicosis and ranks as one of the most destructive diseases of sheep. It also affects cattle. Its occurrence is seasonal, with most cases occurring during the autumn. The disease occurs typically in warm temperate climates. In NZ the disease occurs in the lowland warm areas of the North Island but occasionally extends south to the northern areas of the South Island.

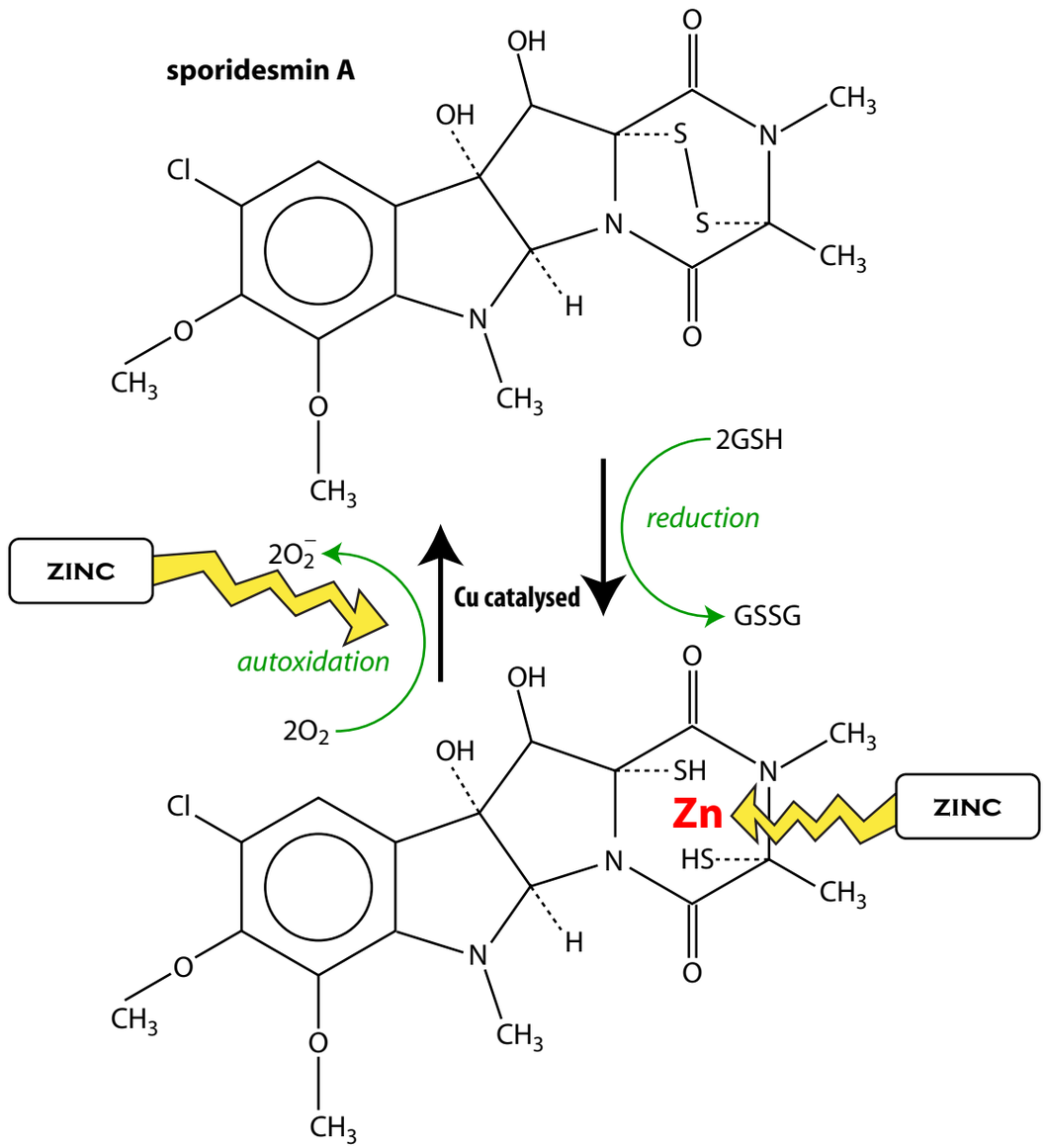
Aetiology and Pathogenesis

The disease is a hepatogenous photosensitization caused by the hepatotoxin sporidesmin which is produced by the saprophytic fungus Leptosphaerulina chartarum (formerly Pithomyces chartarum) Under the warm moist conditions of autumn, L. chartarum proliferates on pasture litter producing the toxin sporidesmin. At sporulation the sporidesmin is translocated into the spore and it is consumed by ruminants especially under close grazing conditions.

The sporidesmin is rapidly absorbed from the upper gut, and is concentrated in the liver and hepatic bile. Here the molecule undergoes a glutathione-linked, copper-catalyzed cycle of oxidation and reduction to produce the toxic free radical superoxide, and other free radicals. This superoxide radical production causes necrosis of the ductular epithelium in the early stages, later the ducts become occluded by fibrous tissue, causing obstruction of the bilary system. The resulting liver injury, particularly of the biliary system, blocks the excretion of phytoporphyrin (phylloerythrin), the breakdown product of chlorophyll. Endogenous porphyrins, e.g. haemoglobin and myoglobin, accumulate giving the clinical condition of jaundice. Accumulation of phytoporphyrin leads to photosensitivity on exposed nonpigmented skin. The concentration of the major liver enzyme, gamma glutamyltransferase is used in the diagnosis of the disease and in the selection of F.E. resistant animals.

The reduction and autoxidation of sporidesmin generates an “active oxygen”. The reaction involves the disulphide bridge of the mycotoxin, which is readily reduced by interaction with thiols, including glutathione (GSH). The di-thiol formed by reduction is unstable in the presence of oxygen and autoxidises back to the parent compound, generating a super-oxide radical in the process. The reaction is dependent on metal catalysis and copper in particular. The copper must be catalytically active, chelated or protein bound copper will not catalyse the superoxide formation. It is believed that copper is found in an active state as either newly absorbed metal or in transit in the intracellular pool to be involved part of the toxic process. Hence if the pool of free copper can be modified the toxicity of sporidesmin should be reduced. Zinc is known to inhibit copper absorption from the intestines. Zinc admini-

DIAGRAM 3.11.1 Facial eczema



Sporedesmin reduction and oxidization, catalysed by copper, produces free radicals which damage cells. Zinc interferes with this in several ways.

stration decreases the size of the hepatic copper transport pool and reduces the severity or prevents toxicity from occurring. Zinc is also capable of forming a stable sporidesmin-zinc mercaptide, which prevents autoxidation and superoxide radical formation.

Zinc is used as a preventative, it has no antidotal activity once liver damage has occurred, hence zinc treatment should be administered at least 10 days before the onset of dangerous pasture spore counts.

Paracetamol (Acetaminophen)

Paracetamol, also known as acetaminophen in the USA, is a common OTC analgesic and antipyretic drug that is different than NSAIDs. First of all it does not have anti-inflammatory properties. It does NOT block prostaglandin formation. It reduces fever by direct action against endogenous pyrogens. Paracetamol does not produce stomach upset like aspirin and other NSAIDs because it has no activity against prostaglandins. It does not interfere with platelet aggregation.

Toxicity

Paracetamol is normally conjugated with glucuronate, conjugated with sulfate, or a small percentage is metabolized by the liver to a toxic intermediate. This toxic intermediate is conjugated with glutathione and excreted as a biologically inactive compound. If the amount of paracetamol exceeds the limited amount of glutathione than the toxic metabolite in the hepatocyte will react with cellular structures resulting in cell death. This toxic metabolite can also produce damage in other tissues including RBCs. In cats the problem is compounded because of their limited ability to conjugate paracetamol to glucuronate. One paracetamol tablet (500 mg) will produce toxic signs in cats. A toxic dose for cats is 50–60 mg/kg. Dogs need a higher dose (150+ mg/kg) before toxic signs appear.

Clinical Signs

Initial clinical signs include anorexia, salivation and vomiting. Methemoglobinaemia, red blood cell haemolysis and classic Heinz body anaemia develops. The mucous membranes show characteristic brown color from methemoglobinemia. Liver necrosis occurs more often in dogs than in cats and is characterized by icterus, weight loss, and death. Facial and paw oedema have been reported in dogs and cats. Haemoglobinuria may occur.

Treatment

Depending on the time since ingestion induction of emesis may be beneficial. Activated charcoal (1-4 gm/kg) administered with a laxative is also indicated after oral ingestion. Administer drugs that have sulphydryl groups or contribute sulphate to substitute for the missing glutathione, e.g. N–acetylcysteine (Parvolex). Parvolex is given IV or PO at a loading dose of 140 mg/kg body weight followed by 70 mg/kg for 3–5 more treatments. Sodium sulphate is an alternative to Parvolex (see Current Veterinary Therapy Volume IX page 190 for more information).

Ragwort & pyrrolizidine alkaloids

Sources

Ragwort (Senecio jacobaea) is widely distributed on North and South Island. Paterson's Curse (Echium plantagineum) is also widely distributed and common in the South Island (no reported poisonings in NZ).

Toxicity

- pyrrolizidine alkaloids (PA) exists in the plant as a non-toxic free-base or a N-oxide.
- the free-base is converted into highly reactive alkylating pyrroles by liver microsomal enzymes.
- The reactive pyrrole crosslinks with DNA and prevents liver cells from reproducing.
- Increasing numbers of liver cells are damaged resulting in a cirrhosis-like liver condition with blocked bile ducts and veins.
- severe or cumulative exposures = liver failure and death of the animal.
- The toxicity may not be apparent until months after the animal has eaten the ragwort.
- PAs are toxic even after being dried (as in hay).

Clinical Signs

Cattle: Indefinite illthrift-loss of condition.

Diarrhoea and rectal prolapse

Nervous signs: depression, ataxia, irritability

Photosensitisation has been reported.

Sheep:Chronic hepatic disease which may lead to copper toxicity

Horses: Not so common today. Dullness, unsteadiness, aimless wandering and masticating food slowly and deliberately. Pass dark urine and show signs of jaundice.

Pathology

Cattle: Ascites with oedema of mesentery, intestinal and gall bladder walls and a small fibrotic liver.

Atrophy of the liver parenchyma with zonal or diffuse megalocytosis of hepatocytes; biliary duct hyperplasia with portal tract fibrosis; perivascular fibrosis affecting central veins.

Essentially the same changes in sheep and horses.

Sheep are known to be more resistant to PA poisoning and are used to reduce ragwort in pastures. Sheep can enzymatically alter the PA in their rumen to enough of a degree to decrease the likelihood of poisoning.

Treatment

Treatment is usually unsuccessful. Animals should be removed from access to the plant. It has been suggested that laxatives and a high protein (quality) diet formulated for liver disease may be useful.

Xylitol

Sources

Xylitol is a sugar substitute found in many sugar-free candies and gums. While having little to no effect on humans, dogs are extremely sensitive to xylitol. Ingestion promotes insulin release and can cause hypoglycaemia with ataxia, collapse and seizures. Hypokalaemia may occur. Hepatic necrosis and death are known to occur after xylitol ingestion.

Toxicity

Anecdotal information suggests that IV doses of xylitol at 0.2 to 0.4 g/kg cause hypoglycaemia. Some chewing gum contains 1-2 grams of xylitol per piece. One or two pieces of gum could poison a 10 kg dog; however, much larger ingestions tend to occur when dogs consume whole packets containing 10 or more pieces.

Clinical Signs/Effects

Clinical signs may include anorexia, dehydration, depression, haemorrhage, icterus, PU/PD, vomiting and weakness.

Hypoglycaemia does not occur in all cases. Some dogs have slightly elevated liver enzymes 8-12 hours post ingestion but usually recover. Other dogs develop acute liver failure, haemorrhage and disseminated intravascular coagulation with or without signs of hypoglycaemia and have a guarded to poor prognosis.

Treatment

There is no antidote for xylitol toxicity. Usual decontamination procedures are recommended when ingestion is recent, except that activated charcoal is ineffective in binding xylitol.

Symptomatic and supportive treatment is recommended. It is not known if compounds such as S-Adenosylmethionine (SAMe), ursodeoxycholic acid or Vitamin E are beneficial. SAMe is a precourser of glutathione, which has antioxidant properties and detoxifies compounds in the liver. Ursodeoxycholic acid has several effects including antioxidant properties. Vitamin E protects the liver against lipid peroxidation.

Antibiotics may be indicated in acute liver failure. Amoxicillin, cephalexin or other penicillins/cephalosporins are recommended as liver metabolism is not required.

Monitor liver enzymes and clotting time (PT) for 48-72 hours after ingestion.

Cases

Case 1

Give the aetiology of Facial eczema.

What are the clinical signs and subclinical effects of facial eczema in sheep?

What is the mechanism of toxicity which causes clinical signs?

Describe the rationale for the prevention of facial eczema in sheep.

Case 2

A farmer calls you to his farm to look at several calves out of a group of 60 (3-4 month old) calves. You arrive midday to find four dead calves and several calves with signs of severe abdominal pain, depression, anorexia, weakness, staggering

gait and diarrhoea. The farmer found them ill this morning. They had appeared to be fine yesterday. A search of the surroundings indicates a dumping site has been disturbed by the calves. The site includes old equipment parts, batteries and discarded oil in containers that have been spilled.

1. What is the likely cause of this scenario?
2. What would you do for the affected calves?
3. What would you expect to find on post mortem?
4. How would you confirm your diagnosis?

Case 3

Pest control operators laid poison bait around a dairy farm to control possums. White phosphorus (1%) in an apple pulp base was placed in the trees. The farmer allows the working dogs to run loose during the day. Several dogs have died over the last four days. The dogs were depressed, vomited and appeared to be in pain. One dog had a haemorrhagic diarrhoea and vomited six hours before death. This morning the farmer found two dogs eating a dead possum (less than two hours ago). The dogs have not vomited, but they have abdominal pain.

a. What treatment would you give these dogs?

b. What would you do to establish a diagnosis of phosphorus poisoning?

Case 4

A new dairy herd was established in June. From early September some cows became anorexic, lost condition and their milk production decreased. They had diarrhoea and developed scaly, roughened skin, especially of the udder. Twelve cows died within 2-3 weeks of these signs first appearing. Serum gamma glutamyl transferase levels were measured in 12 cows. Five cows had serum values within the reference range (0 to 32 U/l). The remaining cows were up to 159 U/l. Liver histology revealed a diffuse hepatopathy.

What questions/investigations would you initiate to determine your diagnosis?

Neuromuscular junction

commonly used drugs

none

NMJ blockers

- ☑ occasionally used during anaesthesia
- ☑ they must not be given to conscious animals
- ☑ animals must be artificially ventilated
- ☑ do not use these drugs unless you have equipment for IPPV and know what you are doing

The main veterinary relevance is muscle relaxation during anaesthesia. Myaesthenia gravis is a rare disease of dogs where the number of receptors for acetylcholine is reduced: this may be congenital (Jack Russel terriers) or acquired (autoimmune). The usual treatment is to give anticholinesterases (pyridostigmine) to increase the amount of acetyl choline or immunosuppressant drugs if appropriate. Some toxins will interfere with acetylcholine synthesis or release, causing muscle weakness.

NMJ blockers

These are only used in anaesthesia to relax the skeletal muscles. Their original use was rather different - they were arrow poisons derived from several species of *Chondrodendron* creepers used by various tribes in the Amazon and Orinoco valleys. They were called wooari (later corrupted to curare) meaning “flying death”!

Animals must be unconscious before use.

These drugs paralyse all the skeletal muscles - the animal lies still but these drugs have no effect on consciousness. Among other effects the animal is unable to breathe and must be ventilated. Do not use these drugs if facilities for artificial ventilation are not at hand. These drugs will rapidly kill animals in a particularly nasty way if used incorrectly. They are not drugs for beginners.

There are two main classes:

- depolarising (non - competitive) blockers
- non - depolarising (competitive) blockers

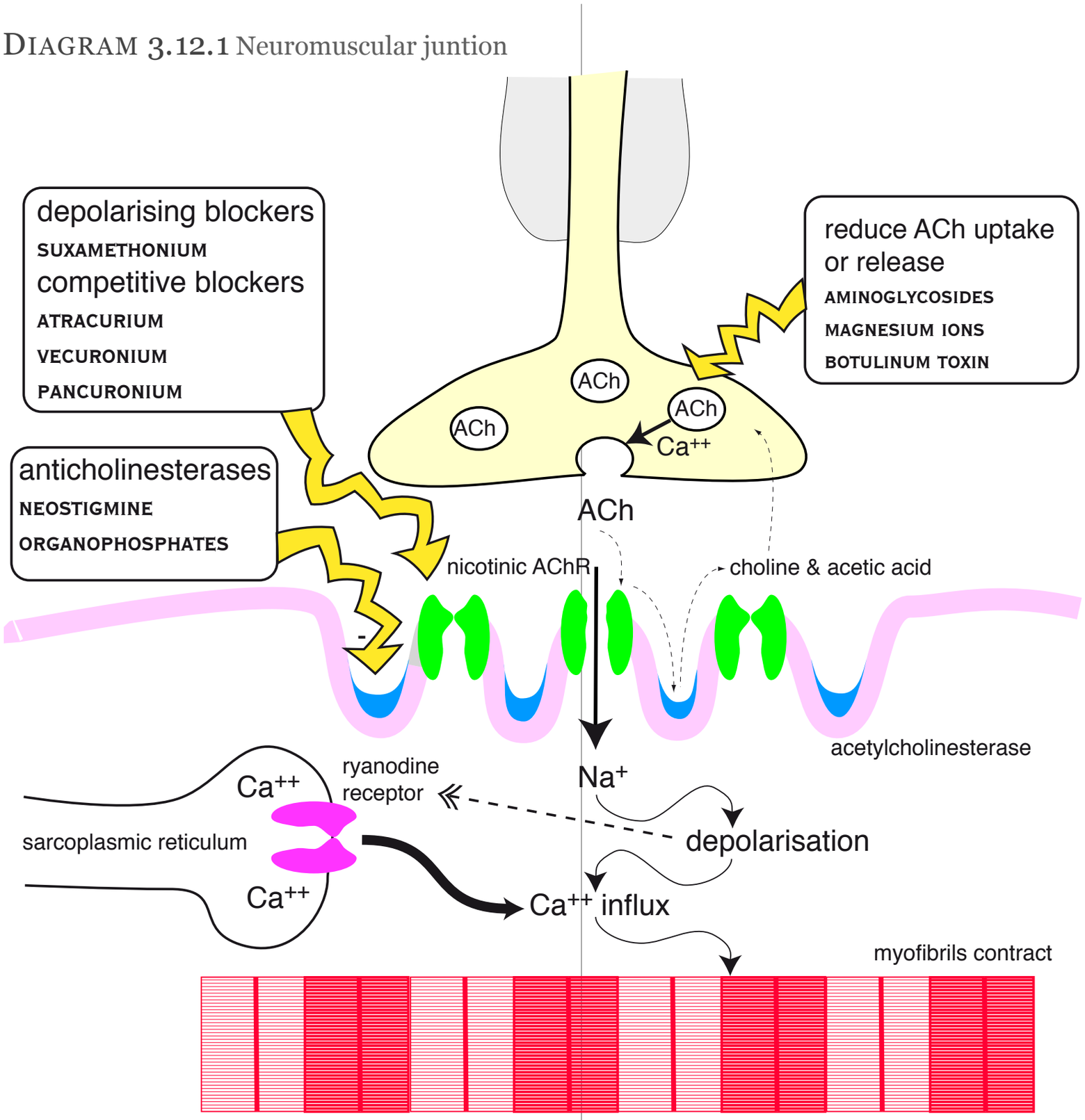
Depolarising Blockers

Suxamethonium (succinylcholine USAN) is the only useful drug in this class. It is an acetylcholine analogue which binds to receptors and causes depolarisation (like acetylcholine). Suxamethonium dissociates from the receptors slowly leaving them in an inactivated state and unable to respond to acetylcholine. Its action ends when it diffuses out of the synapse. The end result is that the muscle fibre twitches once then relaxes.

Pharmacokinetics

acts in one circulation time; duration of action in most species except dog is about 2 - 3mins (dog 20 mins) but broken down by plasma (butyryl)cholinesterase not

DIAGRAM 3.12.1 Neuromuscular juntion



Sites of action of drugs used to alter muscle contraction.

acetylcholinesterase. These are both inhibited by organophosphate insecticides (for fleas) in which case its duration may be >24 hrs.

does not cross the placenta

Indications

used in cats and dogs, (rarely pigs, horses and rabbits) as part of a crash induction technique for anaesthesia (relaxes larynx to allow intubation)

cats: useful for intubation to overcome laryngeal spasm

dogs: not used much - duration of action 20 mins (but remember OPs) - sometimes used for caesarian section

horses: not used much any more - some horses have an excitable induction with thiopentone - low dose suxamethonium given with thiopentone to block this; used to be used in Australia for restraint

pigs and rabbits are difficult to intubate without muscle relaxants

Contra - indications

•if no means of artificially ventilating animal is available

•if there is any doubt that the animal is unconscious

•organophosphate administration in last month

Precautions

The initial depolarisation causes muscle fasiculation which can damage muscle fibres. This may cause an increase in plasma K^+ and CPK, and post operative muscle pain.

- transient bradycardia may occur.
- some breeds of rabbits are very sensitive to its effects
- attempted reversal with anticholinesterases will prolong the block
- may trigger malignant hyperthermia in susceptible pigs

Clinical use

The animal is given an induction dose of anaesthetic. When it loses consciousness, the suxamethonium is injected rapidly iv. The muscles fasiculate as the fibres are depolarised and then relax, allowing rapid intubation. If the animal is not intubated rapidly, it must be ventilated by mask. After intubation, the animal is ventilated with low doses of inhalation anaesthetic agent until the block wears off. If the block does not wear off, ventilation must be continued.

Competitive Blockers

These act as antagonists at the NMJ nicotinic receptors, ie compete with acetylcholine for the receptors.

Indications

dogs for thoracic / upper abdominal ops (pancuronium, atracurium, vecuronium) to allow better access for surgeon

(horses for thoracic ops (rare)(atracurium)

(experimental animals)

Pancuronium is cheap, duration 20 - 40 mins: atracurium is possibly best, duration 15 - 20 mins, used in sick animals - broken down by Hofmann degradation in the plasma so no liver function required. Vecuronium is short acting - 10 mins. Obselete drugs not used any more include tubocurarine (releases histamine in dogs), gallamine, alcuronium (drops blood pressure), fazadinium etc. Newer drugs such as mivacurium and rocuronium have not worked into veterinary use yet. Rocuronium has an extremely fast onset of action in people which can be quickly terminated by chelation with cyclodextrin, so it is close to the ideal drug.

Drug interactions

potentiated by inhalation anaesthetics (unknown mechanism) and aminoglycoside antibiotics, high magnesium, low calcium - reduced acetylcholine release

Precautions

artificial ventilation and adequate anaesthesia required

Clinical use

Given iv after the animal has lost consciousness from the anaesthetic. Paralysis usually takes 1 - 2 minutes and the animal must be ventilated (by mask). Alternatively, they can be given after the animal has been anaesthetised and intubated.

At the end of the procedure neuromuscular blockade is reversed using anticholinesterases - neostigmine (rarely edrophonium) and atropine to block the muscarinic effects (except horses). Neostigmine blocks the breakdown of acetylcholine which then competes with the neuromuscular blocker for the nicotinic receptors. Increased acetylcholine in other parts of the body can cause unwanted effects such as gut spasm, possible rupture of enterotomy wounds and colic in horses.

The shorter acting atracurium and vecuronium tend to be used to avoid having to reverse blockade; the animal is ventilated until the block wears off. This approach is used in human anaesthesia and neostigmine and edrophonium are becoming difficult to obtain in NZ.

Neostigmine and edrophonium are sometimes used to diagnose myaesthenia gravis, the longer acting pyridostigmine to treat it.

Experimental drugs

You may see a bungarotoxin (from kraits) mentioned in the literature. It binds irreversibly to nicotinic NMJ receptors and is used to characterise the receptors. It is not used clinically and you are unlikely to come across snake bites in NZ.

Malignant hyperthermia

MH is caused by a defect in the gene coding for the ryanodine receptor, which releases calcium ions from the sarcoplasmic reticulum. In MH, the receptors open and stay open, uncoupling contraction from excitation. MH is common in some breeds of pig, but probably occurs in all species. It is usually triggered by the anaesthetic halothane.

In the full-blown syndrome there is a rapid and sustained rise in body temperature, without shivering, either in the operating theatre or in the recovery room, in the absence of any obvious cause such as infection or a hot and humid environment. Tachycardia, cyanosis, generalised muscle rigidity, and cardiac arrhythmias are common clinical signs. There may be heating and rapid exhaustion of the soda-lime canisters. Acidosis is an early finding and there may also be hyperkalaemia, hyperphosphataemia, and hypocalcaemia from muscle-cell breakdown. Rhabdomyolysis is an important feature of the syndrome and is best demonstrated by measuring serum CK, which usually peaks on the second or third day after the reaction. Tenderness and swelling of muscles may develop, especially in the thighs. Myoglobinaemia and myoglobinuria are common and renal failure may result from the rhabdomyolysis. Another complication is disseminated intravascular coagulation.

If your pig goes rigid, stop administration of halothane, ventilate with oxygen and cool down with cold water. The definitive treatment is the ryanodine receptor antagonist dantrolene. Unfortunately, dantrolene is expensive with a short shelf life and never available when needed.

Chapter 4

Central nervous system

This part covers the central nervous system and the drugs which interact with it, mainly anaesthesia - related.

*Opium poppy (*Papaver somniferum*), the source of morphine.*

Central neurotransmission

Central neurotransmission

- ☑ the main excitatory transmitter is glutamate acting at AMPA (fast), NMDA (medium) and mGlu (slow) receptors
- ☑ the main inhibitory transmitter is GABA acting at $GABA_A$ receptors
- ☑ neuromodulators act slowly to amplify or reduce transmission, usually by altering membrane polarisation
- ☑ noradrenaline acting at α_2 receptors is mimiced by some important veterinary drugs

The CNS is the most complex organ system in the body: the physiology of the normal CNS is not well understood, and most drugs given for their CNS effects are used empirically. Many more drugs have side effects either directly on the CNS or mediated by it. The action of most drugs at the receptor level is known, but this is not always useful in predicting their effects on the whole animal. These notes concentrate on the major neurotransmitter systems where the information is least confusing.

The effects produced by a neurotransmitter can be very variable for a number of reasons:

•the CNS is not hard wired - connections are continually changing under the influence of growth factors. There are usually several back-up wiring systems - the importance of these can change with time and disease. Receptors are being continuously recycled - thus their numbers change.

•most neurotransmitters have multiple receptor subtypes at which they can work - so the effects depend on the receptors present on the target cell

•the same receptor subtypes sometimes have different signal transduction mechanisms coupled to different effectors

•their effects can be changed by neuromodulators

The good news is that all neurones are thought to obey Dale's law and release the same transmitter at all their terminals (but don't forget co-transmittors).

Calcium is required for neurotransmitter release, so drugs which interfere with calcium movement can alter neurotransmitter function. Magnesium is sometimes used for this effect - eg, it can augment analgesia by an effect at the spinal cord.

Every neurone has a wide range of inputs (usually both excitatory and inhibitory); what it does will depend on the sum of all these inputs.

Disinhibition

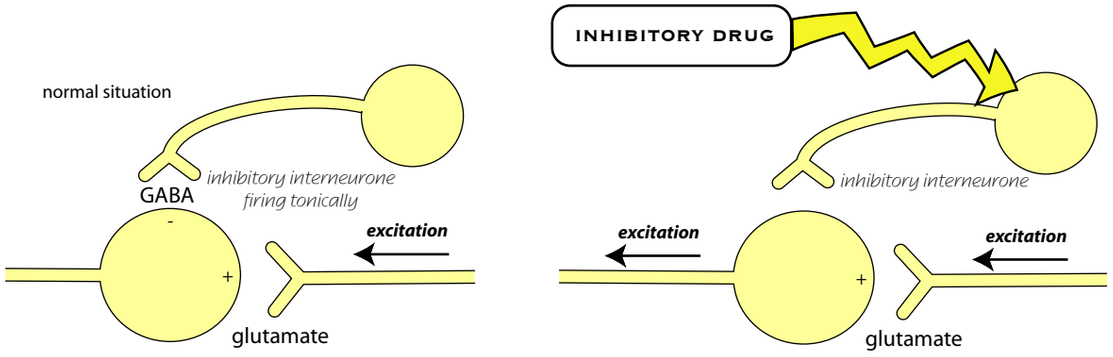
A relatively common cause of confusion is that drugs which are known to be inhibitory can produce excitatory effects in animals under some conditions, eg, anaesthetics. This is usually due to disinhibition.

TABLE 4.1.1 Time course

Time	Purpose	Example
milliseconds	fast transmitters	ACh at NMJ
tens of ms	potentiation	Glu at NMDA R
seconds - minutes	neuromodulators	substance P at primary afferent synapse in cord
minutes - days	receptor up/down regulation	
days - weeks	neurone reconnections	nerve growth factor at TyrK R

Different transmitter and receptor systems are used depending on the urgency of the situation.

DIAGRAM 4.1.1 Disinhibition



A mechanism for inhibitory drugs to produce an excitatory effect.

Excitatory transmitters

Glutamate

Glutamate (and aspartate) will excite virtually all central neurones. It acts at a variety of receptors, usually named after the experimental drug used to characterise them. Fast depolarisation of postsynaptic neurones is caused by activation of the ionotropic (Na^+) AMPA receptor. (The kainate receptor is very similar and is thought to do the same thing, although its distribution in the brain is different.) The NMDA receptor is also a ligand gated ion channel (Na^+ and Ca^{++}) and is an important target of drug action (see below). Metabotropic glutamate receptors (mGluR) (nine subtypes at the last count) are G protein coupled receptors. They are divided into three groups: group I (mGluR 1 & 5) act postsynaptically via IP3, group II (mGluR 2 & 3) act postsynaptically via adenyl cyclase, group III (mGluR 4, 6, 7 & 8) act presynaptically via adenyl cyclase. No useful drugs act specifically at metabotropic glutamate receptors at present but this is likely to change.

Glutamate is released from vesicles in a process that requires calcium. Zn^{++}, and probably other things, are also released from the vesicles.

NMDA Receptors

These are a means of amplifying excitatory signals. They are thought to be responsible for long term potentiation which is the physiological basis of memory. Possibly more important from a veterinary practice point of view, they cause wind up in the spinal cord (and probably the brain stem) which shows up as hypersensitivity to pain (see analgesia notes). They are probably also involved in the propagation of seizures in epilepsy.

They are composed of five proteins, usually one NR1 subunit and four NR2. There are several types of NR2 subunits; NMDA receptors containing NR2B subunits are thought to be important in pain and are being targetted for drug development. Having a variety of subunits to choose from when forming NMDA receptors means that many subtyes of receptors are possible, but the clinical relevance of this is not clear yet.

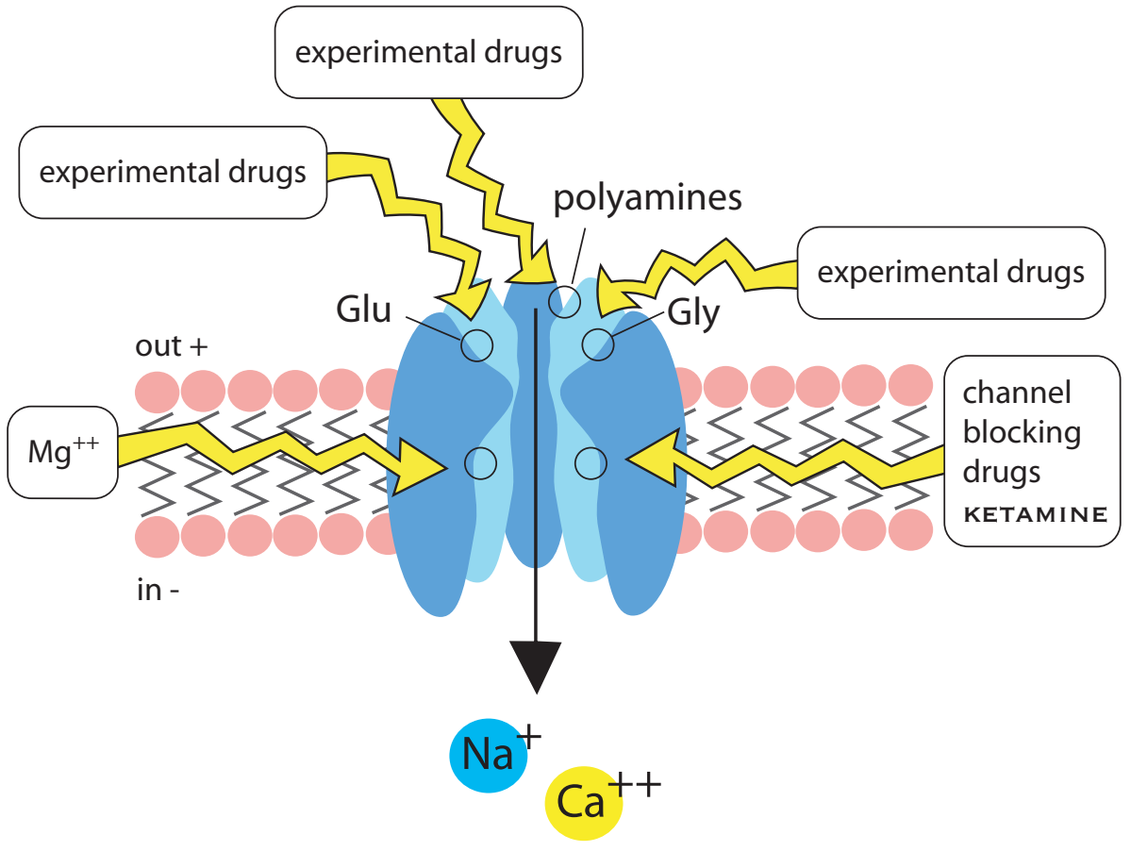
In most forms of neuronal injury, particularly strokes in people, the mechanism of damage is cells leaking glutamate (from energy metabolism) which then acts at NMDA receptors and lets lots of calcium into the cell. This can kill the cell (excitotoxicty). A drug which could prevent this without side effects would be a huge earner, so there is a lot of effort going into research in this area.

MOVIE 4.1 Effects of NMDA receptor activation

Many useful drugs exert their effects indirectly through NMDA receptors, ketamine directly blocks the channel. It would be undesirable in most circumstances to completely block (loss of memory) or open the channel (excitotoxicity), so most new drugs coming along are partial agonists.

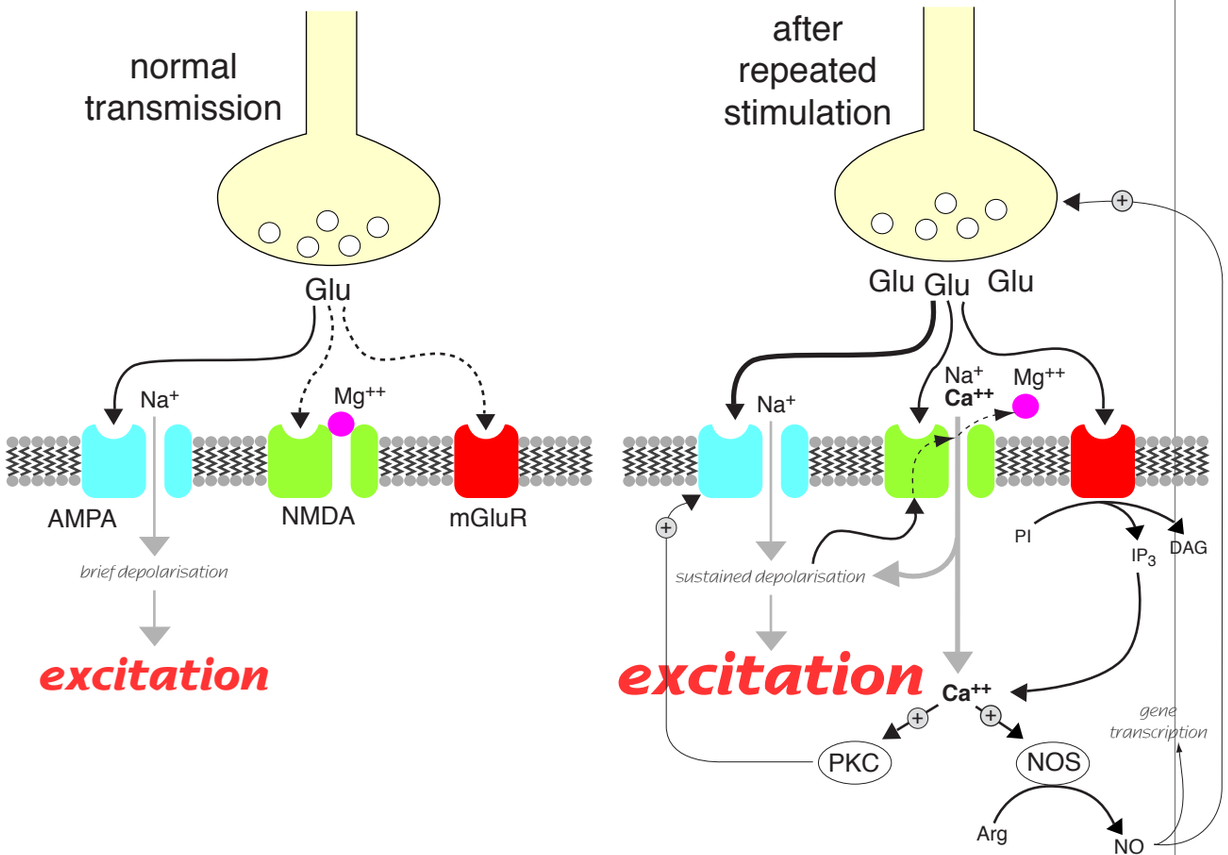
NMDA receptors require glycine to bind to a specific site before the channel can open. In vivo, there is always enough glycine around to allow channel opening, but many potentially useful NMDA antagonist drugs bind to this glycine site. (nb, this is not the same as glycine gated Cl- channels, see below.)

DIAGRAM 4.1.2 NMDA receptor



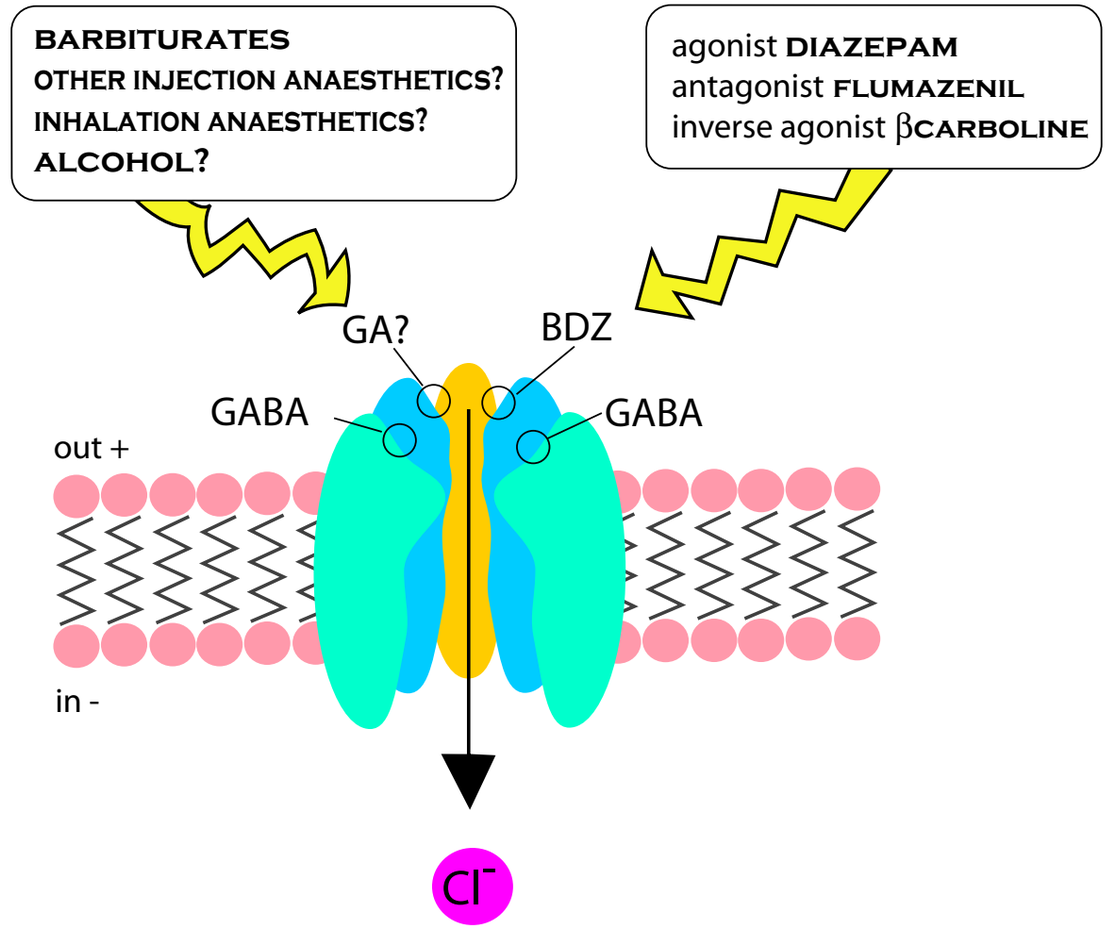
NMDA receptors are ionotropic receptors related to GABAA receptors. Glutamate is the agonist, but glycine is also required for channel opening. Channel opening can be modulated by polyamines, and the channel can be blocked by magnesium and a number of drugs.

DIAGRAM 4.1.3 NMDA receptor activation



NMDA receptor activation after repeated stimulation. Glu = glutamate, PKC = protein kinase C, NOS = nitric oxide synthase, NO = nitric oxide.

DIAGRAM 4.1.4 $GABA_A$ receptor



The GABAA receptor. GA = general anaesthetic binding site, BDZ = benzodiazepine binding site.

Inhibitory transmitters

GABA

GABA (γ aminobutyric acid) is widely used throughout the CNS - virtually every neurone will be inhibited by it. It is mainly contained in short inhibitory interneurones. $GABA_A$ receptors are a major site of drug action, particularly for sedatives, anticonvulsants and general anaesthetics. $GABA_A$ receptors are also present on peripheral neurones but what they do there is not obvious. The $GABA_A$ receptor is a ligand gated ion channel which opens when two molecules of GABA bind to it which causes chloride ions to flow into the cell, causing hyperpolarisation and thus inhibiting firing. Blockade of the chloride channel by experimental drugs and toxins causes convulsions.

As well as binding GABA, $GABA_A$ receptors also bind benzodiazepines (sedatives) and, less strongly, barbiturates (injectable anaesthetics). Both classes of drugs potentiate the effects of GABA by various means and cause postsynaptic inhibition. $GABA_A$ receptors are probably also the site of action of most anaesthetic agents. Some drugs also bind to the benzodiazepine receptor to stop the channel opening (inverse agonists - do not confuse with benzodiazepine antagonists which only block the effects of benzodiazepines and have no effect on their own). Endogenous inverse agonists are thought to exist but their function is unknown - exogenous ones make animals anxious which is not usually desirable.

The $GABA_A$ receptor is composed of five subunits, but 19 different subunits have been cloned and there are probably 500 subtypes of natural $GABA_A$ receptors. Drugs specific for these subtypes are likely to emerge. The commonest contains 2 α subunits, 2 x β and 1 x γ. Different subtypes may explain the different patterns of effects seen with "$GABA_A$ receptor" drugs.

$GABA_B$ receptors have a presynaptic inhibitory action and may be important in the spinal cord but not much is known about their function. They are G protein coupled receptors. There are probably lots of different subtypes.

$GABA_C$ receptors are chloride channels similar to GABAA receptors but slower acting. They occur in the retina but are probably more important in the cortex. They are much more sensitive to GABA, but do not bind any of the anaesthetic or sedative drugs. So far, their function seems to be the regulation of sleep.

Glycine

Glycine is also an important inhibitory transmitter, particularly in the spinal cord. It binds to a chloride channel receptor very similar to the GABAA receptor (ie, different from the glycine receptor associated with the NMDA receptor). This is clinically important as strychnine is a competitive antagonist at the glycine inhibitory receptor - in strychnine poisoning, an animal will start to twitch. Tetanus toxin blocks the release of glycine (and GABA) resulting in continuous muscle contraction.

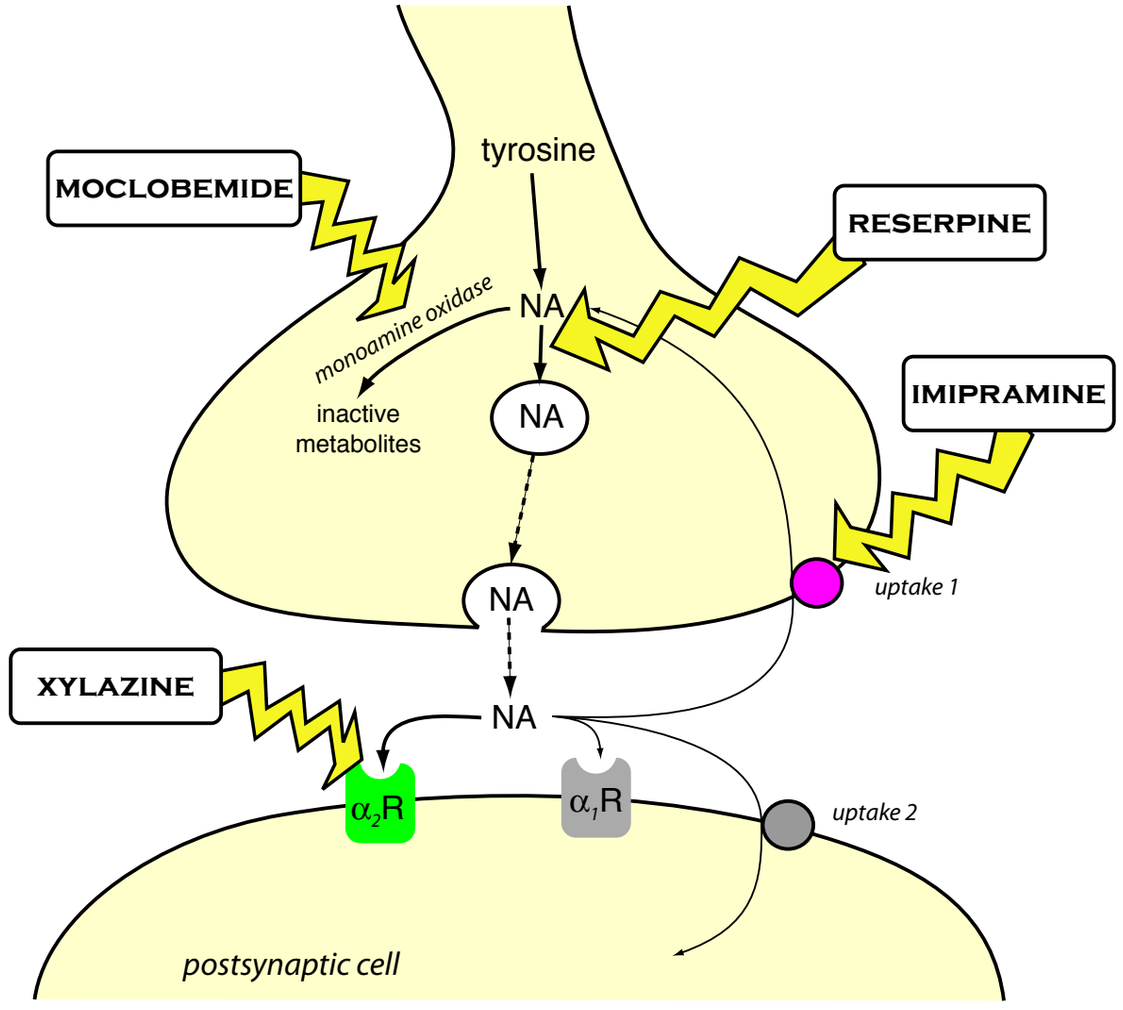
Both the GABA and glycine gated chloride channels are similar to the glutamate gated chloride channels found in invertebrates and which are the target for avermectin parasiticides. In overdose, these commonly used drugs can open GABA and glycine gated chloride channels to cause CNS inhibitory effects in mammals. Avermectins do not usually get into mammalian brains because the P glycoprotein pump in the blood brain barier keeps them out. Some individual animals (particularly collies) are missing the gene for the P glycoprotein and will go into a prolonged coma if given avermectins.

Monoamines

Noradrenaline is an important (mainly inhibitory) neurotransmitter, usually acting at postsynaptic β or α2 receptors (do not confuse with presynaptic α2 receptors in the periphery). Activation of α2 receptors always causes inhibition of the neurone they are on - if the neurone is presynaptic, as in the periphery, the effects can be excitatory. α2 receptors are important in alertness, sleep, blood pressure control and pain transmission; α2 agonists are widely used in veterinary medicine for their CNS effects (see under analgesics and sedatives). The endogenous ligand for many α2 receptors in the CNS may be agmatine rather than noradrenaline, agmatine also binds to imidazoline and NMDA receptors.

5HT (serotonin) is widely used as a neurotransmitter but because it acts at a large number of receptor subtypes (at least five different types in the brain - which may be either inhibitory or excitatory, pre or postsynaptic) its physiological role is not clear. 5HT neurones are concentrated in the pons and medulla with diffuse connections up and down. It is thought to be important for sleep, some sensory pathways,

DIAGRAM 4.1.5 Monoaminergic transmission in the CNS



feeding behaviour, vomiting, mood, etc, etc. Not many veterinary drugs interact with it directly, although the side effects of some are mediated by 5HT.

In man, depression appears to be associated with a functional lack of noradrenaline or 5HT or both. Depression is not recognised in animals, but antidepressant drugs certainly alter animal behaviour and are often given empirically for this reason. Noradrenaline and 5HT have their action terminated by reuptake into the presynaptic neurone; most antidepressant drugs block this reuptake, eg the tricyclic antidepressants. Monoamine oxidase inhibitors were used in the past for the same purpose but have major side effects. Modern, reversible inhibitors such as moclobemide may be better. Some reuptake inhibitors are more specific for noradrenaline (imipramine) or 5HT (fluoxetine) (or dopamine (selegiline)) but most will block the reuptake of all to some extent. Since these transmitters are also important in the peripheral nervous system, antidepressants have many side effects attributable to excess noradrenaline ± 5HT (some of the older drugs have antimuscarinic effects as well).

Dopamine is a neurotransmitter as well as a precursor for noradrenaline. It is involved in three important pathways; nigrostriatal pathway - important in motor control; the mesolimbic pathway to the nucleus accumbens - the “reward pathway” and the tuberoinfundibular pathway between the hypothalamus and the pituitary. Problems with the nigrostriatal pathway lead to Parkinson’s disease in people: this is not recognised in animals but can be induced by dopamine antagonists (many classes of sedatives)! The reward pathway is very important in drug addiction in people, but is probably involved in learning and possibly food intake in animals too. The tuberoinfundibular pathway is important to maintain pituitary secretion (dopamine inhibits pituitary hormone release) - drugs to manipulate this are starting to be used in veterinary practice. Many hormones involved in reproduction are under the control of pituitary derived releasing hormones.

Dopamine also stimulates the chemoreceptor trigger zone to cause vomiting and dopamine agonists are used as emetics.

Dopamine also acts at a large number of receptor subtypes but most known functions are through the D2 subtype family.

Adrenaline is not thought to be very important as a neurotransmitter in the brain. It can still alter CNS function by altering blood flow.

Other fast transmitters

Acetylcholine acting at nicotinic receptors is involved in some inhibitory circuits on motor neurones. Muscarinic receptors play a role in learning and memory. Since animals do not smoke and do not seem to get Alzheimer’s disease, acetylcholine receptors are mainly important in poisoning in veterinary practice - many plants contain cholinergic drugs.

Histamine acting at H1, H2 and H3 receptors can be either excitatory or inhibitory but its physiological role is unclear. It may be involved in sleep. Several histamine antagonists are used in veterinary medicine for their central effects (mainly phenothiazine sedatives), but they all affect other receptor systems as well as histamine.

Purines, ATP (co-released with noradrenaline), AMP and adenosine, have only recently been recognised as neurotransmitters in the brain (as well as doing other things connected to metabolism). Adenosine acts at purinergic A receptors of which there are several subtypes, ATP acts at purinergic P receptors. P2x receptors are important ionotropic receptors (again there are several subtypes), P2y receptors are metabotropic. Expect more new functions for these receptors to be discovered soon. The stimulant effect of caffeine and similar drugs is probably due to an action at purinergic receptors.

Neuromodulators

Peptides tend to be involved in amplifying or damping down signals rather than transmitting signals. Many are involved in inflammation and are released from the peripheral ends of neurones as well as the central ends. They tend to diffuse away from the cells that produce them to affect all the surrounding cells, so they can have a wide range of effects. Peptides such as substance P enhance pain signals leading to hypersensitivity (more later). Encephalins such as β endorphin or endomorphin usually have the opposite effect, although others such as nociceptin, and possibly dynorphin also enhance pain signals. Morphine (and codeine in invertebrates) are possibly also endogenous neurotransmitters, as well as analgesic drugs. Neuropeptide Y is the most abundant neuromodulator in the mammalian brain. It is involved in pain and appetite, among other things. A variety of cytokines and growth factors also act as neuromodulators, as do a number of peptides first isolated from the gut such as cholecystokinin and vasoactive intestinal peptide. The list is getting longer all the time. Numerous drugs interact with one or more of these, usually to produce CNS side effects. There are also a number of anomalies - for instance, capsaicin, the hot substance in chillies, acts at specific receptors in the

spinal cord and the periphery to increase the release of substance P, but no endogenous ligands for these receptors have yet been found. This area is likely to get even more complicated in the future, and there is plenty of scope for drugs which interact with neuromodulators.

Nitric oxide and carbon monoxide are also implicated in neuromodulation. Nitric oxide usually increases excitability, the effects of carbon monoxide are thought to be similar. These gases are produced as needed and rapidly diffuse away. They can be altered by manipulating the enzymes that make them, but appear to be so widely used in the body that increasing or reducing their production causes a vast range of effects.

Arachidonic acid may act as a neuromodulator in its own right, although it is difficult to distinguish its effects from those of its metabolites, the prostaglandins and leukotrienes. PGF2α may be an important neuromodulator in the brain. A variety of commonly used drugs affect arachidonic acid, including corticosteroids and aspirin type drugs.

Various endocannabinoids, of which anandamide is best known, act as neuromodulators in the brain to produce a wide variety of effects, from sleep to analgesia to appetite stimulation to cough suppression (and probably more). Cannabinoids acting at CB1 receptors may be involved in pain processing.

Pain and analgesia

Pain and analgesia

- ☑ pain signals are carried from the periphery to the brain by a number of routes
- ☑ pain signals are subject to modulation at several stages, particularly in the spinal cord (gating) which may increase or decrease the signal
- ☑ most analgesic drugs interfere with endogenous pain modulation systems
- ☑ pain changes over time so drug treatment of pain must change over time
- ☑ analgesic drugs are more effective if given before the pain starts
- ☑ good nursing is a useful adjunct to analgesic drugs

Definitions

Pain: no completely satisfactory definition exists; that proposed by the International Association for the Study of Pain (for people) is the most widely accepted: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." ie, pain consists of both a sensory component and an affective component. Some people also include a cognitive component, but I consider this a response to pain. (Other people deny that animals are capable of thinking.)

Analgesia = a lack of pain.

Nociception = the sensory component of pain. Since it is not possible to definitively prove that animals can feel pain, this term is sometimes misused (particularly by American physiologists) to mean pain in animals. A nociceptor is a nerve fibre used for pain signals.

Hyperalgesia and allodynia These are conditions which occur after pain perception has been altered by central or peripheral sensitisation. Hyperalgesia occurs when a stimulus which would have been painful before is now more painful; allodynia is when a previously innocuous stimulus (such as light touch) becomes painful. Sometimes these conditions persist after the injury has healed (hyperpathia).

Algogenic = something which produces pain.

Placebo = Latin “I will please” = inactive drug given to people who believe that it will do some good.

Nocebo = Latin “I will hurt” = inactive drug given to people who believe that it will cause problems. Animals which have been inappropriately treated in the past tend to behave as though any future treatment will hurt, too.

Assessment of pain

In animals, it is only ever possible to measure the response to pain, usually by assessing behaviour. **Beware - lots of drugs will alter behaviour without affecting pain**. Some people have attempted to assess pain objectively in animals by measuring autonomic function (heart rate, blood cortisol concentrations, etc.) but this only measures stress. Pain will cause stress, but so will many other things, including handling the animal. If there is any doubt that an animal is in pain, it should be given analgesic drugs. A response to the drugs in-

dicates that it probably was in pain (but remember the effects on behaviour): a lack of response may mean the the animal was not in pain or that the analgesia was insufficient.

It is unethical not to treat pain in an animal under your care.

You must be able to recognise pain and know how to treat it in any species you are likely to come across.

Pain pathways

Blocking the afferent pathway or stimulating the inhibitory pathway can provide analgesia. These pathways are not hard wired, ie, the importance of each part can change in the short term and neuronal connections can change in the long term. This is sometimes (confusingly) called plasticity.

afferent excitatory pathways

injury stimulates Ad and C fibres - polymodal nociceptors

- Aδ - sharp localised pain, mechanical stimuli
- C - burning pain, heat or cold

→ dorsal root

→ substantia gelatinosa of spinal cord

→ spinothalamic / spinoreticular tracts

→ thalamus

→ (cortex) affective rather than sensory?

descending inhibitory pathways

cortex?

→ thalamus

→ brainstem

→ dorsal horn of cord

Recommended reading

Julius & Basbaum, 2001, Molecular mechanisms of nociception, *Nature*, 413, 203 - 210 A good review of the pathophysiology of pain which is up to date but still readable.

Gate theory

Nociceptive signals may be enhanced or inhibited (gated) in the dorsal horn of spinal cord (and also in the thalamus, although the higher up the pathway one goes, the less is known). Placebo is an important effect in people (much more important than the pharmacodynamic effect for some drugs such as codeine); this must be mediated by the cortex. Placebo effects probably occur in animals, but nocebo may be more important. Animals tend to recognise vets who have done nasty things to them and seem to expect more of the same. This is likely to affect the action of analgesic drugs adversely. Many analgesics mimic or inhibit the action of the endogenous transmitters involved in gating at the spinal level.

Response to injury

When injury occurs a cascade of effects follows.

1) *direct stimulation of nociceptors* - message passed on to brain, reflex withrawal of part stimulated

2) *descending inhibition* - often before the stimulus is perceived as pain

3) *release of chemical mediators* - bradykinin, prostaglandins, leukotrienes, 5 - hydroxytryptamine, substance P, thromboxanes, platelet activating factor, noradrenaline, free radicals, histamine, etc, etc

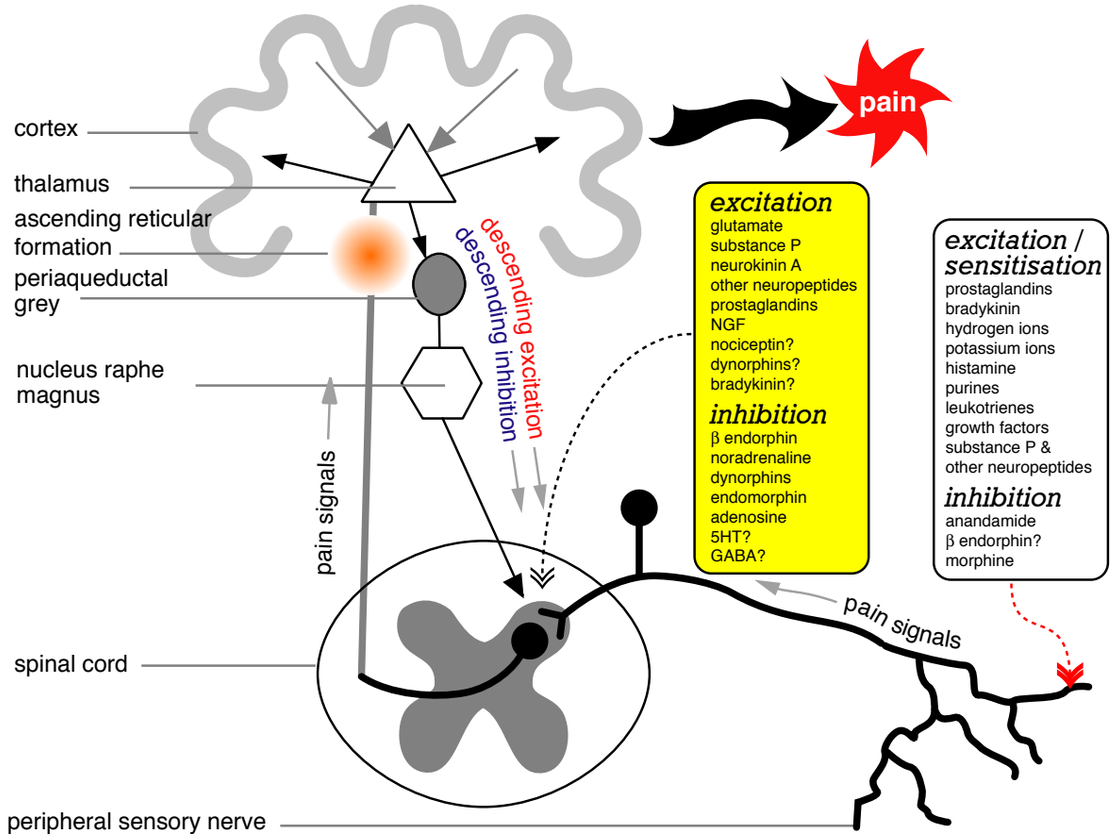
4) *sensitisation of nerve endings* - by the combination of chemical mediators (bradykinin + prostaglandins may be most important)

5) c*entral sensitisation* - NMDA receptors, tachykinins, (metabotropic glutamate receptors??) ± excitotoxicity with loss of inhibitory neurones?

6) r*ecovery of normal sensitisation* - may fail causing chronic pain

All this means that pain will vary over time and thus the drug requirements to relieve pain will vary over time. There is pretty good evidence in most species that drugs work better (more effective and longer lasting) if given before sensitisation occurs.

DIAGRAM 4.2.1 Pain pathways



Analgesic drugs work by manipulating these at various points.

This process may apply to other problems apart from pain. There is good evidence that inflammatory bowel disease involves similar processes.

Analgesia

Types of pain

The effects of analgesic drugs depend on the pain that they are used to treat. There are lots of different ways of classifying pain; probably the most commonly used in people is to divide pain into nociceptive (ie, in response to a noxious stimulus) and neurogenic (where nerve damage produces abnormal signals which mimic pain signals and there is not any obvious damage to tissues). Different types of drugs are used to treat the two types of pain in man but most types of pain in animals are assumed to be nociceptive. This may change as we learn more about pain.

TABLE 4.2.1 Gating at the spinal cord.

Transmission	Transmitter	Receptor	Analgesic
normal	glutamate	AMPA	(local anaesthetic) (Ca channel blockers) (experimental AMPA antagonists)
enhanced	glutamate	NMDA	ketamine antidepressants (experimental glycine antagonists)
	substance P	NK1	(capsazepine)
	neurokinin A	NK2	(experimental drugs)
	nociceptin	ORL1	nociceptin antagonists (4 aminoquinolines)
reduced	encephalins	μ & κ opioid	opioids (acupuncture?)
	noradrenaline	α_2	α_2 agonists
	5HT	$5HT_3$?	antidepressants?
	GABA	$GABA_A$	anaesthetics (TENS - Aβ fibre stim)

Pain can also be classified as somatic, visceral or central. Central pain is assumed to be neurogenic; there is some evidence that visceral pain (eg, colic) is produced by a different mix of neurotransmitters than in the periphery.

Assessing the intensity of pain, and thus the effectiveness of analgesics, can be tricky. A variety of pain scales have been advocated, which assign numbers (subjectively) to the severity of the pain. Beware statements such as “drug X is twice as good as drug Y since it halves the pain scale”.

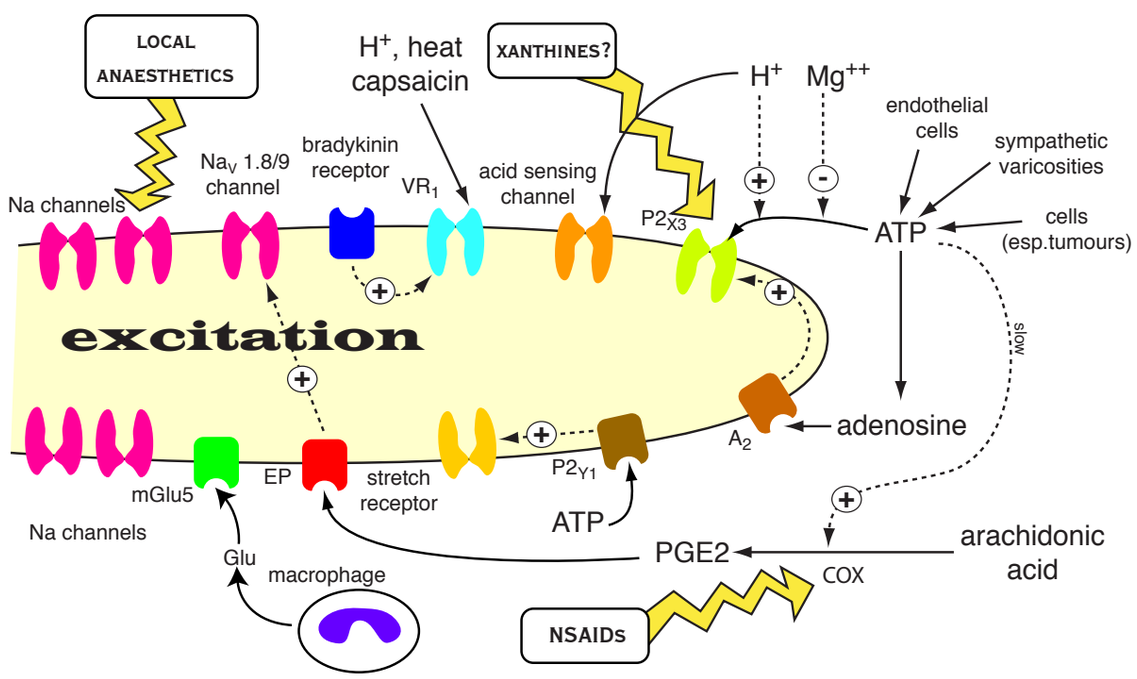
Management of pain

Successful management of pain requires more than just analgesic drugs. Other things to be considered include:

- emotional aspects - nursing, food, warmth
- treat the condition!
- physiotherapy??
- TENS? / acupuncture?

If pain cannot be successfully treated, euthanasia must be considered. If an animal's owner refuses analgesia on the grounds of expense. this is the only option.

DIAGRAM 4.2.2 Initiation of pain signals.



A greatly simplified diagram of a peripheral nerve ending and some of the mechanisms which may cause excitation. Most of the ion channels conduct Na+ or Ca++ or both. EP receptor activation causes sensitisation rather than excitation.

Groups of drugs

Many drugs have analgesic effects but few are clinically useful. No drug works in every case. The commonly used groups of drugs are:

- opioids
- NSAIDs
- local anaesthetics
- α2 agonists

There are many other drugs used in people which are less useful in animals (but may be used as adjuvants to one or more of the above drugs):

- psychotropics (mainly used for neurogenic pain in man) - tricyclic antidepressants (TCAs), anticonvulsants
- odds and sods - capsaicin etc

Sites of action

peripheral nerve endings	local anaesthetics, NSAIDs (opioids?)
peripheral nerve	local anaesthetics (opioids? GABA agonists?)
spinal cord dorsal horn	local anaesthetics, opioids α2 agonists (NSAIDs??)
brain stem	opioids, α2 agonists, TCAs, carbamazepine
ventral tegmental area	opioids
cortex	opioids, α2 agonists, TCAs, carbamazepine

It is usually a good idea to use combinations of drugs which work at different sites (balanced analgesia), but more of that later.

Pre op analgesia

Drugs are more effective if given before central sensitisation occurs; ie, before the pain starts (sometimes incorrectly called pre-emptive analgesia). After central sensitisation has occurred higher doses are required. Ketamine may be able to reverse central sensitisation, presumably by blocking NMDA receptors. This means that for surgical pain, animals should be given an analgesic in their premed.

Clinical use

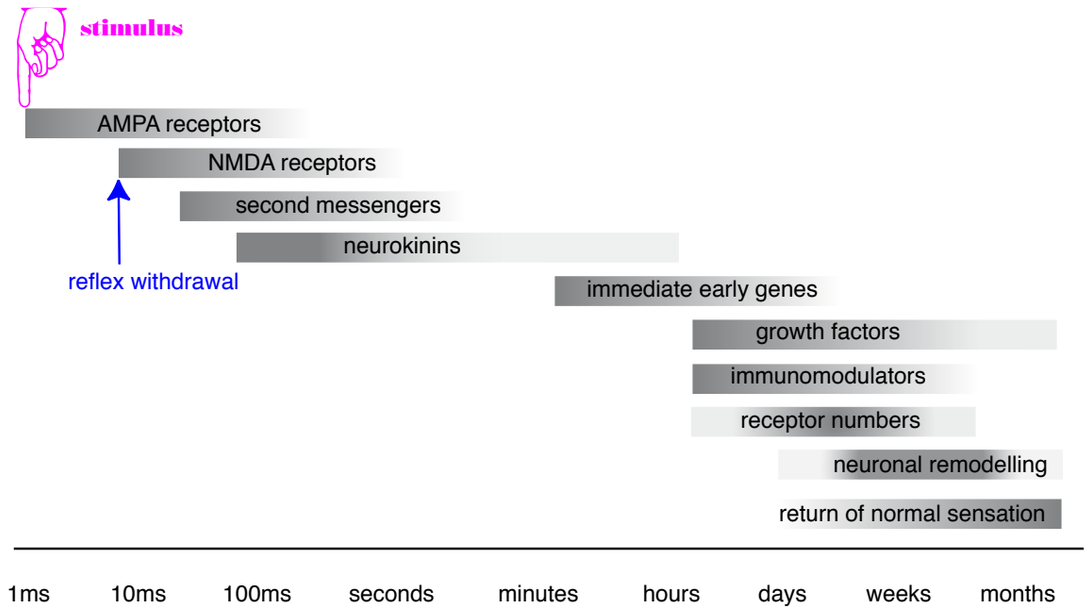
- mild pain - NSAIDs
- inflammatory pain - NSAIDs
- severe pain - opioids
- surgical pain - opioids + local + NSAIDs, depending on op

Analgesia in food animals can cause problems; giving drugs nearly always involves withholding times for meat or milk (as well as cost), but as a vet you will have a responsibility to try to relieve pain. Persuading farmers that animals in pain are not productive may help.

Further reading

Pain Management in Animals. eds. Flecknell and Waterman, W.B.Saunders, 2000

DIAGRAM 4.2.3 Time course of pain signalling.



Local anaesthetics

commonly used drugs

lignocaine (lidocaine USAN)

Local anaesthetics

- ☑ stop action potentials by blocking sodium channels
- ☑ are weak bases which get into cells in the unionised form, become ionised and bind to the channels in the open or inactivated state.
- ☑ show use dependence - rate of onset and depth of block are dependent on action potential frequency
- ☑ are mainly used for analgesia - particularly in ruminants
- ☑ block most excitable tissues if you give too much

Anaesthesia comes in several different forms. Local anaesthesia (= local analgesia) also comes in several different forms: regional anaesthesia / analgesia, spinal anaesthesia / analgesia, specific nerve blocks and local infiltration.

General anaesthesia is different again - more later.

Some local anaesthetics are used as anti-arrhythmics or anti-convulsants (see cardiovascular notes).

Chemistry

Many drugs have some local anaesthetic effect but the useful drugs all have an aromatic (lipophilic) end joined to a basic amine (hydrophilic) end by either an ester or, more commonly, an amide group. These different links are important in metabolism as this is where the molecule is split to inactivate it.

Mechanism of action

Blockade of voltage gated sodium channels in nerve axons. The sodium channels can exist in three states: closed (normal), open (only for milliseconds) and inactivated (after opening). The local anaesthetic binds to the channels in the open or

MOVIE 4.2 Sodium channels in action.

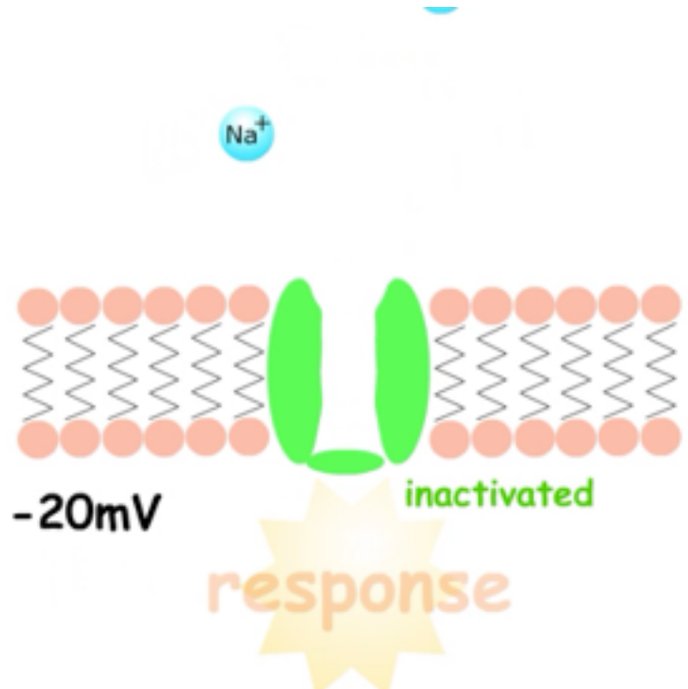


TABLE 4.3.1 Sodium channel subtypes

Tissue	Sodium Channels
CNS	Na_V 1.1, 1.2, 1.3
dorsal root ganglia	Na_V 1.8, 1.9
peripheral neurones	Na_V 1.7
neurones & CNS glia	Na_V 1.6
skeletal muscle	Na_V 1.4
heart	Na_V 1.5

Current local anaesthetics block them all.

inactivated states. More channels will be in these states if the nerve is actively firing, so local anaesthetics work better in active neurones (use dependance).

MOVIE 4.3 Local anaesthetics at the sodium channel

A variety of subtypes of sodium channels have been discovered. Some drugs are marginally selective for some subtypes. In future, drugs which just block the selected type of nerve may be clinically available. There is a lot of research on Nav1.7 blockers to treat chronic pain (in people), but no useful drugs yet. Current local anaesthetics are not selective and will block voltage gated calcium channels too - these may be important in C fibres.

Pharmacokinetics

Absorption

Local anaesthetics are unusual in that they are normally applied directly to the site of action. However, most of them still have to get into nerve cells to work. pKa is important for penetration into neurones, most local anaesthetics have a pKa of 8 - 9. Most local anaesthetics cross the neurone cell membrane (in the unionised form) and get to their binding site from the inside. Some unionised drug may go directly from the outside through the cell membrane to the binding site.

Distribution

The action of local anaesthetics is terminated by redistribution. They are rapidly distributed away from the site of action unless vasoconstrictors are given at the same time (adrenaline, felypressin). These are contra - indicated where the blood supply to an organ may be compromised by vasoconstriction, eg a cow's teat or a dog's toe. Adrenaline is much less stable than most local anaesthetics and has a short shelf life.

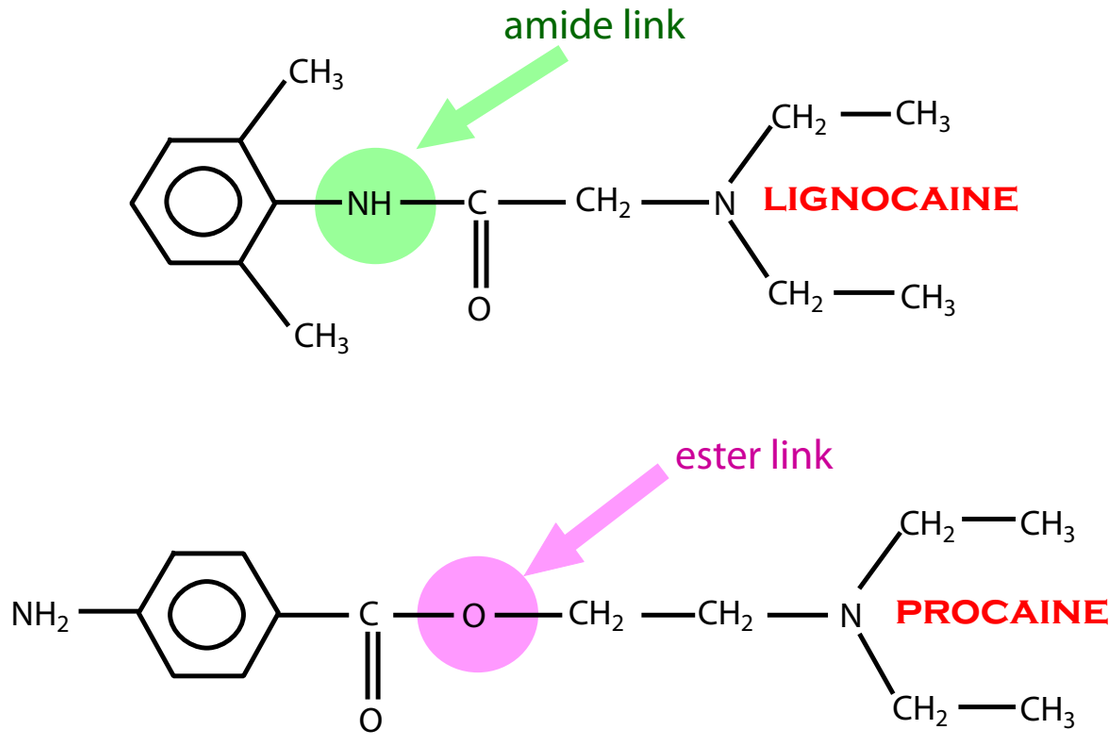
Metabolism

Esters are rapidly broken down by plasma cholinesterase, amides are broken down more slowly (but still pretty fast) in the liver. Lignocaine (an amide) is amost completely metabolised in one pass through the liver - it cannot be given orally.

Use dependence

Since local anaesthetics get into the sodium channel more easily when it is open and bind to the channel more tightly in the inactivated state, if the channels are cycling through the three states (ie action potentials are passing along the nerve) the local anaesthetics will work better. Thus rapidly firing nerve fibres will be preferentially blocked. Nerve fibres carrying pain signals tend to be firing more rapidly than others, but use dependence is mainly important in the anti-arrhythmic and anticon-

DIAGRAM 4.3.1 Local anaesthetic metabolism



Esters and amides are metabolised differently.

vulsant effects of local anaesthetics. In these situations it is sometimes possible to block rapidly firing cells while having no effect on cells firing more slowly.

Differential block

The onset of blockade follows a regular pattern: small myelinated fibres (Aδ) are blocked first, followed by small unmyelinated fibres (C) and then large myelinated fibres (Aα). This means that pain and sympathetic transmission is blocked before motor transmission. This is obviously desirable but is difficult to achieve reliably in clinical situations.

However, at a steady state, a 2 - 4 times higher concentration is required to block C fibres compared to Aα fibres. The discrepancy may be because C fibres have different subtypes of NaV channels and also possess CaV channels.

Toxicity

Usually occurs after accidental iv injection, but some types of block require large doses - it is particularly easy to overdose sheep. The toxic dose of lignocaine in most species is about 7mg/kg.

•sedation
•convulsions
•cardiotoxicity
  - automaticity depressed
  - myocardial toxicity (especially bupivacaine)

Indications

- operative analgesia (usually need sedation except in ruminants)
- postoperative analgesia
- diagnosing lameness (usually horses)
- (arrhythmias - not with adrenaline!)
- (convulsions)

Administration

•**topical** (eg., eye, larynx) (skin - Eutectic Mixture of Local Anaesthetics, EMLA) - blocks local nerve endings. Remember that most drugs are weak bases so they are dissolved in acid - ie, they sting when put into eyes!!!

•**local infiltration** (eg., L block for caesarian section) - blocks nerve endings in area to be desensitised. Use a fine needle!

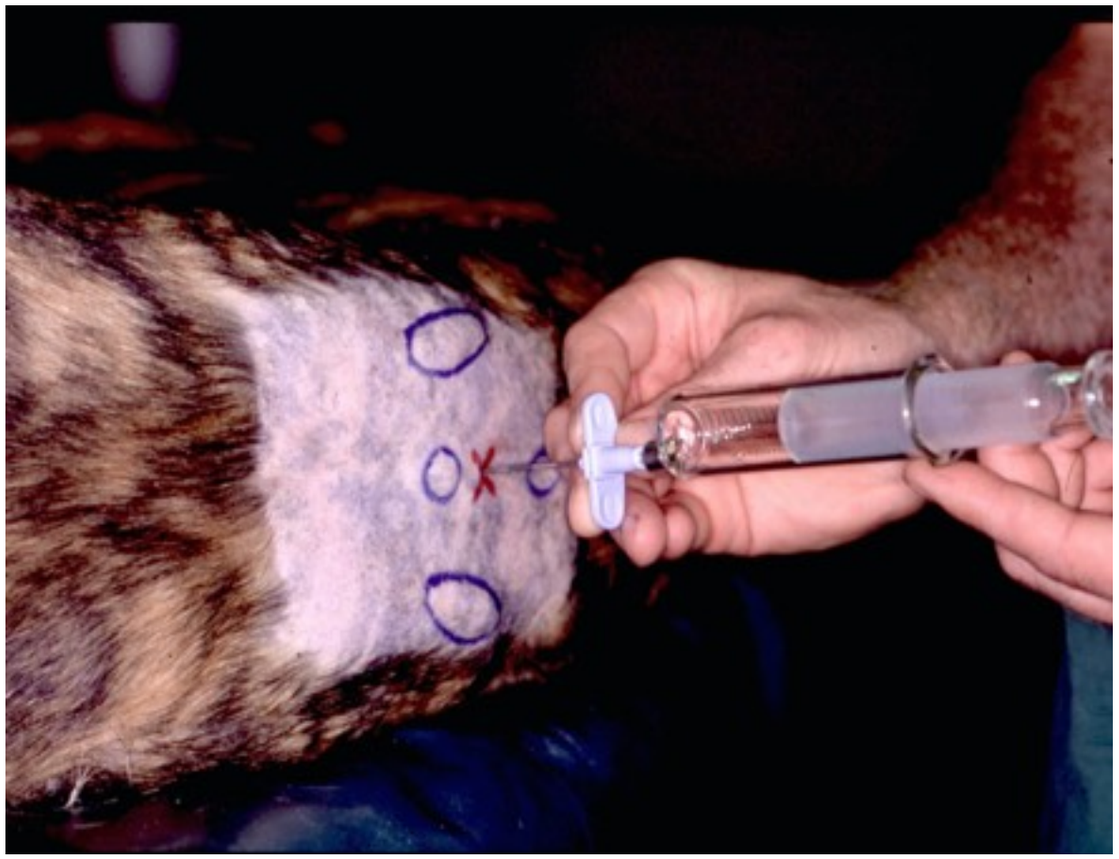
•**nerve block** (eg., paravertebral for caesarian section) - blocks transmission in a specific nerve (and thus the area it supplies). Needs some knowledge of anatomy!

•**epidural** and

•**intrathecal** - block the area supplied by the nerves arising from the affected part of the spinal cord. Needs more knowledge of anatomy or spinal cord can be damaged. Also blocks motor nerves.

•**Bier's block** (Intra Venous Regional Anaesthesia, IVRA) (eg., for foot operations) - injection into a vein below a tourniquet - blockade of most of the tissues below the tourniquet. nb. analgesia stops when the tourniquet is removed

IMAGE 4.1 Epidural injection



Checking that the needle is in the epidural space using the loss of resistance method.

•**intra-articular** - mainly the synovial membrane. Be extemely careful not to introduce bacteria into joints.

Since iv administration usually causes side effects, care should be taken that the drug is not injected into a vein; ie aspirate before injecting.

Drugs

Lignocaine

By far the most commonly used drug is lignocaine (lidocaine USAN). It is chemically stable (can be autoclaved), spreads through tissues, used as 1 or 2% solution parenterally, 4% topically. It has a rapid onset - 5 min, medium duration of action - 30 - 40 minutes. This can be prolonged to 1 hour with adrenaline, although premixed combinations are no longer sold in NZ. Remember that adrenaline can cause ischaemic necrosis in extremities. Depending on the type of block being used, it is possible to give toxic amounts (maxiumum dose 7mg/kg). It is cheap.

Prilocaine

Prilocaine is very similar to lignocaine but less toxic - it is used for Bier's blocks (IVRA). Mepivacaine again is very similar to lignocaine but less irritant - used in horses for diagnostic nerve block (some horses produce a local inflammatory reaction to lignocaine).

Bupivacaine

Bupivacaine is a long-acting drug with a slow onset time (peak effect occurs within 30min). The duration of action varies from 2–6h, depending on route of administration and the dose, but it has an onset time of about 20min. It is used as a 0.25% or 0.5% solution. It has been used widely in dogs. It is more cardiotoxic than equieffective doses of lignocaine: the dextro isomer has a specific toxic effect on the heart. Clinically, this is manifested by ventricular arrhythmias and myocardial depression after inadvertent iv administration or overdosing in small animals. Levobupivacaine is sometimes used in people but is very expensive.

It can be useful to give mixtures of bupivacaine and lidocaine to acheive a fast effect which lasts for several hours.

Ropivacaine is very similar to bupivacaine but is much less toxic (and even more expensive).

Amethocaine

Amethocaine (tetracaine USAN) is the only ester used clinically. It is usually given topically in the eye. Proxymethacaine is similar. Cinchocaine is sometimes used for spinal blocks but is pretty toxic (it has been used in combination with phenobarbitone for euthanasia). Benzocaine is an insoluble local anaesthetic sometimes found in powders applied topically to stop animals itching.

Procaine

Procaine is obsolete - slow onset, poor penetration of mucous membranes, toxic - do not use. The similar chloroprocaine may be better but is not available in NZ. The only good point about these is that they are not metabolised to 2, 6 xylidine (see below). This has led to their re-introduction in the UK.

Articaine

Articaine has taken over in human dental anaesthesia. It has a fast onset and long duration, and at least three different routes of metabolism, none of which produce anything nasty (see politics, below). It may become useful in food animals. It is always used with adrenaline.

Future directions

There are a number of subtypes of Na_v channels, which are located on different neurones. Drugs which are specific to Na_v 1.8 and 1.9 on sensory neurones but not Na_v 1.5 on myocardial cells are being sought, although at present, only some spider venoms are specific for the different subtypes. Another approach to specificity is to use TRPV1 agonists (see below), which are probably only present on C nociceptor fibres, to open the ion channels and allow local anaesthetics into the neurone.

Experimental drugs

Tetrodotoxin (TTX) from puffer fish, blue ringed octopus, etc (produced by symbiotic *Vibrio* spp) and saxitoxin (STX) from toxic algae are large organic molecules which bind very specifically to (some) sodium channels from the outside and are used to study sodium channels in the laboratory. They are widely used *in vitro* to block action potentials and are very toxic. They are not used therapeutically, but experimental use shows that they can produce up to 20 hours block in people. They may rarely be seen as poisoning cases (usually saxitoxin - there are probably no blue ringed octopus in NZ).

A variety of obscure spider and scorpion toxins also affect sodium channel gating in such a way as to mimic block clinically - hopefully you will not come across these except in scientific papers.

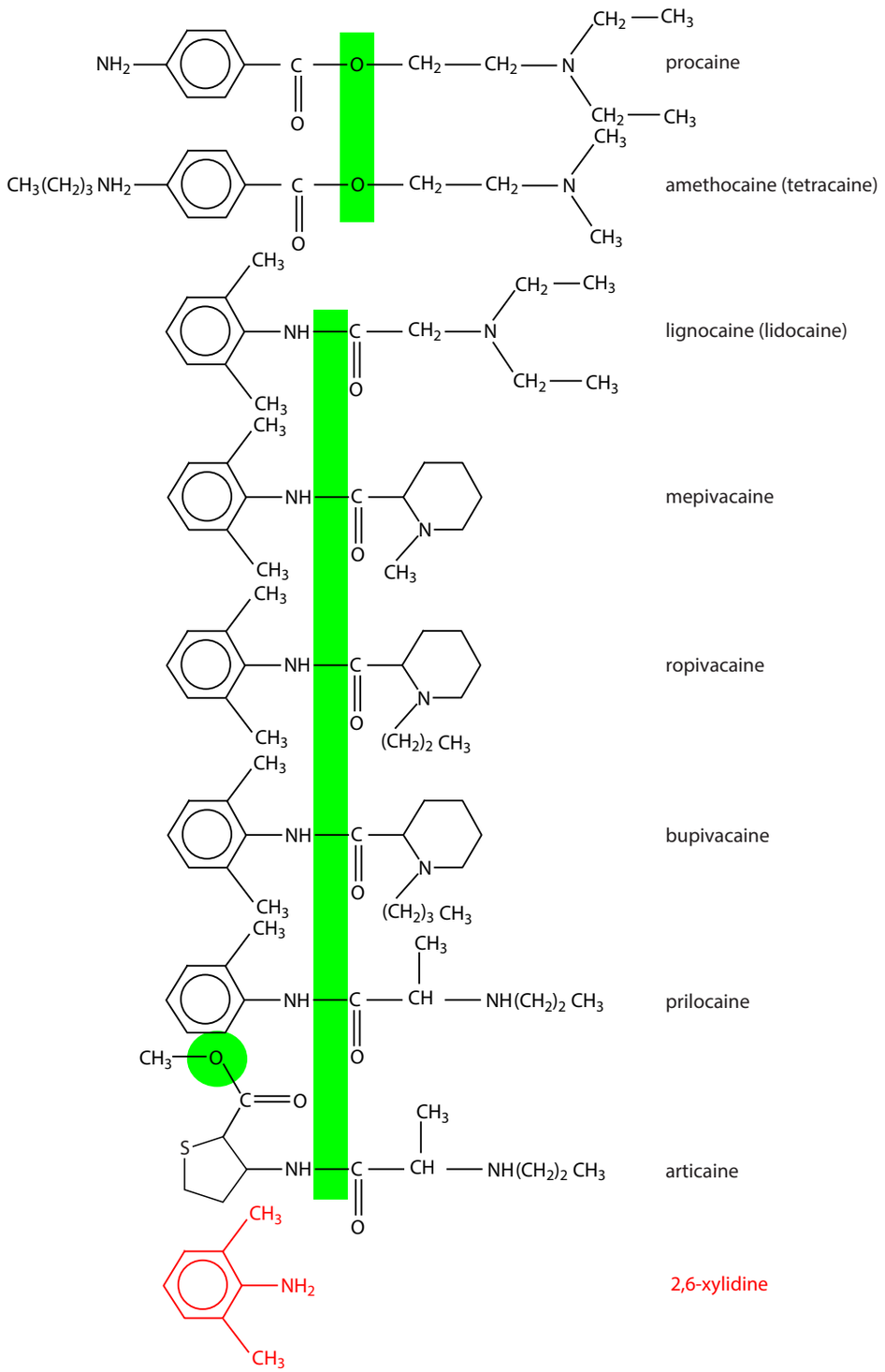
Sodium channel openers

Veratridine is used experimentally; a variety of insecticides such as DDT and pyrethrums have similar effects. Although not used for their effects in mammals, these are occasionally seen as poisoning cases eg, sea anenome poisoning.

Politics

One of the metabolites of most local anaesthetics is 2,6 xylidine, which is a common industrial contaminant and causes nasal tumours in rats at high doses. This has led to lignocaine being banned in Europe for use in food animals, although it is still the most widely used local anaesthetic in people.

DIAGRAM 4.3.2 Local anaesthetics and 2,6 xylidine



Green areas indicate where drugs are metabolised. 2,6, xylidine is a potential metabolite of most amine local anaesthetics except prilocaine and articaine. It is probably carcinogenic.

Opioids

commonly used drugs

morphine

Opioids

- ☑ the main group of strong analgesics
- ☑ main effects analgesia and euphoria
- ☑ interact with anaesthetics and sedatives to increase sedation
- ☑ side effects - vomiting and possibly respiratory depression. Not usually seen in animals in pain.
- ☑ overdose causes excitement in cats and horses
- ☑ morphine is metabolised very slowly in cats
- ☑ if in doubt about an animal's pain - give it morphine

IMAGE 4.2 Opium poppy

Opioids (note spelling) are not quite the same thing as opiates. (Opioids bind to opioid receptors: opiates are derived from opium poppies.) This is the main class of drugs used to produce potent analgesia.

Morphine, the prototypical drug in this class, is a complex plant alkaloid produced by the opium poppy *Papaver somniferum*. Most other clinically used drugs are semi-synthetic derivatives based on the morphinian backbone, or phenylpiperidine derivatives (fentanyl etc). The chemistry has implications for metabolism.

Opioid receptors

See table below. Subtypes of all these receptors have been described but their role is not yet clear. σ receptors are not always recognised as opioid receptors.

Most clinically useful drugs are μ agonists:

- morphine (& papaveretum - a crude extract of morphine) and its derivatives heroin (diamorphine) & M6G
- pethidine and its derivatives fentanyl, alfentanil, sufentanil, lofentanil, carfentanil
- methadone & dipipanone

Most of these notes refer to μ agonists, particularly morphine.

Useful effects

- analgesia
- euphoria

Mechanism of action

Opioids reduce firing in cells carrying pain signals (mainly in the spinal cord, but also in the brain stem): they hyperpolarise neurones by opening K+ channels (GIRK2 (Gprotein coupled inward rectifying potassium channels)). There are sex differences in these channels.

Opioids also reduce transmitter release by closing N type Ca^{++} channels and may directly reduce neurotransmitter release at nerve endings.

μ opioids cause mood effects by stimulating the ventral tegmental area which projects to the reward pathways in the nucleus accumbens via a dopaminergic pathway using D2 receptors.

There is increasing evidence that morphine has analgesic and anti-inflammatory effects in the periphery. There is also some evidence that morphine injected intra-articularly in horses causes formation of large glycopeptides such as hyaluronic acid. (see anti-inflammatory notes). Opioid peptides may also have a role in control of reproductive hormones and inflammatory cells; they are expressed on macrophages in inflammation. Watch this spot! (or read Br. J. Anaes., 2005, 95, 42.)

A variety of worms and other animals which are unlikely to feel pain possess opioid receptors, but what they do is anyone's guess. Opioid receptors as a means of producing analgesia is probably a fairly recent evolutionary development.

TABLE 4.4.1 Opioid receptors

Receptor	Endogenous Ligand	Main Effects	Agonists	Partial Agonists	Antagonist
μ (MOP)	β endorphin endomorphins	analgesia, respiratory depression, euphoria	morphine, pethidine, fentanyl etc	buprenorphine (etorphine)	naloxone (diprenorphine) (CTOP)
δ (DOP)	enkephalins	analgesia, hormonal effects	(DPDPE)	(etorphine)	naloxone high dose (diprenorphine) (naltrindole)
κ (KOP)	dynorphins	analgesia, dysphoria, diuresis	(U69593, CI977)	(etorphine)	naloxone very high dose (diprenorphine) (nor-binaltorphine)
ORL_1 (NOP)	nociceptin	increases pain	(Ro646198)		(J113397)
σ		psychotic effects, analgesia?	(phencyclidine) ketamine??		

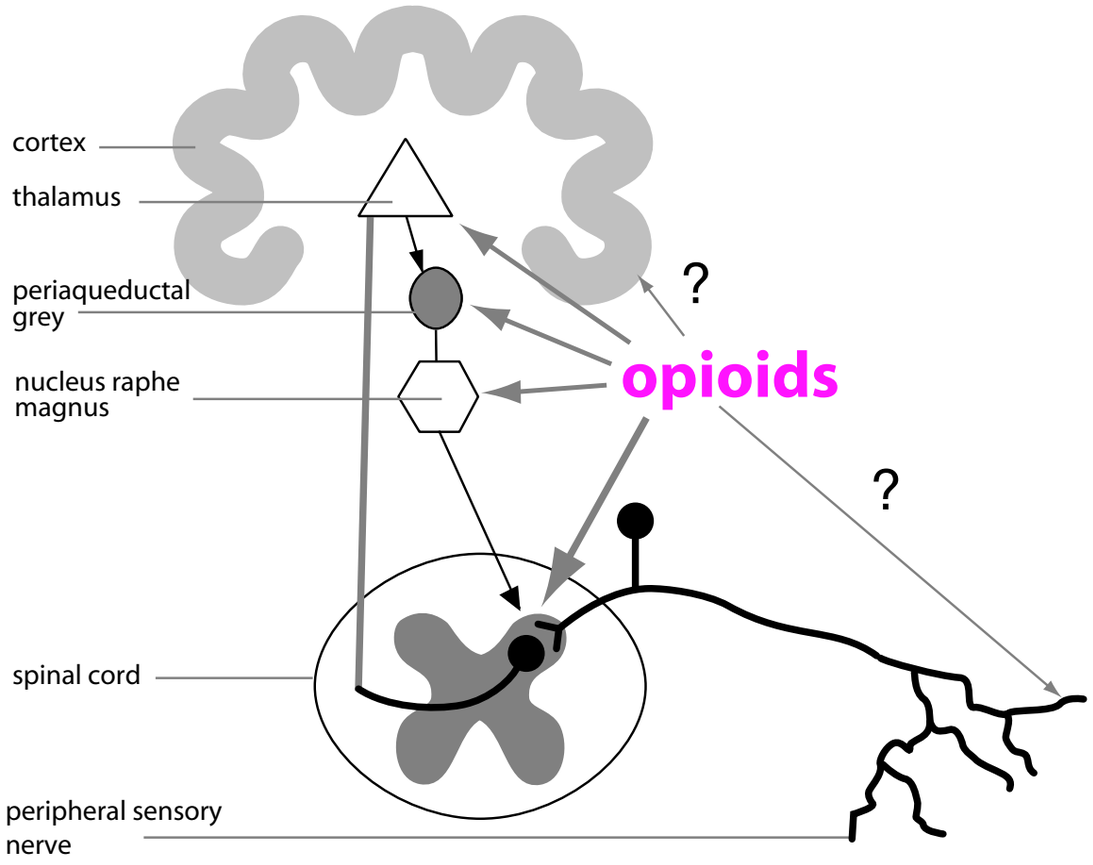
The sigma receptor is no longer regarded as an opioid receptor, but I put it in here anyway. There have been several attempts to rename these receptors, none of which have stuck.

Side effects

Although the range of possible side effects is large, animals in pain show remarkably few of them, even after high doses. Healthy dogs usually vomit after morphine.

- vomiting - stimulate dopaminergic pathways in the chemoreceptor trigger zone

DIAGRAM 4.4.1 Sites of action of opioids.



The main site of action is probably the spinal cord, with possibly synergistic actions at the thalamus.

- sedation (usually only at high doses in normal animals)- non specific inhibition in the ascending reticular formation??
- euphoria - opioid receptors on dopaminergic neurones in the ventral tegmental area project to the nucleus accumbens - the “reward pathway”
- gut effects - slowed peristalsis and sphincter spasm leading to constipation - mainly mediated through the myenteric plexi but also central and direct effects on the smooth muscle cells
- muscle rigidity - mechanism unknown - worse with fentanyl
- respiratory depression - reduce sensitivity of respiratory drive to PCO_2 , made worse by anaesthetic drugs
- urinary retention - increased sphincter tone
- cough suppression - probably mediated by a different receptor system
- increased intra-cranial pressure - mechanism unknown
- addiction - caused by a combination of the euphoric effects of the drug and the unpleasant effects of withdrawal
- histamine release - sometimes occurs after iv morphine administration in the dog - use another route
- bradycardia can occur after large doses - depression of vasomotor centre - give atropine
- miosis - stimulate oculomotor nucleus to increase parasympathetic tone - this effect is often opposed by the effects of excitement
- excitement - mainly cats and horses at high doses - reaction to euphoria??
- segmental pruritus can occur after it morphine. There is a definite link between itch and pain - both may be carried by C fibres - bur exactly hoe morphine produces this is not clear.
- chewing behaviour - sheep and rats

Pharmacokinetics

Absorption

Usually given im or iv. Oral absorption is variable - morphine is about 20% bioavailable. Since the major action is in the spinal cord, opioids are sometimes given intrathecally or epidurally to get direct to the site of action (and stay there). Morphine is best by these routes, but transfer to the brain in the CSF can lead to prolonged respiratory depression.

Fentanyl is available in patches which are stuck on the skin and slowly absorbed.

Distribution

There are large differences in fat solubility; morphine is relatively hydrophilic, fentanyl derivatives are relatively lipophilic.

Metabolism

Morphine is conjugated with glucuronide to produce morphine 3 glucuronide (M3G) and M6G (potent analgesic) Remember cats do not possess glucuronyl transferase! One dose is enough in this species.

Elimination

Large differences between drugs and species, but glucuronidation is important in most. Remember cats! Most opioids also undergo some enterohepatic recirculation.

Indications

- analgesia
- anaesthetic premedication
- (anti-diarrhoeals)
- (anti-tussives (stop coughing))

as with all analgesics, opioids are more effective if given before pain starts

Contra-indications

- severe head injury? - opioids raise intracranial pressure
- upper respiratory tract injury? - block cough reflex thus may cause inhalation of blood clots, teeth, etc.
- unconsciousness - unable to feel pain???

Chest injury is sometimes cited as a contraindication for opioids on the theoretical grounds that they inhibit respiration, however, rib injuries are extremely painful and opioids often result in better respiration in animals with chest injuries.

Drugs

Morphine is the oldest drug and probably still the best. It is certainly the cheapest. An im dose will last about 4 hours in the dog and horse, and up to 24 hours in the cat, **but the duration of action will depend on the pain**. Morphine produces less obvious analgesia in ruminants, but works in pigs (short acting - about 1 hour after normal doses). It is not licensed for use in food animals. Intrathecal morphine lasts up to 24 hours, but sometimes produces itching of the areas supplied by the cord segments affected. Use sc or im rather than iv in dogs, where it causes histamine release. If you really must give it iv, use low doses given very slowly. If you have to give something iv, fentanyl is better.

Methadone is very similar to morphine but more expensive. It is traditionally used in horses because of a myth that it causes less excitement than morphine. It is very long acting in some people, but not in animals. It may cause less vomiting in dogs, so is used in situations where vomiting would be disastrous, such as cervical instability. It has zero bioavailability if given orally in dogs.

Pethidine (meperidine USAN) works well in people but is very short acting in most animals (30 - 40 mins in the dog): high doses need to be given often. It is metabolised relatively easily by the cat. One metabolite, norpethidine, can cause excitation in people, usually only when it accumulates in renal disease or when pethidine is given regularly. This could be a problem in animals with renal disease. Pethidine is abused by people because it penetrates the CNS rapidly.

Fentanyl is a highly potent opioid usually given by intermittent iv injection or infusion for intraoperative analgesia. Fentanyl has a rapid onset time (2–5min) after iv injection and a short duration (5–20min) depending on the dose given. It is a potent respiratory depressant, which means that its use in anaesthetised animals requires low doses often, or an infusion, if mechanical ventilation is to be avoided. At high doses it induces bradycardia, which may be prevented by an antimuscarinic drug. Muscle rigidity has been reported in humans with the use of high doses of fentanyl; this can also occur in conscious dogs given high doses. Fentanyl can also be given by the transdermally. Skin patches designed for use in humans containing fentanyl released at different rates have been applied to dogs, cats, pigs and horses. They can produce plasma fentanyl levels at the lower end of the analgesic range recognised in humans after 24h (so they must be applied in advance), although there is considerable inter-animal variation. Great care is required to ensure that they are in close contact with the skin; the hair underneath must be clipped and shaved. However, excessive shaving which damages the stratum corneum can result in fast absorption. They are probably best used to provide background analgesia with other routes or drugs used on top if the pain breaks through. Their use in humans is restricted to chronic pain therapy.

Fentanyl is available in a combination product along with the butyrophenone tranquillisers fluanisone (Hypnorm) or droperidol (Innovar). It is used as an im neuroleptanaesthetic / neuroleptanalgesic mixture in rats, rabbits, mice and guinea pigs or occasionally for sedation in dogs

Alfentanil is only administered by iv injection, either as a bolus or more commonly by infusion. It has a short elimination half-life (0.4–2h depending on the species), a small volume of distribution within the body and a moderately fast clearance and so is well suited to administration by iv infusion. Like fentanyl, it is a potent respiratory depressant and induces significant bradycardia at clinical doses; animals should be pretreated with an antimuscarinic drug such as atropine or glycopyrrolate before use. Its duration of action is very short (2–5min). Alfentanil has also been used as a bolus before induction of anaesthesia with a barbiturate or propofol to reduce the dose of induction drug. It is most commonly used to provide intraoperative analgesia in small animals, given by iv infusion. When used this way, it reduces the requirement for inhalational or iv anaesthetic drug maintenance, although not in horses.

Sufentanil is a thiamyl analogue of fentanyl with greater analgesic potency. It is used iv in humans as a bolus and by infusion, and is also given epidurally and intrathecally to provide spinal analgesia. The cardiovascular and respiratory effects are similar to those of fentanyl. Its use by infusion in dogs with nitrous oxide has been described.

Remifentanil is similar, but shorter acting. It has been developed for use by infusion during anaesthesia. It is an ester which is hydrolysed in plasma and thus is very short-acting (1 - 2min, depending on dose) and requires no liver function. Pharmacokinetic studies in dogs show that the drug is rapidly cleared, the volume of distribution is small and the contribution by the liver to the overall clearance was very low. It is useful under anaesthesia where it is infused iv at a rate to match surgical stimulation.

Carfentanil is similar but longer acting, it is usually used for chemical immobilisation of large animals (including deer).

This group of drugs was originally developed for chemical warfare, so there may be others out there which could be useful transdermally.

Codeine is a weak analgesic but useful antitussive and antidiarrhoeal. It is sometimes used in dogs as a mild analgesic. **Oxycodone** is used in people in NZ in similar situations.

There are a number of other opioids peculiar to America, **oxymorphone** and **hydromorphone** are widely used there as a substitute for morphine, and **hydrocodone** as a substitute for codeine.

Heroin (diamorphine) is not used in animals, and only very rarely in people in NZ. It is a drug of abuse, although not common in NZ (at the moment). It is much more lipid soluble than morphine and gets into the CNS faster (so works better at producing euphoria), but once there it is thought to be metabolised to morphine and exert its analgesic effects as morphine. It is used in human cancer patients in the UK.

Residues

Only pethidine is registered in food animals, but does not work very well. It is probably best to use α_2 agonists in ruminants. Opioids work well in pigs but are usually shorter acting, sometime **much** shorter acting, than in other species.

Other considerations

Most μ agonists are controlled drugs because of the potential for abuse (in people). This means that they have to be locked away and their use recorded (see notes on the law) so that they can be tracked all the way from ordering from the wholsaler to administration to the patient. It also means that drug addicts will attempt to break into clinics to steal them.

The euphoric effects in a drug addict depend on a high concentration getting into the brain quickly. This means that lipid soluble drugs such as heroin, or to a lesser extent pethidine, are favoured over relatively water soluble drugs such as morphine. However, any drug addict desperate enough to break into a vet clinic is unlikely to be choosy.

Mixed agonists

Sometimes called partial agonists. These drugs were developed 40 years ago in the hope of producing analgesics which did not produce respiratory depression or addiction potential. They are falling out of fashion because they are no less respiratory depressant than morphine at equianalgesic doses and many of them produce dysphoria rather than euphoria. Most are κ receptor agonists and have side effects such as diuresis and occasionally motor effects in people (no information on domestic animals).

Buprenorphine is probably the only one worth using. It is a potent μ selective partial opioid agonist which has a particularly high affinity for its receptor. The association of the drug with the receptor is slow and this is reflected in the slow onset time of action of the drug (30–60min). For this reason, buprenorphine is usually given by sc or im injection rather than iv. It can be given sublingually in humans, which allows rapid absorption but by-passes the liver during the absorptive phase. However in animals, this route is really only practical in cats, where the injection formulation can be given into the cheek pouch. Administration of the drug orally results in very poor bioavailability, between 3 and 6%. Transdermal patches have been tried in animals, but did not work.

Buprenorphine is extensively metabolised in dogs, with only 1% unchanged buprenorphine appearing in the urine and bile. The main metabolite is buprenorphine glucuronide which is excreted in bile. Buprenorphine has a long elimination half-life in dogs, 4.5 - 42h, a large volume of distribution and moderately fast body clearance. The slow terminal half-life of buprenorphine in dogs is not reflected in a particularly long duration of action (4h at normal doses), and for some types of pain at

least, may not be dose related. The elimination of buprenorphine is faster in sheep and the duration of action is shorter (c. 3h). The actions of buprenorphine are not readily reversed with opioid antagonists. It is best used as a premedicant before moderately painful surgery, as increasing the dose or adding a full μ agonist to treat severe pain is not usually sucessful.

At higher doses, it is also a ORL1 agonist, and analgesia can be reversed. You are unlikely to see this in practice though.

It is used in opioid addicts, particularly in the USA.

Butorphanol is a partial opioid agonist with activity at both μ and κ receptors. It was used in humans but dysphoria and variable analgesia resulted in limited use by the parenteral route although it is available as a nasal spray. Butorphanol is rapidly and almost completely absorbed after im or sc injection in dogs and reaches a peak plasma concentration within 30–45min. The drug is lipophilic and is well distributed throughout the body, particularly in dogs and cows. Body clearance is high in dogs, cattle and humans, but considerably slower in the horse. The elimination half-life was short in dogs, cattle and horses (1–2h), although even at low doses, butorphanol can be detected in cows' milk for 36h. Analgesia is of short to moderate duration (if detectable at all) when butorphanol is used to control postoperative pain in dogs and cats (1–2.5h), although data from experimental pain studies suggest a longer duration of action (6-8h). Analgesia for visceral pain appears to be better than for somatic pain, although not consistent. The intensity of analgesia can be variable to non-existant and its use is best restricted to animals in mild to moderate pain. Butorphanol appears to enhance the sedative effects of acepromazine. In the horse, butorphanol given alone induces an increase in locomotor activity (sometimes dramatic), and it should be given with α_2 adrenergic sedatives. Licensed doses in the dogs and cat are lower than those suggested by experimental studies.

Recent work in people indicates that it may produce analgesia in women but pain in men.

Tramadol has recently become popular in English-speaking countries, although it has been in use in Germany for many years. Tramadol is not usually classified as a mixed agonist: one of its stereoisomers is a μ agonist; the other isomer is a monoamine reuptake inhibitor. Increased noradrenaline and 5HT have a synergistic effect on analgesia. Tramadol may also act as an NMDA antagonist. However, although the main metabolite of the first isomer has a higher affinity for the μ receptor, this M1 metabolite is produced by cytochrome P450 2D6, which is deficient in dogs. This means that it has a measurable, but minor effect in dogs compared to people. In contrast to morphine, it does not potentiate the sedation of acepromazine. It is probably best avoided for acute pain and reserved for oral use in situations where NSAIDs do not produce adequate analgesia for chronic pain.

Etorphine (M99) is not available in NZ; it is sometimes used overseas in a neuroleptanalgesic mixture ("Immobilon" sold for horses, occasionally used in wild animal immobilisation). **Beware - self injection is likely to be fatal; several vets have died using this drug.** The lethal dose for people is 30 - 120μg. It is a class A controlled drug (see law notes).

Antagonists

Opioid antagonists are sometimes used to reverse the effects of overdose. They will also reverse analgesia as well as side effects, so it is usually better to just deal with the side effects of the opioid. If you are using potent drugs such as carfentanil in the field where there is a chance of accidentally injecting yourself, you must have some naloxone available (and know where your veins are).

Naloxone is a human drug used for accidents and overdoses. This should be on hand if using carfentanil or other potent opioids for immobilisation - people are more susceptible to the respiratory depressant effects of opioids than common domestic species. Only lasts about 20 mins. It is very expensive.

Naltrexone is similar to naloxone but has a longer duration of action.

Diprenorphine is an antagonist at all the main receptor types. It is only used to reverse etorphine. It is not available in NZ.

naloxone human dose

0.8 - 2mg (2 - 5 ml of 0.4mg/mL solution) iv to effect. Max dose 10mg

Nalorphine and laevorphanol are partial agonists rather than antagonists and are obselete.

Remember that the partial (mixed) agonists will also act as partial antagonists, and partially reverse the effects of pure agonists.

Antidiarrhoeals

Opioids reduce passage of gut contents by a combined effect on the myenteric plexus and the CNS. Codeine, loperamide, diphenoxylate and morphine & kaolin are used for this (see gut pharmacology notes).

TABLE 4.4.2 Opioid specificity

	μ	κ	δ
morphine	+++	+	0
pethidine	++	0	0
fentanyl	+++	0	0
alfentanil	+++	0	0
methadone	+++	0	0
etorphine	+++	+++	+++
buprenorphine	(+++)	- -	0
butorphanol	(++)	+++	0
nalbuphine	- -	++	0
tramadol	+	0	0
naloxone	- - -	- - -	- -
diprenorphine	- - -	- - -	- -

Opioid receptors and drug specificity. + agonist, (+) partial agonist, - antagonist, 0 no effect. nb specificity depends on the test used!

Antitussives

Depression of coughing may not be mediated by opioid receptors but is produced by most opioids with a similar structure to morphine. Codeine (cheap) and butorphanol (expensive) are sometimes used in dogs. (see respiratory notes).

NSAIDs

commonly used drugs

lots

NSAIDs

- ☑ analgesic and anti-inflammatory
- ☑ inhibit cyclooxygenase
- ☑ beware gut ulceration (common) and kidney failure (rare)
- ☑ use with care in situations where blood pressure is likely to be low

Non-steroidal anti-inflammatory drugs (NSAIDs) (sometimes called aspirin like drugs) are a very large group of drugs of diverse chemical structure with the common property of inhibiting cyclo-oxygenase, and thus reducing prostaglandin production. Prostaglandins perform many functions in the body, including mediating inflammation and sensitising peripheral nerve endings.

There are other groups of anti-inflammatory drugs which are also not steroids - I have referred to them as anti-arthritis drugs. All anti-inflammatory drugs are covered in more detail in the anti-inflammatory notes.

Effects

- anti-inflammatory (see anti-inflammatory drug notes)
- analgesic
  - peripheral
  - central?
- antipyretic
- anti-endotoxic??

Mechanism

The way that NSAIDs produce analgesia may be different from the way they produce their anti-inflammatory effects. Both may be due to cyclo-oxygenase (COX) inhibition in various sites (althogh most NSAIDs have other effects which may also contribute to analgesia). nb. cyclo - oxygenase inhibition is usually assessed by measuring the reduction in circulating thromboxane B2 rather than PGE2 levels in the relevant tissue, which may well be different.

Steroids also reduce prostaglandin production (by acting higher up the cascade) but are not directly analgesic - they are potent anti-inflammatories and by removing inflammation they can reduce pain. NSAIDs are different in that they can produce analgesia in the absence of inflammation.

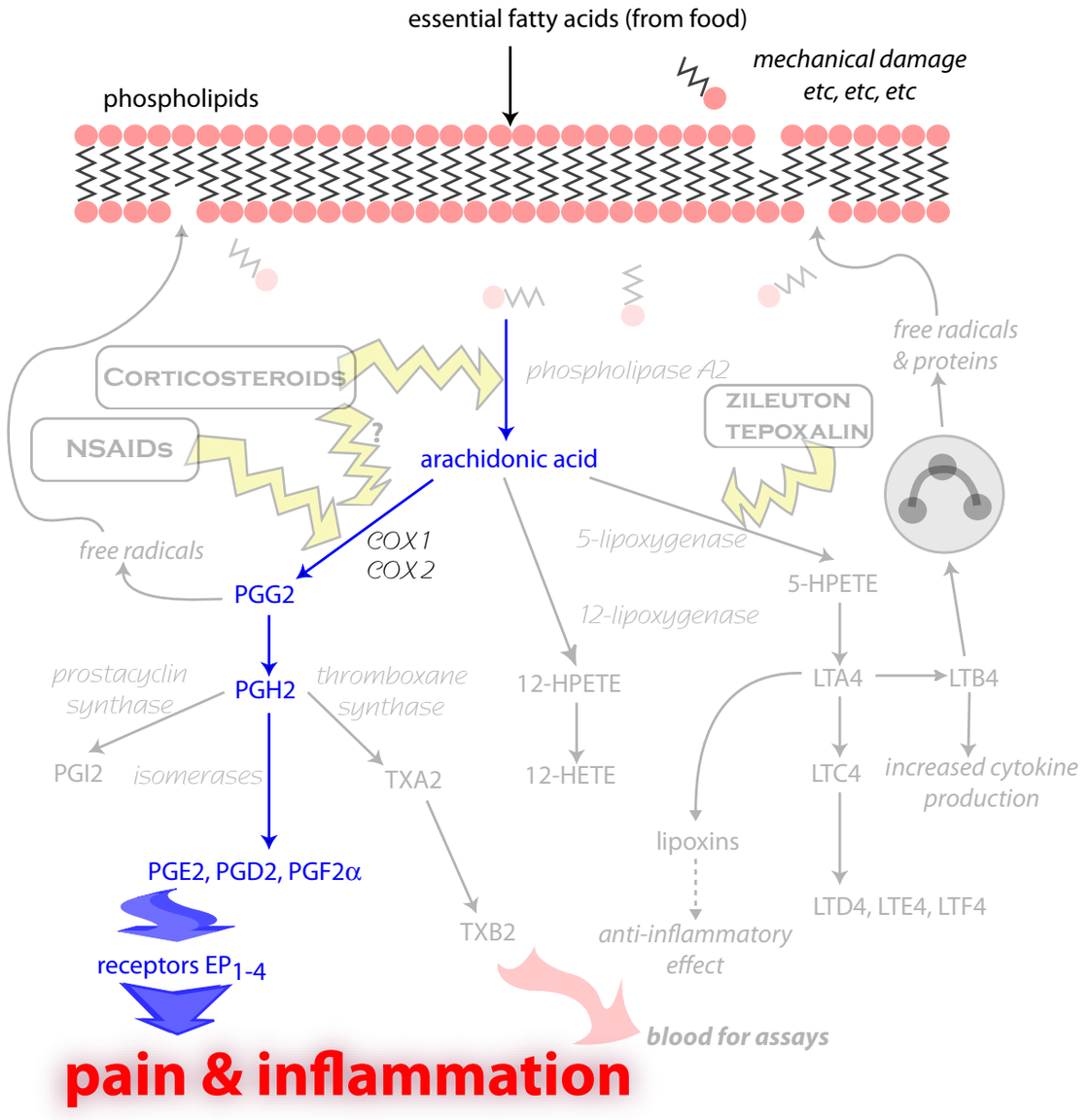
Cyclo-oxygenase exists in at least two forms:

COX1 - constitutive - responsible for physiological production of PGs

COX2 - inducible - produces PGs during inflammation

A variation on COX1 (COX3) has been reported. It is involved in the action of paracetamol in dogs, but probably not other species. Its significance is unknown at present.

DIAGRAM 4.5.1 NSAIDs



The arachidonic acid cascade.

All currently used veterinary drugs inhibit both COX1 and COX2 (but to different degrees). Since most side effects are caused by inhibition of COX1, drug development is focussing on finding drugs which only inhibit COX2. Carprofen, firocoxib and deracoxib are the only veterinary drug which comes close so far (in dogs), meloxicam is some way behind. Celecoxib and rofecoxib are COX2 inhibitors for people, but they may not be specific for COX2 in other species - there are big species differences.

There has been a recent scare about the cardiovascular effects of coxibs in people. This seems to be only a problem with high dose chronic use (usualy to prevent chronic inflammation becoming cancer), but see *Br. J. Anaes*, 2005, 95, 281 for all you ever wanted to know on this.

Prostaglandin receptor pharmacology is a developing field. The situation is confused at present; the receptors responsible for some effects (but not the sensitisation of neurones) have been elucidated. However, it is clear that PGD2, E2 and I2 can all sensitise peripheral neurones to the pain producing effects of bradykinin and other mediators.

Some (most??) analgesia may be produced in the CNS (probably the brain rather than the spinal cord). There is evidence that prostaglandins interact with several types of glutamate receptors to increase nociception, NSAIDs may block this.

All currently used drugs also have other effects unrelated to cyclo-oxygenase inhibition which could contribute to analgesia. Many scavenge free radicals, which will also reduce inflammation.

Side Effects

when used as analgesics

gastric ulceration - limits use of most drugs to about 5 days at normal doses. Very common but not usually serious.

Normal production of mucus in the stomach depends on PGE2 (produced by COX1), if mucus production is stopped then the stomach acid will cause ulceration. This can be prevented by giving PG analogues or PGE1 with the NSAID (see gut pharmacology notes).

kidney damage - but usually only in combination with other factors:

- hypotension / hypovolaemia (shock, poor anaesthesia, etc.)
- chronic kidney failure
- old age
- urinary tract obstruction

Kidney failure is rare but often fatal.

When the mean pressure in the renal artery falls below about 65mmHg there is not enough pressure across the glomerulus for filtration to take place. The body re-

sponds by producing angiotensin II which constricts the efferent arteriole to keep the pressure in the glomerulus up, but in the long term, this would reduce blood flow through the proximal tubular capilliaries and cause ischaemic damage. To stop this, PGE2 causes emergency vasodilatation in the kidney (until blocked by NSAIDs). NSAID induced renal failure can usually be prevented by keeping the blood pressure at normal levels (usually with iv fluids ± vasoconstrictors).

The papilliary necrosis associated with NSAIDs is probably caused by interference with COX2, although COX1 may also be involved. COX2 knockout mice die of kidney failure, but of a different sort.

other side effects

- increased bleeding time (mainly aspirin)
- liver damage (some drugs have specific hepatotoxic effects)
- agranulocytosis - very rare

side effects sometimes seen in people

- asthma
- dermal reactions
- uricosuric effect

Analgesic NSAIDs

All NSAIDs have some analgesic effect, but some appear better clinically than others. Carprofen, ketoprofen meloxicam and flunixin are the drugs most often used for analgesia rather than an anti-inflammatory effect, but analgesia depends on type of pain and situation of use. Carprofen and flunixin have very different effects on PGE2 production but seem to produce similar analgesia. Coxibs are used in this way in people, but the jury is still out on these in animals. Comparative trials of NSAIDs are as rare as hens' teeth in veterinary medicine,so nearly all the evidence behind clinical use is anecdotal.

Older drugs with more analgesic than anti-inflammatory effects include paracetamol (acetaminophen USAN) and dipyrone (only available here as a mixture with hyoscine).

The distinction between analgesic and anti-inflammatory effects may be less obvious than it would appear from the clinical use of these drugs. Recent evidence indicates that small pain fibres play an important part in the inflammatory response.

Indications

• mild musculo-sketetal damage - strains, osteoarthritis, etc. Inhibition of COX1 can cause increased degradation of articular cartilage by reducing subchondral blood flow and thus speed up the progress of the disease, but the benefits of analgesia usually outweigh this risk. The anti-inflammatory effects of NSAIDs are also useful here.

• mild pain

• equine colic - not all NSAIDs are suitable. Flunixin can be too effective and mask pain (often a sign of gut ischaemia) leading to a false sense of security. Do not use flunixin unless you have reached a definitive diagnosis.

• postoperative pain - not all NSAIDs are suitable; not all ops are suitable for NSAID analgesia. In man, the pain from dental and orthopaedic ops usually responds well to NSAIDs.

• acute inflammation - calf pneumonia, etc (see anti-inflammatory notes)

Pharmacokinetics

(see also anti-inflammatory notes) Half lives are very variable between species. Use with extreme care in unlicensed species.

Beware aspirin and paracetamol in cats, phenylbutazone in cattle, naproxen in dogs: unexpectedly long half lives.

Aspirin has an unexpectedly short half life in cattle.

Several NSAIDs have had withholding times established and are registered for use in food animals.

Clinical use

Acute pain - onset of analgesia about 15 mins after im / iv injection. Be careful of shock causing hypotension leading to kidney failure. Remember also that bad anaesthesia has similar effects to shock!

Chronic pain - usually osteoarthritis - dosage regime must be arranged to minimise gastric ulceration. Give tablets with food, only give as necessary rather than continuously, use anti-ulcer drugs (see gut pharmacology notes).

Recommended reading

Lees, May and McKellar (1991) Pharmacology and therapeutics of non steroidal anti-inflammatory drugs in the dog and cat: 1 and 2. *Journal of Small Animal Practice*, 32, 183 - 193 & 225 - 235

α2 agonists

commonly used drugs

xylazine (large animals)

(dex)medetomidine (small animals)

α2 agonists

- ☑ analgesic and sedative
- ☑ major cardiovascular side effects
- ☑ use with care in sick animals
- ☑ probably the best general analgesic drugs in ruminants

Adrenergic α2 agonists are widely used, especially in large animals, for chemical restraint. They are also effective analgesics and possibly the most effective class of analgesic drugs in ruminants.

These drugs are especially useful in large animals and have superceded everything else as sedatives.

Effects

- analgesia
- sedation
- bradycardia
- rise then fall in arterial blood pressure
- spasm then relaxation of gut
- muscle relaxation
- vomiting (30% of dogs & 40% of cats, depending on dose)
- hypoxaemia (ruminants)
- hypothermia

Mechanism

There are four receptor subtypes, $\alpha_{2a\text{-}d}$. α_{2d}s are thought to be the rat equivalent of α_{2a}R in other species. α_{2a}R are involved in analgesia and sedation, α_{2b} in the cardiovascular system.

Adrenergic α2 receptors are G protein coupled receptors which increase K^+ conduction in same way as opioids (and probably at the same ion channels (GIRK2)) and so hyperpolarise neurones.

Sites of action

analgesia - spinal cord, (locus coeruleus)(some species differences in number and distribution of receptors)

sedation - locus coeruleus (ascending reticular formation)

cardiovascular effects - This can cause confusion. These drugs cause hypertension and bradycardia followed by hypotension. The hypertension is caused by a direct effect on the vascular smooth muscle in resistance arterioles in some vascular beds such as the skin (big arteries are unaffected). The hypotension is caused by an

inhibition of the vasomotor centre in the medulla, the thoracic sympathetic outflow and the release of noradrenaline at sympathetic nerve endings. The hypertension usually causes marked vagally mediated reflex bradycardia which is potentiated by reduced release of adrenaline and noradrenaline.

Cardiac output can be reduced by up to 70%.

Most of the clinically used drugs contain an imidazoline ring and so bind to imidazoline receptors. The exact function of these is unknown but I1 receptors are thought to be involved in blood pressure control - some imidazolines which are not also adrenergic α2 agonists have been used to lower blood pressure in man. Imidazoline I2 receptors appear to be on monoamine oxidase B and may also be involved in depression. I3 receptors are involved with insulin release from the pancreas. α2 agonists certainly reduce insulin production and thus cause a temporary hyperglycaemia.

respiratory effects - xylazine appears to cause bronchoconstriction (and possibly pulmonary artery constriction) in ruminants; it may also cause pulmonary oedema. Animals become hypoxic, sometimes severely. It will kill about 1.7 deer in 1000. This also occurs with the other drugs, but their use in ruminants is not sufficient for it to show up. It is probably caused by the release of various inflammatory mediators from pulmonary intravascular macrophages, which are probably confined to ruminants.

This hypoxia can be easily treated by giving oxygen intranasally.

Respiratory depressant effects are minimal.

Routes of administration

usually im (small animals), im or iv (large animals)

poorly absorbed sc - blood vessel constriction

spinal administration gives long lasting analgesia without side effects and is clinically useful in ruminants and horses

(dex)medetomidine in particular (at low doses) is useful as part of a balanced analgesia mixture, sometimes given as an iv infusion.

α2 antagonists are available (see sedative notes) and are usually used to reverse sedation but will also reverse analgesia. This is rarely desirable.

Drugs

Xylazine has been around for longest (1960s) and is still widely use in a variety of species. Ruminants are much more sensitive to xylazine than other species for some unknown reason - they require much lower doses. Rams and bulls are much more variable in their dose requirements than females and castrated males. Xylazine appears to cause bronchoconstriction in cattle and sheep; it may also cause pulmonary oedema. It will produce a delayed hypersensitivity reaction in many deer; this is fatal in 1.7 animals in 1000. It may be metabolised to 2, 6 xylidine (carcinogenic).

Detomidine was introduced for use in the horse and is now the standard sedative in this species, although it works in most other species too. A derivative, **medetomidine** is used in small animals (only one isomer, **dexmedetomidine** is active, it is also used as an anaesthetic premed in people). Medetomidine is slightly more sedative than the others but it is not possible to produce anaesthesia with it alone in most of the species we deal with (cf. rats and man). **Clonidine** was the original (human) drug; it was first marketed as a nasal decongestant until it was noticed that it reduced blood pressure. It was then marketed as a hypotensive until it was noticed that it also produced sedation and analgesia, when it began to be used in anaesthesia and pain clinics. The moral of this story is that these drugs have lots of side effects! **Romifidine** is a clonidine analogue which was developed at the same time but shelved because of its sedative side effects. It has now been resurrected for horses. It is similar to the others but longer acting.

One attraction of α2 agonists, particularly in small animals and deer, is that it is possible to reverse the sedation with antagonists. **Atipamezole** (small animals) and **yohimbine** (deer) are used, although there are many more specific experimental drugs such as idazoxan (α2 antagonists were examined as antidepressants for man a few years ago). Remember that all the effects of the α2 agonist will be reversed, including any analgesia. This is rarely desirable.

Balanced analgesia

commonly used drugs

morphine + NSAID + medetomidine

morphine + lignocaine + ketamine

Balanced analgesia

- ☑ combinations of analgesics in low doses to avoid side effects
- ☑ evidence for efficacy (or safety) lacking for most combinations

Balanced analgesia involves using several drugs at low doses so that the analgesic effects are additive or synergistic but the side effects are reduced. Combinations usually include an opioid or α2 agonist and possibly an NSAID plus one or more of the following:

dissociative anaesthetics

Ketamine is the only drug easily available, tiletamine mixed with zolazepam (a benzodiazepine sedative) could be used. Their analgesic effects (on their own) only become obvious at anaesthetic doses but ketamine potentiates other analgesic drugs at very low doses. Ketamine is an NMDA antagonist. It stops / prevents wind up in spinal cord and is also amnesic in man (blocks memory of pain). High doses in combination with α2 agonists will cause anaesthesia. It is a controlled drug and abused by some people.

dopamine antagonists

Butyrophenones such as droperidol (usually used as sedatives) produce deep sedation in combination with opioids. Enhanced analgesic effects have been reported but are dubious. These drugs produce unpleasant subjective effects in people, and are probably best avoided. Lots of side effects.

inhalation anaesthetics

All cause unconsciousness but some cause profound analgesia at low doses. Nitrous oxide is the most widely used (50% mixture with oxygen is probably the single safest analgesic - see anaesthetic notes for details). Methoxyflurane and trichloroethylene are good analgesics at low doses. Their mechanism(s?) are unknown but may involve endogenous opioids. They are inconvenient to give except under general anaesthesia.

Drugs Used For Chronic Pain In Man

These may sometimes be useful in animals as part of a balanced analgesic technique, or when all else fails.

tricyclic antidepressants

These block reuptake of noradrenaline and 5HT which then act on α2 and 5HT3 receptors in dorsal horn of cord. Amitriptyline works best in man at doses well below the antidepressant dose. It also blocks NMDA receptors at clinical doses, and this may account for its analgesic action.

sodium channel blockers

These are used for causalgia in people. Lignocaine given intravenously has been used this way in horses, but is metabolised too quickly after systemic administration to be much use. Longer acting sodium channel blockers(see antiarrhythmic drugs) are used in people after testing the effects of iv lignocaine.

topical analgesics

Capsaicin (the hot substance in chillies) depletes C fibres of substance P - causes burning pain first but then blocks pain for days - months

EMLA cream - eutectic mixture of local anaesthetics (lignocaine and prilocaine) - will penetrate skin to cause analgesia. Used in needle shy children, but also useful for repeated blood sampling etc. Useful in laboratory animals. (see also drugs used in the eye).

gabapentin

This is used for neuropathic pain in people. How it works and if it works at all in animals are still undecided.

Clinical use

Combinations of drugs should be chosen for the circumstances of the individual animal. Pain changes with time: different drugs and combinations may work more effectively at different times. Remember local analgesia too. In severe pain, particularly neuropathic pain, finer control can be achieved with an iv infusion. Ideally this should be with an infusion pump, but just sticking your drugs into a bag of saline and adjusting the drip rate to suit works very well. Remember to label the bag!

The aim of giving combinations of analgesics is to achieve synergy. This is practically impossible to show clinically and very difficult experimentally, partly because there is no widely accepted statistical technique. So far there is only good experimental evidence for synergy between opioids and α2 agonists (but only by the spinal route) and opioids and NSAIDs. This is a hot research area so things will change in the near future!

Sedatives

commonly used drugs

acepromazine

medetomidine (dogs and cats)

xylazine (large animals)

Sedatives

- ☑ acepromazine produces mild sedation with some cardiovascular depression.
- ☑ diazepam is unreliable on its own (except in ruminants) but safe.
- ☑ a2 agonists are best in large animals but cause cardiovascular depression and vomiting in small animals.
- ☑ combinations of a sedative with an opioid produce deeper sedation (neuroleptanalgesia).
- ☑ deeply sedated animals need to be monitored as for general anaesthesia.

Lots of different terms are used for these drugs, usually derived from their effects at the normal dose in people. For instance, ataractic (do not confuse with analgesic), hypnotic, narcotic, neuroleptic, sedative, tranquilliser, etc.

In veterinary practice, the distinctions between these classes of drugs is usually not clear - I will refer to them all as sedatives.

Indications

- chemical restraint
  - mild sedation
  - heavy sedation
  - neuroleptanalgesia
  - general anaesthesia
- to potentiate anaesthetic drugs
- (travel sickness)

Selection of drugs or technique will depend on

- procedure to be carried out, eg.,
  - examination - very mild sedation only (usually!)
  - radiography - animal must lie still with reasonable muscle relaxation
  - lancing abscess - muscle relaxation less important than analgesia
- species (and sometimes breed and sex)
- animal's temperament

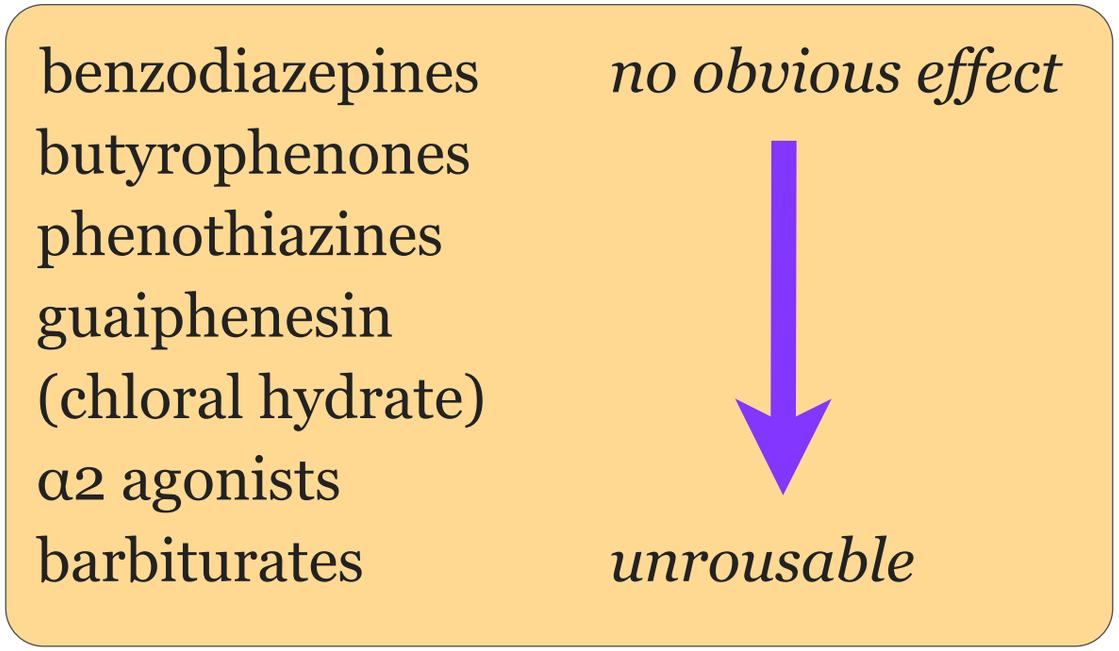
All sedative drugs have a smaller effect if the animal is excited before you give them. Calming the animal down and treating them gently are well worth while!

Drugs

There are many drugs used - see below under the different classes.

Mechanism of action

Most drugs have effects on a wide variety of receptor systems but probably work by by the final common pathway of reducing input to the ascending reticular formation. Activation of the ascending reticular formation will increase arousal and is thought to be be responsible for consciousness.



Knowledge of the receptors affected by these drugs is important to predict interactions (these drugs are often used in combination) and side effects.

Phenothiazines

Acepromazine is by far the most widely used sedative in all domestic animals. Chlorpromazine was the original drug of this class, and although it is still sometimes used in people (for schizophrenia), it is not used in animals any more. It is only mentioned here because the effects of acepromazine have never been properly assessed - it has always been assumed to be very similar to chlorpromazine. Methotrimeprazine (levomepromazine INN) is a human drug sometimes used to sedate children - it is supposed to have some analgesic effects. It is usually used in veterinary practice as an antihistamine, as is promethazine.

These drugs probably cause sedation by an effect at dopamine D2 receptors. They are also potent **α**1 receptor antagonists - blood pressure!

Effects

- sedation
- anti emetic
- vasodilatation - can be profound!
- lowers temperature
- analgesic / hyperalgesic (depending on the particular drug)
- anti muscarinic
- anti histamine
- extra pyramidal stimulation (Parkinson's disease)

Contra-indications

- stress
- epilepsy / convulsions - D2 antagonism causes dyskinesias which can look like convulsions

Care with

- shock
- cardiovascular disease - a1 antagonism causes hypotension
- Boxers - collapse - vagal syncope? give with atropine
- stallions - prolapse of the penis, sometimes irreversible

Clinical use

Use the smallest dose which works. Bigger doses prolong the effect rather than increase the depth of sedation. Avoid getting the animal excited before administration. Animals excited after injury would be better sedated by an opioid analgesic.

Use in combination with opioids will markedly increase sedation.

Alpha 2 Agonists

See under analgesics. The most commonly used class in large animals.

Benzodiazepines

A large family of drugs which are very widely used in humans as sedatives and anxiolytics, they are not good sedatives in domestic animals but potentiate other drugs. When given alone, they sometimes cause paradoxical excitement - probably by making the animal forget it is supposed to be tame! Many also have active metabolites.

Mechanism

Bind to $GABA_A$ receptors and potentiate chloride conductance thus hyperpolarise neurones. This can cause generalised reduction in neuronal activity (sedation), or at lower doses can reduce activity in specific pathways, eg, the tonic inhibitory pathway from the ventromedial hypothalamus to the appetite centre in the lateral hypothalamus.

Effects

- sedative in ruminants, only sedative in combination with other drugs in other species
- anticonvulsant
- appetite stimulant - useful in cats and possible cattle
- anxiolytic?

These are useful emergency drugs for sick animals as they do not depress the cardiovascular or respiratory systems at normal doses.

Indications

- emergency treatment for convulsions
- potentiate anaesthesia
- stimulate appetite in cats & cattle
- sedation in shocked animals

An antagonist, flumazenil, is available but too expensive to use.

Drugs

The short acting water soluble drug **midazolam** is useful as an intravenous premed, although it will not induce anaesthesia on its own in most animals (as it will in man). The most widely used drug is **diazepam**. It has a medium duration of action in most species (about 20 minutes) although active metabolites may prolong this, especially in combination with other sedatives. Brotizolam has recently be licensed as an appetite stimulant for cattle.

As a pharmacological curiosity, benzodiazepine inverse agonists (eg β carboline) also exist. These bind to the receptor but produce the opposite effects to an agonist such as diazepam, ie, excitement and anxiety. They are not used clinically!

There is also a plethora of benzodiazepine like drugs on the human market, usually used as sleeping tablets (eg zopiclone). Most of these have not been used in domestic animals but you may sometimes see animals which have eaten their owners' sleeping pills!

Butyrophenones

Azaperone (and fluanisone overseas) are used in veterinary practice, droperidol and haloperidol are human drugs.

They sometimes (often!) cause excitement rather than sedation. Azaperone is traditionally used in pigs to control fighting when mixing groups, and for anaesthetic premed. It has also been used in dogs.

They are useful anti-emetics in dogs at very low doses, and are sometimes used in neuroleptanalgesic mixtures.

In man these are used as antipsychotic drugs (mainly for schizophrenia) - in the past when they were used as anaesthetic premeds, they caused subjective feelings of aggression but prevented the patients doing anything! Dogs and chimps given these drugs can behave aggressively for months afterwards.

They are potent D2 antagonists and often produce twitching, usually ascribed to extrapyramidal stimulation - ie, iatrogenic Parkinson's syndrome.

Use something else if possible.

Obsolete Drugs

Chloral hydrate was used in large animals, either iv, oral or per rectum. It is very irritant extravascularly, must be given in large volumes, tastes nasty and is very long acting. It must be converted to trichloroethanol to produce sedation - takes about three mins in horses. **Use α2 agonists instead**.

Guaiphenesin is still sometimes used in horses at induction of anaesthesia. It also has to be given in large volumes but does not have all the other disadvantages of chloral. It may be muscle relaxant rather than sedative **Use α2 agonists instead for induction**. The only time it may be useful is as a component in "triple drip" anaesthesia.

Phenobarbitone is sometimes useful po in very vicious dogs but is very long acting and easy to overdose. **Use only when nothing else works**.

Do Not Use As Sedatives

Reserpine - although sold in NZ to "calm" horses, it probably produces the same sort of psychoses as in man. This may make behaviour problems worse.

Magnesium - muscle relaxant rather than sedative. (Low dose magnesium may have a place as part of a balanced analgesic mixture, but it is also very effective at reducing cardiac output.)

Neuroleptanalgesia

Sedatives can be potentiated by adding an analgesic; the neuroleptanalgesia produced is a very deep sedation bordering on anaesthesia. Most neuroleptanalgesics are a mixture of an opioid with a phenothiazine or butyrophenone. Giving unfamiliar combinations of drugs requires that you know your pharmacology if you are not to get a nasty surprise.

When giving drugs which are potent depressives, the condition of the animal must be closely monitored. Neuroleptanalgesia can be as deep as general anaesthesia, but most sedatives have a large range of side effects, particularly on the cardiovascular and respiratory systems. Animals should be checked for heart or respiratory disease before the drugs are given, and the depression produced by the drugs continuously monitored. Most of the drugs mentioned have a long duration of action - the animal must have its airway, breathing and circulation monitored. In most cases a short acting anaesthetic (with intensive monitoring) is preferable to heavy sedation (with the animal left to look after itself when you have finished).

Species recommendations

These are my personal preferences - many other combinations or techniques will work just as well! Producing the correct degree of sedation is an art rather than a science - it depends on the animal and its handlers as well as the drug and the vet. Excitement and pain will reduce the effects of drugs.

Mild sedation

dog acepromazine (10) -20 - 50µg/kg im or sc (higher doses prolong effects without increasing sedation) but be careful in Boxers and large breeds such as Mastiffs - syncope / excessive duration of action.

cat acepromazine 20 - 50µg/kg & morphine 0.5mg/kg im or sc but sedation may not be obvious - competent gentle handling is probably more effective.

horse acepromazine 20µg/kg iv but sedation may not be obvious. Do not use in stallions - priapism may occur.

cattle xylazine 50µg/kg im The effect is variable in bulls.

sheep xylazine 10 - 20µg/kg im very large individual variation in effect - some rams very sensitive. Beware hypoxia - have oxygen handy for nasal admin.

deer xylazine 0.5-1mg/kg im Beware hypoxia - have oxygen handy for nasal admin.

pigs azaperone 1 - 2mg/kg im - not always effective - quiet handling essential. Heavy sedation probably better for most purposes.

Heavy sedation

dog medetomidine 20 - 80µg/kg im / sc

cat ketamine 10mg/kg im / sc (no muscle relaxation) or ketamine 5 - 10mg/kg & midazolam 0.2mg/kg im

horse detomidine 10 - 40µg/kg iv

cattle xylazine 100 - 300µg/kg im

sheep xylazine 50 - 200µg/kg im very large individual variation in effect - some rams very sensitive. Beware hypoxia - have oxygen handy for nasal admin. (Medetomidine and benzodiazepines produce reliable heavy sedation but not licensed for food species)

pigs ketamine 10mg/kg and midazolam 0.5mg/kg (mixed together) im. Inject through a butterfly or extension set so the needle doesn't come out when the pig jumps.

Very heavy sedation /neuroleptanalgesia

dog acepromazine 20 - 50µg/kg & buprenorphine 6 - 10µg/kg im (any opioid may be used with acepromazine - papaveretum 0.2mg/kg or morphine 0.1mg/kg are cheapest)

very fractious dogs - xylazine 1.3 - 2mg/kg & ketamine 10mg/kg or lots of medetomidine im

cat Not strictly neuroleptanalgesic but xylazine 1.1mg/kg & ketamine 22mg/kg produce very heavy sedation / general anaesthesia

horse heavy sedation may be dangerous for the animal and handlers; xylazine 1.1mg/kg iv followed by ketamine 2.2mg/kg iv will produce light general anaesthesia.

cattle, sheep, pigs general anaesthesia usually used

Special situations

Road traffic accidents

animal will be in some degree of shock - analgesics alone usually provide reasonable sedation

dogs buprenorphine 6 - 20µg/kg im or

morphine 0.2 - 1mg/kg im more potent analgesic (do not mix the two)

cats morphine 0.5mg/kg

Intensive care

most species benzodiazepines eg

midazolam 50 - 500µg/kg iv or as an infusion

Colic

horses xylazine 0.5 -1mg/kg iv but will affect gut motility and thus interfere with assessment (but so will other sedatives & analgesics).

General anaesthesia

General anaesthesia

☑ 1 decide what the animal's requirements are: consider shock, pain, etc.

☑ 2 decide what the surgeon's requirements are: muscle relaxation, fast recovery, etc.

☑ 3 decide on the best drugs

☑ 4 consider availability, cost etc.

Make sure that you know the differences between these terms: general anaesthesia, local anaesthesia (analgesia), regional anaesthesia (analgesia), neuroleptanalgesia, dissociative anaesthesia, balanced anaesthesia. They are not all the same!!

Introduction

A typical anaesthetic may involve:

- **premed** sedative & analgesic (± anticholinergic)
- **induction** injection anaesthetic (may be a mixture of drugs)
- **maintenance** inhalation anaesthetic & oxygen ± muscle relaxant
- **recovery** analgesic ± antibiotics to cover dirty surgery!

ie. lots of drugs which interact!

General anaesthesia was first induced (in man) 150 years ago using ether, although nitrous oxide as an analgesic had been around for a while before. With **ether in man**, the patient goes through a (reasonably) predictable series of stages:

1) analgesia
2) excitement
3) surgical anaesthesia
    plane 1)
    plane 2)
    plane 3)
    plane 4)
4) medullary paralysis
5) death

Stages 4 and 5 are to be avoided!

These are really only applicable to ether anaesthesia in man, although inducing anaesthesia with an inhalation agent such as ether or halothane is rarely done because of the excitement phase. Using combinations of drugs, as is routine these days, will tend to alter progress through these stages. **When monitoring the effects of anaesthetics, you need to consider all the drugs an animal has had**.

Mechanism of action

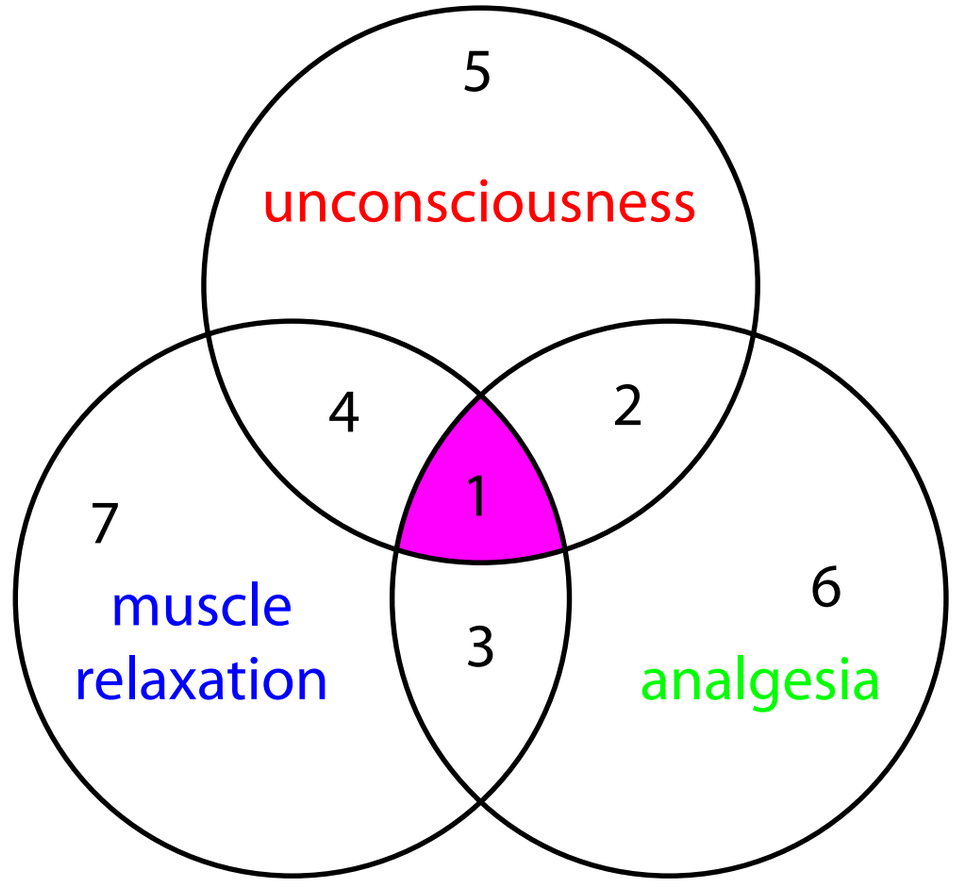
A unitary theory of general anaesthesia has been sought for many years without success. The current consensus is that inhalation anaesthetics bind to the lipophilic residues of various ligand gated receptor proteins, particularly $GABA_A$. They potentiate the effects of GABA with the end result that neuronal activity is decreased, in the same way as with most injection anaesthetics. However, inhalation anaesthetics also have lots of other effects which may be clinically important. An inhibitory effect at neuronal nAChR may be important. Nitrous oxide and xenon preferentially target the NMDA receptor (cf ketamine).

Most injectable drugs bind to $GABA_A$ receptors to facilitate channel opening, and thus hyperpolarise neurones (see neurotransmitter notes). This produces generalised inhibition of neurones, but may also produce excitory effects through disinhibition. Many anaesthetics also have other effects of unknown importance (effects on other receptors and non specific effects). Ketamine is an NMDA receptor channel blocker and is thought to produce its effects by this mechanism.

An endogenous ligand, oleamide, has recently been discovered for the general anaesthetic binding site on the GABA receptor. This may mean that specific agonists and antagonists will be available some time in the future.

There are no safe anesthetic agents, there are no safe anesthetic procedures. There are only safe anesthetists.—Robert Smith

DIAGRAM 4.9.1 Balanced anaesthesia



1 - surgical anaesthesia
2 - may be useful for some things such as lancing abscesses
3 - difficult to achieve ethically
4 - produced by some drugs, can be useful for x rays
5 - natural sleep
6 - you need to know how to produce this
7 - complete paralysis stops breathing

Injection anaesthesia

commonly used drugs

propofol

alphaxalone

thiopentone

ketamine

Injection anaesthesia

- ☑ usually only given iv to induce general anaesthesia, but can be infused for maintenance
- ☑ many factors influence dose required, especially premedication
- ☑ overdose usually causes transient apnoea - intubate & ventilate
- ☑ all drugs are potentially lethal if used incorrectly
- ☑ pentobarbitone is usually used for euthanasia

Anaesthesia is usually induced by injecting a rapidly acting drug intravenously. The advantages of this are that it is easy, a precise dose can be given, there is a rapid onset of anaesthesia (no excitement stage) and only a syringe and needle are required. The disadvantage is that there is no control over waking - if you give too much you are in trouble.

The ideal iv anaesthetic would be reliable, quick acting, produce no excitment on induction, have no side effects, be rapidly metabolised, produce good muscle relaxation, be analgesic, non-irritant and water soluble but it is non existent!

Pharmacokinetics

The minimum dose is given rapidly iv as a bolus for induction, and then the animal usually wakes up as drug is redistributed away from the brain. However, subanaesthetic plasma levels will still be sedative and potentiate other anaesthetic drugs. Most anaesthetics are very lipid soluble (so that they enter the brain quickly) but this means that they redistribute to fat which then forms a depot and releases the drug back into the circulation.

Selecting the correct dose is most important: the dose required for induction depends on

- rate of administration
- route (nearly always iv)
- concentration
- stimulation
- redistribution
- protein binding
- ionisation
- (metabolism)
- (acute tolerance)

The dose required is reduced by: premedication - especially α2 agonists, hypovolaemia, old age, debilitation, low plasma proteins, protein bound drugs - eg NSAIDs, anaemia, individual variation.

Drugs

Barbiturates, and particularly thiopentone (thiopental USAN: all the barbiturates end in al in American), have always been the drugs most commonly used, although

they have recently been overtaken by propofol in both veterinary and human anaesthesia.

Thiopentone

Thiopentone comes as powder mixed with $NaCO_3$. It is unstable when made up as aqueous solution but keeps for three days in a fridge. It is used as 2.5% solution (pH 11) in most dogs, 1.25% in small dogs / cats, 10% in large animals. Use as dilute a solution as possible.

It produces rapid anaesthesia in one circulation time. It is not analgesic, there is some evidence that it is hyperalgesic. It is a potent respiratory depressant. There is usually transient apnoea after an induction dose - ventilate the animal. It produces transient depression (usually only 2- 3 minutes) of cardiac output and blood pressure. It is only used for induction of anaesthesia (cumulation occurs if used for maintenance (half life about 4.5 hours in dogs) - very slow recovery).

Problems with thiopentone are largely caused by overdosage (see pharmacokinetics notes). Muscle relaxation is not always good enough for intubation unless a premed has been given (in people they sometimes use suxamethonium to aid intubation). There are breed variations; **greyhounds and similar dogs have a slow recovery**. Extravascular injection will cause skin necrosis (high pH, especially more concentrated solutions) - inject lignocaine ± saline around area. Intra-arterial injection will cause pain, necrosis and possibly convulsions, probably because the thiopentone crystallises out and causes arterial spasm.

Thiamylal was used in the USA instead of thiopentone but is no longer available, it was clinically indistuingishable from thio.

Propofol

Propofol is not a barbiturate but is clinically very similar to thiopentone. It usually comes as a white emulsion (although an aqueous solution is sometimes available as well) in single use vials under nitrogen which is non irritant (but can cause mild pain in some people, thought to be mediated by P2X and possibly PGE receptors). Its major advantage over thiopentone is that it is metabolised quickly in most species (except some cats) (half life about 40 mins in dogs). Its disadvantages are respiratory depression at least as strong as thiopentone, mild excitatory effects (usually front leg paddling in about 10% of dogs, although opisthotonus can occur) and occasionally rough recovery (especially cats). It can cause hallucinations in people which often takes the form of sexual disinhibition in women! The usual vehicle contains egg yolk and coconut oil and is an ideal growing medium for bacteria - open ampoules must be thrown away. There have been some suspected deaths from septicaemia in dogs after using old propofol. Wound infections are three times more likely after propofol anaesthesia - possibly because people are tempted to use old propofol.

A newer formulation in detergent was available for veterinary use, but there were also problems with the vehicle (it strips the lining off veins) and has been withdrawn.

New derivatives of propofol which are water soluble and more potent are being developed.

Alphaxalone (alfaxalone)

Alphaxalone has been around since the 1970s as “Saffan” (for animals) and “Althesin” (for people). These were a mixture of the steroids alphaxalone and alphadolone. The alphaxalone was thought to produce most of the anaesthesia, while the alphadolone was originally included to help dissolve the alphaxalone. However, recent work indicates that the alphadolone may have a significant analgesic effect. However, the vehicle (polyethoxylated castor oil - "Cremaphore EL") caused massive histamine release in dogs, and sometimes people (and caused the withdrawal of Althesin). Cats sometimes got oedema of the paws and ears after Saffan.

Saffan has now been replaced by a preparation of alphaxalone dissolved in cyclodextrin and water (“Alfaxan”). This is also suitable for dogs (in fact, any animal with veins) and is widely used, especially Australia as it is produced by an Australian company. It is slightly more expensive than the other induction drugs in NZ so is less popular here. It is often worth it for the fast recovery, though. The recovery can be so fast that animals can wake up suddenly, which can be disconcerting! You need to make sure that they are analgesic at this point to avoid excitement.

Alphaxalone takes longer than some other drugs to cross the blood brain barrier and works best if given slowly (over about a minute). It may be less respiratory depressant than other induction drugs. It is quickly metabolised in most species and doesnot accumulate.

Other steroid anaesthetics are under development (although all the candidates so far also cause excitatory effects on recovery or later). They will be water soluble to avoid the problems with the vehicle.

Ketamine

Ketamine is rather different from the other induction agents. It is a dissociative anaesthetic, which means (in people anyway) that the patient is conscious but not aware of what is being done to them. This may be because it is a good analgesic adjuvant and completely blocks the memory! It produces no cardiovascular depression at normal doses (when used alone). It acts rapidly by any route (although it is painful by im or sc injection - pH4). Its main disadvantage is that is produces no muscle relaxation and can actually cause convulsions in dogs and horses. It is sometimes used alone in cats and monkeys and combined with other drugs in other species (see below). It is also abused by some drug addicts, and is a controlled drug in NZ, so it should be locked up.

Tiletamine is a similar drug which comes premixed with zolazepam (benzodiazepine sedative) as Zoletil in NZ or Telazol in the USA.

Obsolescent drugs

Methohexitone is barbiturate which is similar but shorter acting than thiopentone. It usually produces excitation on induction and recovery - heavy premed required. It produces much more respiratory depression than thiopentone. Its only real indication was for induction in greyhounds but it has been overtaken by propofol. It is now difficult to obtain.

Pentobarbitone is rarely used for anaesthesia any more. It gives a slower induction and is longer acting than thiopentone. Its main use is for euthanasia, although it can be used for anaesthesia in sheep - faster metabolism than most species. It is sometimes used for long term sedation in dogs (eg, metaldehyde poisoning). Do not use euthanasia mixtures for anaesthesia - they are not sterile and contain large amounts of various alcohols to help solubility.

Metomidate and the human analogue **etomidate** are not available in NZ and are mainly of historical interest, although etomidate is currently undergoing a revival in veterinary anaesthesia in the USA. They produce anaesthesia but no analgesia and are traditionally used in pigs. Etomidate may be of advantage in sick dogs since cardiovascular depression is minimal. Analgesic premed is required for a smooth induction, and sedative premed to stop twitching - these tend to negate the lack of cardiovascular depression and rapid recovery. Etomidate has been abandoned by human anaesthesia because it causes profound adrenocortical depression.

Obsolete drugs

Laboratory animals are sometimes given these drugs in an attempt to produce long acting anaesthesia with minimal cardiovascular depression. In nearly every case, modern drugs properly administered would be better for the animals and give more reliable results for the experimenter.

α chloralose produces 8 -10 hours of stable light anaesthesia in rodents, but no analgesia. It may have a place in some very limited situations.

Urethane is similar, but has more analgesia. It is carcinogenic. **Do not use**.

Chloral hydrate in overdose will produce a state bordering on general anaesthesia, but with no analgesia. **Do not use.**

Tribromoethanol has nothing to recommend it. It must be given ip and is very irritant. It quickly decomposes to even more irritant metabolites. **It should never be used**.

Combinations

neuroleptanalgesics

sedative & hypnotic

α2 agonist & ketamine

benzodiazepine (midazolam) & ketamine

zolazepam & tiletamine

The sedative overcomes the increased muscle tone produced by the ketamine.

Infusion anaesthesia

With rapidly metabolised drugs like propofol and alphaxalone, it is possible to maintain anaesthesia by continuously infusing the drug (often with a short acting opioid like remifentanil or alfentanil to supplement analgesia). This has become popular in human anaesthesia but requires an infusion pump which is too expensive for most veterinary practices at present. Remember that unless the animal is completely analgesic, the infusion rate has to be varied according to the surgical stimulus. A much less accurate way (in small animals anyway) is to mix all the in-

gredients in a drip bag and drip it in. This is sometimes used in horses with a mixture of xylazine, ketamine and guaiphenesin (“triple drip”). Human anaesthetists who like playing with lots of kit have tried controlling infusion pumps by computer feed back systems for hands off anaesthesia with reasonable success. The way of the (distant) future?

Euthanasia

Small animals are usually killed by giving an overdose of pentobarbitone iv. Note that these solutions are not sterile as dead animals do not worry about septicaemia. The pentobarb causes respiratory depression, the animal stops breathing and death is usually considered to have occurred when the heart stops from hypoxia.

The volume involved in killing large animals this way will not fit easily into a syringe, so other drugs are sometimes added. Various toxic local anaesthetics such as cinchocaine have been used in an attempt to stop the heart; potassium chloride is sometimes used.

Premixed toxic cocktails (T61) have been used which include a muscle relaxant. These should always be given iv as there have been some cases of the muscle relaxant being absorbed before the sedative part of the mix if given im - not a pleasant way to go.

Inhalation anaesthesia

commonly used drugs

isoflurane

Inhalation anaesthesia

- ☑ used to maintain anaesthesia after induction with an injectable drug
- ☑ relatively insoluble drugs (low blood: gas coefficient) produce a relatively fast recovery
- ☑ isoflurane produces dose dependent respiratory and cardiovascular depression but not much analgesia
- ☑ eliminated by respiration - in overdose ventilate with 100% oxygen

After anaesthesia has been induced with an injectable drug it is often maintained with an inhalation drug. This also allows the animal to be given supplementary oxygen (30% minimum). Anaesthesia can also be induced with inhalation agents but is usually slow and unpleasant for the animal since these drugs usually produce an excitement phase before surgical anaesthesia. Some of the newer drugs may change this but it is still difficult to get animals to cooperate when you say "take a deep breath...". One exception is young foals and calves, where it may be possible to place a nasopharyngeal tube and induce anaesthesia with gas.

Advantages of inhalation anaesthesia are control of airway, ventilation and uptake and elimination of drug. The disadvantages are that expensive equipment is needed and possible equipment failure is dangerous for the animal (especially the obsolete and unmaintained equipment which seems to end up in veterinary practices).

Pharmacokinetics

Different from most drugs in that the inhalation agents are taken up through the lungs and excreted (mostly) unchanged by the same route. (Some of the older agents may undergo significant metabolism.)

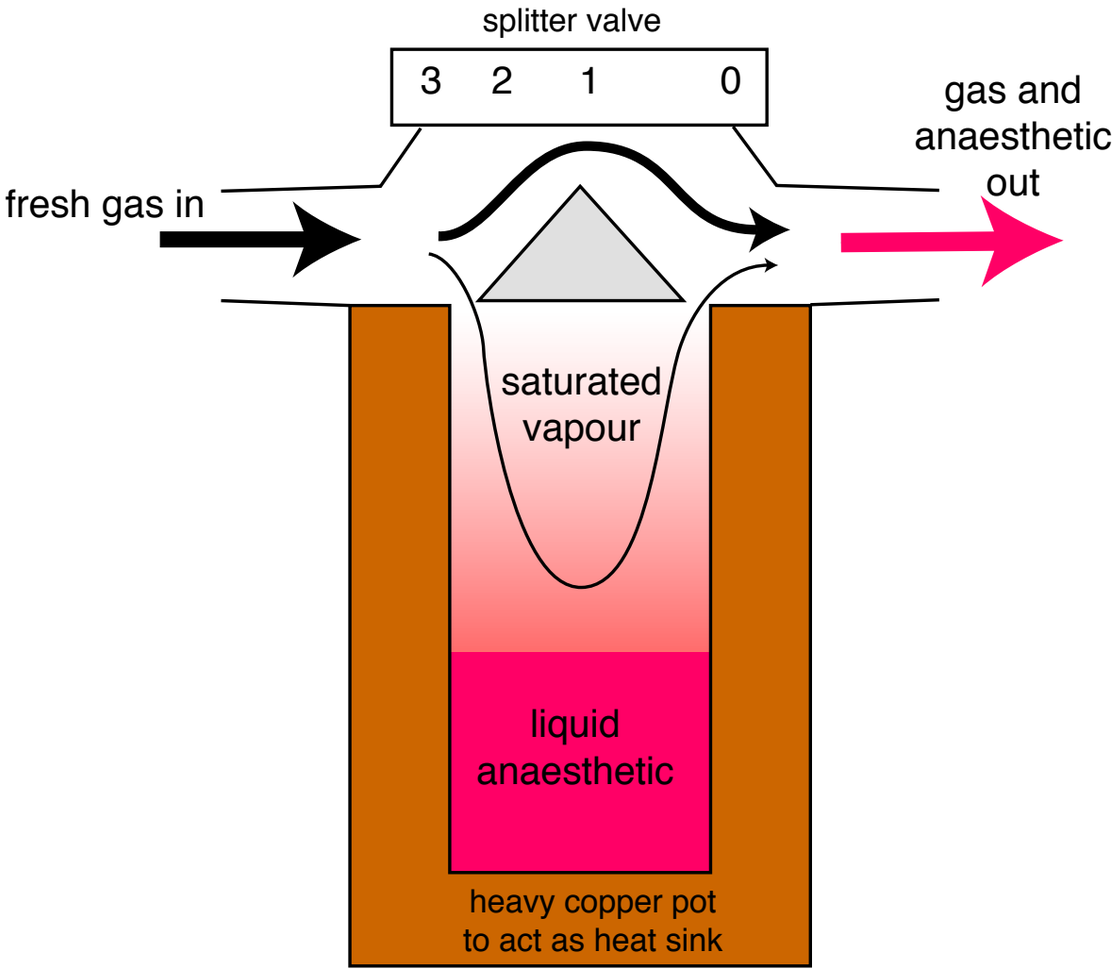
A digression on Dalton

Conventions on dosage of inhalation anaesthetics are slightly confusing. The amount of drug the animal is given is usually expressed as a percentage of inspired gas (sometimes the fraction - F_I drug). Once in the animal it is sometimes expressed as a partial pressure or tension (particularly for gases). This can lead to confusion as there are at least six different units of pressure used in anaesthesia. Remember that at sea level the ambient pressure is approximately 101kPa (the SI unit), 1 atmosphere, 1 bar, 760 mmHg, 15 psi or 1000 cm water! Therefore 4% halothane = 0.04 F_I hal = 4 kPa

Administration

When inhalation anaesthetics were first used, they were administered by pouring some onto a wad of cotton wool and holding this over the animal's nose. Since the effects of these drugs are critically dose dependent, and overdose results in death, precision vaporisers and complicated anaesthetic circuits were invented to try to control the dose the animal receives. **To deliver the correct dose of drug to the animal you must understand how this equipment works** (and how to repair it when it doesn't)!

DIAGRAM 4.11.1 Vaporiser



A precision vaporiser. Since the saturated vapour pressure of each drug is different, a different calibrated vaporiser must be used for each drug. Desflurane vaporisers are different.

Modern precision vaporisers are very accurate but very expensive. In human anaesthesia, there is a trend back towards using simple vaporisers (or even just squirting a bit of inhalation agent in the circuit with a glass syringe) and using sophisticated monitoring equipment to check how much drug the patient is getting. This sort of monitoring equipment is also expensive and is not widely used in veterinary practice (yet - but wait until the first big court case).

Uptake And Elimination

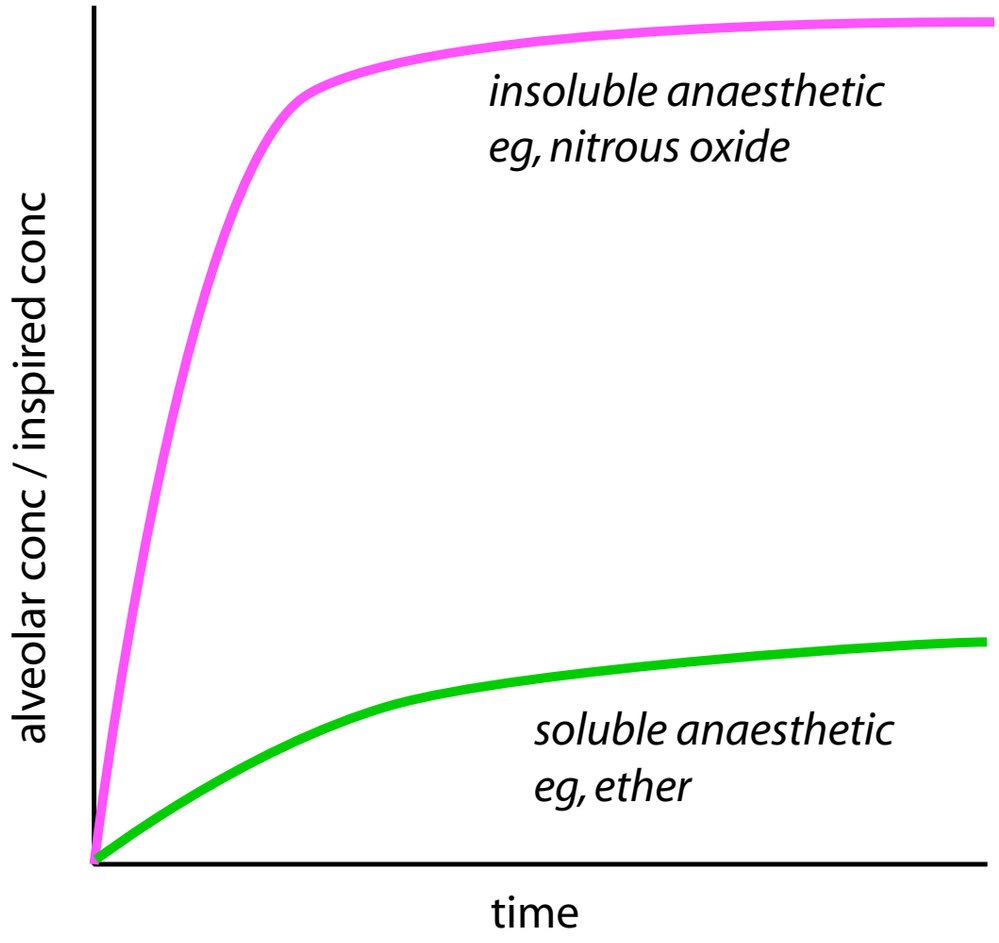
If animal is healthy, alveolar concentration is proportional to brain concentration, but lung disease will slow the uptake of drug. A number of factors influence uptake and elimination:

physical factors (properties of the drug)

• **saturated vapour pressure** - mainly a factor in vaporiser design unless you use a vaporiser with an anaesthetic for which it was not designed (or a non-precision vaporiser). As vaporisers are very expensive, this is sometimes done but is not recommended as there are big differences between drugs. It is useful to express SVP in kPa - this approximates to the maximal concentration (%) you can get out of the vaporiser.

• **blood gas coefficient** (solubility) This determines speed of induction and recovery. A relatively insoluble anaesthetic will quickly reach equilibrium between inspired and alveolar concentration, a relatively soluble anaesthetic will take a long time. A soluble anaesthetic effectively has a larger volume of distribution, so

DIAGRAM 4.11.2 Anaesthetic uptake



Uptake of inhlation anaesthetic agents. Note that the Y axis is a ratio rather than an absolute concentration.

more drug has to be absorbed to fill this volume and this takes longer. Therefore a relatively insoluble agent will give a fast induction and recovery; eg, desflurane (BG coeff 0.4; ie insoluble) will give a faster induction and recovery than ether (BG coeff 12; ie soluble). NB., if a drug is completely insoluble it will not get to the brain and will not be an anaesthetic. Soluble drugs tend to be more potent - anaesthesia can be produced at lower concentrations. If this did not happen, they would not be useful clinically as it can take a very long time for them to reach high concentrations.

- **rubber solubility** - mainly a problem with older agents and rubber tubing. The drug has to pass through lots of rubber / plastic tubing before it gets into the animal.

- **blood brain coefficient** - not clinically significant with current drugs, they all get into the brain very easily.

other factors (properties of the animal)

• **ventilation** - in the most extreme case, if an animal is not breathing, it will not take up any drug. It is common to stop an animal breathing with the induction drug. Beware, during intermittent positive pressure ventilation large quantities of drug can be forced into the animal.

• **cardiac output** - again in the most extreme case, if cardiac output is zero, the blood containing the drug will not leave the lungs and systemic uptake will be zero. A low cardiac output will slow the passage from the lungs to the brain.

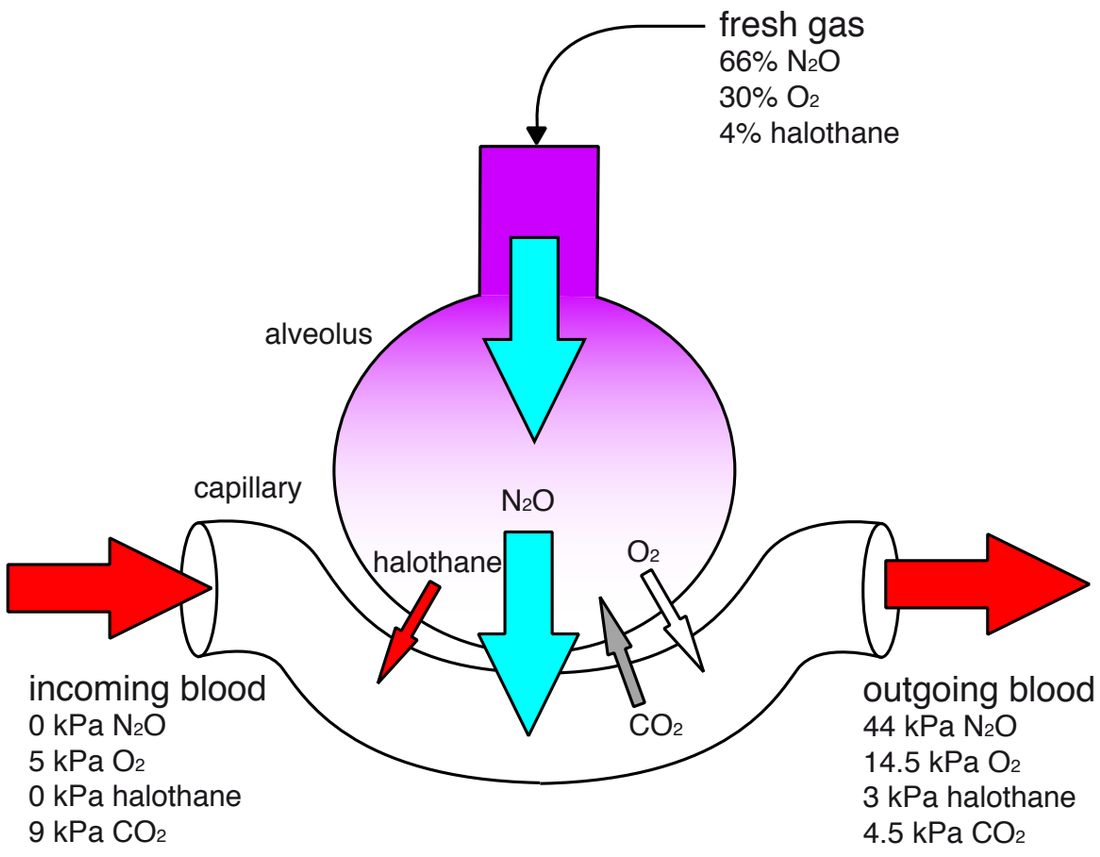
• **lung disease** - thickening of the blood gas barrier in the lungs will slow diffusion. This will mean a slower uptake and elimination of anaesthetic.

• **second gas effect** - probably only important with nitrous oxide, and possibly desflurane. If a large proportion of the volume of the gas in the alveolus moves across into the blood, more fresh gas will move into the alveolus to take its place, bringing more halothane (or whatever) with it. This is a way of getting more halothane into the animal faster, ie, faster induction. This will only happen for the first few minutes - it only takes about 10 minutes for nitrous oxide to equilibrate. The opposite occurs on recovery (Fink effect or diffusion hypoxia) where the nitrous oxide diffuses from the blood into the alveolus displacing alveolar gas (including oxygen); this can give rise to hypoxia. 100% oxygen is usually given for several minutes on recovery from an anaesthetic which has used nitrous oxide.

Minimum alveolar concentration (MAC)

This is an important concept. It is the concentration in the alveolus at a steady state which will prevent purposeful movement in response to a supramaximal stimulus in 50% of individuals (ie, it is a type of ED50). It is lowered by sedatives, induction agents, analgesics, nitrous oxide etc. Usually about 1.3 MAC is required for maintenance but the actual amount required will depend on animal's state of excitement / pain. The MAC is used to compare the potency of inhalation anaesthetics. It also gives you some idea of what to set the vaporiser to at the start of an anaesthetic - but you will have to change the setting according to how the animal responds!

DIAGRAM 4.11.3 Second gas effect



Second gas effect - confusing but not clinically important except when using nitrous oxide.

Drugs

These drugs are usually used in closed anaesthetic circuits with soda lime to absorb carbon dioxide. In the past, the high concentrations of KOH in soda lime caused problems with breakdown products of the drugs. This is not a problem with modern soda lime.

Isoflurane

Isoflurane is similar to halothane but gives a slightly faster induction and recovery. It has more or less taken over from halothane, as halothane is becoming harder to get since it is rarely used in people any more. Isoflurane may also cause MH. It produces *slightly* more analgesia than halothane, and *slightly* less cardiovascular depression. Monitoring cardiovascular depression, in the form of blood pressure, should be carried out routinely. Many dogs object to the smell, so do not use it for masking them down.

Halothane

Halothane is a good general purpose anaesthetic but not a very good analgesic (use with nitrous oxide or injectable analgesic). It is also a poor muscle relaxant. It is best used as the hypnotic part of a balanced anaesthesia technique. Its side effects include:

- respiratory depression (dose dependent)
- reduced cardiac output
- vasodilatation
- sensitises heart to adrenaline - **beware light anaesthesia!**
- (halothane hepatitis)
- (malignant hyperthermia in pigs)

When used alone, to provide surgical anaesthesia (ie, high doses), cardiorespiratory depression can be severe. If not enough halothane is used, the combination of halothane and adrenaline can cause tachyarrhythmias, especially in cats.

Halothane hepatitis is a cause of (unnecessary?) worry in human anaesthesia - halothane has been largely replaced by isoflurane and may be withdrawn in the future. Hepatitis after halothane is not a problem in domestic animals but concern about operating theatre staff may cause controls on atmospheric pollution (see scavenging below).

Malignant hyperthermia occurs in some breeds of pig (and people), particularly Pietrain and some families of Landrace pigs. If the pig starts to go hot and rigid, turn off the halothane immediately and ventilate with 100% oxygen. It may also need to be hosed down with cold water. The problem is caused by a mutation of the ryanodine receptor, which controls calcium flux out of the sarcoplasmic reticulum. The definitive treatment is dantrolene (ryanodine receptor antagonist), but it is rarely available. Malignant hyperthermia can also occur in other species but is rare. Halothane is sometimes deliberately used in pigs to detect if they are carrying the MH genes (MH is also induced by stress and lowers the value of the meat). About 30% of commercial pigs in NZ have the MH gene. Pigs have been extensively studied as a model for MH in people; but little is known about it in other species.

Nitrous oxide

Nitrous oxide (N2O, laughing gas) has been around since the 18th century. It was used as a recreational drug until its analgesic properties were discovered. It is a weak anaesthetic although a good analgesic so it must be used with other agents. It produces a rapid induction - it equilibrates in about 10 mins. A number of problems are associated with nitrous oxide:

- diffusion hypoxia - Fink effect - the opposite of the second gas effect
- diffuses into air filled spaces - beware pneumothorax and colic
- can build up in circle systems - oxygen analyser must be used or run the system semi closed.
- depresses folate metabolism (long term use > 8 hours)

Since it is a gas, it comes in cylinders and requires pressure regulators, flow regulators etc (more equipment to break down!). However, it is well worth the bother. The main reason to use it is that its analgesic properties mean that much less isoflurane / halothane can be used. This either means smoother anaesthesia or faster recoveries, depending on how it is used.

Newer drugs

The newer agents **desflurane** and **sevoflurane** give a very fast induction and recovery. Desflurane is very good in theory but requires special (very expensive) vaporisers, although a solution in propylene glycol may get around this problem. Sevoflurane has been used in more situations in animals and would be my drug of choice if cost was no problem. Some paediatric anaesthetists use them for induction (takes 10 - 60 seconds) and then switch to halothane or isoflurane for maintenance. They may have their use depending on price. Sevoflurane is catching on in human anaesthesia and getting cheaper all the time. These drugs make masking an

animal down a practical way of inducing anaesthesia. Sevoflurane with nitrous and oxygen in an induction chamber is probably the method of choice for small wildlife species.

Minor drugs

Enflurane is a chemical isomer of isoflurane but often produces excitatory effects which make judgement of depth of anaesthesia difficult. It has no obvious advantages and is not often used.

Xenon is occasionally used in people. It blocks NMDA receptors with no effect on GABA receptors and is a very good anaesthetic, but is very expensive. Its MAC in dogs combined with the cost mean that it is very unlikely to be used in veterinary anaesthesia.

Old drugs

Methoxyflurane gives a very slow induction and recovery, but is a very good analgesic and a good muscle relaxant so is useful for long orthopaedic ops. It is extensively metabolised releasing free fluoride ions which may cause kidney damage (particularly in combination with NSAIDs). Dogs seem to be more resistant to fluoride ions than other species.

Methoxyflurane is a byproduct of isoflurane manufacture, and at low doses has been advocated as a safe way of inducing analgesia without anaesthesia. (It was used like this back in the 1960s and the NZ army currently use it this way.) It may yet make a comeback in veterinary medicine!

Most of the other drugs mentioned here are only of historical interest, but if you see them in practice - **avoid**!

Diethyl **ether** (= ether) is almost obselete and should be avoided in most circumstances. It is a good anaesthetic but very inflammable in air, and explosive in oxygen. Its vapour is heavier than air and will roll along the floor and under doors. It gives a slow induction and recovery. The only reason it is still around is that it is the only agent which can be used without supplementary oxygen as it stimulates respiration (but if oxygen is available use it). It is irritant to the airways (peroxide degradation products) - anticholinergic premed required.

Older agents include **trichoroethylene** which is almost obselete but worth using in some circumstances. It is a very good analgesic but a poor muscle relaxant and is best used in combination with another agent such as halothane - low dose halothane keeps the animal asleep and trichloroethylene provides the analgesia. It gives a very slow induction and recovery but good analgesia during recovery. **Do not use in a closed system with soda lime - it reacts to produce phosgene**. (Anaesthetic or HPLC grade trichloroethylene should be used for anaesthesia; it is also one of the commonest industrial solvents but solvent grade is full of toxic impurities.)

Chloroform used to be used in horses because it was cheap. It causes massive liver necrosis in hypoxia and is very good at sensitising the heart to adrenaline. **Do not use**.

Scavenging

There has been concern about the effects of occupational exposure to small amounts of anaesthetic drugs in the atmosphere. In NZ, OSH have recently tightened guidelines on the maximum amounts permissible in room air; in Britain and the USA, there are similar guidelines but with different numbers. There is no good evidence that exposure to trace amounts of these drugs harms human health (with the possible exception of nitrous oxide causing abortion in women) but they smell nasty and are better removed. OSH have recently caught on to the fact that vets do not worry about this - so be warned!

A number of things can be done to reduce pollution:

- fill vaporisers in a well ventilated place (out of doors?) without spillage.
- fill vaporisers at the end of a day before you go home rather than in the morning before you start work
- turn vaporisers off when not in use
- use low fresh gas flow rates
- check equipment for leaks
- anaesthetic agents are good for removing stains from clothes but try to resist the temptation to do this!
- scavenge waste gases - but make sure the system does not impose any extra work for the animal
- in the last resort, open the window!

Fish anaesthesia

When fish have to be anaesthetised, they are given drugs in their water which are absorbed across the gills and could thus be classified as “inhalation anaesthetics”.

Drugs

Tricaine methanesulphonate (tricaine mesylate, MS222) is commonly used and probably best. It comes as a powder which needs to be dissolved in aerated fresh water (not tap water) or sea water as appropriate. **Phenoxyethanol** is an oily liquid which can be useful but may be carcinogenic. It dissolves some plastics. **Benzocaine** (dissolved in ethanol or acetone stock solution) has been used, deep anaesthesia not reliable. A mixture of **clove oil and detergent** (Aqui S) has been developed in NZ to allow handling of salmon. It is sedative rather than anaesthetic and may cause stress (fish generally do not like detergent - it damages their gills).
Ether can be used at a pinch - it is slightly soluble in water.

TABLE 4.11.1 Inhalation anaesthetic drugs

Drug	Induct %	Maint %	MAC %	ML Vap /mL Liq	Svp (kPa)	Blood:gas	$ /100mL Liquid	Problems
halothane	2 - 5	0.5 - 2	0.9 1.1 (cat)	228	33	2.4	$30	malignant hyperthermia
isoflurane	2 - 3	0.5 - 2.5	1.4 - 1.9	189	32	1.4	$120	
sevoflurane	5 - 7	1 - 3	2.5 - 3.4	143	21	0.65	$240	
enflurane	4 - 5	0.5 - 3	2.2	196	23	1.9	$60	excitation
methoxyflurane	not easy!!	0.2 - 0.5	0.15	210	3	11	$222	strong smell
desflurane	4 - 11	2 - 9	7.2 - 10.3	206	89	0.4	$60	heated vaporiser
ether	up to 20	3 - 10	3	232	59	12	$12.50	inflammable / explosive
chloroform	1.5 - 2	0.5 - 1.5	0.8	302	21	8	$9	liver toxicity
trichloro ethylene	max	0.2 - 1.5	0.6	267	8	9	$39.50	+ soda lime = phosgene
nitrous oxide	not possible	66	105 (man) 220 (dog) 255 (cat)	656	5100	0.47	0.7c (vapour)	diffusion hypoxia
xenon	70	70	60 - 71 (man) 120 (dog & pig)	-	-	0.11	$3 (gas)	cost

*(Not all these drugs are easily available in NZ at the moment, and the prices can fluctuate **dramatically**. Use prices for comparison only!)*

Anticonvulsants

commonly used drugs

phenobarbitone (prevention)

diazepam (treating status epilepticus)

Anticonvulsants

- ☑ midazolam or diazepam is used in animals actually convulsing
- ☑ phenobarbitone is used to prevent seizures
- ☑ bromide is added to phenobarbitone as a last resort
- ☑ both diazepam and phenobarbitone potentiate the effects of GABA
- ☑ both suppress fits without treating the cause

Causes of seizures

- idiopathic epilepsy (caused by K^+ channel disease???)
- distemper
  - young dogs - active infection
  - old dogs - ecephalopathy
- head injury
- encephalitis
- CNS tumours
- pyrexia / heatstroke
- poisoning - metaldehyde
- etc, etc

Anticonvulsant drugs can control the signs but cannot treat the cause of the problem.

Epilepsy affects about 0.5% of dogs and cats (same as people). Seizures are classified in people - the situation is confused in dogs and cats but generalised tonic - clonic type (grand mal) type are commonest.

Treatment

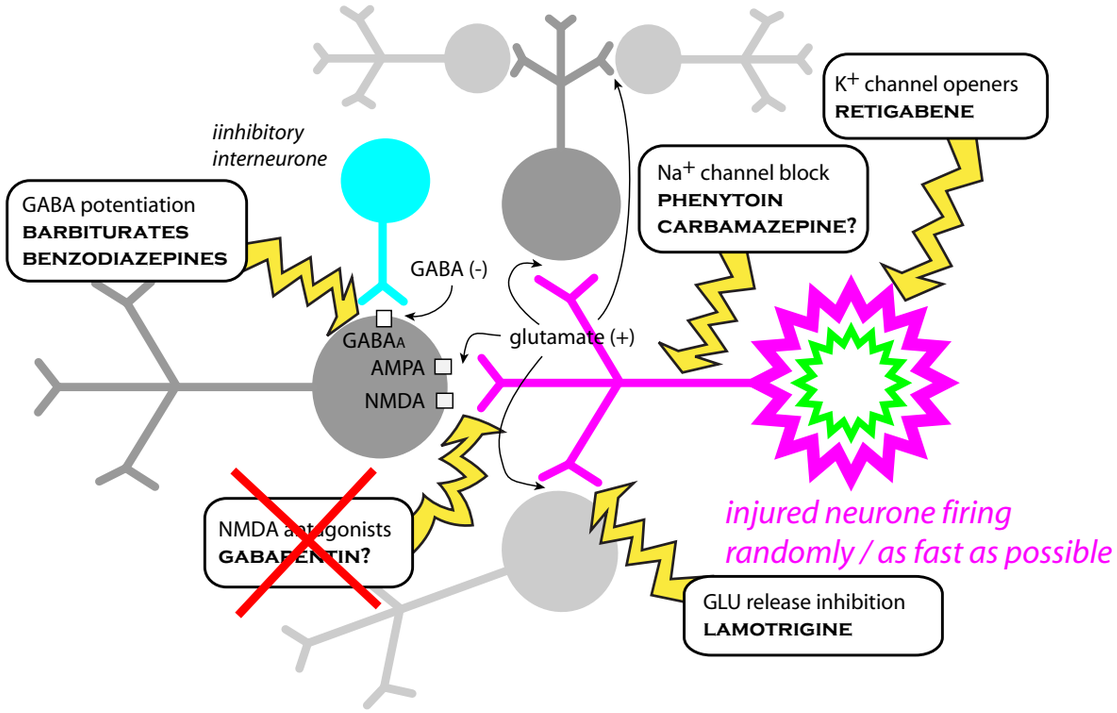
Status epilepticus is an emergency - continuous rapid firing of neurones releases lots of glutamate which is neurotoxic in large quantities, particularly to inhibitory interneurones, making seizures worse. Diazepam or midazolam must be given intravenously immediately. If there is no response general anaesthesia is used (thiopentone / pentobarbitone / phenobarbitone). Other drugs such as lorazepam and fosphenytoin are sometimes used in people. Remember Airway, Breathing and Circulation.

In an emergency, in dogs, cats and foals, give 5 - 10mg doses of diazepam iv to effect. This should stop the seizures for up to 20 minutes and give time for assessment. Diazepam is safe when given iv.

Prevention

Phenobarbitone (phenobarbital USAN) is the most commonly used drug although a variety of others have been tried. These drugs are given long term per os so chronic side effects are important. No drug gives complete control - 33% of dogs have no further fits, 33% improved, 33% not improved after phenobarbitone. Treatment should only be given if fits recur regularly (usually more than one a month).

DIAGRAM 4.12.1 Anticonvulsants



Anticonvulsant drugs' mechanisms of action. Most clinically useful drugs have more than one action.

Drugs

Phenobarbitone is the drug of choice for dogs and probably also cats. It is the cheapest and most effective. It usually produces sedation and ataxia for the first few days then tolerance develops to these effects. It takes 2 weeks to equilibrate. This is one of the most potent drugs for inducing P450 enzymes - metabolism of phenobarbitone and other drugs is greatly increased. Very rarely, it can cause liver damage.

Imepitoin has been recently registered for use in dogs. It is a phenytoin derivative, but is much safer and more effective (similar efficacy to phenobarbitone). It is not cheap.

Levetiracetam is sometimes used in people and is enjoying a fad at the moment in dogs. Only time will tell if it is clinically useful.

Felbamate is a relatively new drug which looks promising in dogs but is still expensive. It has a relatively short half life of 5 - 6 hours. Not available here.

Primidone has been used in dogs for many years. It is metabolised to phenobarbitone which is probably responsible for at least 85% of primidone's effect. Cats don't metabolise it as well so it is less effective. Liver damage occurs after high doses - 70% of clinical cases? Use phenobarbitone instead.

Phenytoin and **carbamazepine** are effective in man but their half lives are too short in dogs. Phenytoin is teratogenic and can cause liver damage, although a newer analogue, fosphenytoin, may be better. Their main mechanism is sodium channel blockade - use dependent block stops high frequency firing. They induce liver enzymes in about a week - faster metabolism.

Sodium **valproate** has a very short half life in the dog but may work in cats - no enzyme induction. It stops GABA breakdown / reuptake.

The **benzodiazepines** (diazepam) are not much use in dogs as they become tolerant in a few hours - days but may be useful in cats. There are many other benzodiazepine type drugs used in man - most do not work reliably in dogs and cats or are so short acting that they are useless.

Bromide passes through GABA receptors more easily than chloride and hyperpolarises cells in the same way. It is cheap and is unlikely to kill the dog, but has little else to recommend it. It is effective in about the same proportion of cases as phenobarbitone (~ 70%) but sometimes works when phenobarbitone does not (and vice versa). It has not been used for 30 years in people because of unpleasant subjective side effects but is being revived as a treatment for dogs in the USA. It is ethically dubious to make an animal's remaining life a misery with drugs in order to avoid being sued for killing the animal. It should be avoided in cats as it is less effective than in dogs and makes approximately 50% of them cough, which can lead to irreversible lung damage and death.

Gabapentin and **lamotrigine** are newish drugs which work well in people, but are also metabolised too quickly in dogs to be of much use. Gabapentin is sometimes added to combinations for dogs.

Topiramate is sometimes used in people. It is supposed to be synergistic with phenobarbitone but there is no experience of its use in dogs.

Combinations

Combinations of older drugs are a last resort - in people these combinations are no better than an adequate dose of one drug. In veterinary practice, combinations of phenobarbitone and bromide (at low doses) are sometimes used. Combinations of phenobarbitone and more modern drugs may be useful, but there is very little information on this as yet. These are usually used as a last resort before euthanasia. Remember that most anticonvulsant drugs will potentiate anaesthetics, but enzyme induction will shorten their effect. This can provide nasty surprises.

Treatment failure

Seizures occurring while an animal is taking an anticonvulsant drug do not necessarily mean that the drug is not working. The original disease may be getting worse, the dose may be too low, the animal may have developed tolerance or the owner may have forgotten to give the drug. Monitoring plasma levels is a useful way of checking (see formulary for therapeutic plasma levels).

Remember that these drugs only suppress seizures; they do not treat the causative disease, which may be progressing.

Drugs which may trigger epilepsy

Avoid phenothiazines and butyrophenones - they lower seizure threshold and can cause extra pyramidal effects which can easily be confused with seizures. Several anaesthetic drugs can lower seizure thresholds, but this is not usually a problem under anaesthesia. Avoid fluoroquinolone antibiotics, especially in combination with NSAIDs in dogs prone to epilepsy.

The future??

Response to drugs in man is similar to dogs - ie a large proportion of cases are not improved. This has led to the development of lots of new drugs which have not yet been evaluated in domestic animals, particularly NMDA antagonists. The drugs of choice for dogs could change radically in a few years.

Electrical stimulation of the cervical vagus works in many people with epilepsy which is refractory to drugs. This has not been reported in dogs yet! Stimulation of various parts of the brain, either electrical or magnetic, appears to work in some people and some models of epilepsy, as does chopping out bits of the brain (usually parts of the hippocampus).

More interestingly from a pharmacological point of view, a ketogenic diet has been shown to be effective at preventing epilepsy in children. If the mechanism of this was understood, new drugs might follow.

In the longer term, gene therapy to replace defective potassium channels is a possibility in people.

TABLE 4.12.1 Anticonvulsant pharmacokinetics

	Dog	Cat	Man
phenobarbitone	42 - 100 (24 - 30)	34 - 43	70 - 100
primidone	2 - 7		6 - 12
phenytoin	2 - 4	24 - 108	15 - 24
carbamazepine	1		24 - 48
valproate	1.5 - 3	8.5	8 - 15
ethosuximide	17		16 - 70
diazepam	2 - 5	2	24 - 72
clonazepam	1 - 5		24 - 36
felbamate	12		23
bromide	25 - 46 days		11 days

Elimination half lives of some anticonvulsants (hours - except for bromide)

Stimulants

CNS stimulants are occasionally given to animals, but there are practically no indications for them.

Doxapram is sometimes used as a respiratory stimulant, particularly in new born animals. However, its effects are not confined to the respiratory centre, and it will cause general CNS stimulation (and increased energy requirements). Most respiratory problems in new born animals are caused by airway obstruction: giving a drug which increases cerebral oxygen requirement will make the situation worse. The only indication for doxapram is to counteract the effects of a respiratory depressant drug where it is not possible to perform IPPV for some reason. However, if it is not possible to perform IPPV, you should not be giving respiratory depressant drugs!

Amphetamines are widely used drugs of abuse in people, and probably in racing animals, particularly greyhounds. There are no indications for them in animals, and it is unethical, and in most cases illegal, to give them to animals (or even possess them). You may see cases where animals have eaten their owner's P.

Methylphenidate (Ritalin), a cocaine analogue, is given to children in a similar way to behaviour modifying drugs are given to dogs and cats. Its only possible indication in animals is narcolepsy, which is very rare. **Modafinil**, a stimulant with an unkown mechanism of action is also used in people for narcolepsy. There is no experience of its use in domestic animals. It is sometimes abused in people as a "cognition enhancer".

Methylxantines, such as **theophylline**, have a mild stimulant effect, but are usually used for their other effects. If you need to use a CNS stimulant in an animal, use one of these. Theobromine seems particularly toxic to dogs.

Psychopharmacology

commonly used drugs

diazepam

amitriptylline

Psychopharmacology

- ☑ Make a specific diagnosis
- ☑ use drugs as an adjunct to environmental change and training
- ☑ beware diazepam - can make bad behaviour worse!

The use of drugs to treat behaviour problems in animals (psychopharmacology) is in its infancy. Much of the available data is anecdotal and based on individual clinical cases treated successfully (unsuccessful cases are not written up). The drugs used are usually not registered for use in animals. There is a tendency to prescribe drugs used in the treatment of human psychiatric disorders for the treatment of animals but there have been very few trials in which the use of such drugs in cats and dogs was examined scientifically. Behavioural treatment should be used in combination with drugs.

Beware side effects: many of the drugs used to alter behaviour act on monoamines, an effective overdose of noradrenaline or 5HT can have severe cardiovascular effects (serotonin syndrome).

Problems in cats

Inappropriate marking

Anxiolytic drugs, antidepressants and progestins have been used. They reduce the anxiety and stress being experienced by the cat. This allows the cat time to become habituated or desensitized to the stressor and the owner time to modify the environment to reduce the stressor. Drugs assist in the treatment of inappropriate marking but may be ineffective if used without environmental modification.

Many drugs are used to reduce anxiety in humans. The definition of anxiety in domestic animals remains unclear but it is widely accepted that inappropriate marking in cats is often due to anxiety. The most commonly used anxiolytic in the cat is diazepam 1 to 2 mg/cat (0.2 - 0.4mg/kg) twice daily for 4 weeks then once daily for 4 weeks then decreased by half.

Many cats revert to inappropriate marking when diazapam is stopped. It improves the problem in 55 to 75% of cats and is as effective in males as females. Longer acting benzodiazepines, lorazepam, oxazepam or clonazepam may also be useful.

Sedation may leave the cat more vulnerable to road traffic accidents and predatory dogs. Increased appetite and weight gain are common. Interestingly, increased affection is regularly seen. Fatal hepatic toxicity has been reported in cats within 11 days of receiving diazepam.

Buspirone is a $5HT_{1A}$ antagonist used as an anxiolytic in people. It may be effective in the treatment of inappropriate marking in cats (0.5 - 1mg/kg po 2 - 3 times daily). Buspirone has little sedative effect and appears to produce little tolerance in humans. It does not cause withdrawal symptoms. If the cat does not respond to

treatment then use something else. Buspirone was effective in 55% of cats in one study.

Tricyclic antidepressants are the most commonly used drugs in the treatment of depression in humans. They have minimal interference with short term memory and thus are useful in behaviour therapy in animals. Amitriptyline, clomipramine and fluoxetine are commonly used. Treatment should continue for 2 to 3 weeks after the undesirable behaviour has stopped. The medication should then be gradually reduced over an eight week period. Amitriptylline stopped inappropriate marking in 80% of cats in one study. Sleepiness was seen initially but it wore off during the first two weeks of treatment.

Progestins, such as megoestrol in tablet form and medroxyprogesterone in injectable form, have antiandrogenic and antianxiety effects. They are commonly used for sexually dimorphic problems which have not responded to neutering. They may work by selective binding to sites in the hypothalamus which reverse the action of testosterone sensitive action centres. They should not be used initially in the treatment of inappropriate marking because of their side effects.

In the treatment of inappropriate marking it is the antianxiety effect of progestins which is utilised. They are reported as being effective in about 30 to 50% of neutered cats however other reports conclude that they are effective in 48% neutered males and 18% spayed queens. If the treatment is successful then results should be seen within the first week after initiation. It has been suggested that if megoestrol acetate does not work then medroxyprogesterone may or vice versa.

Progestins should be used as a last resort since the risk of side effects is high.

Problems in dogs

Aggression

There are several different types of aggression and it is important to diagnose the cause of aggression before initiating treatment. In addition the social milieu in which aggression occurs must be considered before treatment is embarked upon. Behavioural therapy and castration are often effective in reducing or eliminating aggression but on occasion drugs are needed to supplement these. Painful conditions, especially those of the ears, shoulders and hips are probably more important in the development of aggression than we usually recognise.

Male aggression, especially intermale aggression, may respond to castration. If castration is not possible or if aggression continues afterwards then progestins (medroxyprogesterone) may be effective .

Acepromazine may be effective in the short term control of aggression (0.5 - 2.0 mg/kg po every 8 to 36 hours).

The anti-androgenic progestagen delmadinone (Tardak) may also be effective. It is thought to work by inhibiting pituitary gonadotrophin release and by affecting a behavioural centre. The effects are reversible. Dose dogs <10 kg - 1.5 - 2.0 mg/kg, 10 to 20kg - 1.0 - 1.5 mg/kg, >20kg - 1 mg/kg bodyweight by sc or im injection.

An effect should be seen within 5 days. If not seen within 8 days repeat treatment. Otherwise repeat treatment at 3 to 4 weeks. Thereafter repeat as required. Do not use in dogs with history of poor libido or poor fertility if such dogs are to be used later for stud purposes. Do not use if other steroids are being given.

The use of diazepam for the treatment of fear aggression in dogs is not recommended as it sometimes acts to cause aggression, probably by reducing fear.

Obsessive compulsive behaviour

The obsessive-compulsive behaviour in dogs which include tail chasing (Bull Terrier types), flank sucking (Doberman), fly biting (Cavalier King Charles Spaniels) and acral lick granuloma are similar to stereotypic behaviour seen in humans such as hair pulling and hand washing. The pathological background to these activities remain ill defined but it is believed that aberrant serotonin metabolism is involved although some attribute the activity to abnormal endorphin metabolism. It is suggested that the anatomical focus of the disorder is the limbic system and studies have implicated the basal ganglia in the region of the caudate nucleus in humans.

Obsessive compulsive behaviours are characterised by being repetitive behaviours in excess of requirements and often interfering with normal activities.

Differential diagnosis of obsessive compulsive behaviour in dogs include the following;

•boredom - responds to increased activity, environmental enrichment, increased human attention

•attention seeking behaviour - responds to increased attention and desensitization or counter conditioning

•hyperactivity usually responds to increased exercise levels. True hyperactivity is extremely rare and affected dogs only stop their activity when exhausted. These dogs respond to treatment with methylphenidate (Ritalin) 5 mg orally every 12 hours (up to 20 to 40 mg daily) or amphetamines (dextroamphetamine) 0.2 to 1.3 mg/kg orally as required (not recommended for ethical reasons). These drugs stimulate non-hyperactive dogs to become hyperactive and hyperactive dogs are calmed. Treatment is usually for life though it may be suspended for a week or two every 6 months to determine if hyperkinesis returns. NB. these are drugs of abuse in people.

•anxiety especially separation anxiety (see below)

•infectious or metabolic disease. Distemper may cause repetitive activities.

•neurological disease. Nerve conduction dysfunction has been implicated in cases of self mutilation. CNS neoplastic conditions may also cause repetitive activities. Epilepsy.

•self mutilation due to dermatological or other medical reasons.

•self mutilation due to aberrant endorphin metabolism may be treated by naltrexone (dog) 2.2mg/kg orally every 12 or 24 hours (cat) 25 - 50 mg/ cat every 12 to 24 hours. If naltrexone doesn't block the response then it is probably not due to aberrant endorphin metabolism.

Obsessive compulsive behaviour may be the appropriate diagnosis if the dog or cat does not respond to the therapies discussed above and if it interferes with normal behaviour.

Obsessive compulsive behaviour disorders have been treated with tricyclic antidepressants; amitriptyline (1-2 mg/kg twice daily for dogs); clomipramine (can cause arrhythmias and should be used only after the dog has had a thorough cardiac examination). Because it is potentially dangerous, treatment should start at about 0.5mg/kg every 12 hours increasing over a 5 week period to 3mg/kg or 200mg per day whichever is less. Should any side effects develop the treatment should be stopped or the dosage reduced. Usually treatment should last for 5 weeks to determine how succesful it is. If clomipramine is successful it will have to be continued for life. Imipramine and fluoxetine (0.5 - 1mg/kg once daily) have also been used, as has doxepin 3-5mg/kg orally every 12 hours increasing to a maximum of 150mg/kg every 12 hours. The minimum dose is given for 10 days and should be doubled if no effect seen.

Separation anxiety

A common problem in young dogs and may be expressed as persistent barking or destruction / digging when the owners are absent. This type of anxiety is usually treated by counter-conditioning and habituation. However counter conditioning for the treatment of anxiety is usually more successful if combined with medication. Two drugs considered to be particularly useful in the treatment of seperation anxiety in dogs are; clomipramine (1 - 2mg/kg twice daily) and amitriptyline (1-2 mg/kg twice daily). Both are very useful for dogs which bark or groom excessively when alone. Usually given about 1 hour before everyone leaves the home. Treatment continued for up to 3 months and then tailed off gradually. Fluoxetine (1mg/kg once or twice daily) is also useful.

Phobias

Diazepam given before or during a storm may be useful in reducing the expression of the phobias. However diazepam does change some dogs behaviour for the bad and they may become aggressive and destructive. Use with caution in nervous dogs!

Chapter 6

Cardiovascular system

This part covers drugs which act on the cardiovascular system, or are used to treat cardiovascular problems.

Heart failure

commonly used drugs

cardiac arrest - adrenaline

acute heart failure - inotropes, fluids, antiarrhythmics

Heart Failure

☑ priorities for cardiopulmonary resuscitation

Airway, Breathing and Circulation

☑ sympathomimetics are often used for acute heart failure in intensive care situations. They must be given by intravenous infusion and effects must be monitored.

☑ congestive heart failure is treated with diuretics, vasodilators, inotropes and possibly antiarrhythmics

The cardiovascular system is one integrated system - changing one aspect with drugs alters everything else. The system is normally controlled within very fine limits by a variety of mechanisms - a knowledge of cardiovascular physiology is essential to understand cardiovascular pharmacology and use cardiovascular drugs safely.

		Problem	Drugs used
heart	conducting system	arrhythmias	anti-arrhythmics
	myocardium	reduced contractility	positive inotropes, vasodilators, diuretics
	blood supply	ischaemia	vasodilators, diuretics
	valves	regurgitation	vasodilators
	neural control	rate	chronotropes
blood vessels	hypertension	vasodilators	
blood	volume	hypovolaemia	colloids (crystalloids)
	red blood cells	haemorrhage	whole blood
	proteins	various problems	colloids, clotting factors
	ions	various problems	crystalloids

Heart disease is common in all species but is usually only treated in dogs, cats and horses. The pattern of disease seen does not reflect the incidence in animals; most cases of cardiac arrest (and probably acute heart failure) which occur outside the clinic will die. Acute heart failure ± cardiac arrest commonly follow poor anaesthesia - it can be embarassing to take in a healthy animal and give it back to the owner in a black plastic bag.

Types of heart failure

1. cardiac arrest
2. acute heart failure
3. chronic heart failure (usually presents as congestive heart failure)

The treatment of these is different, although chronic heart failure can (and finally does) progress to acute heart failure then cardiac arrest.

Cardiac Arrest

You must know how to carry out cardiopulmonary resuscitation since if an animal goes into cardiac arrest you do not have time to consult your notes!

Drugs are not usually needed until the recovery phase - when a knowledge of pharmacology really is required!

Prevention of cardiac arrest is much better than cure!! Prevent hypoxia and acidosis. Print out the page overleaf and stick it up on the wall where you can refer to it in an emergency.

Priorities in cardiac arrest

Airway - usually intubation

Breathing - intermittent positive pressure ventilation, preferably with oxygen

Circulation - external cardiac massage (fluids ± vasoconstrictors)

and only then

Drugs are used as necessary (usually given iv (occasionally down the endotracheal tube for some drugs) since blood flow to the tissues will be reduced). Drugs are not usually effective for starting a heart that is stopped (although they may be used as adjuncts): in nearly every case the most effective treatment is restoration of the flow of oxygenated blood to the myocardium by external cardiac massage.

Drugs are most useful for supporting the heart after resuscitation when the animal is effectively in acute heart failure.

- positive inotropes
  - adrenaline, dobutamine
- antiarrhythmics
  - lignocaine
- fluids
  - bicarbonate, crystalloids, colloids

ECG is usually useful as myocardial damage is common after CPR

Acute Heart Failure

Causes:

- anaesthetic overdose
- pericarditis
- metabolic illness

Cases which occur outside the clinic will probably die. Animals must be handled with extreme care as excitement may well cause cardiac arrest.

Drugs used include positive inotropes (usually β1 agonists), iv fluids, antiarrhythmics and vasodilators (usually nitrates). They are given intravenously to effect and the animal is monitored very closely in intensive care.

Congestive Heart Failure

This is commonly seen in practice in dogs and cats: these are usually treated as outpatients. It is a syndrome of low cardiac output which can arise from a number of causes. Endocardiosis, usually resulting in leaky valves, occurs in 30% of dogs over 10. As a very broad genralisation, dogs get dilated cardiomyopathy and cats get myocardial hypertrophy. Accurate diagnosis is essential (usually ultrasound), as some drugs used for one type will make the other type worse.

Heart failure is sometimes classified into backward and forward failure, which is of some use when deciding on drugs:

- backward failure - increased right atrial pressure from lack of forward flow through the heart causes blood to dam back to capilliaries. This pressure causes leakage which is seen as oedema.

TABLE 5.1.1 CPR chart

Cardiopulmonary resuscitation

If the animal has stopped breathing (do not count gasps) and there is no peripheral pulse, check apex beat.
If there is no apex beat, start CPR; if there is an apex beat ventilate with 100% oxygen.

	Concurrent activity
Airway Visually check / insert endotracheal tube, or, Emergency tracheotomy (14SWG catheter through cricothyroid membrane), or, Extend neck and pull tongue forward. Stop giving anaesthetic drugs, flush circuit with oxygen and set high oxygen flow.	Shout for help. Note time.
Breathing Squeeze bag 3 times checking for chest expansion - if chest expands, check pulse again: if no chest expansion, check airway again, or, Ventilate mouth to nose. Ventilate every 5 seconds; allow chest to deflate between breaths.	When an assistant arrives, they take over ventilation.
Circulation Lay animal on right side. Extenal cardiac massage at 2 beats / second. Continue ventilation. Stop and check for pulse every 2 minutes. Internal cardiac massage is only justified if chest is open or if there are major chest wounds.	Establish iv access - big catheter in a big vein - cut down if necessary. Start fluids at a slow rate to keep vein open.
Drugs No drugs necessary in the first 5 minutes, then: adrenaline 20µg/kg iv, or 100µg/kg intratracheally. Repeat every five minutes with a double dose if no response. atropine 20µg/kg iv, or 40µg/kg intratracheally once. After 10 mins CPR: sodium bicarbonate 1mEq (=mmol)/kg slowly iv into running infusion, preferably 0.9% NaCl. Do not give intratracheally! Repeat 0.5mEq/kg iv every 10 minutes of CPR. In hyperkalaemia or hypocalcaemia only: calcium (boro)gluconate 1mg/kg iv - do not give with bicarbonate. Stop CPR after 20 minutes if no response.	Attach ECG Flush drugs in with 5 - 50mL saline Check potassium first.
After heart restarts Continue ventilation with 100% oxygen and consider:	monitor ECG
positive inotropes: adrenaline 5 - 10µg/kg/min iv - titrate to effect on blood pressure, / dobutamine 2.5 - 10µg/kg/min iv - titrate to effect, / dopamine 1 - 10µg/kg/min iv - titrate to effect	
fluids: sodium bicarbonate in normal saline, Hartmann's, colloids - beware overdose!	monitor blood gases and central venous pressure
antiarrhythmics only give if absolutely necessary: *tachydysrhythmias* lignocaine (without adrenaline) 1mg/kg slowly iv; repeat every 10 mins if necessary up to 3 times, then 20µg/kg/min if necessary verapamil 20µg/kg iv over 10 mins, repeat if necessary. *bradydysrhythmias* isoprenaline 20 - 200µg/kg/min iv, or, dobutamine 2.5 - 10µg/kg/min iv to effect	monitor ECG

- forward failure - not enough blood flows to the tissues so oxygen demand outstrips supply. This is seen as excercise intolerance.

Backward and forward failure can be further classified into left and right sided failure.

- left backward - pulmonary oedema and cough
- left forward - poor tissue blood flow - kidneys - drug excretion
- right backward - ascites, hepatic congestion (reduced drug metabolism), peripheral oedema
- right forward - poor blood flow to lungs - left side filling reduced - left out put reduced

Treatment of congestive heart failure

Dogs commonly develop valvular incompetence or dilated cardiomyopathy, while cats usually get hypertrophic cardiomyopathy. However, as a general rule, the treatment given depends on the severity of the disease rather than the cause. Animals with severe congestive heart failure are usually hospitalised and treated for acute heart failure until stable. Excitement can cause congestive heart failure to become acute!

Treatment

- (rest)
- (low salt diet)
- diuretics
- vasodilators (ACE inhibitors)
- positive inotropes
- antiarrhythmics if necessary

Treatment is required when the normal homoeostatic mechanisms fail to keep arterial blood pressure within the normal range, or when the cardiac output is inadequate for normal tissue perfusion, or when treatment will help decrease the progression of disease.

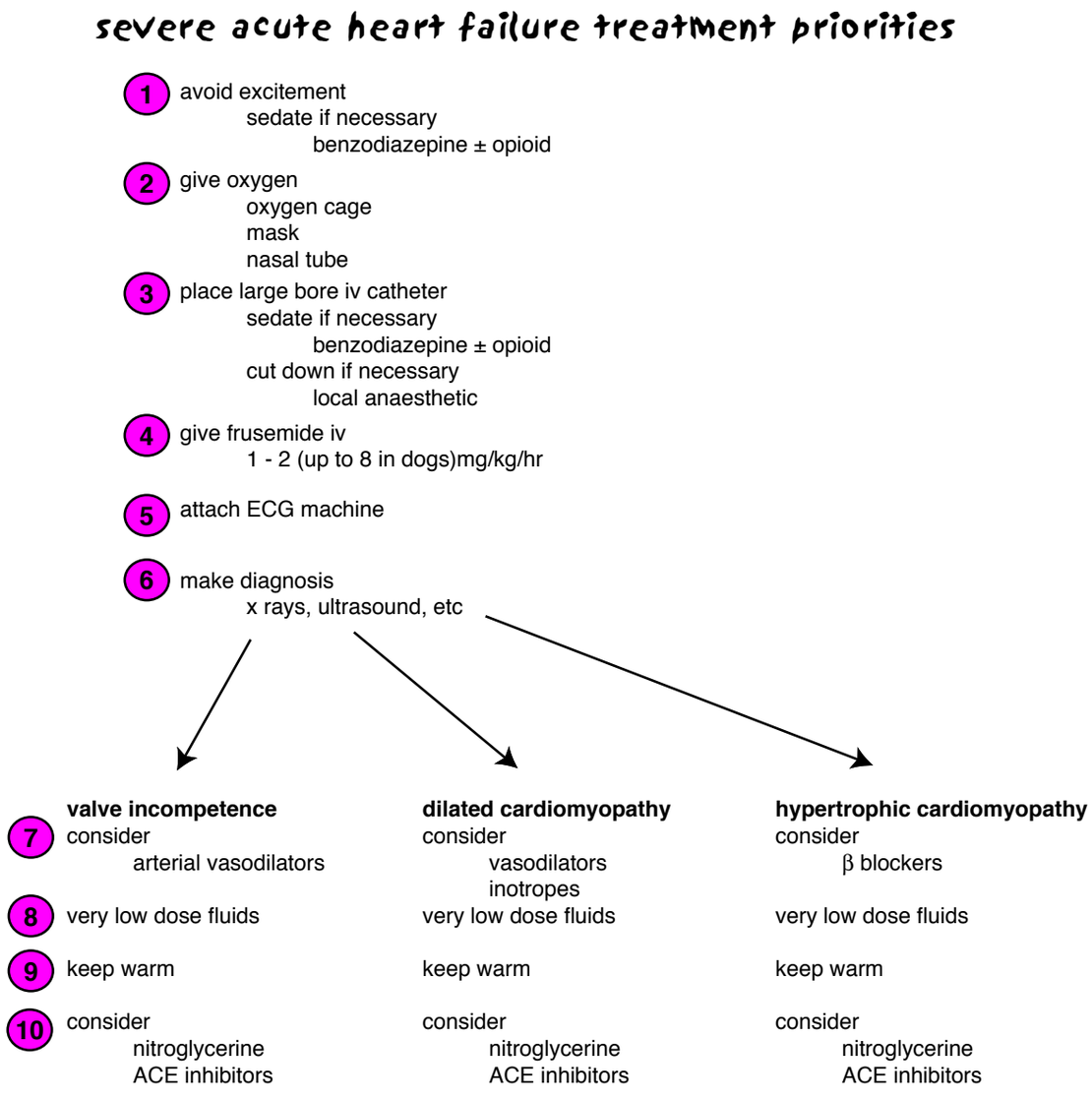
Therapy has four principal goals:

- improve tissue circulation
- maintain tissue oxygenation
- adjust fluid compartments and venous flow to maintain blood flow but prevent

congestion

- normalise cardiac rhythm

DIAGRAM 5.1.1 acute heart failure treatment algorythm



Treatment of congestive heart failure in people has changed in the last 10 years; veterinary treatment may eventually catch up. As well as diuretics and ACE inhibitors, most people with CHF will receive β blockers (± phosphodiesterase inhibitors in the short term). A number of other treatments are coming along:

- endothelin antagonists such as bosentan are particularly useful in CHF with pulmonary hypertension
- endothelin converting enzyme inhibitors such as phosphoramidon
- vasopeptidase inhibitors such as omapatrilat - inhibit ACE and stimulate ANP which causes vasodilatation and natriuresis
- recombinant brain natriuretic peptide

You may have to (re)learn your cardiovascular pharmacology in a few years' time!

Positive inotropes

commonly used drugs

sympathomimetics - adrenaline, dopamine, dobutamine

PDIs - pimobendan

cardiac glycosides - digoxin

Positive inotropes

- ☑ sympathomimetics infused iv for acute heart failure in anaesthesia and intensive care
- ☑ phosphodiesterase inhibitors infused iv for acute heart failure in anaesthesia and intensive care, or given orally for congestive heart failure
- ☑ cardiac glycosides were given orally for congestive heat failure but have very low therapeutic index; beware low potassium

Positive inotropes are drugs which act primarily by increasing myocardial contractility, i.e. they increase the force of myocardial contraction. They require the existence of a cardiac reserve, i.e. a completely decompensated heart will not respond to these drugs. Diseased cells may or may not respond to the influence of the inotropes, depending on:

- method by which the drug increases contractility
- potency of the drug
- type of deficit resulting in a loss of contractility
- severity of the defect present in the cell
- number of cells involved

The successful use of these drugs results in improvement to either the quality (ie. alleviate clinical signs at rest) or quantity (ie. increase survival time) of life.

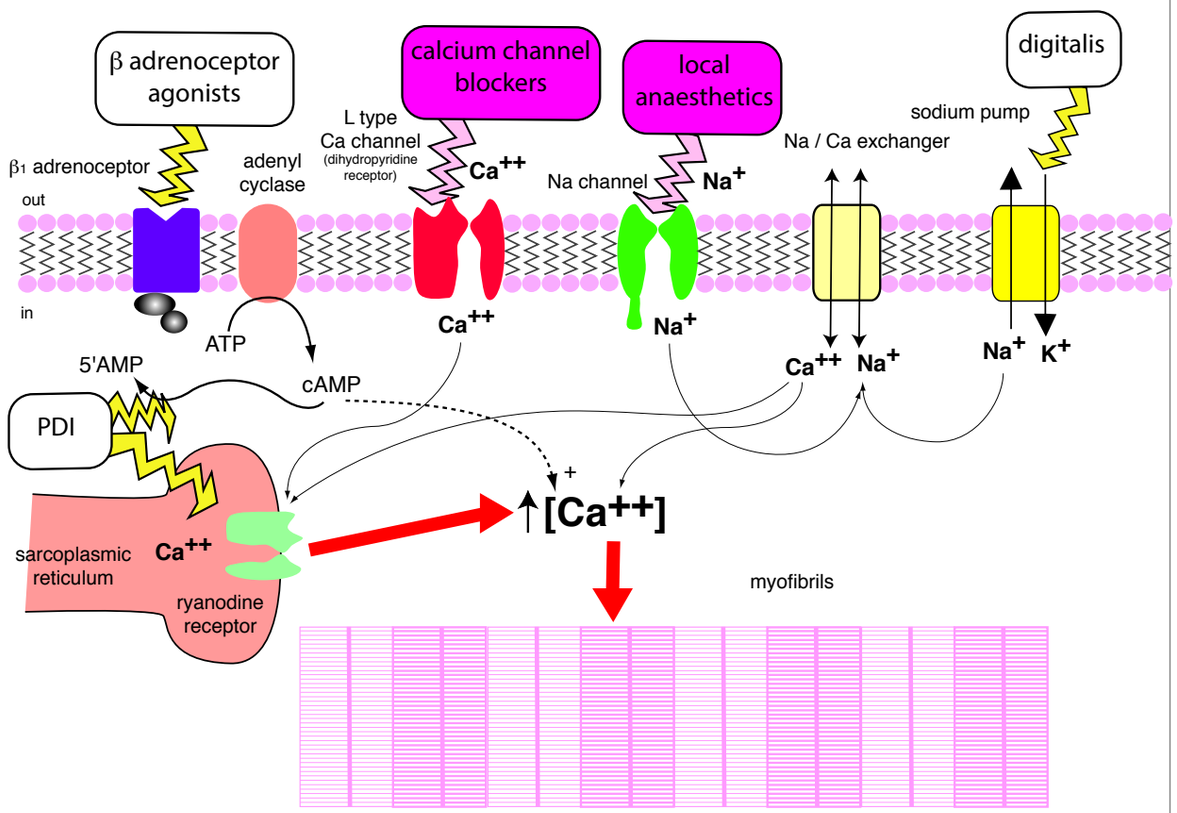
There are three main groups of drugs: cardiac glycosides, phosphodiesterase inhibitors and sympathomimetics. As a general rule, cardiac glycosides and phosphodiesterase inhibitors are used for chronic heart failure, sympathomimetics for acute heart failure.

The mechanisms of action vary from class to class. Most drugs are thought to work by increasing the concentration of free calcium ions in the sarcoplasm, usually by triggering release of the calcium stores in the sarcoplasmic reticulum through ryanodine receptors.

Sympathomimetics

Sympathomimetics may be used for short term inotropic support of a failing myocardium. They have a very short half life and therefore are only really useful as either an iv bolus or as iv infusions; ie in intensive care. They are therefore normally used only in acute heart failure. Traditionally, dobutamine has been used in dogs and horses, and dopamine in people, but there is no good reason for this. Adrenaline is cheap, and is the best drug to treat anaphylaxis in the field. This means that it should always be available and **you must memorise the dose rate**. Sympathomimetics are primarily used as inotropes, usually for their β1 agonist effects, but β1 receptor activation also increases automaticity of myocardial cells so ventricular ectopic beats are a common sign of overdose. These may progress to ventricular tachycardia or even ventricular fibrillation, so **ECG monitoring is necessary**. Since the object of therapy is to increase arterial blood pressure, this is usually monitored directly.

DIAGRAM 5.2.1 Positive inotropes



Mechanism of action of positive inotropes (white boxes) and negative inotropes (pink boxes). PDI = phosphodiesterase inhibitors.

TABLE 5.2.1 Sympathomimetic effects

Effect On	Rate	Force	SVR	ABP
adrenaline	++	+++	+++	+++
noradrenaline	-	0/+	+++	+++
dopamine	0	+++	0/-	++
isoprenaline	+++	+++	-	-
dobutamine	+	+++	+	+++
dopexamine	0/+	+++	0	+++

nb: different effects occur at different doses (SVR = systemic vascular resistance; ie, vasoconstriction: ABP = arterial blood pressure)

Tolerance to β1 receptor activation can occur after as little as 8 hours so long term use is usually limited to 3 days maximum.

Drugs

Adrenaline (epinephrine USAN - not to be confused with ephedrine) is an agonist at β1 and α1 receptors in the heart (positive inotrope and chronotrope) and all adrenergic receptors peripherally (predominantly arteriolar constriction and a subsequent increase in afterload). It is cheap and should be readily available for emergencies.

Adrenaline usually comes as a 1:1000 solution in brown ampoules (it is light and oxygen sensitive), but it should be diluted to at least 1:10,000 before use. It can be mixed with most iv fluids for infusion, although anything containing calcium is best avoided.

Indications

•cardiac arrest:

to increase the efficacy of electrical defibrillation

(asystole and severe bradyarrhythmias) use atropine first

•inotropic infusion in intensive care (must monitor ECG)

Dose of adrenaline

Dilute to 1:10,000 (100µg/mL)

- **20 µg/kg im or**
- **5 - 20 µg/kg iv or**
- **20µg/kg intratracheal, or as a last resort only**
- **2 µg/kg intracardiac (avoid if possible)**

This may have to be given in an emergency - memorise the dose!

•anaphylaxis / analphylactoid reactions (often to drugs) - im or sc bolus injections usually used in the field

Side effects

tachyarrhythmias leading to ventricular ectopic beats and ultimately ventricular fibrillation in overdose - monitor ECG and feel pulse for irregularities. nb tachyarrhythmias are more likely in the presence of halothane.

Other drugs

Noradrenaline (norepinephrine USAN) is mainly an α agonist (vasoconstriction) but has some useful β1 effects at higher doses. It is indicated for haemostasis of mucosae and has been used for systemic vasoconstriction. It is contraindicated in heart failure (increases afterload).

Isoprenaline (isoproterenol USAN) is a synthetic β1 and β2 receptor agonist which increases heart rate more than other catecholamines. It decreases peripheral vascular resistance by its β2 effects. This may cause a decrease in blood pressure. It has no real place in the treatment of heart failure as it has a positive chronotropic effect ie. increase heart rate, and a potential to cause malignant ventricular dysrhythmias. It is occasionally used to increase heart rate in third degree heart block (but a pacemaker is better).

Dopamine is an endogenous precursor of noradrenaline but also has direct effects. At a low dose (2μg/kg/min) it is a dopamine receptor agonist and causes renal, mesenteric, (coronary, cerebral) arteriolar vasodilatation. At a medium dose (2 - 5μg/kg/min) it acts at β1 receptors to produce positive inotropy. At a slightly higher dose (5 - 10μg/kg/min) it acts at β1 receptors to cause positive chronotropy and increased automaticity as well. At high doses (>10μg/kg/min) it affects α1 receptors, either directly or by causing the release of noradrenaline, and causes vasoconstriction.

Since it must be given by infusion, dopamine is usually only used in intensive care, as a positive inotrope in acute heart failure or in shock when renal and mesenteric flow is decreased from vasoconstriction.

Side effects are dose dependent and include tachycardia, supraventricular and / or ventricular arrhythmias, vomiting, hypotension, and vasoconstriction. Since it is used by infusion and it has a very short half life treatment of toxicity is by slowing or stopping it

Contraindications - ventricular fibrillation & uncorrected arrhythmias

It is always given by infusion, starting at a low dose (1 μg/kg/min). Effects are monitored (ECG, ABP) and rate increased until the desired effect has been reached or toxicity (tachycardia, ventricular ectopic beats) occurs. Accurate control of infusion rate requires an infusion pump.

Dobutamine is a synthetic catecholamine with predominant β1 agonist effects which increase contractility and is relatively non-arrhythmic. It favours cardiac output redistribution to coronary and skeletal muscle beds. Renal and mesenteric flows also increase due to a total increase in cardiac output. It enhances AV conduction resulting in mild positive chronotropic effect

It is used to increase contractility in patients in acute heart failure (horses under anaesthesia), and for short term stabilisation of chronic heart failure until longer acting drugs can take effect.

Side effects are similar to dopamine.

Dopexamine is similar to dopamine but longer acting. Not available in NZ at present.

Calcium

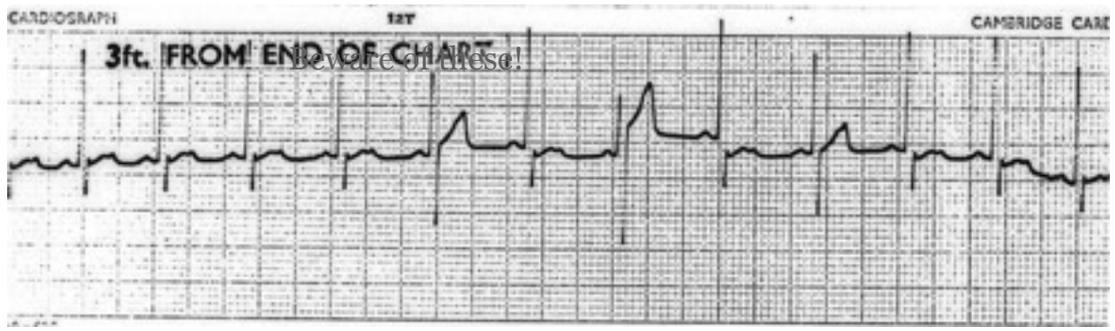
Do not use this!

Since most inotropes act to increase intracellular calcium, it seems logical to use calcium salts (gluconate or chloride) as inotropes. They can be effective and used to be used for this purpose, especially after cardiac arrest, but they are much better at causing contraction of smooth muscle than cardiac muscle. This means that they produce intense vasoconstriction - in the coronary and cerebral vessels this will potentiate or even cause ischaemia. Calcium has been shown to reduce survival in acute heart failure and should not be used as an inotrope. Indeed, modern practice is to use calcium channel blockers to cause coronary and cerebral vasodilatation in cardiac intensive care, despite the small reducution in cardiac output they cause.

Phosphodiesterase inhibitors

This group of drugs includes such familiar substances as caffeine (coffee), theophylline (tea) and theobromine (chocolate). Most of the drugs used in veterinary practice are esters of theophylline, such as aminophylline or etamiphylline. Newer PDIs specific for cardiac phosphodiesterase have been produced for human use, these include amrinone, milrinone and enoximone. “Viagra” (sildenafil) started out as one of these until its interesting side effects were noted. Oxpentifylline (pentoxyfylline USAN) is a theophylline type drug which is rather more specific for PDE 4 and has a number of different effects such as TNFa antagonism. It could be useful in CHF but is not usually used.

IMAGE 5.1 Ventricular ectopic beats



Beware of these!

Mechanism of Action

(See inotropes diagram) Phosphodiesterase normally inactivates cAMP. Inhibition of cAMP degradation leads to increases in intracellular cAMP concentration, and consequent increases in activity of cAMP-dependent protein kinase. This activates many intracellular enzymes by phosphorylation. Calcium dependent enzymes are also activated, leading to stimulation of contractility due to increased effects of intracellular calcium. Their effects are additive with digoxin.

These drugs increase the rate and force of myocardial contraction. They also cause some bronchial and systemic arterial dilatation and increase the alertness of the animal, all of which is useful in dogs with CHF. There are at least 11 different types of phosphodiesterase (and numerous subtypes), so the range of effects is large.

The cardiac specific phosphodiesterase inhibitors (PDI3s) were initially widely touted as an alternative to digitalis in man but are going out of fashion as although they alleviate congestive heart failure, they reduce survival time in man. They seem to improve the quality of life but increase the chances of sudden death, probably from arrhythmias. This is probably acceptable in animals.

PDI4s are currently undergoing investigation as anti-inflammatory drugs. Sildenafil is a PDI5.

Methylxanthines

Methylxanthines (usually theophylline esters such as aminophylline or etamiphylline) are also adenosine A2 receptor antagonists. Adenosine is secreted by most cells in response to high energy usage compared to oxygen availability, and acts as an autacoid to decrease the oxygen demand and to increase oxygen availability through alterations to blood flow.

Effects

Methylxanthines act as weak positive inotropes, but more importantly they relax smooth muscle in bronchi and pulmonary vasculature. They induce diuresis both by increasing cardiac output and hence renal blood flow, and by increasing renal blood flow directly through blockade of adenosine's vasoconstrictive actions in renal vessels. Methylxanthines may also cause central stimulation which is probably a major part of their clinical effect (a previously lethargic dog becomes active again). The relative importance of these effects is different for each drug.

Side effects

- CNS excitation - restlessness to convulsions
- tachycardia which can lead on to ventricular tachyarrhythmias and sudden death
- tachypnoea

Indications

mild congestive heart failure, for bronchodilator effects in patients with myocardial failure, pulmonary oedema or asthma.

Care

use with caution in animals with

- severe cardiac disease
- gastric ulcers as it induces gastric acid secretion
- hyperthyroidism
- renal or hepatic disease

antagonises β blocker effects

Dose

Theophyllines have a low therapeutic index so determine dosage correctly. Dose obese animals on their lean body weight. Sustained release products offer the advantage of less frequent dosing, better owner compliance and less fluctuation in blood levels but results may be erratic in animals. im injection is painful; iv injection must be very slow, though because of good bioavailability of oral preparations it is rarely used.

TABLE 5.2.2 Phosphodiesterase subtypes.

Enzyme	Subtypes	Tissue	Inhibitors
PDE1	A, B, C	CNS, blood vessels	
PDE2	A		
PDE3	A, B	myocardium, blood vessels	milrinone, pimobendan,
PDE4	A, B, C, D	airways, inflammatory cells, CNS, stomach	rolipram, oxpentifylline,
PDE5	A	blood vessels, platelets	sildenafil,
PDE6	A, B, C, D, G, H	retina	sildenafil,
PDE7	A, B	skeletal muscle	
PDE8	A, B		
PDE9	A		
PDE10	A		
PDE11	A		

Phosphodiesterase isoenzymes. Theophylline (and papaverine) are non-specific inhibitors.

Other drugs

Amrinone was the first specific cardiac phosphodiesterase inhibitor but is no longer available in NZ. An intravenous bolus of amrinone in dogs leads to a 60 -100% increase in cardiac contractile force which lasts 5 - 20 minutes, and a 10 - 30% increase in systemic arterial blood pressure. In humans amrinone improves left ventricular performance and this effect is sustained. Withdrawal of therapy results in cardiac decompensation. It was used for short term management of congestive heart failure refractory to other treatment. Its long term efficacy for congestive heart disease has not been evaluated in animals, in people long term survival is reduced.

Milrinone is the only cardiac specific PDI available here. It is a methylcarbonitrile derivative of amrinone which is 20 to 30 times more potent than amrinone. Its cardiovascular effects are reported to be similar to those of amrinone but without increases in heart rate. In one trial approxiamately 70% of dogs with myocardial failure responded well to this drug.

Its short half life and duaration of action in dogs mean that it usually has to be given four times daily so is not really practical for outpatients.

Milrinone has a large therapeutic ratio. Ventricular arrhthymias occur in < 5% of dogs with myocardial failure.

Pimobendan is a similar drug which is most commonly used in dogs. In addition to PD inhibition, it is also supposed to “sensitise” the myocardium to calcium. This effect is likely to be useful since it involves no extra oxygen consumption and the myocardial calcium modulation is impaired in CHF. It prolongs life in dogs in dilated cardiomyopathy but not in valvular insufficiency. It is usually used in combination with ACE inhibitors and frusemide. Like the methylxanthines, its major effect may be in the CNS to make the dog feel better.

There are lots of analogues of pimobendan currently undergoing clinical trials in people.

Oxpentifylline (pentoxyfylline USAN) is not normally used to treat CHF, but may be useful, both as a PDE inhibitor and as a tumour necrosis factor α antagonist (reduces myocardial inflammation).

Cardiac glycosides

Cardiac glycosides are complex molecules present in a variety of plants, a number of which have been used therapeutically including digoxin (the only one available in NZ), digitoxin, oubain (which is probably the endogenous ligand) and lanatoside C. Other cardiac glycosides are usually only encountered as toxins: convallotoxin (from lily of the valley) and squill (from sea holly; previously used as rat poison).

They consist of a steroid nucleus with a lactone ring (responsible for activity) to which are attached three sugars (different with the different drugs) which influence solubility and binding.

Effects

- positive inotrope
- negative chronotrope

Mechanism of Action

IMAGE 5.2 Foxglove

Foxglove (Digitalis purpurea) the traditional source of cardiac glycosides.

positive inotropic effect: Digitalis glycosides bind to the K+ binding site of the sodium pump. This inhibits Na+ being pumped out of the cell; the extra Na+ is exchanged for Ca++ resulting in an increased intracellular Ca++ concentration which increases contractility (see diagram). Numerous other mechanisms have been proposed but this is currently thought to be the main one.

negative chronotropic effects: Thought to be due to stimulation of central vagal nuclei and potentiation of the effects of acetylcholine in atrial myocardium and in AV conducting tissue. Together this results in an increase of vagal tone. In the atria this increased parasympathetic tone decreases atrial automaticity, depresses atrial conduction and increases the effective and functional refractory periods. At the AV node, increased parasympathetic tone decreases atrio-ventricular conduction slowing ventricular response to atrial fibrillation and flutter. The most pronounced ECG change therefore, is prolongation of the P-R interval (first degree heart block), although total heart block can occur.

Indications

- congestive heart failure caused by dilated cardiomyopathy
- supraventricular tachycardias especially atrial fibrillation or flutter

There are no large scale studies in dogs but in people, digitalis only benefits a proportion (different in each trial) of patients in sinus rhythm with congestive heart failure.

Pharmacokinetics

Absorption - may be decreased by food. Time to peak plasma concentrations vary depending on the formulation and dose

Distribution - digoxin is approximately 20% bound to serum proteins (species dependent) and the remainder is free in the serum. Digoxin is strongly bound to skeletal muscle but is also distributed widely, with the highest concentration in kidney, heart, intestine, liver and skeletal muscle. Lowest concentrations are found in the plasma and brain. The half life in the dog varies between 14 - 56 hours, in the cat it is between 33 - 58 hours, ie plasma concentrations take several days to stabilise.

Metabolism - approximately 15% is metabolised by the liver. (remember there is decreased hepatic function in both right and left sided heart failure) In some people, metabolism by gut bacteria is important, and antibiotic induced changes in gut bacteria may lead to digoxin toxicity.

Elimination - the remaining 85% is excreted renally by glomerular filtration and tubular secretion so be careful with patients in renal failure and adjust the dose appropriately using therapeutic drug monitoring.

Severe heart disease will affect all aspects of pharmacokinetics - care is required!

Clinical use

Though this is rarely done, in life threatening supra-ventricular tachyarrhythmias it is possible to rapidly "digitalise" a patient. **This process risks inducing serious ventricular arrhythmias**, but may be life saving on rare occasions. More usually, digoxin is administered at the maintenance dose rate, allowing the animal to come to steady state over a period of several days. Maintenance therapy doses are usually calculated on the basis of body surface area (see pharmacokinetic notes).

Dosage with cardiac glycosides will vary considerably with the following factors:

•age: as older animals have less skeletal muscle and therefore less binding of drug. Glomerular filtration rate decreases with age and with decreased cardiac output

- obesity: as digoxin is not very lipid soluble, then dosage must be based on lean bodyweight. Conversely, digitoxin is lipid soluble so dosage is unchanged
- electrolyte imbalances: because these drugs compete with K^+ for binding to the Na/K ATPase, in hypokalaemia the dose must be reduced and visa versa for hyperkalaemia (monitor serum electrolytes or look at T wave on the ECG). Dosage should also be reduced for hypernatraemia and hypercalcaemia. However, it is better to correct the underlying fluid/electrolyte imbalance first.
- concurrent drug administration
- myocardial failure: If the animal is in myocardial failure or is hypoxaemic they are more sensitive to digitalis. This may be at least partially caused by changes in blood flow to liver and kidneys.

Monitoring digoxin treatment

Steady state peak and trough concentrations should be maintained between 1.0 - 2.5ng/ml (dog) and 0.9 - 2.0ng/ml (cat).

Mild toxicity is seen at concentrations of 2.5 - 6 ng/ml. Severe toxicity is seen at > 6 ng/ml.

Contraindications

- digitalis intoxication
- ventricular fibrillation
- pericardial disease
- (hypertrophic cardiomyopathy)

Care

animals with renal failure or lung disease

Safety and Toxicity

Digitalis has a very low therapeutic ratio. Sudden calcium influx can cause arrhthymias due to electrical instability in myocardial cells, so work up to a steady state on a maintenance schedule and do not use loading doses.

Mild toxicity - anorexia, nausea, vomiting, and diarrhoea. Appropriate treatment is to withdraw digoxin for 24 hours, then give maintenance at 50 % of the initial dose for 12 hours. Use therapeutic drug monitoring to check.

Digoxin can be directly irritant to the gastric mucosa, causing vomiting. This is worse with the tablet formulations, and can be difficult to clinically differentiate from toxicity due to high plasma concentrations. Try using elixir formulations if tablets are causing irritation.

Serious toxicity - increased excitability - ventricular ectopic beats, especially bigeminy, ventricular tachycardia. Give lignocaine or similar drug (and monitor ECG!!).

Treatment of acute toxicity

Atropine will help to block the increased vagal tone. Anti-arrhthymic drugs may be used: phenytoin or lignocaine are the drugs of choice. Procainamide or propanolol may also be useful. Digoxin antibodies which mop up the drug are available but difficult to obtain and extremely expensive.

Drug interactions

Do not use quinidine or verapamil as they may increase serum digitalis concentrations. Frusemide decreases renal blood flow and blood volume, requiring a reduced dosage of glycosides due to slower elimination. Frusemide also causes an increased loss of K^+, as do other diuretics (especially thiazides), and thus potentiate digitalis. Drugs that induce or inhibit hepatic microsomal enzymes may also affect dose levels.

Digitoxin is not available in NZ. It is similar to digoxin but as it is primarily metabolised in the liver, could be useful in patients with renal insufficiency (instead of digoxin). It is 70 - 90% protein bound (cf. digoxin which is only 20% protein bound) and has a much shorter half life of between 8-12 hours in the dog. This means that it is possible to achieve therapeutic concentrations on a maintenance schedule in 24-36 hours and if toxicity occurs reduce it in 8-12 hours. This more rapid clearance is one of the reasons some cardiologists prefer this drug to digoxin. The half life in the cat is >100 hours and so do NOT use in this species. (It also has a long half life in man.)

Vasodilators

commonly used drugs

benazepril

Vasodilators

- ☑ reduce afterload and can prolong life in CHF
- ☑ angiotensin converting enzyme inhibitors block production of angiotensin 2 and are probably the best drugs to use in CHF as a first line treatment
- ☑ nitrates are converted to nitric oxide and have very potent acute effects
- ☑ hydralazine is sometimes used if nothing else works

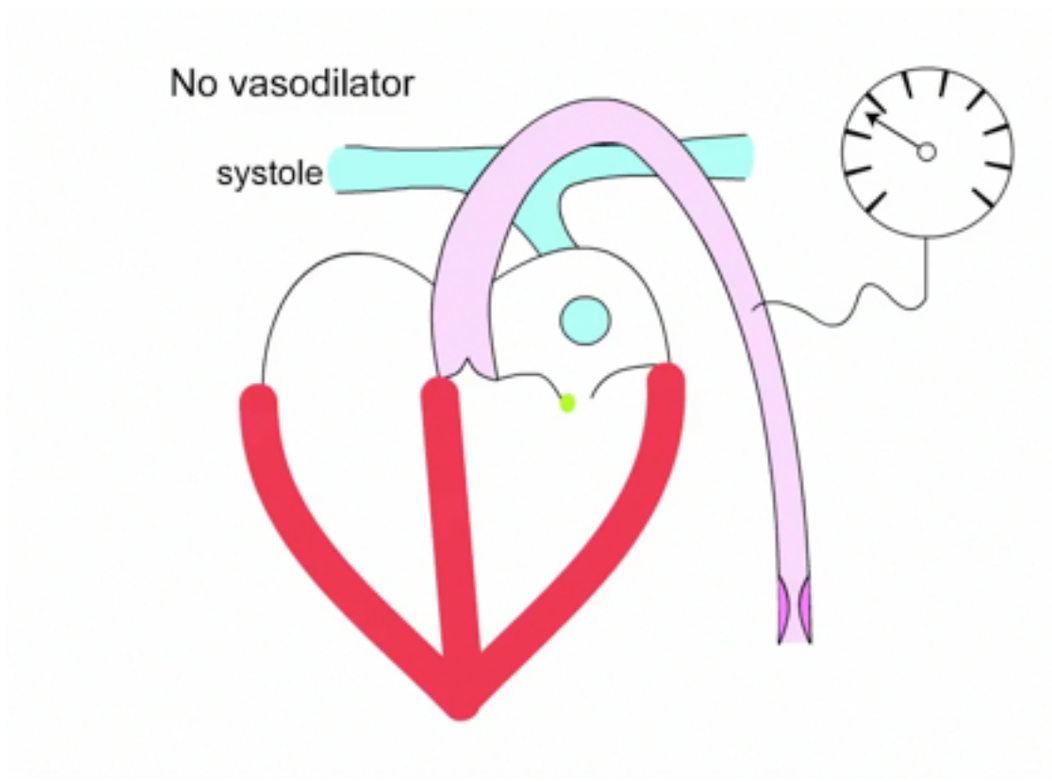
- These have become the treatment of choice for treating congestive heart failure in people and dogs, since they have been shown conclusively to prolong life.

Late congestive heart failure leads to vasoconstriction by a variety of mechanisms including increased sympathetic tone, renin - angiotensin system activation and increased ADH concentrations. Arterial vasodilatation reduces afterload, myocardial work, oxygen consumption, pressure across the mitral valve and thus increases cardiac output. Venous vasodilatation reduces preload and oedema.

Vasodilator indications

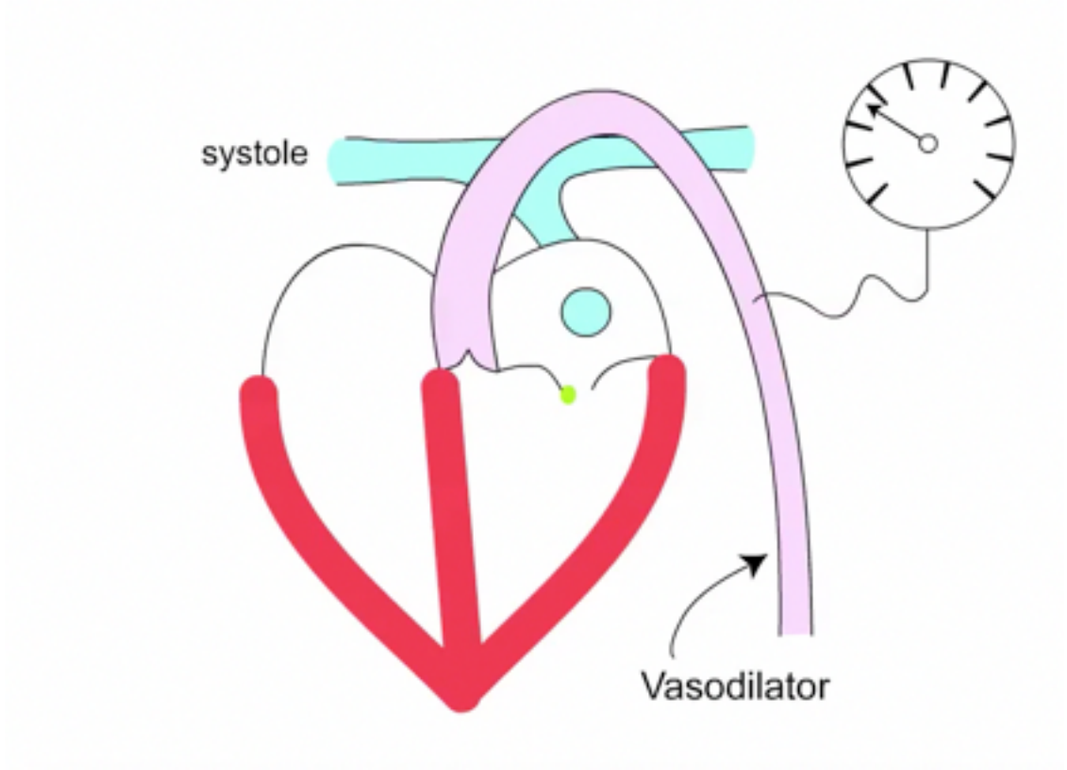
- congestive heart failure
- mitral regurgitation
- control of ABP during anaesthesia
- navicular disease (isoxuprine)
- (essential hypertension - not recognised in domestic animals)

MOVIE 5.1 Valve failure, no vasodilator



Vasocontriction keeps blood pressure up at the expense of forward flow.

MOVIE 5.2 Valve failure with vasodilator



Blood pressure is reduced but forward flow increased.

-

Vasodilator side effects

- hypotension
- reflex tachycardia
- plus effects specific to individual drugs

Drugs

A very large number of drugs can cause vasodilatation; it is usually regarded as an undesirable side effect. The main group of vasodilators used for chronic heart failure is the angiotensin converting enzyme inhibitors. These are given orally for long term treatment. Nitrates and calcium channel blockers are less commonly used for both acute and chronic heart failure. They can be given by a variety of routes. Great care is needed if they are given iv in acute situations. A range of other drugs are used rarely, usually in a desparate attempt to find something that works!

Angiotensin converting enzyme inhibitors

These are some of the few drugs proven to prolong life in dogs. Many ACE inhibitors are available, there is no obvious difference between them apart from duration of action (and price!).

Physiology

The renin - angiotensin - aldosterone system is an important mechanism for maintaining blood pressure in the face of various challenges. Renin release from the juxtaglomerular apparatus is stimulated by a fall in blood pressure, reduced renal blood flow, reduced sodium concentration in the distal tubule, increased renal sympathetic activity and a host of other factors poorly understood. β agonists and PGI2 also stimulate renin production. Atrial natriuretic peptide reduces renin production: angiotensin II does the same, possibly by the same mechanism. Renin then converts angiotensinogen to angiotensin I.

ACE inhibitors block the enzyme which converts angiotensin I to angiotensin II. Most of their effects can be attributed to a reduction in ATII levels. ATII produces most of its effects at the confusingly named AT1 receptors (see diagram).

ACE is also responsible for breaking down bradykinin which can act as a vasodilator by stimulating PLA2 which results in the production of prostacyclin, and by causing the release of nitric oxide from endothelial cells.

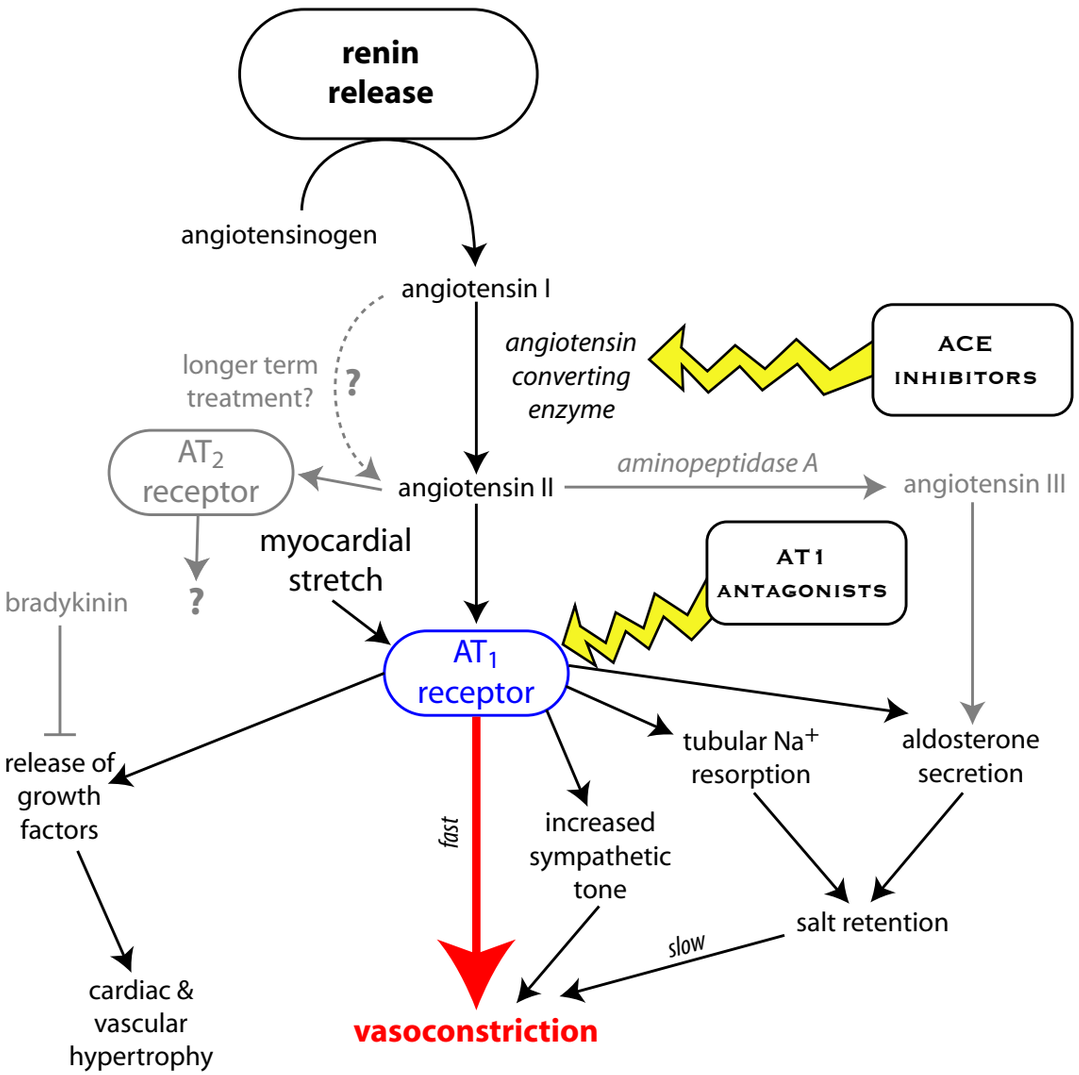
Most ACE is bound to the surface of endothelial cells, but it can occur in other tissues such as cardiac muscle. ACE inhibitors tend to reverse the cardiac hypertrophy seen in heart failure.

Effects

In normal healthy animals and people, ACE inhibitors have no effect after a single dose and cause only a small drop in blood pressure after several days' treatment. It seems likely that there has to be increased renin release (and thus more ATI available for conversion to ATII) before ACE inhibitors have much effect. Most dogs with congestive heart failure will have increased sympathetic tone, and may also have reduced arterial blood pressure leading to increased renin release. Some dogs may be on low salt diets in an attempt to cause sodium depletion.

The end result in dogs with CHF is that there is a decrease in venous and diastolic intra-cardiac pressure with a concurrent decrease in afterload and so a resultant increase in cardiac output. They relax both capacitance and resistance vessels, but preferentially affect the kidney heart and brain. They are often used with diuretics

DIAGRAM 5.3.1 ACE inhibitors



The renin - angiotensin - aldosterone system. The pathways in grey are of unknown importance.

such as frusemide (although frusemide probably has some vasodilator action of its own), but the interactions can cause kidney failure (see below). ACE inhibitors have their own mild diuretic and natriuretic effect.

The vasodilatation produced by increased bradykinin may also be important in heart failure.

Indications

vasodilator in the treatment of congestive heart failure, especially valvular disease

Side effects

- hypotension in overdose
- anorexia, vomiting and diarrhoea
- at high doses glomerular lesions and renal failure (monitor BUN and serum creatinine) may be induced
- since they also inhibit aldosterone they may cause a hyperkalaemia therefore monitor electrolytes especially if using potassium sparing diuretics as well

In people, ACE inhibitors often cause coughing - thought to be caused by increased bradykinin in the airways.

Precautions

care in renal insufficiency patients

Inside the kidney, there are lots of AT1 receptors on the vasa recta. ATII can alter glomerular filtration rate by constricting the afferent arteriole, by contracting the mesangial cells or by constricting the efferent arteriole. In normal animals, the end result of ATII on GFR is not much change, but in hypotension the effects on the efferent arterioles are thought to predominate. (This is inferred from two experiments using small numbers of dogs which were also sodium depleted, either by dietary restriction or frusemide administration and dietary restriction. They were also anaesthetised, heparinised and subject to very invasive surgery and extracorporeal circulation.) An alternative theory is that the afferent arterioles constrict in direct response to being stretched by increased blood pressure, resulting in constant glomerular flow rates and GFR.

Acute renal failure has been reported after ACE inhibitors in man, but usually in cases of renal artery stenosis, which lowers the pressure in the afferent arteriole. Only two cases have been reported in dogs, both of which also had frusemide (one had digoxin (at toxic levels) as well). It seems likely that the frusemide was at least as much to blame as the ACE inhibitor in these cases. Both had low plasma sodium concentrations (132 & 137mM) which were probably caused by the frusemide. Since ATII helps maintain blood pressure in low sodium states, they were probably hypotensive as well (not measured). Since GFR will depend on the pressure in the afferent arteriole, in the absence of a downstream constriction, that will depend on arterial blood pressure. Thus reduced GFR will result in a reduced amount of urea filtered. However, there is some evidence that in sodium depletion active uptake of urea occurrs to try to maintain the hyperosmolarity in the medulla (normally 66% due to sodium, 33% urea). The dehydration caused by overdosing with frusemide will also cause uraemia (nb. dogs are usually given 4 - 20 times the human mainte-

nance dose of frusemide). If the uraemia causes nausea and vomiting and stops the animal drinking, then a vicious circle will have been set up.

- caution in hyponatraemia, pre-existing haematological abnormalities or a collagen vascular disease ie. systemic lupus erythematosus
- breeding / pregnant dogs (uterine relaxation)
- teratogenic in women

Captopril has a short half life in the dog (3 hours), so must be given two or three times daily. **Enalapril** is basically the same as captopril except that it is a prodrug, which is metabolised by plasma esterases to the active metabolite enalaprilat. This active drug has a longer therapeutic duration than captopril, enabling once daily dosing in dogs. It has been proven in clinical trials to increase the life span of dogs with congestive heart failure (in combination with the diuretic frusemide). **Benazepril** is similar to the other ACE inhibitors, suitable for once daily dosing. The human drug **quinapril** is sometimes used in dogs because it is cheap.

There are dozens of other ACE inhibitors in human use, which probably also work in animals.

AT1 receptor antagonists such as **losartan** and **candesartan** are starting to be used in people. They may be slightly more effective (AT11 can be formed by other routes than ACE) and have fewer side effects. They are used mainly in patients who do not tolerate ACE inhibitors, and there is no experience in domestic animals.

Nitrates

Converted to nitric oxide (Endothelial Derived Relaxing Factor) in endothelium which diffuses into smooth muscle cells and causes relaxation by increasing cGMP activity. They mainly produce venous dilatation but also arterial at slightly higher doses.

Sodium nitroprusside has a very short half life and is only used in anaesthesia / intensive care in critically ill patients having a hypertensive crisis, acute heart failure secondary to mitral regurgitation, severe refractory cardiac heart failure or for cardiovascular surgery. Do not use unless ABP is being monitored continuously - it is very easy to overdose. It is becoming difficult to obtain in NZ.

Pharmacokinetics

Almost instant response from an iv infusion though will return to pretreatment levels in 1-10 minutes once infusion stops.

Metabolised in blood and tissues to cyanide which is converted in the liver to thiocyanate and eliminated in the urine, faeces and exhaled.

Half life is 2-7 mins though this may increase if there is renal impairment or hyponatraemia.

Solutions are unstable and must be protected from light (wrap drip bag & giving set in aluminium foil).

Side effects and Toxicity

hypotension in overdose - give dobutamine

(cyanide toxicity at very high dose rates)

Nitroglycerine (glyceryl trinitrate) can be used like sodium nitroprusside as an iv infusion in intensive care or applied as ointment or patch for more chronic use.The injection is used for acute control of arterial and venous dilatation; the ointment for venous dilatation in cardiogenic pulmonary oedema.

The ointment is designed to be slowly but continuously absorbed with onset of action within 1 hour, duration of action of 2 - 12 hours. Metabolism is rapid - duration of action of iv injection 7 - 10 mins. The ointment is designed to cross human skin - make sure you use gloves and give the animal's owner some.

Overdose will cause hypotension and decreased cardiac output. It should not be used in shock.

Isosorbide dinitrate is very similar, but in tablets.

Other vasodilators

Dihydropyridine calcium channel blockers such as **nifedipine** and **nicardipine** are widely used in people, but not often in animals. These have less cardiac affect than verapamil and diltiazem.

Hydralazine's mechanism of action is unknown but it is a potent direct acting arteriolar vasodilator. This effect is not the same in all vascular beds: - there is more of a decrease in cerebral, coronary, renal and splanchnic vascular beds then in muscle or skin. The increase in renal blood flow causes an increased GFR and helps increase total cation excretion.

It is used in left sided myocardial failure and mitral regurgitation.

Prazosin is now obsolescent. It is an α1 adrenoreceptor antagonist which dilates both arterioles and veins. It produces less reflex tachycardia and less activation of the renin-angiotensin system (ie. Na retention) than with hydralazine.

It is usually only used for adjunctive therapy of congestive heart failure particularly secondary to mitral or aortic valve insufficiency when hydralazine is not effective or not tolerated, treatment of systemic hypertension or pulmonary hypertension in the dog, or in dogs that do not respond well to other agents.

Side effects and Toxicity

- hypotension
- may get syncope (orthostatic hypotension)
- CNS signs, GIT signs
- tolerance develops
- Care is required in chronic renal failure

Doxazosin is a modern α1 antagonist used in man.

Isoxuprine can be used for navicular disease in horses. Its mechanism of action is unknown, but it has some β2 agonist effect. It is contraindicated in pregnancy, and in mares up to 2 weeks post partum. Its main side effect is tachycardia.

Beraprost is a prostacyclin analogue used to treat pulmonary hypertension in people. It has shown promise in cats with chronic kidney disease, where presumably the vasodilatation increases blood flow and oxygen delivery to the kidney.

Other drugs not likely to be used for vasodilator effect

- potassium channel openers
- diazoxide
- β2 adrenergic agonists
- salbutamol
- α2 adrenergic agonists
- clonidine (used in man)
- xylazine, etc
- β1 adrenergic antagonists
- labetolol
- indirect sympathetic blockers
- many drugs
- ganglion blockers
- hexamethonium

This list is not exhaustive!!

Antiarrhythmics

commonly used drugs

Class 1 - lignocaine, quinidine

Class 2 - propranolol, atenolol

Class 4 - verapamil, diltiazem

Others - atropine, adrenaline, digoxin, adenosine, calcium

Antiarrhythmics

- ☑ I - sodium channel blockers
    1. Ia - atrial fibrillation
    2. Ib - ventricular ectopic beats
- ☑ II - beta blockers - stress induced tachycardias
- ☑ III - not used much
- ☑ IV - calcium channel blockers - atrial tachycardias
- ☑ other antiarrhythmics

    digoxin - atrial fibrillation

    adenosine - supraventricular tachycardias

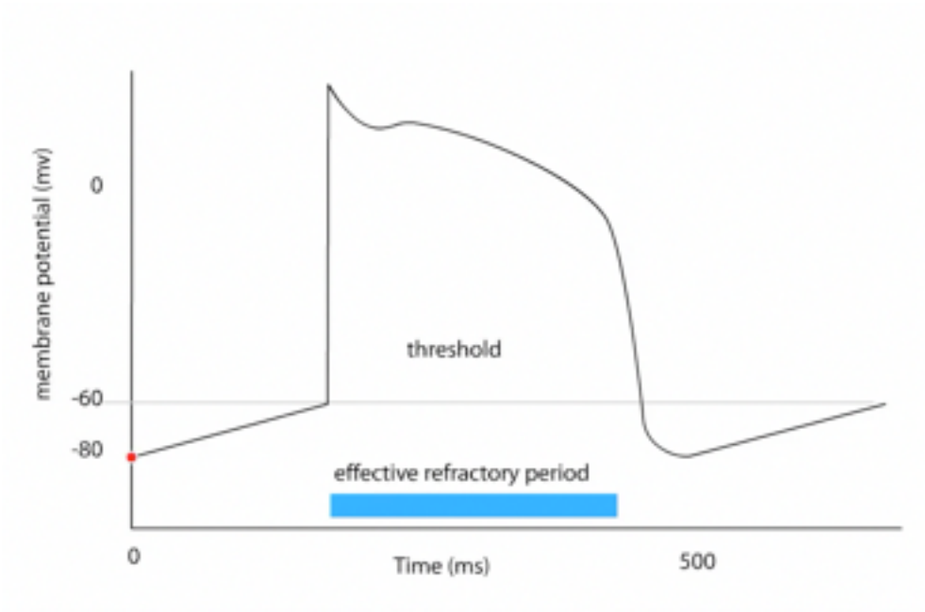
    calcium - ventricular tachycardia due to high potassium

Arrhythmias may not affect the heart's efficiency as a pump and require no treatment, eg sinus arrhythmia which is normal in fit animals. Other arrhythmias eg ventricular fibrillation are immediately life threatening. Most arrhythmias fall between these extremes. (nb, all antiarrhythmic drugs decrease cardiac output to some extent, and may also cause arrhythmias, so you have to be sure that the presenting arrhythmia is worse for the animal than the treatment.)

Causes

- other heart disease
- hereditary
- autonomic system
- metabolic disease
    - hypoxia
    - acidosis
    - electrolyte imbalance (particularly K+)
- drug toxicity (including antiarrhythmics!)

MOVIE 5.3 Cardiac action potential



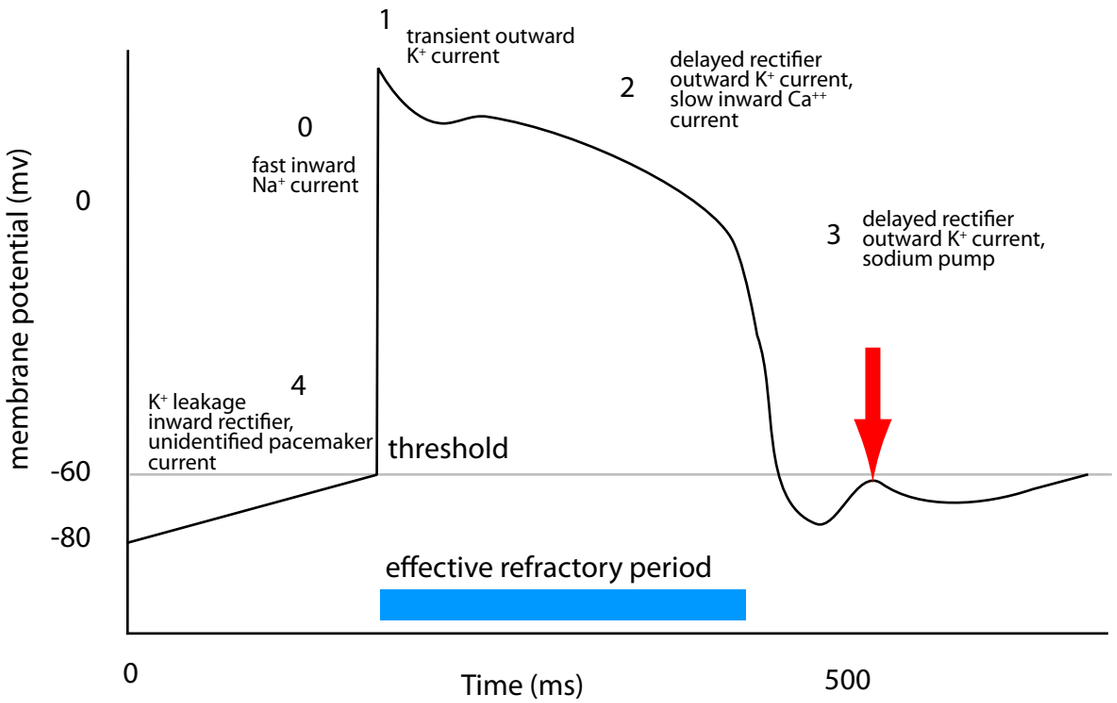
Cardiac action potential in conducting tissue. Numbers refer to the phases of the action potential. The resting membrane potential depends on the extracellular K+ concentration, as K+ rises it approaches the firing threshold.

Mechanisms Of Arrhythmia

Delayed afterdepolarisation

This is usually caused by excessive intracellular calcium, which can be a result of excessive adrenergic stimulation (natuaral, sympathomimetics or phosphodiesterase inhibitors) or digitalis overdose.

DIAGRAM 5.4.1 Delayed after depolarisation



If the second spike reached the firing threshold, an ectopic beat will occur.

Re-entry

This occurs when there is a damaged piece of myocardium which conducts the action potential more slowly than usual. If the surrounding syncytium has repolarised, the slow action potential may propagate through the repolarised tissue in a circular manner.

MOVIE 5.4 Re-entry

Slow propagation through damaged tissue can cause re-entry arrhythmias.

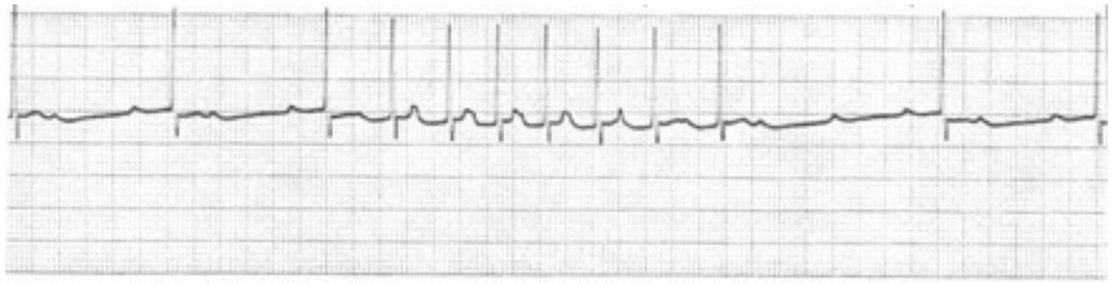
Abnormal pacemaker

This is where a damaged piece of tissue is unable to maintain polaraisation much below the firing theshold and the damaged tissue tends to fire early. Atrial fibrillation or ventricular tachycardias are the result.

Heart block

Not every action potential gets through the conducting system, particularly the AV node, at the normal speed, or at all. The heart block can be 1° - slowed conduction through the AV node, seen as a prolonged p-q interval, 2° - not every p wave causes a qrs complex and 3° where there are normal p waves but ventricular escape complexes.

FIGURE 5.1 *Second degree heart block*



Note that not every p wave causes a qrs complex.

Vaughan Williams classification

I sodium channel blockers (reduce excitability of conducting tissue)
- Ia eg quinidine
- Ib eg lignocaine
- Ic eg flecainide

II β blockers (reduce automaticity) eg propranolol

III potassium channel blockers (prolong action potential) eg amiodarone

IV calcium channel blockers (block nodes & damaged muscle) eg verapamil

nb. many drugs have several effects and do not fit neatly into one class.

Drugs

Class 1 - Sodium Channel Blockers

These can be subclassified on receptor kinetics:

- class 1b interact with sodium channels and dissociate again in less than 1 sec
- class 1a 1 - 10 secs
- class 1c > 10 secs.

Effects

Increased firing threshold, increased effective refractory period. The action potential may be either slightly prolonged or slightly shortened. Action potentials triggered by after depolarisations are inhibited.

Effects on animals will vary according to the heart rate, the tissue and its health (in general, these drugs have a greater effect on diseased tissue). This means that class 1 drugs can have a wide range of effects.

Class 1a antiarrhythmics

Quinidine is mainly used in horses because it is cheap enough to give horse size doses. It is used in supraventricular arrhythmias especially atrial fibrillation.

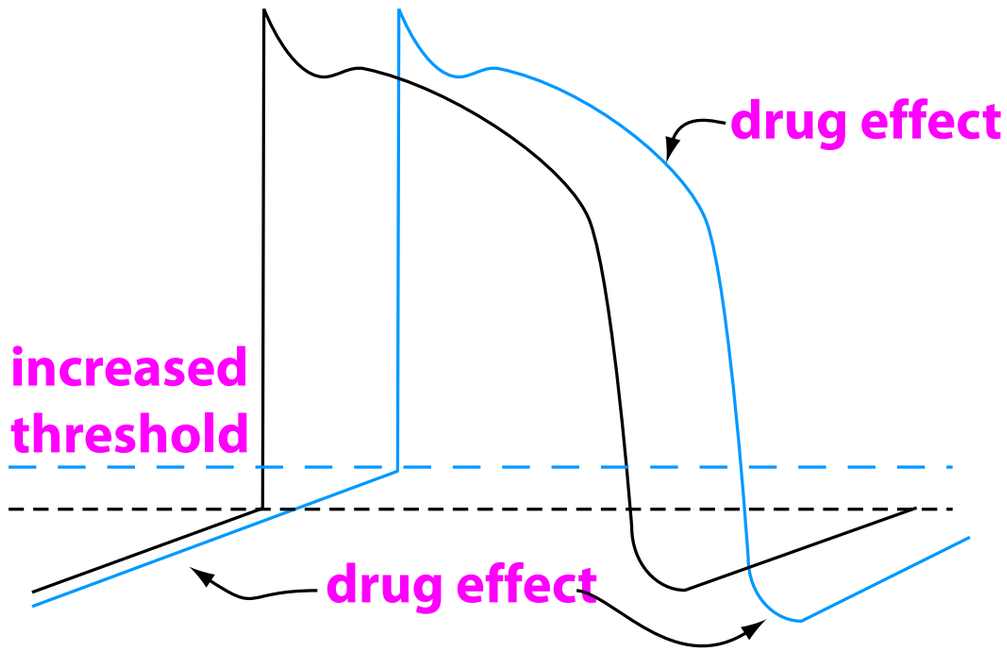
Quinidine has a short half life in dogs and cats so is not much use for maintenance. It is poorly tolerated by dogs.

Side effects and toxicity

- anorexia, vomiting, diarrhoea
- QRS duration and Q-T intervals are increased - if there is a 50% increase in the QRS then remove drug promptly ie. need to monitor with ECG
- ventricular arrhythmias - increase in Purkinje fibre automaticity
- sudden death from ventricular fibrillation possible

All these are potentiated by hypokalaemia.

DIAGRAM 5.4.2 *Class 1 antiarrhythmics*



Contraindications

myasthenia gravis, complete A-V block, intraventricular conduction defects, symptoms of digitalis toxicity

Care is required in acid-base disorders, hypokalaemia, hypoxia, and renal or liver insufficiency

Interactions

increases digitalis plasma levels - displaces digoxin from skeletal muscle binding and reduces digoxin plasma clearance

increased chance of arrhythmias with diuretics which induce hypokalaemia, ie frusemide and thiazides.

Procainamide is effective against ventricular tachyarrhythmias and was used primarily for these but may be effective against supraventricular arrhythmias in high doses. No longer available in NZ.

Class 1b antiarrhythmics

Lignocaine (lidocaine USAN) is used in life threatening ventricular arrhythmias, particularly ventricular tachycardia and ventricular premature complexes. **Do not use lignocaine with adrenaline** - this is only for local anaesthetic use.

Pharmacokinetics

Absorption - onset of action after iv injection is within 2 minutes and duration of 10-20 minutes

Distribution - rapidly redistributed into highly perfused organs - heart failure may decrease the volume of distribution (Vd is about 4.5 l/kg in the dog)

Metabolism - short half life - 90 - 100 minutes - rapidly metabolised by the liver to active metabolites. This may be prolonged by liver disease or poor hepatic perfusion ie. cardiac disease. If given po, lignocaine is 100% metabolised on the first pass through the liver.

Elimination - less then 10% of a parenteral dose is excreted unchanged in the urine.

Side effects and Toxicity

CNS effects - drowsiness, emesis, nystagmus, muscle twitching and seizures - can be very severe in the cat

methaemoglobinuria especially in cats

Treat by withdrawing drug; may need to use diazepam or barbiturates for seizure control as well.

Contraindications

severe SA, AV, or intraventricular heart block

caution in patients with liver disease, congestive heart failure, shock, hypovolaemia, respiratory depression or hypoxia

Tocainide and **mexilitine** are similar to lignocaine but longer acting and are designed to avoid first pass metabolism so can be given by mouth. They are used sometimes for oral treatment of ventricular tachyarrhythmias. Phenytoin is again similar to lignocaine but longer acting with more side effects. Not often used.

Class 1c antiarrhythmics

Flecainide is the only one available in NZ. Occasionally used in atrial fibrillation and other supraventricular tachycardias.

Class 2 β Adrenergic Blockers

Dozens of β adrenergic antagonists (mainly specific β1 blockers) are available for people but propranolol is the only drug widely used in animals (because it is cheap, not because it is a great drug).

Propranolol is a non specific β adrenergic antagonist - ie, it blocks both β1 and β2 receptors. Its anti-arrhythmic effects are caused by decreasing catecholamine dependent automatic rhythms and slowing conduction in abnormal ventricular myocardium - also increase the refractory period of AV nodal tissue, so slowing down the ventricular response to atrial fibrillation and flutter and effectively abolishing supraventricular arrhythmias due to A-V node re-entry. By decreasing contractility it also decreases myocardial oxygen consumption.

Indications

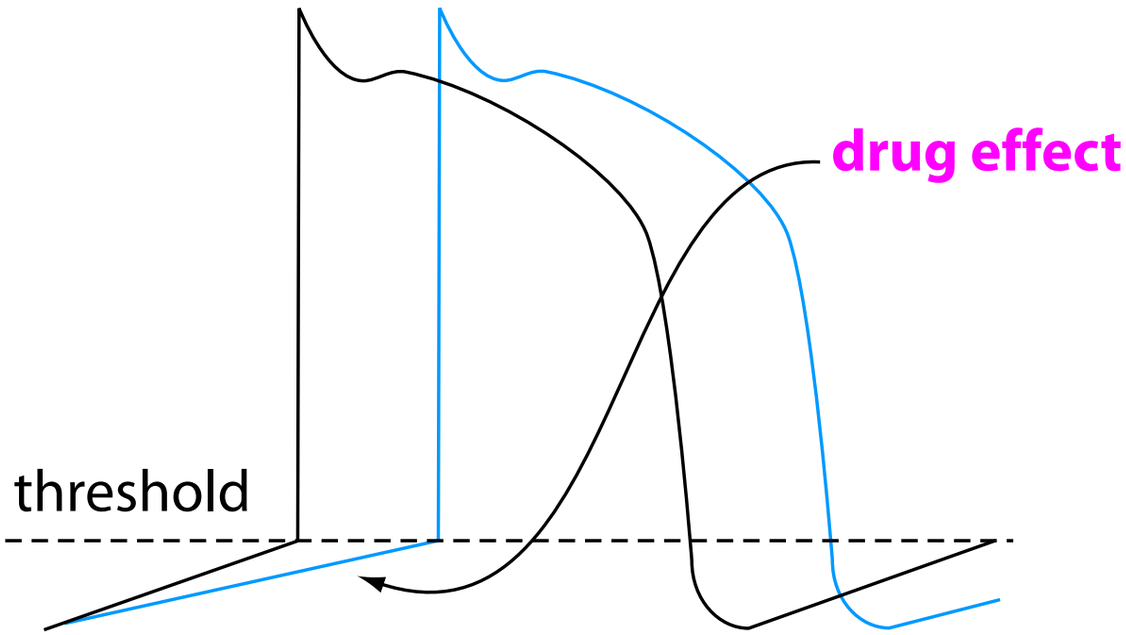
- supraventricular tachyarrhythmias
- feline hyperthyroidism to prevent myocardial hypertrophy
- (used for congestive heart failure in people)

Pharmacokinetics

Absorption - oral - well absorbed and almost complete - biavailability between 2 - 17% after first pass effect in the liver

Distribution - highly lipid soluble and readily crosses the blood brain barrier

DIAGRAM 5.4.3 Class 2 antiarrhythmic drugs



Metabolism - has extensive first pass effect in the liver: half life in dog is 1-2 hours. Effects seen longer than half life because of active metabolites and receptor binding

Elimination - renal with less than 1% unchanged

Side effects and Toxicity

bradycardia, myocardial depression - may make congstive heart failure worse, hypotension, bronchospasm (β2 block - usually only with older, non-selective drugs such as propranolol)

Exacerbation of side effects with acute withdrawal of therapy can occur.

Contraindications

- overt heart failure
- greater than first degree heart block
- asthma or chronic lower airway disease due to beta blocking as it may further constrict airways
- caution in diabetics as get decreased sympathetic compensation for hypoglycaemia
- care in patients with renal or hepatic insufficiency
- care when using in combination with digitalis

Class 3 Potassium Channel Blockers

Rarely used in either man or animals, but most new experimental drugs fall into this class so that situation may change. **Amiodarone** (a thyroxin analogue) is the main drug of this class used in people but has a very long half life and lots of side effects; **bretylium** is sometimes used in dogs with refractory ventricular arrhythmias.

Sotalol is a beta blocker which also acts as a class 3 drug and has been used in dogs.

Side effects can include tachyarrhythmias.

Class 4 Calcium Channel Blockers

Note that some (**verapamil**, **diltiazem**) are more specific (but not completely specific) for the heart and others (dihydropyridines: nifedipine etc) are more specific for blood vessels (as vasodilators). They block the inward Ca++ current across membranes of myocardial cells and vascular smooth muscle. This inhibits both phase 4 of the action potential and the contractile mechanisms of vascular and smooth muscle. They also slow phase 0 in SA and AV nodes

Verapamil is the drug of choice for severe acute supraventricular tachyarrhythmias and may help with atrial flutter or fibrillation.

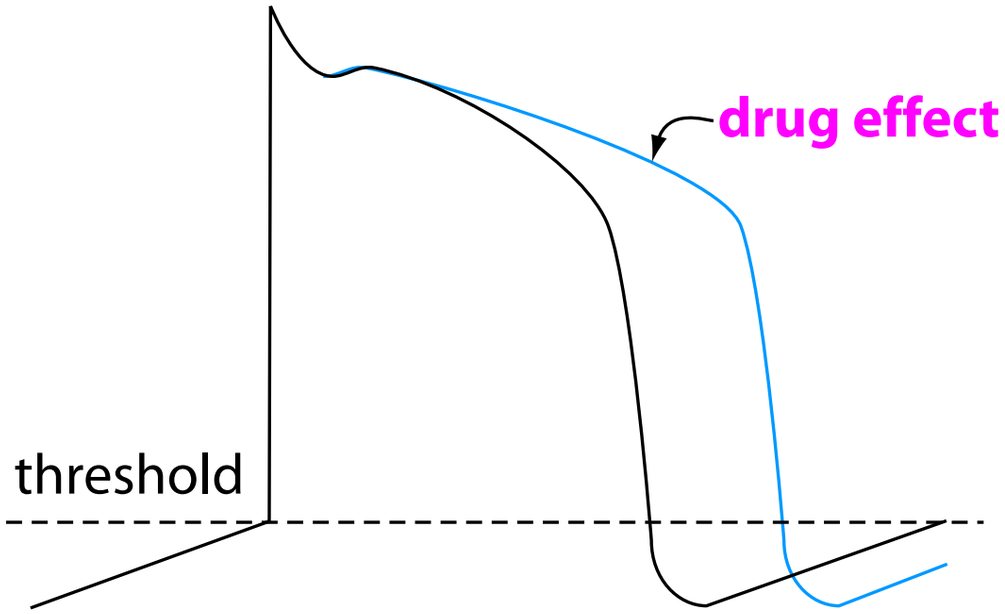
Side effects

- peripheral vasodilation - hypotension
- decreases myocardial contractility
- bradycardia

Contraindications

- severe congestive heart failure
- hypotension
- sick sinus syndrome

DIAGRAM 5.4.4 Class 3 antiarrhythmic drugs



- 2nd or 3rd AV block
- digitalis intoxication
- do not use with propanolol

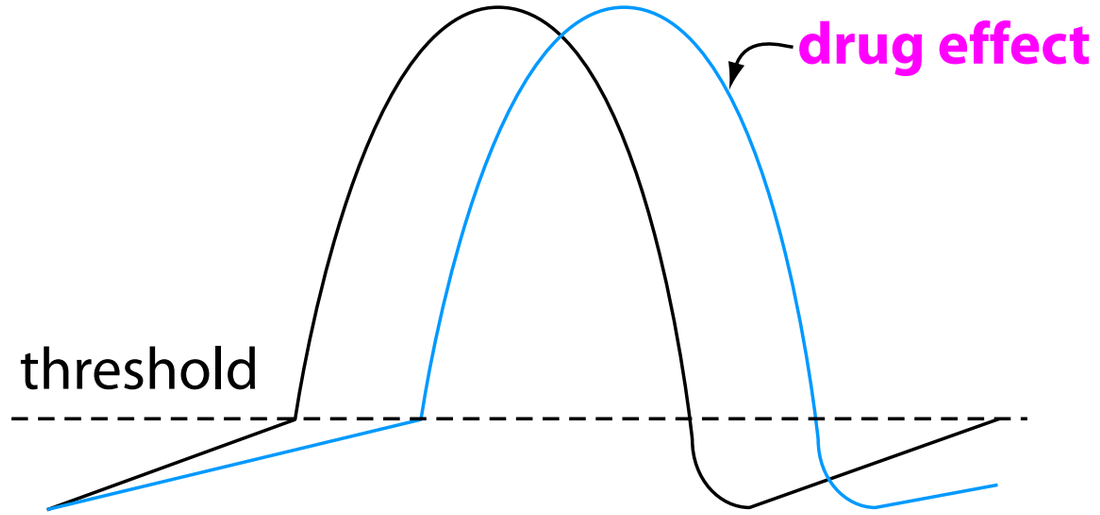
Diltiazem is similar in most respects to verapamil except that it has more favourable pharmacokinetics, and has been reported to be more effective in feline idiopathic dilated myocardopathy than verapamil. It is usually preferred for long term oral use.

Other Antiarrhythmics

Muscarinic antagonists such as **atropine** are used in bradyarrhythmias. **Glycopyrrolate**, which does not cross into the brain, is a bit more specific for the heart and longer acting but expensive. These drugs are often given since they are relatively safe (although tachycardia will lead to myocardial hypoxia). In people, tachycardia is usually of more concern than bradycardia, as tachycardia can indicate silent myocardial infarction. Beta blockers or drugs such as **ivabradine**, which blocks I_f channels in the SA node, are used to slow the heart rate.

Digoxin (see inotrope notes) is often used as an antiarrhythmic in man for atrial fibrillation, and to a lesser extent in dogs (do not use in horses for AF - hye usually have a slow ventricular rate and digoxin will make it worse).

DIAGRAM 5.4.5 Class 4 antiarrhythmic drugs



Adrenergic β1 agonists (usually isoprenaline) are very occasionally used to treat bradyarrhythmias but reduce the efficiency of contraction (ie, oxygen use increases more than the force of contraction) which is not what is wanted in a hypoxic myocardium. Antimuscarinics are better in the short term, pacing in the long term.

Adenosine is sometimes used for supraventricular tachycardias. It must be given by rapid iv bolus as it is metabolised very quickly. May produce transient asystole!

In hyperkalaemia, calcium is sometimes used to control arrhythmias. The hyperkalaemia needs to be corrected as well though - usually by giving insulin & glucose together.

Clinical use

Arrhythmias are usually diagnosed by ECG: **resist the temptation to treat the ECG rather than the animal**.

1. Identify and remove the cause
   hypoxia, electrolyte disturbances, other drugs eg. digitalis or frusemide.
2. Establish the goals of treatment
   Can be anything from improving the quality of life to producing a normal ECG. Determine if treatment is necessary ie. assess the risk/benefit.
3. Decide on the best treatment
   which may include:

- drugs
- physiological manouveres
- cardioversion (DC shock)
- pacemaker
- combination of drugs and other treatment
- no treatment at all (often most appropiate)

Combinations of drugs are sometimes used but should be avoided if possible - many can cause severe drops in cardiac output.

There is plenty of dispute about when to use which drug: my preferences are:

sinus bradycardia *- atropine, glycopyrrolate*
atrial flutter / fibrillation *- all classes, digoxin*
supraventricular tachycardia *- Ia, IV, adenosine*
junctional tachycardia *- all classes except Ib*
ventricular ectopic beats *- III (II, Ib)*
ventricular tachycardia *- III (II, Ib)*
heart block *- pacemaker (isoprenaline)*

TABLE 5.4.1 Summary of antiarrhythmic drug effects

	Ia	Ib	II	III	IV
SA node automaticity	o/-	o/-	--	+/-	o/+
AV node conduction	-	o	-	-	---
Purkinje fibres AP duration	+	-	o	++	-
refractory period	+	++	o	++	-/o
membrane response	---	--	-	o	-/o
automaticity	-	---	-	o	-/o

nb. all will reduce cardiac output to some extent

The kidneys

commonly used drugs

frusemide

The kidneys

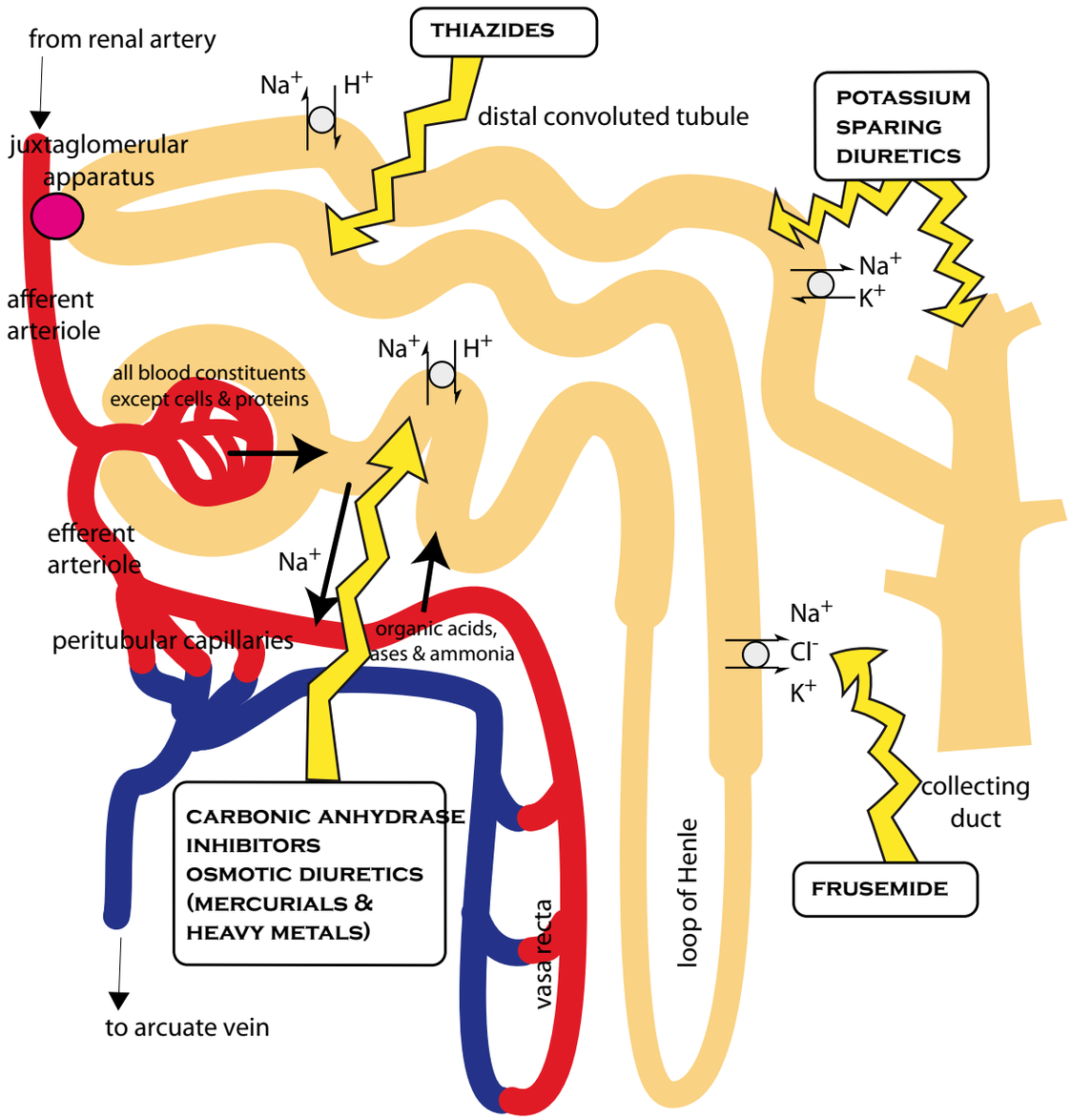
- ☑ loop diuretics most important in veterinary practice
- ☑ main indication is oedema of whatever cause
- ☑ very potent - beware overdose
- ☑ hypokalaemia potentiates digoxin
- ☑ mannitol - beware accidental perivascular injection

Diuretics are drugs which cause increased urine production, ie, water and sodium loss. They are used to reduce preload in congestive heart failure and for life threatening situations like pulmonary and cerebral oedema. Most act by increasing sodium ion concentration in the urine and thus drawing water out too. Only frusemide (furosemide USAN) is commonly used, the others are occasionally used in specific situations.

Drugs

- Loop diuretics
  - frusemide - most commonly used drug by far
- Thiazides
  - hydrochlorthiazide
- Potassium sparing diuretics
  - amiloride
  - triamterene
  - spironalactone
- Carbonic anhydrase inhibitors
  - acetazolamide
- Osmotic diuretics
  - mannitol
  - glycerine
- (Mercurials)
  - obsolete - do not use!

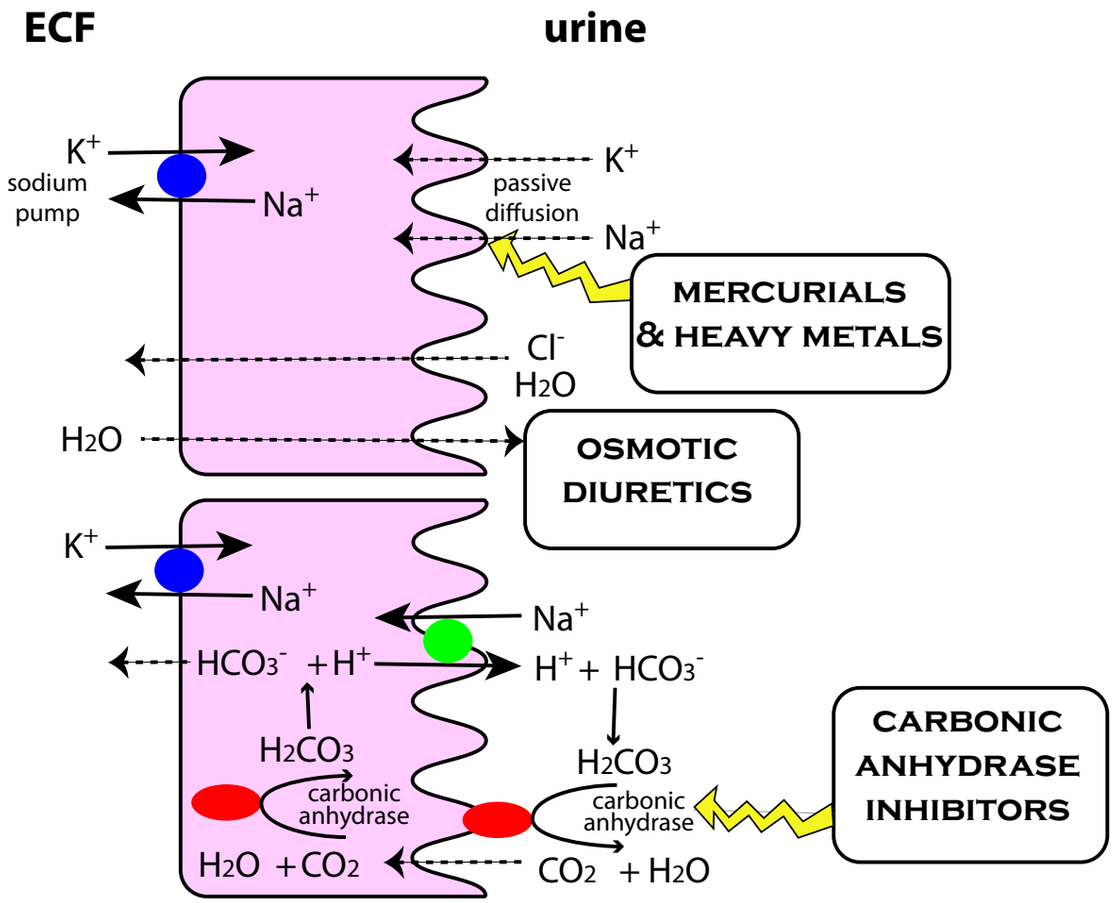
DIAGRAM 5.5.1 Sites of action of diuretics



Sites of action of diuretics - the downstream ion pumps are important!

Drugs Acting In The Proximal Convoluted Tubule

DIAGRAM 5.5.2 Diuteritcs acting on the PCT



Only osmotic diuretics are used clinically to any extent.

Carbonic Anhydrase Inhibitors

Not much used except for glaucoma (see eye notes) because of low efficacy as a diuretic. Acetazolamide is the only one in common use, although newer drugs are available.

Osmotic Diuretics

These drugs are filtered through the glomerulus, have limited tubular resorption and are pharmacologically inert. Mannitol is the only drug commonly used, al-

though occasionally glycerol (glycerin) is given by mouth. Glucose can be used in anuric or oliguric renal failure to try and establish urine production as it is metabolised if not excreted.

They are freely filtered at the glomerulus and poorly reabsorbed from the tubule causing an increase in osmotic pressure in the tubule and preventing the reabsorption of water. As well as water, there is an increase in sodium, other electrolytes, uric acid and urea secretions due to decreased bulk flow resorption. They may increase renal blood flow and glomerular filtration by causing renal arteriole dilation, decreased vascular resistance and decreased blood viscosity . Because mannitol is not metabolised its use in oliguric renal faliure should be confined to one dose only unless diuresis is achieved.

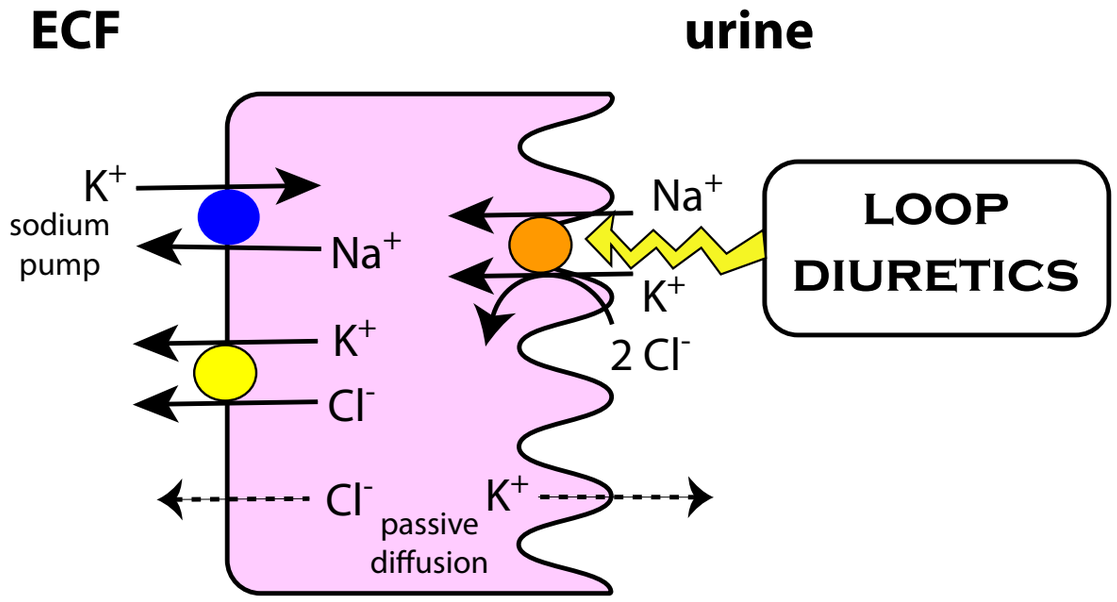
They are used in cerebral oedema and glaucoma, and are contra-indicated in heart disease - colloids raise venous pressure. Mannitol will cause sloughing if given perivascularly.

Mercurials

Obselete - do not use. You may come across heavy metal poisoning causing renal problems.

Drugs Acting In The Loop Of Henle

DIAGRAM 5.5.3 Loop diuretics



Very commonly used.

Frusemide (furosemide USAN) is the most widely used diuretic in man and animals, almost to the exclusion of everything else.

It inhibits active chloride transport in the thick ascending limb of the loop of Henle which decreases the total resorption of Na+ and Cl- and K+. This decreases osmolality of the medulla and increases the osmolality of the filtrate presented to the DCT (normally this is hypo-osmalar) to help water resorption, but it is now iso-osmolar and therefore much more water goes through to the distal tubules to the collecting duct. Sodium loss can be dramatic.

Frusemide redistributes blood flow from the juxtamedullary area to the outer cortical regions - it may also act as a venodilator and increase systemic and/or pulmonary venous capacitance.

Indications

It is used as the main diuretic in all species and when there is fluid retention secondary to heart failure:

small animals - congestive cardiomyopathy, pulmonary oedema, cerebral oedema, hypercaluric nephropathy, uraemia, hyperkalaemia and occasionally for hypertension

cattle - post-parturient udder oedema

(horses - to help reduce epistaxis by depleting circulating blood volume further, one of the main drugs used illegally in racehorses)

Pharmacokinetics

Absorption - iv onset in 5 minutes, peak effect in 30 minutes, duration 2 hours

oral onset in 1 hour, peaks at 1-2 hours, duration 6 hours

Distribution - highly protein bound - 95 %

Metabolism - half life 15 min - 2 hours, may be increased in renal failure, uraemia, congestive heart failure and neonates. Not very much metabolised

Elimination - small fraction filtered by the glomerulus, rest secreted into the proximal renal tubules by an organic anion pump which is inhibited by probenecid

Side effects

This drug is very potent and is easy to overdose. Overdosage leads to dehydration which may be severe. This may also decrease the clearance of concurrently administered drugs and has the potential to cause toxicity eg. digoxin.

- Hypokalaemia which may be predisposed to by anorexia (remember digoxin)
- Hyponatraemia
- Tolerance develops

Caution

pre-existing electrolyte imbalances or conditions that may lead to these eg. vomiting, diarrhoea

Interactions

aminoglycosides, tetracyclines, cephaloridine to increase proximal convoluted tubule nephrotoxicity. Potentiates the effects of digoxin. Possible interactions with ACE inhibitors (see earlier).

Bumetanide is similar to frusemide but more potent. May be more useful in large animals.

Drugs Acting In The Early Distal Tubule

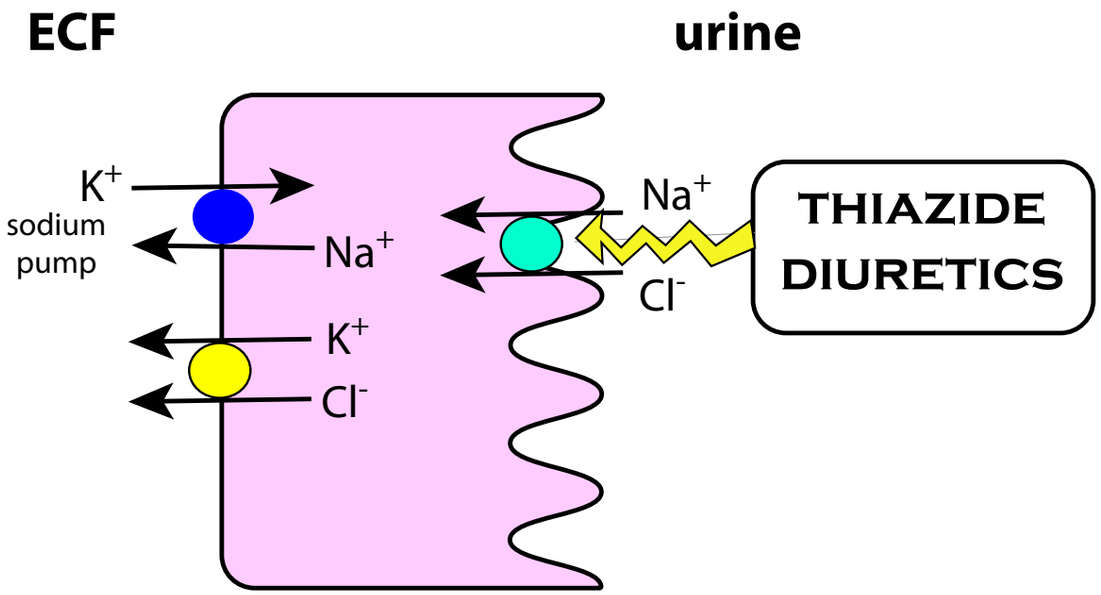
Thiazides

Thiazides were the standard diuretics before frusemide came along, and are still used occasionally, mainly because they are very cheap. Older drugs such as chlorthiazide and hydrochlorthiazide are most widely used in animals but newer drugs such as methcyclthiazide and cyclothiazide are used in man.

They inhibit resorption by decreasing membrane permeability to Na+ and Cl- which promotes a large increase in urine Na+ and Cl- concentration and mild to moderate increases in urine volume. They also cause secretion of K+ and increase the excretion of other ions ie. Ca++, Mg++, PO_4 and iodine. Plasma renin and aldosterone levels increase which also increases K+ excretion. All the thiazides produce a similar level of diuresis. They have anti-hypertensive effects, mechanism is unknown. They can be combined with other diuretics since they work in different parts of the kidney. They are also weak carbonic anhydrase inhibitors but this is not clinically important.

Paradoxically, thiazides reduce the urine output in patients with nephrogenic or pituitary diabetes insipidus, possibly by over compensation of Na+ resorption in the proximal tubule - this effect is achieved only with a low sodium diet.

DIAGRAM 5.5.4 Diuretics acting in the early DCT



These are only used rarely.

Indications

nephrogenic diabetes insipidus

general diuretic for moderate diuresis

systemic hypertension

prevent recurrence of calcium oxalate uroliths in dogs

post-parturient udder oedema in dairy cattle

Contraindications

Renal failure or compromised renal function - they reduce renal blood flow and glomerular filtration rate. In azotemic animals measure BUN and/or serum creatinine levels before treating.

Overuse causes changes in electrolytes and/or fluid balance, particularly hypokalaemia - remember digoxin.

Drugs Acting In The Late Distal Tubule / Early Collecting Duct

Potassium sparing diuretics

Aldosterone is a steroid hormone which binds to a nuclear receptor which stimulates transcription mRNA which codes for the basolateral Na/K-ATPase pump and the luminal Na+ channels. This leads to an increase in Na/K-ATPase pump activity and therefore an increase in Na+ resorption. K+ is lost in exchange for resorbed Na+ to maintain electronutrality.

Spironolactone is structuraly similar to aldosterone and acts as a competitive antagonist of aldosterone. Therefore spironolactone inhibits aldosterone's action on the cells located between the distal renal tubules and the collecting ducts called the "principal cells of cortical collecting ducts" and causes an increased excretion of Na+, Cl- and water and a decreased excretion of K+, NH4, P04 It has no effect on carbonic anhydrase or renal transport mechanisms. It has its greatest effect in patients with hyperaldosteronism. It usually elicits only mild diuresis. It is useful in congestive heart failure because of its interactions with the RAAS, but also interacts with oestrogen and testosterone receptors and is going out of fashion in people because of this.

Indications

limited degree of diuresis when used on its own

- used in combination with other classes, especially loop diuretics, in patients where hypokalaemia due to other diuretics is likely to cause serious problems especially if on digitalis or if unable to supplement with dietary potassium
- used in combination with other classes in cases of severe fluid retention eg. refractory ascites, pulmonary oedema secondary to heart failure which is non-responsive
- used for heart failure in people ± ACE inhibitors - too expensive in animals.
-

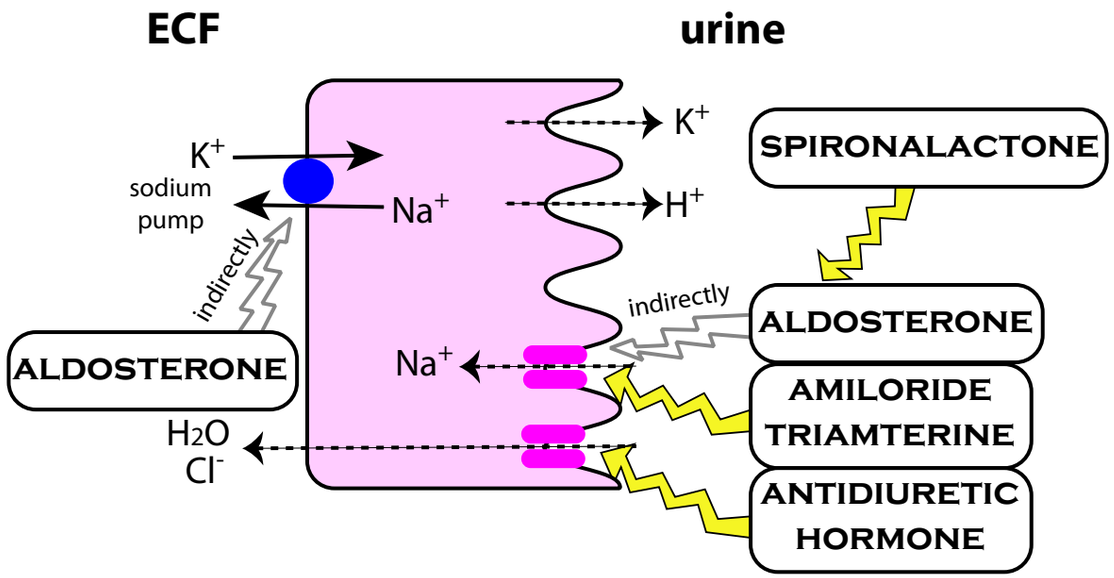
Pharmacokinetics

Absorption - gradual onset of action, peak at 48-72 hours, duration for 2-3 days after therapy has stopped

Distribution - 98% bound to plasma protein - CBG - corticosteroid binding globulin and albumin

Metabolism - rapidly metabolised to a number of metabolites one of which (canrenone) is thought to also have diuretic activity. Spironolactone has a short tl/2 of 1-2 hours in humans whereas canrenone has a tl/2 of about 20 hours

DIAGRAM 5.5.5 Diuretics acting inlate distal tubule / early collecting duct



Some of these are commonly used in people but not animals.

Triamterene and **amiloride** directly block sodium channels on apical (luminal) membrane and therefore decrease Na+ flux which in turn causes a decrease in K+ transport. This only occurs if Na/K transport is increased ie. using other diuretics or there is a physiological defect. They have no effect on normal animals. They act within 2 hours, peak 6-8 hours, duration 12-16 hours

These drugs can produce hyperkalaemia if they are combined with potassium supplementation or ACE inhibitors.

Poisons affecting the kidneys

Metals and Inorganics

- cadmium
- zinc
- boric acid
- mercury
- copper (see toxicants causing gut toxicity)
- uranium
- bismuth
- -phosphorus (see toxicants affecting the liver)

Organic Compounds

- vitamin K3 (menadione) (in the horse)
- cantharidin (blister beetles)
- sulphonamides
- amphotericin-B
- nephrotoxic antibacterials (except sulphonamides)
- oxytetracycline
- bacitracin
- polymyxin-B
- gentamicin
- neomycin
- carbamate fungicides
- carbon tetrachloride
- phenolics
- diquat (herbicide)
- stillage liquid from ethanol production (in cattle) (not confirmed)
- analgesic nephropathy (nonsteroidal anti-inflammatory drugs)
- ethylene glycol (antifreeze)
- oxalic acid
- vitamin D, especially vitamin D3 (cholecalciferol)
-

Plants

- vitamin D containing plants
- Cestrum diurnum

- Solanum malacoxylon
- soluble oxalate containing plants
- beets (Beta)
- rhubarb (Rheum)
- halogeton (Halogeton)
- greasewood (Sarcobatus)
- curlydock (Rumex)
- lambsquarters (Chenopodium)
- Kochia scovaria
- other nephrotoxic plants
- pigweed (Amaranthus retroflexus)
- oak, acorns (Quercus spp.)
- cocklebur (Xanthium)
- lily (Lilium) and daylily (Hemerocallis)
- raisins and grapes

Nephrotoxic Mycotoxins

- ochratoxins
- fumonisins
- citrinin
- hybrid Sudan or Sudan grass (Sorghum spp.) (equine cystitis, ataxia syndrome) secondary to paralysis and ascending pyelonephritis)

Cholecalciferol

(Vitamin D3)

Source

Commercial product available for possum control. Plant toxin

Toxicity

reported from as low as 2 mg/kg, Serious toxicity at >10 mg/kg

LD50 is reported as 13 mg/kg by Rumbeiha et al

Cats are more sensitive than dogs and younger animals are more sensitive.

Toxicokinetics

Absorption - well absorbed from jejunum (small intestine)

Bile salts are required

Distribution - lymph before blood than highest concentrations seen in Plasma, lymph, kidneys and fat.

Binds to alpha 2 globulin (protein)

gets across placenta-will cause supravalvular aortic stenosis in rabbits born to does treated with D3

Metabolism - by liver and kidney see textbook for metabolic cascade, metabolites have LONG half-lives

Excretion - primarily in faeces, some enterohepatic circulation

a small amount (2%) excreted in urine

D3 and metabolites have a long half-life which means treatment may be prolonged for several weeks to control hypercalcaemia.

Physiological Effects

Vitamin D3 or cholecalciferol is a positive regulator responsible for calcium homeostasis in the body. An excess of cholecalciferol results in the following:

- Hypercalcaemia
- Increased absorption of CA and P from Small Intestinal Tract
- Mobilise Ca from bone
- Decrease renal excretion

Hypercalcaemia slows the heart rate; conduction dysfunction QT shortened and PR prolonged when Calcium is greater than 3.49 mmol or 14 mg/dl (depending on the value the lab reports)

Calcium deposits throughout body tissues, heart, blood vessels, kidney and lungs

Vasoconstriction results in an increase in vascular resistance which increases renin release, which can lead to severe renal ischemia and tubular necrosis.

Decrease in ADH levels (inhibited by hypercalcaemia)

- PU/PD
- Dilute urine
- Electrolyte disturbance Na and K+ losses

- Renal failure and calcium deposits in the renal medulla especially the Loop of Henle and the collecting ducts.
- Heart conduction failure

Calcitriol in the GIT

- binds to intracellular receptor in the intestinal cells which stimulates the synthesis of carrier protein

- mobilises calcium from the bone (active transport of Ca in osteocytes)

Calcifediol and Calcitriol

-enhance reabsorption of Ca and Phosphorus from the proximal tubules (kidney)

Clinical Signs

- Latent period of about 8-24 hours after ingestion before clinical signs appear.
- 12-24 hours clinical pathological changes of hypercalcaemia and hyperphosphataemia
- Progressive clinical signs resulting from hypercalcaemia:
- Initially lethargy, weakness, and anorexia,
- then vomiting, polyuria, polydipsia, constipation and dehydration
- urine is hyposthenuric
- Severe GIT signs may have blood in faeces
- Haematemesis is a grave sign
- Azotaemia
- Cardiac abnormalities like bradycardia, ventricular arrhythmias, PR interval prolonged and QT shortened
- Sometimes dyspnoea due to bleeding into the lungs
- Neurological: Twitching, seizures-uncommon but reported, depression and stupor

Diagnosis

Clinical signs often develop 12-36 hours after consumption of a toxic dose.

Laboratory diagnosis

A serum calcium level higher than 4.99 mmol/L is characteristic and highly suggestive of cholecalciferol toxicosis.

An elevated serum phosphorus level may precede the hypercalcaemia by as much as 12 hours and could serve as an early nonspecific indicator.

The urine specific gravity is 1.002-1.006.

Increased BUN and creatinine levels are common as the toxicosis continues.

Cholecalciferol poisoning

- Hypercalcaemia and Hyperphosphataemia
  - Enterohepatic circulation (repeat use of activated charcoal)
- Renal Failure but.....
  - cardiovascular effects
  - gastrointestinal effects
  - CNS depression/ ± seizures
- Treatment
  - Fluids
  - Frusemide
  - Prednisone
  - ± calcitonin depends on the severity of hypercalcaemia
  - Avoid sunlight
  - Low Calcium diet
  - Phosphate binders (aluminium hydroxide)

• Long treatment period

• note: new research has indicated some value in using pamidronate disodium (Pamisol)

Excessive active 1,25-dihydroxyvitamin D metabolites are present in renal tissue, but the analysis is difficult and few laboratories would be able to perform it.

Post Mortem

Gross lesions include petechial haemorrhages in tissues, pale streaks in kidney tissue, and raised plaques in the intima of large vessels, haemorrhagic gastritis.

Microscopic lesions may include mineralisation of the kidney tubules, coronary arteries, gastric mucosa parietal pleura, pulmonary bronchioles, pancreas and the urinary bladder. The renal tubules may be necrotic or degenerative.

Treatment

Detoxification therapy is essential when the exposure is recent (3-4 hours). The first treatment with activated charcoal should include or be followed by a laxative.

Activated charcoal is essential and should be repeated for several days due to the enterohepatic circulation.

Treat the hypercalcaemia with fluid therapy of normal saline, frusemide for diuresis.

Saline diuresis promotes calcium excretion

Frusemide for diuresis (5 mg/kg IV initially then 3 mg/kg q8h)

If the hypercalcaemia is not responsive consider using pamidronate

Corticosteroid administration of prednisone (2 mg/kg q8-12h) inhibits the release of osteoclast-activating factors, reduces intestinal calcium absorption and promotes hypercalciuria. May not be necessary if using pamidronate.

Pamidronate (Pamisol)1.3-2 mg/kg when serum calcium levels are high (superior to calcitonin)

Salmon calcitonin (4-6 IU/kg subcutaneously q3-6h increase to 10-20 IU/kg if the animal does not respond) may be administered to reduce excessive serum calcium levels

Avoid Sunlight.

Prognosis is generally guarded to poor depending on severity and responsiveness of the hypercalcaemia. In animals presenting with haematemsis the prognosis is grave.

Treatment is continued until for at least two weeks (frusemide and prednisone). Remove treatment for 24 hours and check calcium levels. If elevated continue frusemide and prednisone and monitor at weekly intervals. If calcium level is normal after 24 hours, monitor at 48 hours and 72 hours.

Ethylene Glycol

Systems Affected:

- Respiratory - acidosis
- Urinary
- CNS

Sources

- Radiator antifreeze
- other automotive and heat exchange uses

Susceptible Species

Birds and mammals - particularly dogs and cats

Toxicity

(Lethal Dose):

95% EG Diluted 50:50 EG:water

Feline 1-2.5 ml/kg 15 ml

Canine 4-5 ml/kg 13.2 ml/kg

Poultry 7-8 ml/kg

Cattle 2-10 ml/kg

ADME / Pathogenesis

- Unmetabolised EG is rapidly absorbed; same toxicity as ethanol.
- Peak blood levels 1-4 hours post exposure
- Plasma half-life of EG is 2.5-3.5 hours
- EG excreted unchanged in the urine, first 4 hours up to 24 hours.
- Metabolism of EG critical to therapy

Liver:

Disposition of glyoxylic acid:

oxidation to oxalic acid (.25-3.7%)

Oxalic a. + Calcium = calcium oxalate crystals

3 Stages of Toxicity:

1. 30 min to 6 hours CNS/ethanol-like

diuresis-dehydration and polydipsia

DIAGRAM 5.5.6 Ethylene glycol toxicity

Stage 1

1 - 2 hours after ingestion
- vomiting
- CNS depression
- ataxia

3 - 5 hours after ingestion
- acidosis (blood pH< 7.3)

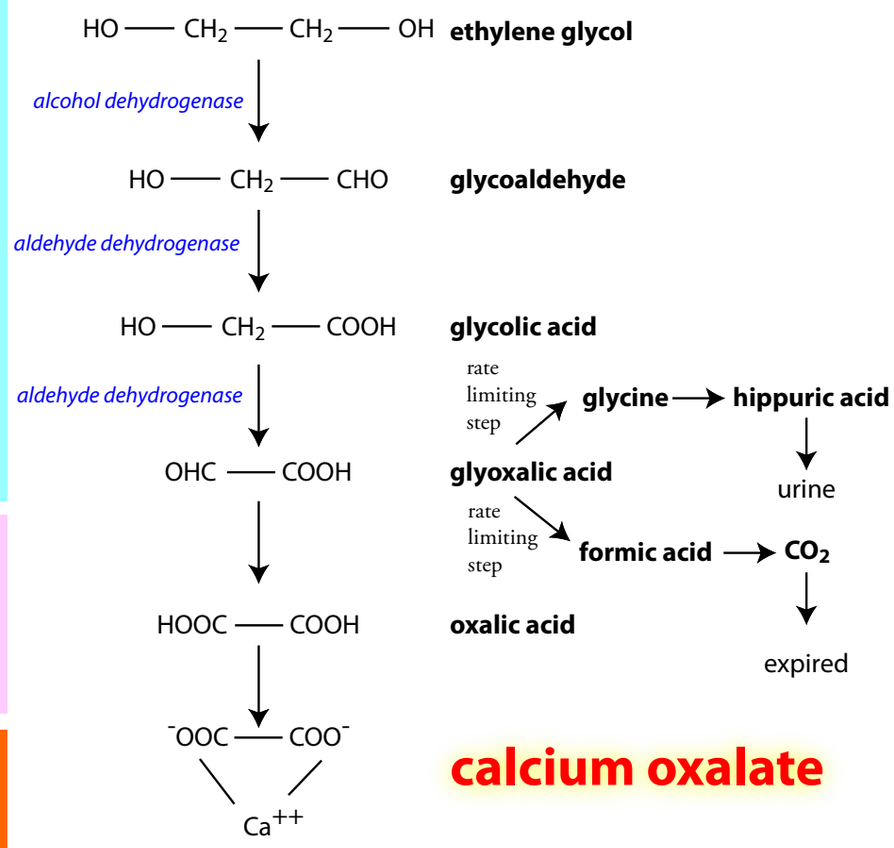
- nervous effects
- greater acidosis
- depression worsens

Stage 2

6 hours after ingestion
- calcium levels drop
- tremors develop

Stage 3

- birefringent crystals deposited in kidneys
- blocked tubules
- increased BUN & creatinine
- anuria



Clinical stages and pathogenesis.

2. 12-24 hours -Cardiopulmonary effects

heart and respiratory rate increase

3. 12-72 hours oliguric renal failure

ocular lesions-detached retina, oedema and anterior uveitis

*rate limiting steps (different species favor different metabolic pathways)

Toxicity

Glycoaldehyde is more toxic than ethylene glycol, but it is rapidly metabolised to glycolic acid.

Glycolic acid is believed to cause metabolic acidosis and probably nephrosis., more toxic than EG.

Glycoxylic acid is more toxic than any of the other metabolites, but it has a short half-life that it does not appear to accumulate in concentrations high enough to have toxic effects.

Oxalic acid combines with calcium to form calcium oxalate crystals which may precipitate in the renal tubules and to a lesser extent in the brain vasculature and other tissues. The presence of oxalate crystals does not correlate with the nervous system effects. Surviving animals usually make complete recovery of the CNS.

Differential Diagnosis

head trauma, encephalitis, drug overdose, acute nephritis, acute diabetes mellitus

Clinical Pathology

Mild lymphopenia and neutrophilia (mature)

Haemoconcentration (PCV. Total Protein)

Blood Urea Nitrogen, creatinine, phosphorus, glucose

calcium, blood Ph < 7.3

Hyperkalaemia

Hypochloraemia, low bicarbonate

metabolic acidosis

Anion gap and Serum Osmolality useful

Anion gap > 25 meq/L (normal 10-15)

Osmolality > 10 mOsm/L (normal ± 5-10)

Urine specific gravity- isothenuric or dilute

Birefringent crystals

Diagnosis

history of exposure with clinical signs

blood or urine analysis if early < 24 hrs

anion/osmolality

A plasma EGT spot test is available for quick determination of EG ingestion.

Gross Pathology

dehydration

hyperaemia of GI, swollen kidneys and pulmonary oedema

uraemia and evidence of renal failure

Microscopic Lesions

calcium oxalate or hippurate crystals-kidney, but brain and muscle ± renal tubules dilated ± crystals; Birefringent crystals

Treatment

Stage 1: (Early exposure/no clinical signs)

emetics, activated charcoal, gastric lavage

Ethanol (depression) < 18 hours

Bicarbonate

Stage 2 and 3:

Bicarbonate, fluids

Peritoneal dialysis (haemodialysis better)

diuretics?

Ethanol Therapy

Ethanol competes with ethylene glycol for alcohol dehydrogenase

Dogs

20% ethanol in saline IV 5.5 ml/kg

Repeat every 4 hours for 5 times, then every 6 hours for 4 times

+ 5% bicarbonate IV at 8 ml/kg**

(**IF metabolic acidosis; if values are available, calculate base deficit and treat with bicarbonate as required).

Evaluate ionised calcium levels and supplement as needed

Cats: Ethanol Therapy

5 ml/kg of 20% ethanol in saline solution IV

every 6 hours for 5 treatments, then every 8 hours for four treatments.

6 ml/kg of 5% bicarbonate (see note under dogs on base deficit and calcium requirements)

(NB this treatment prolongs EG's half life)

Sodium bicarbonate therapy should be based on serial plasma bicarbonate levels when available:

Bicarbonate Deficit (mEq)

0.5 X B.W. (kg) X [24 - Plasma Bicarb (mEq/L)] = mEq of sodium bicarbonate needed

To prevent overdose give only 80% of the calculated dose---very slowly preferably in fluids

Alternative Ethylene Glycol Treatment:

fomepizole (4-Methylpyrazole, 4 MP): for dogs only; in place of ethanol therapy

More effective and safer treatment than ethanol.

Inhibits alcohol dehydrogenase

Treatment must be started within 8 hours of EG ingestion.

Cases

Case 1

Feracol, a cholecalciferol-based possum bait, is ingested by your client's working dog several hours ago.

- What treatment is indicated?
- What is the mechanism of toxicity of Campaign®?
- What serum biochemistry(ies) is/are altered by Campaign® toxicity?
- What clinical signs might you expect to see with this poison?
- What treatment is recommended for a dog presenting with clinical signs of poisoning?
- What is the prognosis for a dog with clinical signs?

Give a brief explanation of your answer.

Blood

commonly used drugs

platelet inhibitors - aspirin

anticoagulants - heparin, acid citrate dextrose

coagulants - vitamin K1

Blood

- ☑ anticoagulants are used in small quantities to prevent blood clotting in iv catheters (heparin) or after collection (ACD or PCD)
- ☑ anticoagulant rat poisons are a major problem in dogs - give vitamin K1
- ☑ There are numerous causes of anaemia - an accurate diagnosis is required for rational treatment

The usual therapeutic aims in veterinary medicine are to encourage blood clotting at the site of injury and prevent clotting in the circulation, ie, thrombosis. Thrombo-embolism is rare, or at least rarely diagnosed, but potentially serious / fatal.

Possible targets:

- vascular smooth muscle - vasoconstriction restricts flow to the affected area
- platelets - platelet adhesion and aggregation forms a viscous mass (platelet plug)
- clotting factors - activation of clotting factors results in polmerisation of fibrin to form a stable clot

Anticoagulant poisoning is commonly seen in dogs which have eaten coumarin rat poisons (eg, warfarin).

Haemostasis

The normal response to haemorrhage is:

- blood vessel constriction
- platelet aggregation to form a plug
- followed by activation of the clotting cascade to form a fibrin thrombus

In veterinary practice, bleeding can be reduced using

- Good surgical practice. Far and away the most important way of preventing and stopping bleeding.
- Artificial substrates for clots (usually as pads applied to large bleeding areas, eg liver)
  - calcium alginate
  - oxidised cellulose
  - absorbable gelatin
  - microfibrillar collagen
- Exogenous clotting factors supplied as whole blood or fresh frozen plasma. After extensive haemorrhage and replcement by colloids, the clotting factors may be so diluted that they no longer work. Topical fibrinogen and thrombin sprays and bandages are under trial in the US.
- Topical vasoconstrictors - adrenaline and noradrenaline. Usually applied to mucous membranes or other large areas which are oozing blood.

- Anticoagulants such as heparin are used in disseminated intravascular coagulation (where bleeding is caused by all the clotting factors being used up). Should not be used for haemostasis in other situations
- (Hypotensive anaesthesia) No longer used for haemostasis but it is useful to remember that if an animal stops bleeding under anaesthesia its blood pressure may be dangerously low / zero!
- Parenteral haemostatics are not much use except in special circumstances. They include **tranexamic acid**, which binds plasminogen thereby preventing its cleavage to plasmin - antifibrinolytic. Small intravenous bolus dosing stimulates the chemoreceptor trigger zone and reliably elicits vomiting in dogs and cats without any generalized CNS depression or excitment often associated with other emetics such as xylazine and apomorphine.

Tranexamic acid is indicated in treatment of overdose with fibrinolytic agents, low plasma fibrinogen, haematuria, (uncontrollable haemorrhage) and poisoning (to induce emesis). It is contraindicated in pregnancy and where there is intravascular clotting. Massive overdoses cause few immediate or untoward effects. The possibility of inducing multiple intracirculatory thromboses must be considered.

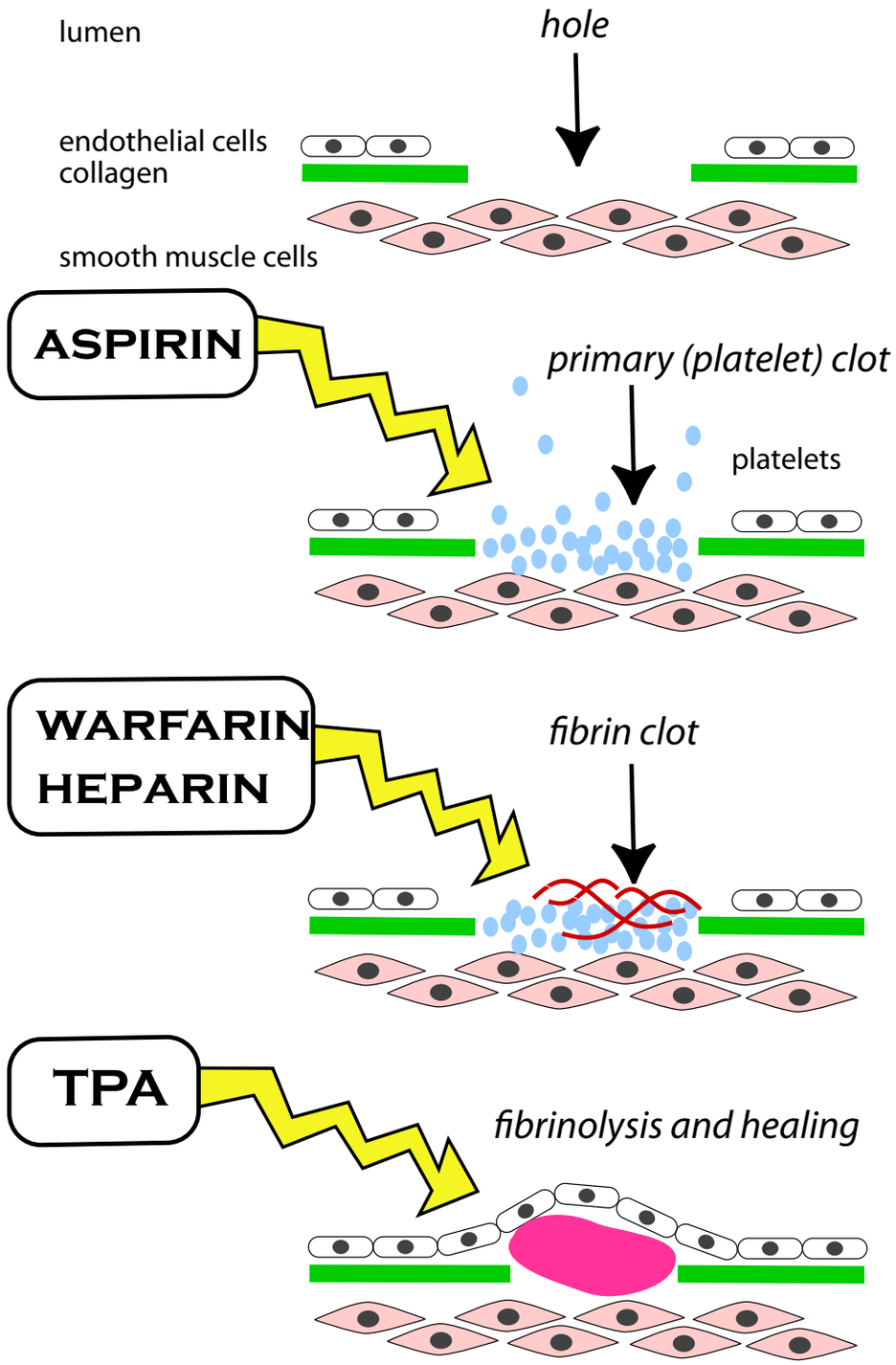
Drugs used to treat clots

There are many drugs used in people to break clots down and restore blood supply to areas distal to the clot (mainly used in myocardial infarction). These are not usually used in animals because they are very expensive and the damage is very gross / irreversible when the animal is presented for treatment (drugs usually have to be given within 3 hours to be effective). In veterinary practice it is usual to try to prevent further clotting using anticoagulants or antiplatelet drugs. All these drugs can cause massive bleeding - animals have completely bled out after their use. As a broad generalisation, anticoagulants are used to treat venous thrombosis, antiplatelet drugs for arterial thrombosis.

Parenteral Anticoagulants

The only common drug is **heparin**. It is a high molecular weight glycosaminoglycan isolated from cattle lungs or pigs' guts. Only five sugar residues are required for action, so low molecular weight heparins are sometimes used. It is rapidly metabolised (2 hours). Clotting times are usually monitored during use.

DIAGRAM 5.6.1 Blood clotting



Drugs affecting clots. Aspirin and warfarin prevent clotting, tissue plasminogen activator breaks down clots.

Mechanism of action
Binds to antithrombin III to activate it. The complex rapidly inactivates circulating thrombin, and to a lesser extent factors XIIa, XIa, IXa and Xa.

Indications
- maintaining iv catheter patency - catheters are flushed with saline containing a small amount of heparin
- prevention of clotting in response to other intravascular hardware (mainly people at the moment)
- venous thrombosis
- disseminated intravascular coagulation

Side effects
bleeding, hypersensitivity reactions (reduced with low molecular weight heparins)

Contraindications
- liver disease, haemorrhage (except DIC)
- do not give im - haematoma formation. iv is best.

In overdose give protamine sulphate, 1mg/100units heparin by slow iv injection (causes hypotension if given fast).

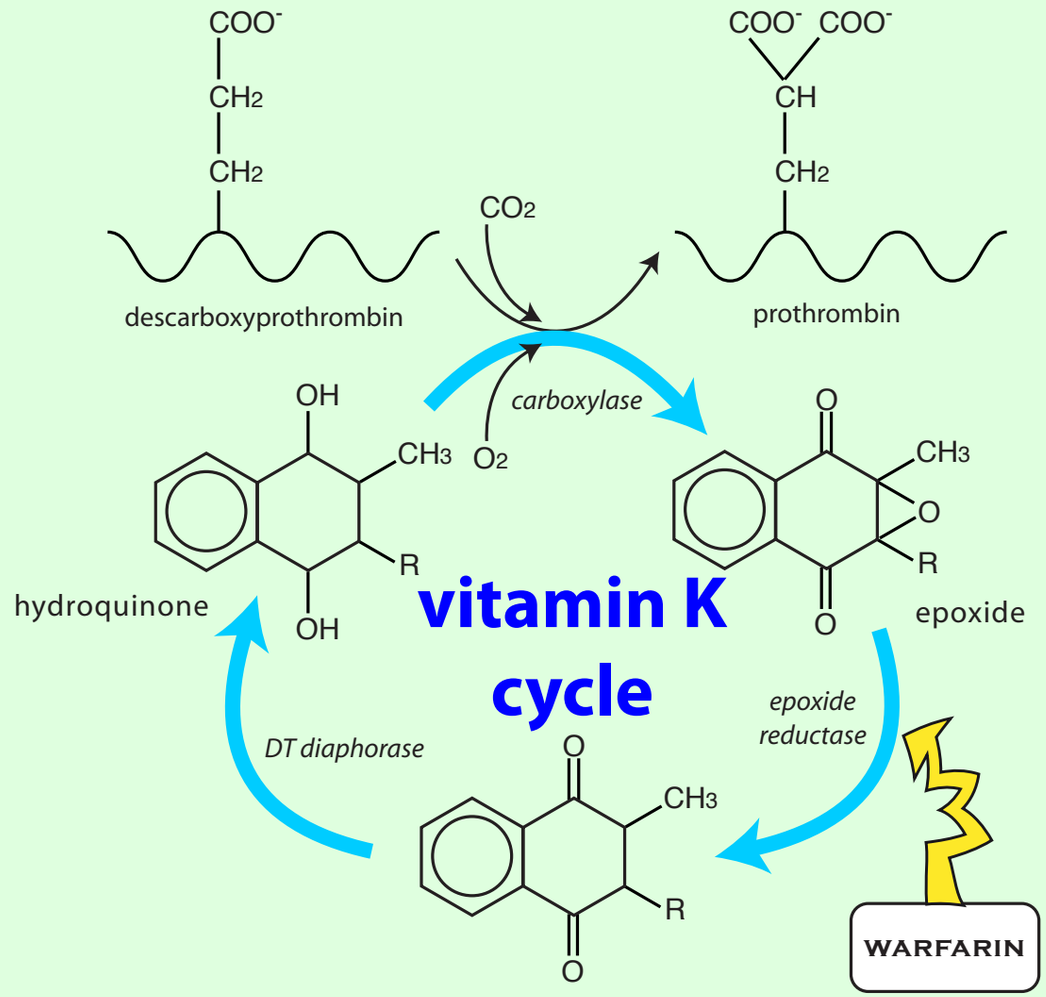
Oral Anticoagulants
These are nearly all coumarins, of which **warfarin** was the first to be widely used (as a rat poison). Some rats have developed resistance to warfarin, and there are a variety of second generation coumarins such as brodifacoum used as rat poisons now. These generally have a much longer duration of action. The most modern drugs in this class (not in NZ yet) have half lives of weeks in dogs.

Warfarin is typical of the coumarin group. It is a stable analogue of vitamin K. Although widely used as an anticoagulant in people, it is mainly seen as a poison in veterinary practice. It competes with vitamin K for the recycling enzymes and inhibits vitamin K dependent clotting factors (prothrombin, VII, IX, X).

When used therapeutically, clotting times must be monitored

Indications
- venous thrombosis
- thromboembolism in cats
- disseminated intravascular coagulation
- navicular disease ?

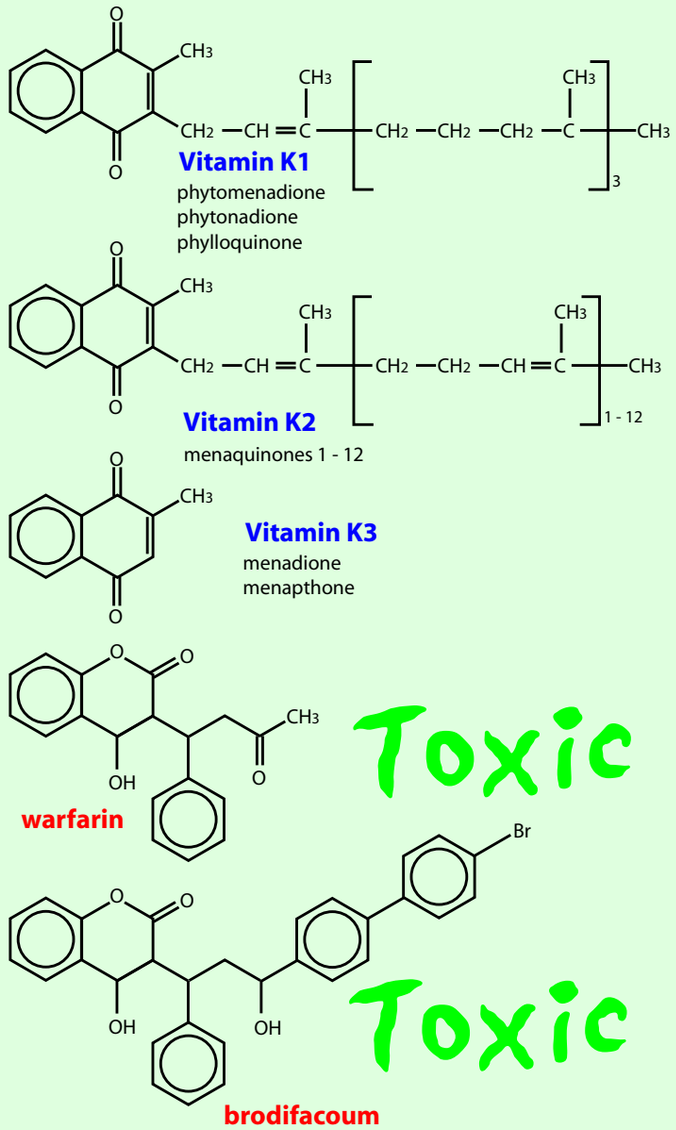
DIAGRAM 5.6.2 Vitamin K cycle



Vitamin K cycles between the hydroquinone and the epoxide in the process of making prothrombin (and factors VII, IX and X). Coumarins block this cycle and prevent the production of prothrombin. Exogenous vitamin K is taken up in the quinone form.

Contraindications
malnutrition, haemorrhage

DIAGRAM 5.6.3 Vitamin K and analogues



Note: only K1 is useful to treat warfarin overdose in dogs.

Pharmacokinetics

highly plasma protein bound - can be displaced by other highly bound drugs eg phenylbutazone.

Since it interferes with the production of clotting factors, existing stocks must be used up before any anticoagulant effect is seen - usually 8 - 10 hours.

Side effects

bleeding - not necessarily in an obvious place!

Treatment of warfarin overdose

In severe cases a transfusion of fresh blood ± intensive care may be necessary. **Phytomenadione** (vitamin K1, phytonadione USAN, phylloquinone, etc.) competes with warfarin for the binding site (other forms of vitamin K are much less effective). In mild cases it will start to work in about 30 mins after iv injection but no signs of improvement may be evident for more than 2 hours. It is usual to continue with oral K1 for 10 - 14 days after warfarin overdose; 30 days after brodifacoum. Assessing prothrombin times will show if treatment can be stopped.

Vitamin K comes in many different forms, all of which have many different names. K1 is probably the only one which works in dogs, avoid K3 (menadione, menaphthone) even though it is cheap (it works in chickens and is added to their feed by the ton).

Further reading

Walker and Royston, 2002, *British Journal of Anaesthesia*, Thrombin generation and its inhibition: a review of the scientific basis and mechanism of action of anticoagulant therapies. 88, 848 - 863

All you ever wanted to know about coagulation and more!

Anti platelet drugs

These are used to prevent the formation of thrombi. **Aspirin** is the only drug widely used in veterinary practice, usually for thrombo-embolism in cats. It inhibits cyclo-oxygenase in platelets and blocks production of thromboxane A2 (which causes platelet aggregation). It can cause bleeding. The dose required is usually low enough to avoid other side effects. Since it irreversibly acetylates platelets, it is only given once every 3 - 4 days.

Clopidogrel does a similar job by a different mechanism. It is widely used in people and is starting to be used in cats.

Prostacyclin (PGI2, epoprostenol) ia a physiological antagonist of thromboxane A2. Very expensive.

Fibrinolytics

Not often used in veterinary practice - too expensive. The dose is critical - too much and the animal will bleed out.

Alteplase is recombinant human tissue plasminogen activator. It breaks clots down and is much better in people than streptokinase or urokinase. It can cause bleeding so do not use if there has been recent trauma or a major operation, hypertension, bacterial endocarditis or acute pancreatitis. Plasmin is starting to be used in people instead.

Streptokinase is isolated from *Streptococcus haemolyticus* B strain. It is antigenic and may produce hypersensitivity. Binds to plasminogen but not preferentially bound to fibrin and will lyse everything . It is not a PA inhibitor. It is degraded by the reticuloendothelial system. Urokinase is isolated from human renal cells Does not need to bind to be active. Not preferential to fibrin, much more expensive than streptokinase, cleared by the liver.

Stanozolol is an anabolic steroid which may have fibrinolytic properties that may be helpful in feline aortic thromboembolism. (clinical studies yet to be done).

Tranexamic acid is an antifibrinolytic sometimes used in people. It is not a substitute for surgical haemostasis.

Anticoagulants for collecting blood

These drugs are not given to animals directly but used to stop blood clotting during collection for storage (in fridge) and infusion later. They work by chelating calcium. Long term storage is largely for RBCs, clotting factors only last a few hours (plasma must be separated rapidly and frozen to preserve clotting factors).

With **acid citrate dextrose**, RBCs keep 3 weeks (in fridge) - the citrate is metabolised in the TCA cycle, dextrose in RBCs. **Citrate phosphate dextrose** - RBCs keep 4 weeks, citrate - RBCs keep 3 days.

Since these drugs chelate calcium, it may be necessary to give extra calcium to ensure normal clotting after infusing large amounts of blood (give 2mmol Ca^{++} to 4 units blood).

Ethylenediaminetetraacetic acid (always called **EDTA**) damages platelets - it is used for *in vitro* blood samples for haematology only. (It is only used parenterally in severe cases of heavy metal poisoning - see toxicology notes).

Poisons affecting haemostasis

Vitamin K

- damaged or mouldy sweet clover (Melilotus)
- mouldy Lespedeza (Lespedeza)
- coumarin and indandione anticoagulant rodenticides and pharmaceuticals
- idiopathic, vitamin K-responsive coagulopathy in swine

Liver and 2° coagulopathy

- Aflatoxin
- Many others

Bone marrow damage

- bracken fern (Pterydium)
- trichloroethylene-extracted soybean oil meal
- benzene (bone marrow effect)

Severe shock / DIC / other coagulopathy

- Garbage Toxicoses

Pit Vipers

Anticoagulant Toxicity

See Veterinary Clinical Toxicology textbook

First Generation – First product a coumarin (warfarin), in NZ coumatetralyl used

Indanediones-“first” generation – pindone, diphacinone and now difethialone in NZ

Second Generation – brodifacoum (Talon), bromadiolone, flocoumafen (Storm)

Sources

Rodenticides, Pesticides

Mechanism Of Action

Interference with the normal blood clotting factors as a result of impaired synthesis leading to reduced concentrations of clotting factors II (prothrombin), VII, IX AND X, due to competitive inhibition of the enzyme vitamin K epoxide-reductase leading to the prolongation of OSPT,. APTT and ACT. The clotting factor precoursers to II, VII, IX, & X are called PIVKA (proteins induced by vitamin K antagonism) proteins. Vitamin K is required for the addition of dicarboxylic acid groups

to the clotting precoursers and for calcium binding to form clots. PIVKA is elevated in vitamin K responsive coagulopathies.

Death due to a generalised bleeding disorder.

ADME

• Absorption rather complete but slow, insoluble in water so small intestine is the likely site of absorption but very little animal data is available.

• Peak plasma levels in 6-12 hours

• Warfarin highly bound to plasma protein

• Liver, spleen and kidney may have high concentrations

In the dog the plasma half-life is 14.5 hours for warfarin, 4.5 days for diphacinone and 6 days for brodifacoum.

Clinical Signs

Signs rarely appear before 24 hours after ingestion usually a lag of 3-5 days

- Death without other clinical signs due to cerebral haemorrhage or other internal haemorrhage
- Depression
- Anorexia
- Anaemia (Pale mucous membranes, dyspnoea)
- Epistaxis, tarry faeces, other sites of bleeding
- Heart rate, pulse - result of anaemia
- Bleeding into joints-lameness
- Abortion
- Icterus if prolonged toxicosis

Diagnosis

History is important

Evidence of haemorrhage

Collect blood from both the patient and a normal animal and submit to the laboratory in citrate blood tubes. (check with lab first as normals not always required)

One stage prothrombin time (OSPT) earliest changes in clotting cascade due to extrinsic pathway (also common) and T½ of Factor VII 6.2 hours or APTT-which measures intrinsic pathway (and common) T½ of Factor IX is 13.9 hours. (Factor X 16.5 hours and Factor II 41 hours) NB Bruere's notes (1990) have a typographical error onT1/2 for clotting factors. These half-lives are for dogs. New edition has corrected values.

(Elevated prothrombin time from 24-48 hours post ingestion);

Chemical Analysis of blood or liver

Treatment

• If recent exposure-within last several hours and no clinical signs use emetics

• If dose calculated is potentially toxic, need to use Vitamin K1 therapy

If clinical signs are present: Parenterally (SQ or IV-only with fluids, slowly); then orally

• Severe clinical signs-transfusions + Vitamin K parenterally.

In poisoning by second-generation anticoagulants prolonged treatment will usually be necessary. This is because the second-generation anticoagulants have a long biological half-life.

a) In animals which are showing advanced clinical signs of intoxication, fresh whole blood transfusion (10-15 ml/kg body weight) is recommended accompanied by parenteral (i.e. subcutaneous) administration of vitamin K1 (2-5 mg/kg body weight/day). Some clinicians recommend dividing this dose and giving it twice daily. Note: plasma or synthetic products may be substituted for fresh blood as appropriate.

Where transfusion is not undertaken a reduced dose of vitamin K1 can be administered intravenously. Care must be taken that this procedure does not induce anaphylaxis and to avoid the risk the dose should given in a 5% dextrose solution and diluted to 1 mg/ml.

Parenteral administration of vitamin K1 should be continued for 1-2 days or until the animal is stable (based on observation and clinical tests such as the one-stage prothrombin time assay (OSPT). Thereafter, oral doses of vitamin K1 are recommended for a period of up to four weeks. The dose can be gradually reduced over

this period. The animal must be closely observed for any recurring clinical signs during treatment and for a month after treatment. The animal should be taken off the vitamin K1 for at least 48 hours to measure the OSPT. If the OSPT is normal, a second test in 36-48 hour may be necessary. If OSPT is normal at that time then vitamin K1 may be discontinued but advise the clients to keep a close eye on the animal. If the OSPT is prolonged than the vitamin K1 should be reinstituted immediately and continued until the OSPT remains normal. After oral dosing the improvement in clotting times may be delayed for 6-12 hours.

b) In animals showing early signs of intoxication and where anticoagulant poisoning is highly suspected (e.g. Flocoumafen, (Storm)) but in which the condition does not warrant blood transfusion, parenteral administration of vitamin K1 (2-5 mg/kg bodyweight/day) is recommended initially. This treatment should be followed by the oral administration of vitamin K1 for a further four weeks, with the dose gradually decreasing over this period. Vitamin K1 absorption is enhanced by feeding with fatty foods. Blood samples should be taken where practicable, to monitor coagulation during treatment. Frequent observation should be continued for at least a further month.

c) If it is suspected that an animal has consumed anticoagulant rat bait, the induction of vomiting is only recommended when very recent ingestion is suspected. Close observation for a week is recommended and vitamin K1 can be given orally as a prophylactic measure. Where there is strong evidence that rat bait has been ingested, close observation and the monitoring of blood coagulation, as outlined earlier, is recommended. Orally administered vitamin K1 is recommended for a period of four weeks.

Summary of treatment of anticoagulant toxicosis in domestic animals.

Anticoagulant Poisoning

- Main clinical sign is haemorrhage
- Competitive inhibition of Vitamin K epoxide reductase
- OSPT increased first
- Warfarin/1st generation shorter T½
- Brodifacoum long T½ (dog 6 days) requires long treatment of 30+ days
- Pindone leaves muscle and other tissue residues
- Vitamin K1 therapy
- Menadione (K3) can be toxic
- Wait at least 48 hours after vitamin K1 is withdrawn to check OSPT.)

Cases

Case 1

"Bouncer", a 15 kg dog is presented to your clinic at 7.30 am. The owner observed the dog eating rat bait left in the garage after its morning walk at around 6.30 am.

a. What treatment would be indicated at this time?

b. What do you need to know to establish your plan of action?

c. If the dog ate approximately 200 gm of Talon, which is .05 gm/kg, did Bouncer get a toxic dose?

Case 2

A 30 kg labrador is presented with epistasis from the nose and rectum. You examine the dog and note tachypnoea, tachycardia, pale mucous membranes and abdominal distention. A PCV and clotting time is ordered STAT. The owner tells you that a rodenticide was left in the garage a week ago. This morning the client noticed that the boxes (2) are empty, but it is unknown if the dog or mice have eaten it. The product name is TalonR.

The PCV is 15 and the clotting time is prolonged. What is your treatment plan for this dog?

What advice do you give the client about the duration of treatment and reevaluation?

Anaemia

Anaemia can be caused by a number of factors which come down to decreased RBC production caused by nutritional deficiencies or bone marrow abnormalities (non regenerative anaemias); and increased RBC removal caused by haemolysis or chronic bleeding (regenerative anaemias). In severe cases blood transfusion may be necessary but the definitive treatment depends on the cause of the condition. Autoimmune haemolytic anaemia is relatively common in small animals and is treated with immunosuppressive drugs.

Iron Compounds

Iron deficiency anaemia is mainly a disease of piglets kept under intensive conditions. They require about 7mg iron / day which would normally be obtained from eating soil; sow's milk does not contain this amount. If untreated, piglets will develop clinical signs at 3 - 6 weeks old, they are usually given a depot injection of iron in the first week (by the farmer). This is becoming less important as piglets are weaned younger (sometimes 3 weeks old). Rarely, the sow is given iron (must be ferrous salt) most of which passes through her; the piglets obtain the iron by eating the sow's faeces.

Too much circulating iron in the piglet encourages bacteria to grow (iron is necessary for most bacteria and is often a limiting factor in their growth) causing problems like polyarthritis.

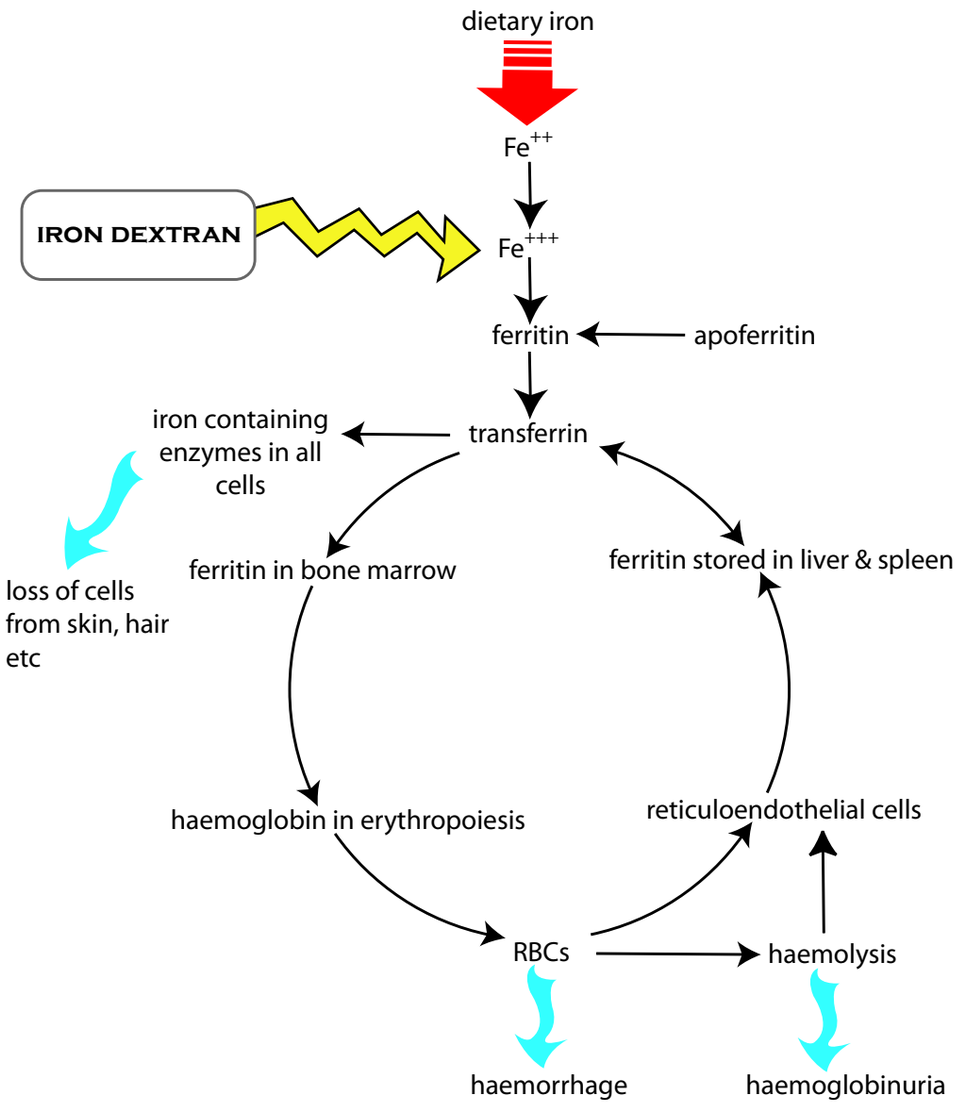
Iron dextran is the main form of injectable iron for the treatment of iron deficiency in piglets at 3 days old. It stains meat (and everything else!) yellow so should be injected behind the ear rather than the gluteals.

Gleptoferron is not available in NZ, it is used in same way as iron dextran in piglets.

Various "tonics" for horses are marketed containing ferric (ammonium) citrate; iron must be in the ferrous form (usually ferrous gluconate) to be absorbed orally.

Copper is also necessary for iron utilisation. Ruminants can be deficient in copper and are usually given oral supplements of a variety of trace elements.

DIAGRAM 5.6.4 Iron utilisation in the body



Iron must be in the ferrous form for absrption from the gut.

B Vitamins

Vitamin B12 acts sequentially in the pathway (with vit C & folic acid) which leads to the synthesis of nuclear proteins in cell division. In deficiency, erythropoiesis is arrested and megaloblasts (large nucleated RBC's which contain more haemoglobin and do not function normally) are released. Deficiency is caused by malabsorption in gut disease so it must be given parenterally.

TABLE 5.6.1 Causes of anaemia.

Cause	Species	Treatment
acute anaemia of unknown cause	all	whole blood (fresh)
nutritional deficiencies		
iron	piglets	iron preparations
vitamin B12	dog & cat	parenteral B12
cobalt (required for B12 synthesis)	ruminants	oral cobalt
folic acid	dog & cat	oral folates
bone marrow abnormalities		
chronic renal failure	dog & cat	anabolic steroids
(reduced erythropoetin production)		erythropoetin
aplastic anaemia		
iatrogenic	all	stop the cause!
oestrogens	dog & ferret	withdraw drug
anticancer drugs	dog & cat	reduce dose?
toxins	all	
infections	all	
excessive RBC destruction		
autoimmune haemolytic anaemia	dog & cat	immunosuppressives
drug reactions	all	withdraw drug
infections		
parasites, eg Haemobartonella	all	treat infection
viruses	all	symptomatic

Cobalt is required for synthesis of vitamin B12 by ruminal micro-organisms. Low cobalt in pasture leads to bush sickness on volcanic soils. Treatment is a slow release cobalt bullet or pasture top dressing.

Folic acid deficiency occurs in steatorrhoea and chronic diarrhoea. Requirements are increased in pregnancy.

Anabolic Steroids

Stimulate erythropoiesis. (See also growth promoter notes). They may be used (especially **nandrolone**) to treat anaemia of some chronic diseases, especially chronic renal failure where their main effect may be to reduce the uraemia which depresses erythropoiesis. Binds to cytoplasmic protein receptor and enhances protein synthesis and diminishes urinary nitrogen excretion.

Discretionary use is illegal in food animals.

Anti-catabolic effects

- inreases nitrogen retention and utilisation
- stimulates appetite and haematopoiesis
- increased retention of calcium, phosphorus and potassium
- Improves blood flow and perfusion,
- reduced blood pressure in microcirculation.

but nutrition must be adequate

General Indications

- stimulate erythropoiesis in anemia due to renal failure and other causes.
- aid in convalescence
- appetite stimulant
- promotion of healing in bones, tendons and surgical wounds.
- antagonise catabolic effects of glucocorticoids
- enhance conditioning of performance horses
- growth promoters

General Precautions

- potential to cause excessive retention of water and Na, Ca, K, Cl, and phosphate.
- may suppress clotting factors II, V, VII and X - •potentiates anticoagulants - may increase prothrombin time
- requires dose adjustment if insulin is used (decreased insulin requirement)
- reproductive problems (decreased fertility)
- virilisation at high doses (most are testosterone derivatives)
- renal or hepatic dysfunction affect pharmacokinetics, which is important to withdrawal times
- potential hepatotoxicity in overdose
- potential for human abuse

Interactions

Potentiate anticoagulants

Laboratory or non-significant findings:

decreased protein-bound iodine

decreased T4 and thyroxine-binding globulin

creatinine and creatine secretion may be decreased

blood glucose may be decreased (therefore may decrease insulin needs)

affect liver function tests (BSP retention, ALT, AST, bilirubin and alkaline phosphatase)

Monitoring

Response to all drugs used to treat anaemia is usually monitored by assessing the PCV. For all anabolic steroids, some monitoring is necessary - clinical or chemical assessment, monitor for androgenic changes, fluid electrolyte imbalance, liver disease, red cell response, weight changes and appetite.

There is anecdotal evidence that **nandrolone** is clinically superior to other anabolics for erythropoiesis. Nandrolone is believed to directly stimulate red cell precoursers in the bone marrow and enhance erthropoietin synthesis in renal failure. Also promotes body tissue building and reverses catabolism and has some androgenic effects.

Ethylestrenol is an orally active anabolic steroid with high anabolic: androgenic ratio (19:1) sometimes used for erythropoisesis. Effects will take at least a week to appear. **Stanozolol** has an anabolic: androgenic ratio 4:1. It may enhance fibrinolysis and so be useful in feline thromboembolism.

Other erythropoietics

Erythropoietin (EPO) is the main regulator of red cell production. It is an endocrine hormone synthesised in the kidney-peritubular cells of the proximal convoluted tubules (a small amount is synthesized in the liver in some species). Synthesis increases with decrease in PO2, inhibited by increase in PO2 (responds to anemia via decreased PO2). It acts on a bone marrow receptor-erythroid progenitor cells but the exact mechanism of action is unknown. It also increases synthesis of haemoglobin. Concentrations are usually reduced in chronic renal failure.

The commercial product is recombinant human EPO: It is prohibitively expensive at the moment. It is a 30,000 MW glycoprotein with human albumin as a carrier: allergic reactions can occur, may manifest as a lack of response to treatment.. Animals must have proper nutritional support. Iron and other essential nutrients must be adequate for EPO to work.

Animals should respond in 2-6 weeks. The use of anabolic steroids may enhance the effect on haematopoiesis.

Erythropoietin is widely abused by human athletes; there ia also potential for this use in horses and greyhounds. In horses it works well for a few weeks then it provokes antibody production which eventually induces anaemia.

Lithium (carbonate) has been reported to stimulate erythropoiesis and has been suggested to aid in the recovery of dogs with oestrogen-induced bone marrow hypoplasia. Blood concentrations must be monitored because of its potential (probable) toxicity.

Polycythaemia

Absolute polycythaemia can occur due to:

- Disease
- Myeloproliferative
- Polycythaemia vera
- elevated EPO in response to:
    - pulmonary disease
    - high altitude
    - cardiovascular disease
    - testosterone
    - decreased PO2
    - renal neoplasia
    - hyperadrenocorticism

Treatment

Try to eliminate cause

Relative polycythaemia is usually caused by dehydration: treatment is iv fluids.

Fluids and electrolytes

commonly used drugs

Hartmann's solution (lactated Ringer's solution)

normal saline

Fluids and electrolytes

- ☑ in emergency any iv fluid is useful to expand plasma volume
- ☑ colloids stay in blood vessels, crystalloids redistribute to other compartments
- ☑ care required in animals with heart failure
- ☑ use oral fluids rather than iv where possible
- ☑ avoid parenteral nutrition - use pharyngostomy tube
- ☑ prevent metabolic disease in ruminants rather than wait and then try to cure it.

Although salty water is not considered a drug by everyone, it is the single most useful way of treating sick animals.

The main function of the blood is to transport oxygen and nutrients to the tissues and take waste products away. To do this there must be adequate volume for the heart to pump, adequate lung function to get oxygen into the blood and adequate tissue blood flow to get oxygen to the cells.

In some situations, vasoconstrictors will also be required.

Composition of blood

- plasma
  - water
  - proteins
    - albumin
    - globulin
    - clotting factors
  - electrolytes
  - glucose
  - waste products
- cells
  - red blood cells
  - white blood cells
  - platelets

Problems can arise from deficiencies or (rarely) excesses of any of these components.

Fluid loss

The distribution of body water (very rough figures):

- total body water - 65% body weight (adults)
  80% body weight (neonates)
- intracellular fluid - 45% bw
- extracellular fluid - 20% bw
- blood volume - 9% bw
- plasma volume - 5% bw

In very fat animals these figures will be lower.

Common routes of fluid loss:

- haemorrhage (not necessarily external)
- vomiting
- diarrhoea
- not drinking
- anaesthesia (breathing dry gas)
- laparotomy / thoracotomy (evaporation)
- burns

The body will adjust the fluid compartments to try to maintain blood volume to preserve blood flow to the vital tissues. Eventually this breaks down and shock results.

Shock

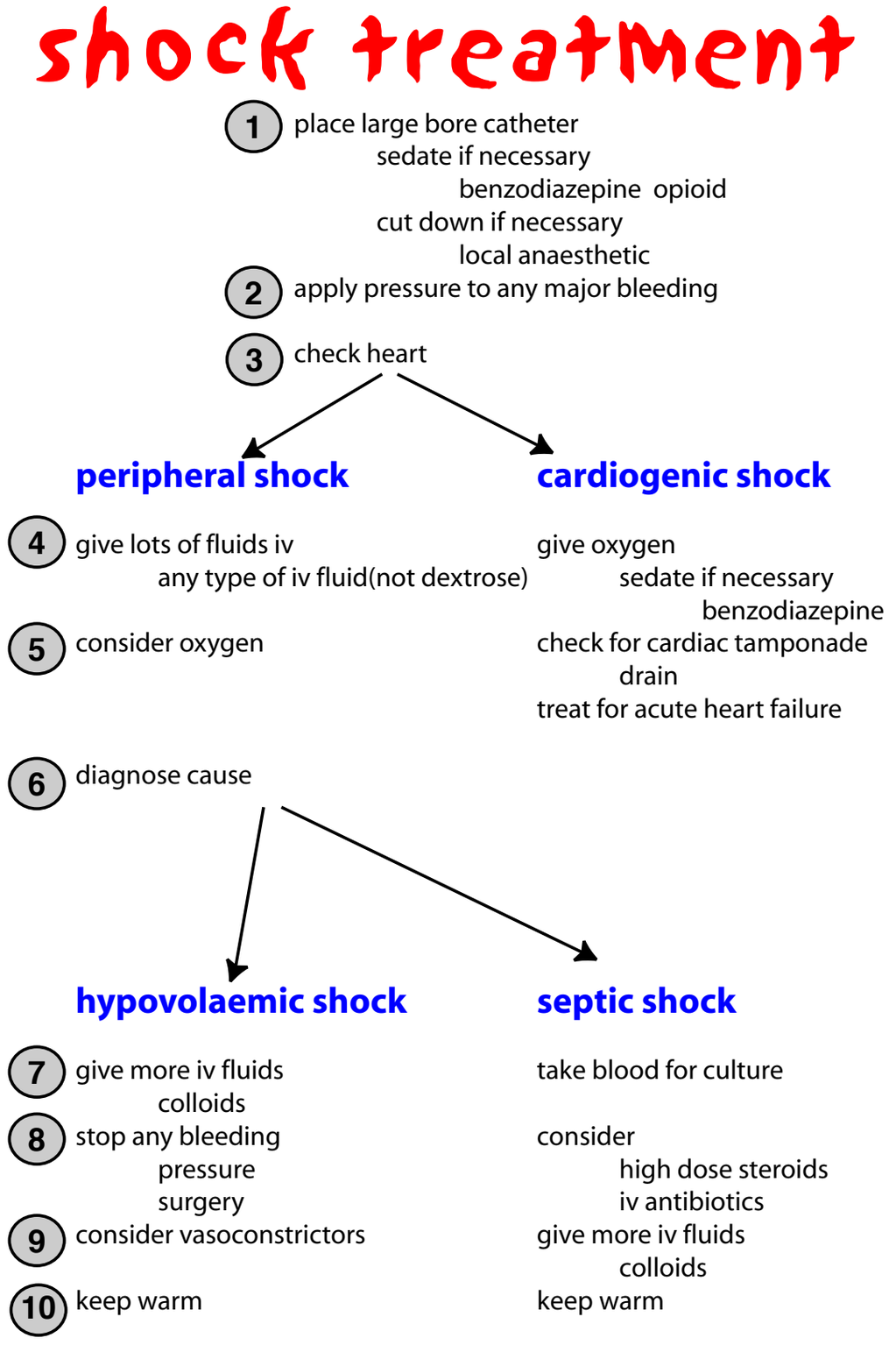
Shock is a state of generalised failure of perfusion of tissues. This is the end stage of most diseases although it is sometimes classified by the causative factor eg endotoxic shock, cardiogenic shock. Initially the body copes by directing most of the cardiac output to the vital organs and drawing water into the cirulation from the interstitial and intracellular fluid compartments but the condition may progress to the point where the compensatory mechanisms are inappropriate and result in positive feedback.

Every body system is affected by shock. Reduced blood flow to the tissues means that anaerobic respiration takes place and lactic acid builds up. The arterioles of non - essential tissues are vasoconstricted by sympathetic outflow and adrenaline but the acidic conditions will eventually cause vasodilatation releasing hydrogen ions into the circulation and reducing cardiac output and thus arterial blood pressure.

The first priority in most types of shock is to treat the hypovolaemia with fluids (almost any fluid will do to start with). The acidosis can then be corrected with bicarbonate and the cause of the shock treated. Treatment of cardiogenic shock is different - see diagram.

A huge number of drugs have been advocated for use in shock but there is no convincing evidence that any of them have any useful effect. Corticosteroids in high doses are sometimes given in the hope that they will do something despite the fact that they have only been shown to improve the outcome if given before shock develops.

DIAGRAM 5.7.1 Shock treatment algorhythm.



Parenteral vs oral fluids

Regulation of water and electrolytes (and thus blood volume) is a function of the kidney. If there is not enough blood flow to the kidney, this regulation breaks down. However, if the kidneys are working and the animal is not vomiting, oral administration is best - the kidneys are better at working out the animal's requirements than most veterinary surgeons. The commonest situation where oral fluids are used is diarrhoea.

In most other circumstances, intravenous administration (via a large bore indwelling catheter) is best. If the animal's blood volume is low, a vein may be hard to find. The answer is to do a sterile cut down onto the vein (see next page); this is quicker and better for the animal than prolonged poking about in the region of the vein followed by administration of fluids by an inappropriate route.

If all else fails, fluids can be given intraperitoneally. Since the peritoneal cavity is only a potential space under normal circumstances, the chances of hitting an organ with the needle are high.

Subcutaneous administration is not a good way to give fluids because if the animal has a low blood volume / acidosis the blood vessels supplying the skin will be constricted. This is done to divert blood to vital organs but also means that the fluid will not be absorbed. Some fluids (dextrose 5%) will cause vasoconstriction directly and actually draw fluid out of the circulation into the subcutaneous depot.

Intraosseous administration has been advocated in puppies and kittens. Injections by this route are extremely painful in man, when a neonatal animal is so sick as to be unable to fight back it is hardly sporting to subject it to excruciating pain as well. Infection is another problem when using this route - the consequences are likely to be disastrous.

General indications for fluids

for oxygen carriage:

- whole blood
- packed cells

for volume expansion:

- colloids
    - plasma
    - gelatins
    - starches
    - hypertonic saline
    - (dextrans)

(but almost any fluid will do in an emergency)

for water and electrolyte replacement:

- crystalloids
    - NaCl 0.9%
    - NaCl 0.18% & dextrose 4%
    - dextrose 5%
    - Ringer's solution
    - Hartmann's solution
- concentrated electrolyte solutions
    - KCl (**must be diluted**)
    - $NaHCO_3$- 8.4% (**must be diluted**)
    - Ca (boro)gluconate
    - Mg hypophosphite (often with Ca)
    - $MgSO_4$

for parenteral nutrition:

- lipid emulsions
- amino acid solutions
- propylene glycol (**ruminants only**)
- Na propionate (**ruminants only**)
- glycerol (**ruminants only**)

Dose calculations

Start by assessing:

- existing deficit - careful history, clinical examination, laboratory tests
- continuing losses - measured directly
- maintenance requirements - 40ml/kg/day

After fluid replacement starts the animals should be assessed regularly and the dose adjusted according to clinical progress. Remember that not all animals have read the book - some will need more than others!

Rate of administration

This depends entirely on the seriousness of the condition. A maxiumum rate of 90ml/kg/h iv is sometimes quoted but the limiting factor is usually the resistance (ie, size) of the intravenous catheter / needle. If you want the fluid to go in quickly use a big, short catheter, or better still, lots of them! This can be a problem in horses, as iv catheters only come in human sizes. Some specialized large cathers are available but are expensive.

If the volume of oral fluid administered is greater than the volume of the animal's stomach then the fluid will rapidly come back up and you will find yourself treating inhalation pneumonia.

Oral rehydration fluids

These should be used in preference to iv fluids where possible. They usually come as a dry powder which is made up with tap water into an isotonic/ slightly hypotonic solution just before administration. Constituents vary but usually include:

- Na^+ to draw water with it
- K^+, Cl- to replace losses
- glucose and glycine to activate organic molecule cotransport systems and increase Na+ uptake
- bicarbonate precursors to correct acidosis
    - acetate (1mmol = 1mmol HCO_3^-)
    - citrate (1mmol = 3mmol HCO_3^-)
    - propionate (1mmol = 1mmol HCO_3^-)

They may also contain starches to be metabolised for energy (adding extra glucose would increase osmolarity of solution and reduce water uptake) and flavourings. Palatability is a problem in small animals.

Only sugar and salt are strictly necessary, the other components are just to improve efficiency. The WHO has published a recipe for third world children: 3.5g salt, 2.5g sodium bicarbonate, 1.5g potassium chloride and 20g glucose made up to one litre with water. This could be used in animals if necessary, although the bicarbonate will change stomach pH enough to cause problems with milk clotting if both are given together.

Indications

mild diarrhoea - especially neonatal animals - cheap enough to use in farm animals

water deprivation

Contraindications

vomiting, severe electrolyte imbalances or shock

They are usually given ad lib in place of drinking water (the animal must be well enough to drink), but if giving by stomach tube, give little and often. The dose depends on the size of the animal's stomach - too much will cause regurgitation ± inhalation pneumonia).

Intravenous fluids

Giving fluids iv is the quickest way to get them to where they are required. Some knowledge of physiology is required to get the dose right - overdosing can be fatal. Too much fluid in the circulation will increase preload on the heart. This is not good for animals with heart disease; in normal animals, signs of congestive heart failure may start to show. Pulmonary and peripheral oedema are most obvious. Pulmonary oedema is often fatal unless oxygen and frusemide are given quickly.

Electrolytes such as potassium and bicarbonate are needed inside cells but are given iv - it takes time for them to diffuse into cells. If the solutions are given too quickly, or in too high a concentration, it is possible to have an excess in the blood at the same time as a deficit in the tissues. Since the heart is one of the organs with the best blood supply, this can lead to arrhythmias.

The circumstances in each animal will be different. The only safe way of using fluids is to monitor the effects of treatment closely. Central venous pressure measurement can be useful - at the very least you should look at the large veins to see if they are distended. CVP can be measured with an improvised water manometer (bits of giving set and a 3 way tap) connected to a central vein. Current trends are to use dynamic variables, such as heart rate variability in response to a test dose of fluids, instead of CVP.

MOVIE 5.5 Cutdown for iv access to lateral saphenous vein

This is a really useful technique to learn for use on very sick animals.

Blood

Whole blood is the fluid of choice for major blood loss but it is expensive and time consuming to collect and store. Blood is usually taken into flexible bags containing acid citrate dextrose (ACD) or citrate dextrose phosphate (CDP) (see anticoagulant notes). ACD will preserve red cells in blood stored at 4˚C for 3 weeks, CDP for 4 weeks. Clotting factors and platelets will be degraded in hours.

Indications

used where RBCs or clotting factors are required

- acute bleeding - PCV below 20%
- chronic problems - PCV below 15% (dog), 10% (cat)

Packed cells (what is left after plasma has been removed) are used where only RBCs are required and suspended in saline before use.

Fresh blood (collected using ACD or CPD but not stored) is used where RBCs and / or clotting factors and / or platelets are required. Beware of transfusion reactions (see anaesthesia notes). There is also the potential for spread of infections, parasites and tumours.

There are no satisfactory substitutes for blood yet but since there is a potentially enormous (human) military market a lot of time and money is being expended looking for a fluid which can carry oxygen, be infused without worries about reactions and has a long shelf life. The nearest so far are perfluorocarbon mixtures which do all these things but are not broken down or excreted by the body. One product is on sale in Japan but worries about long term effects mean that it has not been licensed anywhere else. Cross linked haemoglobin solutions (Oxyglobin) have recently been developed overseas and work in dogs but are not available in NZ yet.

Colloids

These stay in the blood vessels where they maintain blood volume.

Fresh frozen plasma, if collected, separated and frozen immediately, is a useful source of clotting factors as well as a plasma expander. Lasts about 12 months at -80˚C or 3 months at -20. Collecting, separating and storing takes time and equipment. There is the possibility of spreading diseases by tranfusing plasma. Human plasma is sterilised to kill HIV, but this is never done in veterinary practice. Mild allergic reactions are common.

Gelatin solutions (Haemaccel, Gelofusin) are the most widely used plasma expanders. Useful duration of effect 2 - 3 hours. They are made form cross linked bovine gelatin from supposedly BSE free countries.

Hydroxyethyl starch solutions are stable, have a long plasma half life (about 8 hours), a long shelf life - almost ideal but expensive. They are becoming unpopular in people because there is emerging evidence that they can cause renal damage occasionally. They have been banned for human use in the EU.

Anaphylaxis to all of these have been seen in people, but not reported in animals.

Dextrans are obsolete as plasma expanders. They interfere with blood clotting and are now only used (rarely) for this purpose. Lower molecular weight dextrans (40kDa) can cause kidney failure. Avoid.

Crystalloids

These move fairly rapidly out of the blood vessels into the ECF, but can still be useful to expand the blood volume in emergency.

Sodium chloride 0.9% solution (normal saline) is distributed throughout the ECF. Its lack of bicarbonate or a precursor tends to lower pH, but in acidosis, increased blood volume may improve kidney blood flow and thus kidney regulation of pH leading to a reduced acidosis. Long term use will require extra potassium.

Sodium chloride 0.18% and dextrose 4% (dextrose saline) solution is useful for sodium and water maintenance.

Dextrose (glucose) **5% solution** is used as a means of supplying water. The dextrose is quickly metabolised; it is not enough to provide significant energy to the animal. Distributed throughout the body water. Do not give sc - electrolytes diffuse into the pool of dextrose solution drawing water with them and making the situation worse.

Ringer's solution is similar to normal saline but with some potassium. Also tends to lower pH. Very rarely used in animals.

Hartmann's solution (compound sodium lactate infusion, very similar to lactated Ringer's) is used for ECF replacement as it contains lactate as a bicarbonate precursor. It will tend to raise the pH. Although Ringer was British and Hartmann American, "Hartmann's solution" is used in the UK (and NZ) and "lactated Ringer's solution" in the USA.

Plasmalyte is similar to Hartmann's but contains acetate and gluconate.

Sodium chloride 7% solution (hypertonic saline) (3% or 5% are sometimes seen) is used as a plasma volume expander. It draws water out of the ECF into the circulation which increases cardiac output and tissue perfusion in hypovolaemia. It may also have a direct stimulant effect on the heart, although this is controversial. Effects only last 20 - 30 mins so normal crystalloids and / or colloids must be given as well. The small volume of injection makes hypertonic saline (4mL/kg iv followed by normal fluids) useful as a first aid measure in large animals - it is not usually practical to carry around equivalent volumes of isotonic saline.

TABLE 5.7.1 IV fluid use

Condition	Loss	Fluid Used
haemorrhage	all blood components	mild: colloids (crystalloids) severe: (fresh) whole blood
dehydration (not drinking enough)	water	NaCl 0.18% & dextrose 4%, dextrose 5% (KCl 10-20mmol/l added after 2d)
vomiting	water, $H^+Na^+K^+Cl^-$	NaCl 0.9%, Hartmann's (KCl 10-20mmol/l added)
diarrhoea	water, HCO_3^- $Na^+K^+Cl^-$	mild: oral fluids severe: Hartmann's - extra KCl & $NaHCO_3$ needed (unless Addison's or acute renal failure)
severe V & D	water, $H^+HCO_3^-$ $Na^+K^+Cl^-$	colloid & Hartmann's
peritonitis	plasma & ECF	colloid & Hartmann's
gut obstruction	water, $HCO_3^-Na^+Cl^-$	colloid & Hartmann's & $NaHCO_3$
urethral obstruction / ruptured bladder	retention of H^+ & K^+	NaCl 0.9% & dextrose 5% (& soluble insulin?)

It is used for first line treatment of hypovolaemia - more dilute solutions / water to drink must be given afterwards; and in head and lung injuries (draws oedema fluid into the circulation). It should not be used in severe dehydration.

Further reading

MacDonald, N., & Pearse, R. M. (2017). Are we close to the ideal intravenous fluid? British Journal of Anaesthesia, 119(suppl_1), i63–i71. http://doi.org/10.1093/bja/aex293

Electrolyte additives

Potassium chloride solution comes in several strengths **which must be diluted before use**. They are usually mixed into a bag of crystalloid. Note that injecting potassium into a bag is not the same thing as mixing it with the bag's contents - a bolus of potassium will rapidly stop the heart. Longer term fluid therapy (>12 hours) usually requires potassium supplementation. Make sure that you label the bag in an obvious way.

Hyperkalaemia can be treated by correcting acidosis, giving insulin in 5% dextrose to promote uptake of potassium by cells and by giving calcium borogluconate to oppose the cardiac effects of potassium.

Sodium bicarbonate 8.4% solution is used because it contains 1mmol/mL which makes the sums easier. If you come across other concentrations you will have to do some more maths. For instance, a 5% solution contains 50g/L. The molecular weight of sodium bicarbonate is 84, so a 5% solution contains 50/84 = 0.6mol/L (mmol/mL).

Bicarbonate must be mixed with other solutions before use. Normal saline is the fluid usually used - bicarbonate is incompatible with anything containing calcium (many other solutions and most drugs) (calcium carbonate is insoluble and precipitates out). Bicarbonate is distributed throughout the body water but administration is calculated to replace the circulating deficit, since correcting the acidosis will lower plasma potassium levels. A blood gas sample is taken and the amount of bicarbonate required is obtained by multiplying the base excess (a negative number in acidosis!) by the blood volume (roughly 10% of body weight).

For example; if a 500kg horse has a base excess of -10mmol/L in a blood (usually arterial) sample, it needs 10mmol/L of bicarbonate to restore acid base balance in the blood. Since its blood volume is about 50L, the amount of bicarbonate required is 50 x 10 = 500mmol or 500mL of 8.4% solution.

Once this amount of bicarbonate has been infused (over 60mins), the base excess is checked again because some will have been redistributed.

Beware of overdose - this will cause a paradoxical acidosis in the CNS. Give too little bicarbonate and reassess teh animal rather than giving too much.

Calcium (boro) gluconate solutions (the boron is added only to improve solubility) are used in cows and ewes for milk fever (40% solution) and in bitches for eclampsia (10% solution). The amount of calcium given to cows does not correct the deficiency; the aim is merely to tilt the balance in favour of homoeostasis. Administration of calcium salts sc causes intense vasoconstriction and sometimes necrosis of the overlying skin so give them iv.

Magnesium sulphate / chloride solutions are used in cows for grass staggers. iv administration causes muscle paralysis and can stop the heart - it should be given sc.

Compound calcium / magnesium / phosphorous mixtures are often given iv to cows where it is not clear which mineral or combination of minerals is deficient. Given iv in grass staggers followed by magnesium solution sc.

Compound trace elements

Usually given as an oral supplement to ruminants. Remember that **animals only need a trace** - any more will probably be toxic. Selenium is very easy to overdose - beware of Se injections in animals which have been dosed orally or been on pasture with Se supplemented fertiliser.

Parenteral nutrition

Avoid if at all possible! Consider enteral feeding by nasogastric or pharyngostomy tube before embarking on parenteral feeding. A dedicated catheter into a central vein is required; maintenance of this catheter and prevention of phlebitis and infection is tricky.

Lipid emulsions and **amino acid**s are expensive, are ideal bacterial growth media and can be irritant. Care is required with iv glucose since it causes an osmotic diuresis.

Drugs for ketosis in ruminants

Ketosis occurs when there is a sudden increase in demand for energy, e.g. at the start of lactation in dairy cows or towards the end of pregnancy with twins in beef cows and ewes. The liver becomes depleted of glycogen and undergoes fatty change which leads to anorexia which exacerbates the problem. **Glucocorticoids** are sometimes used to promote gluconeogenesis but can cause premature parturition. Prevention by sorting out the diet is better than cure.

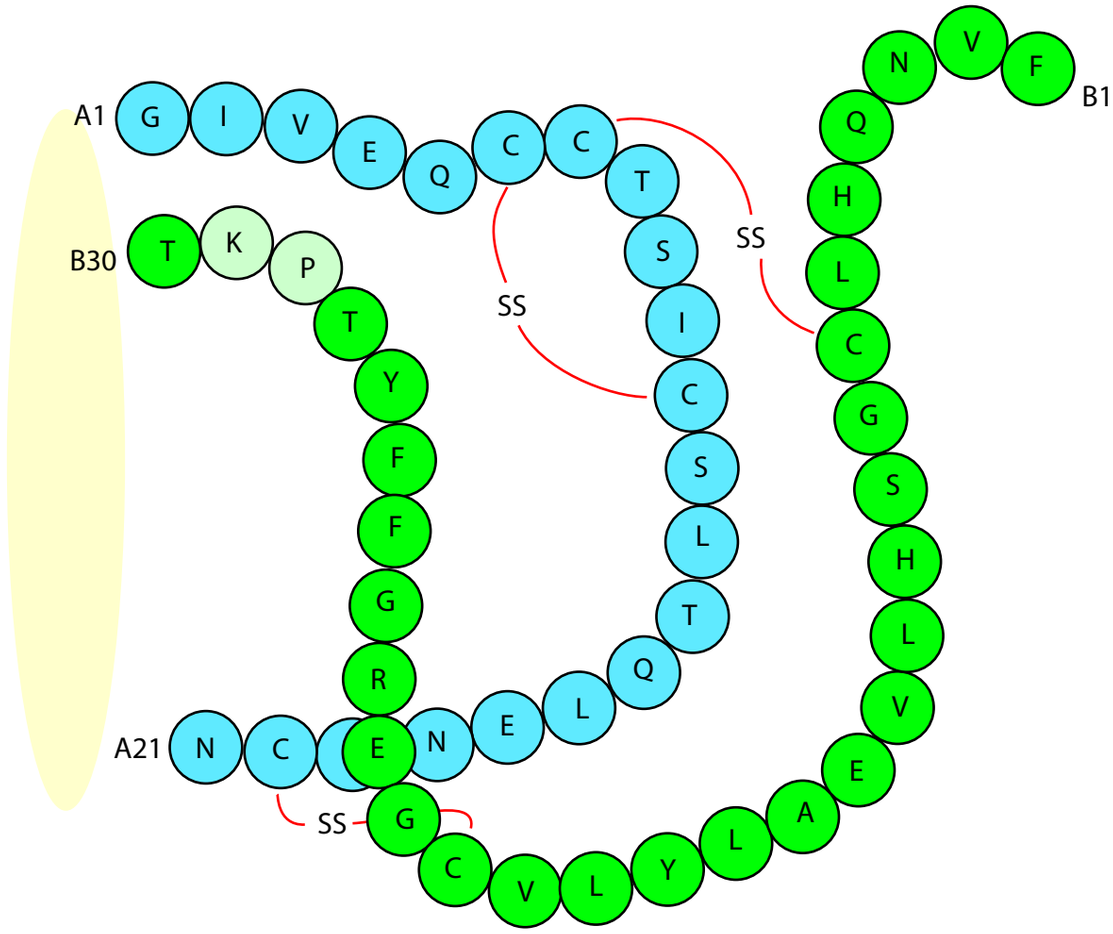
Propylene glycol, **sodium propionate** and **glycerol** are all rapidly metabolised to glucose in cows and ewes. Dose varies with the preparation / severity of the

condition. These drugs are given orally as glucose precursors to prevent ketosis - not to provide all the energy requirements of the animal.

Chapter 6

Inflammation & hormones

This part covers drugs which interfere with the inflammatory process and hormones (and their manipulation).



Insulin

Inflammation is probably the commonest condition that vets are asked to treat. Although inflammation is usually only a sign of injury or infection, the pain and loss of function associated with inflammation mean that the inflammation must be treated (as well as the primary problem). There is a huge (and growing) variety of chemical mediators of inflammation.

Although most of the drugs used today are aimed more or less specifically at prostaglandins, there are thousands of other targets and drugs acting at these are starting to emerge. There are interesting times ahead for anyone interested in pharmacology!

Most hormones also have effects on the immune system, so they are all lumped in together here.

Cancer can also be regarded as a failure of the immune system or a response to chronic inflammation, so it is included here too.

Corticosteroids

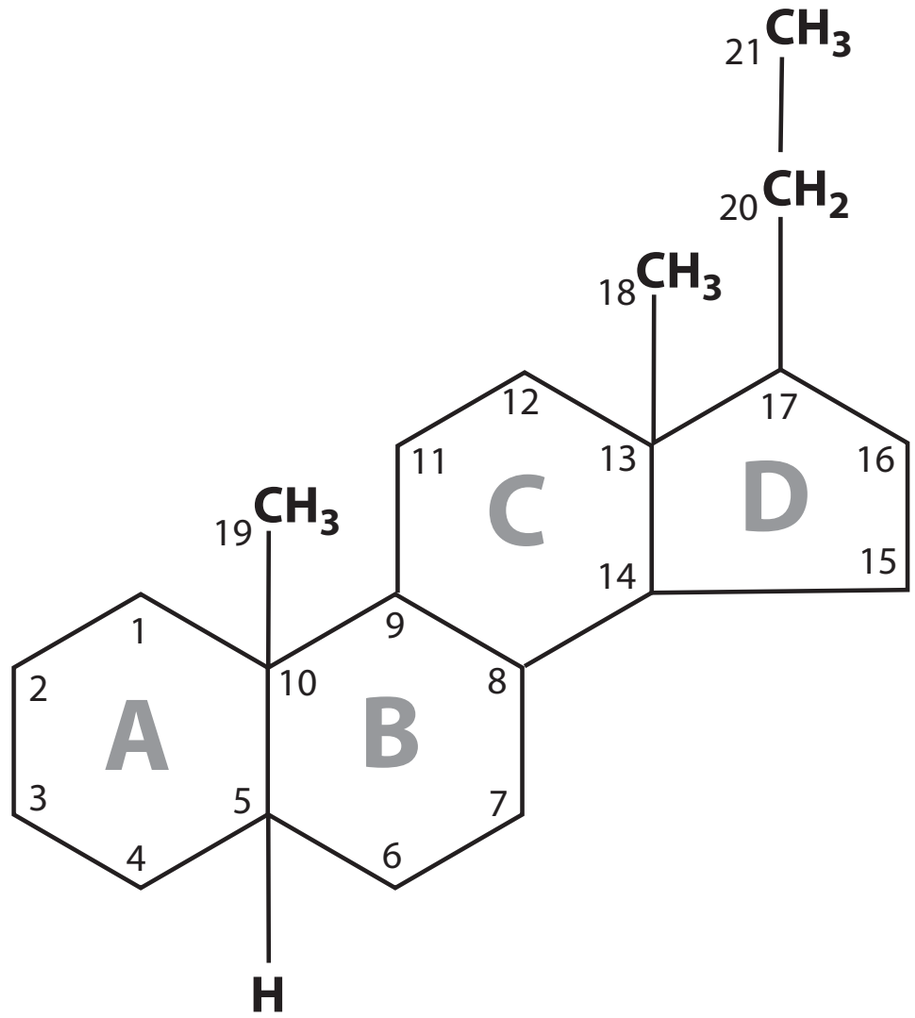
commonly used drugs

glucocorticoids
short acting hydrocortisone
medium prednisolone, prednisone
l*ong acting* betamethasone, dexamethasone
mineralocorticoids fludrocortisone

Corticosteroids

- ☑ indications - all species: inflammation of (almost) whatever cause
- ☑ dogs & cats - immunosuppression (at high doses)
- ☑ (cattle - induction of calving in emergency)
- ☑ beware iatrogenic Cushing's syndrome!

DIAGRAM 6.1.1 Basic steroid structure



Pregnane, the basic structure of the corticosteroids.

Steroids are the main group of drugs used to suppress inflammation and the immune system in veterinary practice.

The word steroid refers to the 19-21 carbon pregnane nucleus common to these substances. Many veterinary drugs are steroids, for instance, the sex hormones, anabolic steroids, some anaesthetics and some muscle relaxants. Digoxin also contains a steroid group.

Corticosteroids are produced by the adrenal cortex and come as two classes; glucocorticosteroids (= glucocorticoids) - produced in the *zonae reticularis* and *fasiculata*; and mineralocorticosteroids - produced in the *zona glomerulosa*

Endogenous glucocorticosteroids are produced by the adrenal cortex in a series of enzymatic steps. The glucocorticosteroids we use therapeutically are mostly structurally modified synthetic analogues of these endogenous glucocorticosteroids. Most of the endogenous glucocorticosteroids and many of the synthetic analogues still retain at least some of both types of effects.

There is a wide variety of preparations available but often the clinical effects are more related to the formulation than the particular drug used. Hydrocortisone (= cortisol) is the only endogenous glucocorticoid used therapeutically; prednisolone and its prodrug prednisone are widely used in dogs, as are the longer acting betamethasone and dexamethasone. Very potent newer drugs such as flumethasone are rarely used. Other drugs, such as triamcinolone are sometimes used. If a mineralocorticoid effect is required, fludrocortisone is most commonly used. Supplies of this have become problematic recently.

TABLE 6.1.1 Relative potencies of steroids.

	Na^+ Retention	Anti-inflammatory
Endogenous		
aldosterone	3000	?
corticosterone	15	0.3
cortisol	1	1
Synthetic		
prednisolone	0.8	4
dexamethasone	0	30
betamethasone	0	35
flumethasone	0	700
fludrocortisone	125	10

Molecular basis of action

Glucocorticoids bind to their receptors in the cytoplasm and the receptor - drug complex is then translocated into the nucleus where it interferes with transcriptional regulation to stimulate or inhibit the transcription of mRNA.

MOVIE 6.1 Steroids mechanism

Cellular mechanism of action of steroids. The steroid receptor complex binds to DNA with its zinc fingers; depending on where it binds, proteins are either produced or production blocked.

Variable responses by different cells to steroids may be explained by variable penetration of cells and tissue types, different receptors, variable access to specific DNA sequences in different cells or other variations in intracellular environments.

Glucocorticoid Effects

Corticosteroids have many effects all over the body!

Energy metabolism

- antagonistic to insulin
- increase gluconeogenesis
- enhance lipolysis
- protein catabolism (to provide amino acids for gluconeogenesis)

Water and Electrolytes

- decrease calcium absorption (gut)
- increase calcium excretion (kidney)
- polyuria (decreased ADH secretion)
- increase water intake (psychological?)
- increase glomerular filtration rate

Blood and Immune System

- decrease lymphocyte numbers
- decrease eosinophil, monocyte, basophil numbers
- increase neutrophil numbers
- increased release from the bone marrow
- decreased extravascular migration
- lower propensity to marginate on vascular endothelium
- decrease virus induced interferon production
- decrease production of interleukin, prostaglandin, thromboxane, platelet activating factor
- may elevate serum enzymes etc.
- serum alkaline phosphatase (common in dogs)
- alanine aminotransferase
- cholesterol
- blood urea nitrogen
- may depress serum thyroxin

Cardiorespiratory system

- chronotropic
- inotropic
- block inflammatory increases in capillary permeability
- permissive to effects of catecholamines
- increase number and affinity of b adrenoreceptors

CNS

- mental dependence
- euphoria
- increased appetite
- depression
- depress chemically mediated pyrexia
- direct inhibition of prostaglandin E2 production in the preoptic hypothalamic vasculature of the thermoregulatory centre

Skin

- calcification of skin
- thinning and weakening of connective tissues

Musculoskeletal system

- inhibition of osteoclast activity
- retardation of growth
- depletion of cartilage matrix
- decreased cartilage compliance
- osteoporosis
- changes to collagen structure

Reproductive system

- normal foetus maturation
- can be teratogenic (cleft palates)
- induce abortion / parturition in some species (alpha substituent group must be present on carbon 16 of the steroid nucleus in order to induce parturition in cattle)
- inhibit spermatogenisis
- inhibit ovulation

Gut and liver

- facilitate absorption of fat
- increase secretion of gastric acid, pepsin, and trypsin
- decreases production and alters the structure of protective mucus
- pancreatitis
- increased fat and glycogen deposits in the liver
- increased serum levels of ALT, GGT and alkaline phosphatase

Anti-inflammatory actions

Glucocorticosteroids exert their anti-inflammatory effects on cells by stimulating or inhibiting the production and effects of:

lipocortin

Lipocortin inhibits phospholipase A2 which mediates release of arachidonic acid from the phospholipids of cell membranes.

LDL receptors

Low density lipoproteins are thought to be a major source of arachidonic acid after the initial release of arachidonic acid from the cell membranes. Glucocorticosteroids inhibit the synthesis and the expression of LDL receptors necessary for transport of LDL into the cell.

COX 2 (inducible cyclo-oxygenase)

Concentrations of COX 2 within inflammatory cells increase dramatically in response to stimuli. The synthesis of COX 2 is directly inhibited by the presence of glucocorticoids. Concentrations of COX 1 are less affected at anti-inflammatory doses.

Cytokines

The production and or effects of some cytokines are inhibited by the presence of therapeutic concentrations of the glucocorticoids:

- tumour necrosis factor (TNF)
- interleukin 1 (IL 1)
- platelet activating factor (PAF)
- a variety of 'growth factors'

Lysosomal membrane stabilization

Stabilization of lysosomal membranes has long been reported as the predominant anti inflammatory effect of glucocorticoids. The extent to which this happens, if at all, and its significance is not really known.

The anti-inflammatory actions of glucocorticosteroids at a cellular level are due to

- inhibition of recruitment of leukocytes
- inhibition of elaborating of inflammatory mediators by damaged and recruited cells
- interference in the synthesis and activation of catabolic enzymes
- suppression of the generation of granulation tissue.

The use of glucocorticosteroids is generally thought to inhibit primary wound healing. Their controlled use, however, can reduce scar formation and reduce the generation of excessive granulation tissue.

Immunosuppressive effects

The different types of leukocytes have differing sensitivities to glucocorticosteroid concentrations and their effects are manifested in different ways. The systemic glucocorticosteroid concentrations required to induce a generalized immunosuppression are much larger than anti-inflammatory concentrations. However, a degree of immunosuppression always follows any systemic glucocorticosteroid therapy. In general you can administer a large single dose of a short to medium acting glucocorticosteroid without any serious adverse affect. However, prolonged systemic therapy can be associated with a number of potentially serious affects. (See immunosuppressant notes below)

Hypothalamic - Pituitary - Adrenal axis

(diagram)

Endogenous adrenal cortisol production is controlled through the effects of the pituitary produced hormone ACTH. Corticotrophin releasing factor (CRF) and arginine vasopressin (anti-diuretic hormone) (AVP, or ADH), produced in the hypothalamus, are responsible for stimulating the production and release of ACTH from the pituitary. The secretion of CRF from the hypothalamus generally follows a diurnal pattern in man and some animal species, peaking in the morning and being lowest in the evening. This is not the case for our domestic species. A pulsatile increased secretion of CRF is in response to stimuli which signal increased glucocorticoid need such as exercise, trauma, and cold. High plasma cortisol concentrations act as negative feedback, reducing further synthesis and release of AVP and CRF from the hypothalamus, and ACTH from the pituitary and inhibit further production. The presence of significant concentrations of exogenous glucocorticosteroids will also inhibit the synthesis and release of AVP, CRF, and ACTH and as a consequence markedly suppress endogenous plasma cortisol concentrations.

Extended administration of exogenous glucocorticosteroids can result in adrenal cortical atrophy. Persistently elevated concentrations may result in a period when the adrenal cortex is non - responsive, or has a diminished response to either stress induced ACTH release, or even exogenous ACTH administration.

Clinical indications

- allergy

- inflammation
- immunosuppression (see later)
    - autoimmune conditions
    - neoplasia
- induction of parturition (used to be common in cows, but now sort of banned)
- endocrine function tests
- replacement therapy in Addison's disease
- trauma - shock therapy (controversial)

Drugs

The glucocorticoid bases in common use are listed in approximately ascending order of potency which corresponds to increasing length of action of the base.

Short acting

- hydrocortisone
- prednisolone
- prednisone

Medium Acting

- methylprednisolone
- triamcinolone

Long acting

- betamethasone
- dexamethasone.

Pharmaceutical Considerations

The glucocorticoid bases are prepared as salts or esters. The pharmacokinetics of the drug product can be markedly affected by the compounding. Glucocorticoid - base - salt(ester) compounds are prepared in different excipient formulations. The formulation can also markedly affect the pharmacokinetics of the product. Therefore, the potency and duration of effect of a glucocorticosteroid are determined by:

- The base
- The base compound
- The formulation

Examples of base-compounds: hydrocortisone sodium succinate, methylprednisolone sodium succinate, and dexamethasone sodium phosphate.

Most glucocorticosteroid bases can be classed as alcohols which are relatively insoluble in water. The sodium salt of the phosphate or succinate ester is generally used to provide water soluble forms for intravenous or intramuscular injection. Acetate and isonicotinate esters are relatively insoluble. They are usually prepared as aqueous suspensions for subcutaneous or intramuscular injections. Because they are insoluble they are absorbed slowly. These are the depot formulations. Acetonides and diproprionates tend to be the least soluble of this group. Fluorination or esterification with fatty acids or cyclic acetonides increases topical anti-inflammatory activity often without increasing systemic glucocorticoid activity.

Formulations

Tablets, aqueous solutions, aqueous suspensions, alcohol solutions, creams, and ointments are available. Formulation characteristics dictate the possible routes of administration and the absorption characteristics from these sites. Variations in particle size, excipient, pH, and physicochemical characteristics can all affect the absorption of the formulation.

Pharmacokinetics

Available pharmacokinetic information doesn't always correlate with observed duration of clinical effect due to the molecular mechanism of action of glucocorticosteroids and because many assays are not sensitive enough to measure pharmacologically significant glucocorticosteroid concentrations e.g. one equine pharmacokinetic report quotes that prednisolone was assayable for 7 days following an intramuscular injection of 200 mg of prednisolone acetate into the gluteal musculature. The same paper reports the endogenous cortisol concentrations were depressed for 21 days following the same injection.

Absorption

formulation effects

oral preparations - available predominantly as free bases

aqueous solutions - most readily and rapidly absorbed

short acting aqueous suspensions - dissolve quickly into body fluids, are relatively rapidly absorbed, produce peak blood concentrations within a few hours after injection and are totally eliminated from the body within 3 days of administration.

organic solutions in polyethylene glycol, e.g. azium solutions = dexamethasone alcohol dissolved in polyethylene glycol. (other organic solvents are also used) - some precipitate at the site of injection and are absorbed at a slightly slower rate and hence produce lower peak plasma concentrations which are maintained for slightly longer

long acting or depot formulations e.g. methylprednisolone acetate - can take from 1 - 4 days to achieve (relatively low) peak plasma concentrations - may take a number of weeks for plasma concentrations to decline to undetectable concentrations - may associated with local tissue damage around the site of injection - major species and individual variations in both the extent and duration of HPA axis suppression - may suppress endogenous plasma cortisol concentrations for only 3 days in the horse but up to 12 weeks in cattle.

Ester/salt effects

hemisuccinate, succinate and phosphate esters are the most water soluble products available. They are used when rapid glucocorticoid effect is desired, when the intravenous route of administration is chosen, and can also be injected intramuscularly and subcutaneously. They are relatively rapidly absorbed.

Alcohol and isonicotinate in propylene glycol have been used intravenously (in the horse) . Their duration of effects are predominantly determined by the glucocorticoid base when administered intravenously. They form depots when injected im.

The acetate, diacetate, trimethylacetate, tebutate and phenylpropionate esters are poorly water soluble; their absorption tends to be slow and sustained. When given by the intra-articular or intra-lesional route, high concentrations will be maintained locally for a long time. When given im, these esters form depots resulting in low plasma concentrations for periods of at least 2 to 14 days, depending on the dose, base, formulation and species injected.

Acetonide esters are used topically and are poorly water soluble. They bind to keratin slowing systemic absorption.

Free bases or the salt of an organic acid form (such as betamethasone benzoate) are also used.

Distribution

Widely distributed in the body both intra and extracellularly. Cortisol is approximately 90% protein bound in plasma. About 75% to the steroid binding globulin transcortin and 10 - 15% to serum albumin. Transcortin has a high affinity, particularly for cortisol or prednisolone, but low capacity, whereas albumin has a low affinity but much higher capacity.

Metabolism

Most glucocorticosteroid compounds are rapidly hydrolyzed in plasma or synovial fluid to release their active base. Methylprednisolone sodium succinate is not readily hydrolyzable in plasma and along with prednisone and cortisone requires hepatic metabolism to be converted into their active form, and thus are unsuitable for local or topical administrations.

Biotransformation is complex, but reduction of the double bond between C4 and C5 occurs mainly in the liver. This inactivates the molecule which is conjugated with glucuronic acid and excreted via the kidneys

Elimination

Very variable. Metabolites are excreted in the urine - very little faecal or unchanged urinary excretion. Elimination of depot preparations is absorption rate limited.

Selecting an appropriate drug

Think about:

- cost
- route of administration
- time to onset of effects
- duration of effects desired /achieved
- importance of sodium retaining effects
- anti-inflammatory potency
- HPA axis effects

Contra-indications

- diabetes mellitus
- pre-existing catabolic disease
- bacterial or fungal infections
- ocular viral infections, corneal ulceration
- growth in young animals
- pregnancy
- surgical (or other) wounds

Drug interactions

- cause microsomal enzyme induction.

- additive with some diuretics or Amphoteracin B in causing depletion of potassium.
- increase digitalis toxicity (K+ depletion)
- insulin antagonism
- decrease metabolism of cyclophosphamide
- erythromycin inhibits the activation of methylprednisolone
- increased risk of gastric ulceration from NSAIDs given concurrently
- may potentiate other drugs inductions of seizures.

Adverse Effects

Therapy of less than 3 - 5 days rarely causes any serious adverse effects unless other risk factors exist, e.g. diabetes mellitus, fulminant bacterial infection.

Some adverse effects occur routinely even with short duration of therapy:

- alteration to haematology - "stress leukogram"
- hepatic enzyme leakage into plasma - elevates ALT and SAP and interferes with diagnostic tests
- depressed total serum thyroxin concentration but the animal remains euthyroid (sick euthyroid syndrome)
- polydypsia, polyuria, polyphagia
- foetal abnormalities especially cleft palate
- abortion (C16 substituted glucocorticosteroids only)
- peptic and gastric ulceration

Some adverse effects occur especially with long term therapy

- increased susceptibility to infections
- myopathy
- behavioral changes
- osteoporosis
- inhibition of growth
- calcinosis cutis
- hyperpigmentation
- thinning of the skin
- collagen diseases

An Addisonian crisis (cardiovascular collapse, respiratory collapse, coma, death) may occur especially with sudden withdrawal of long term therapy due to HPA axis suppression.

Dosing strategies

Serious adverse effects are almost always avoidable. Incorrect or negligent use of these drugs is the most common reason for adverse effects. Adverse effects and toxicity can be largely avoided by use of the correct dose rates and regimens for different indications. In general, an adequate dose should be used by an appropriate route for the required speed of onset, then the dose tapered off to nothing / as low as possible depending on the condition.

•cats and birds are less sensitive and require higher doses than most other species

•if therapy is short duration then tapering of dose rates is not necessary.

•if therapy lasts for longer than 1 - 2 weeks (prednisolone) or 1 week (dexamethasone) then before therapy is interrupted the dose rate must be gradually tapered to a maintenance dose rate and the dose interval must be lengthened to 48 hours to allow the HPA axis to reawaken.

•only short acting glucocorticoids can be used for alternate day dosing (hydrocortisone (12 hr), cortisone (12 hr), prednis(ol)one (12-36 hr), methylprednisolone (12-36 hr)) - long acting glucocorticoids are not suitable for alternate day dosing (dexamethasone, triamcinolone, betamethasone)

Mineralocorticoid effects

Mineralocorticoids are used solely in the treatment of adrenal cortical insufficiency (Addison's disease) since most glucocorticosteroids used in replacement therapy have insufficient mineralocorticoid activity to sufficiently control electrolyte excretion. Drugs such as desoxycorticosterone pivalate (DOCP) (injectable, specific mineralocorticoid, used in USA) or fludrocortisone (tablets, used everywhere else) are used to produce increased extracellular fluid volume, sodium and fluid retention, potassium and hydrogen ion loss and increased glomerular filtration rate. A shortage of fludrocortisone has prompted research on ways of getting more mineralocorticoid effect from glucocorticoids. For instance, liquorice inhibits the enzyme which inactivates glucocorticoids in the kidney and prevents them having a mineralocorticoid effect and may be useful in dogs.

Cushing's syndrome

Cushing's syndrome results from too much circulating corticosteroid. There are three main causes:

- **iatrogenic - the commonest cause in veterinary practice!!**
- excessive production of ACTH from the pituitary (usually a tumour)
- adrenal tumours or hyperplasia

Treatment of iatrogenic Cushing's involves tapering off the dose of steroids (see notes above); the other two are usually treated with trilostane in dogs (surgery in man), although several other drugs are occasionally used, particularly selegiline. Cushing's in horses is usually caused by excessive ACTH production and is treated with dopamine agonists such as pergolide.

Drugs

Drugs which reduce steroid synthesis, such as **trilostane** (a competitive inhibitor of 3-β-hydroxysteroid dehydrogenase) are effective but expensive. This is the most widely used drug in dogs at the moment. 3-β-hydroxysteroid dehydrogenase blocks the conversion of pregnenolone to progesterone, which is an intermediate for cortisol, but also aldosterone and various androgens. It appears to have fewer side effects in dogs than people, but warn pregnant dog owners to be careful (and don't give it to pregnant bitches).

The most commonly used drug in dogs in the past was **mitotane**, but it is an unpleasant drug and safer alternatives are now used. It is becoming difficult to obtain, which is good news for dogs and their owners.

It was discovered in the 1940s that the insecticide DDD (similar to DDT) destroyed the adrenal glands in dogs. The o,p' isomer (mitotane, = o,p' DDD) was found to be responsible. It has a direct cytotoxic effect on the zonae fasiculata and reticularis of the adrenal cortex and probably acts by killing mitochondria. Mitotane also inhibits steroid synthesis.

Mitotane's absorption is poor and variable in dogs. It is best when tablets are crushed up in oily food but this exposes the owner to the drug. Very fat soluble - taken up with fat.

Side effects are a major problem: overdose will cause Addison's disease (low corticosteroids). Some dogs will develop Addison's even at low doses. This often kills dogs. Steroid supplementation may be necessary. Anorexia, vomiting, lethargy and ataxia may also occur.

Other drugs sometimes used in Cushing's syndrome

Drugs which act on the HPA axis, such as **selegeline** (= l deprenyl) which has been licensed in the USA in the dog. It is a monoamine oxidase B inhibitor - stops dopamine breakdown (also stops 5HT breakdown - interacts with pethidine to kill dogs). Other drugs acting on the HPA axis include bromocriptine (dopamine agonist) and cyproheptadine (dirty 5HT antagonist). In horses, pergolide at low doses is the drug of choice.

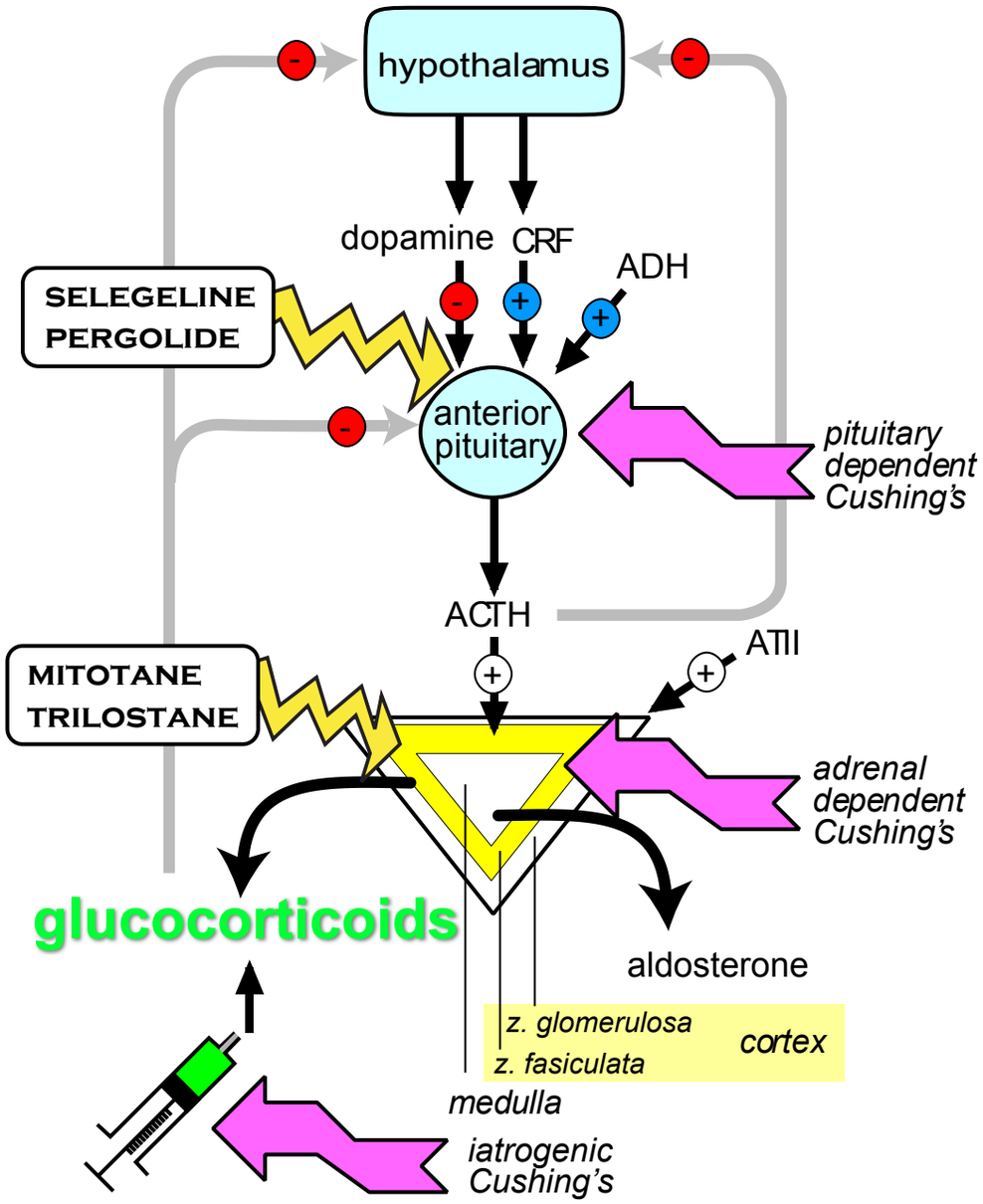
A variety of cytochrome P450 enzymes are used to produce corticosteroids and drugs which block these have been used clinically in a similar way to trilostane. Drugs with these effects include metyrapone, aminoglutethimide and ketoconazole. They are not often used in animals.

Drugs which block steroid receptors, such as **mifepristone** and **aglepristone**. Beware, these will cause abortion in pregnant animals (and women).

Dexamethasone is sometimes given to diagnose Cushing's syndrome (dexamethasone suppression test). It should suppress the production of ACTH and steroid in a normal dog but interpretation of abnormal results can be tricky. Care is required in horses.

CRF blockers are being trialled as antidepressants in people, so there should be lots of new drugs around soon.

DIAGRAM 6.1.2 The hypothalamic-pituitary-adrenal axis.



NSAIDs

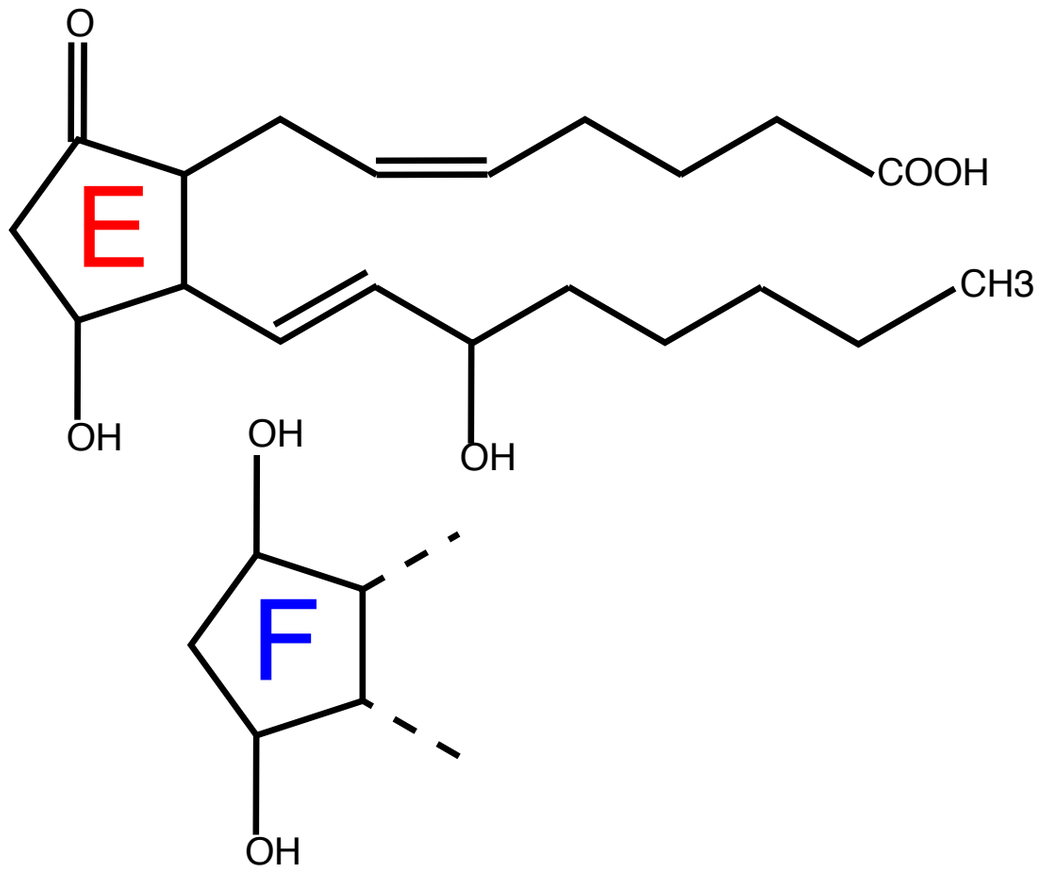
commonly used drugs

aspirin, carprofen, flunixin, ketoprofen, meloxicam, phenylbutazone, tolfenamic acid

NSAIDs

- ☑ widely used in all species for minor pain and injury
- ☑ the major drugs for osteoarthritis
- ☑ do not penetrate into milk well - WHTs
- ☑ gastric ulceration limits long term use
- ☑ care required where kidney perfusion is less than optimal
- ☑ beware paracetamol in cats
- ☑ use corticosteroids if potent anti-inflammatory effects are required

DIAGRAM 6.2.1 Prostaglandin structures and names.



Prostaglandin E2 (top) and F (bottom). The the letter refers to the substituents on the ring: the 2 refers to the number of double bonds.

NSAIDs (non-steroidal anti-inflammatory drugs) are some of the most commonly used drugs in all species. You need to know about them!

NSAID Effects

- anti-inflammatory
- analgesic (see analgesic notes)
- anti-pyretic

Some NSAIDs also have anti-thrombotic and anti-endotoxic effects.

The proportion of each effect is probably different for each drug, but this is difficult to prove. There are major species differences.

Molecular basis of action

The primary mechanism of action is inhibition of cyclo oxygenase (COX) and thus diminished generation of thromboxane, prostacyclin, and the prostaglandins, particularly PGE2. Since these compounds have a huge variety of functions, reducing their production causes a huge number of effects.

Other mechanisms include

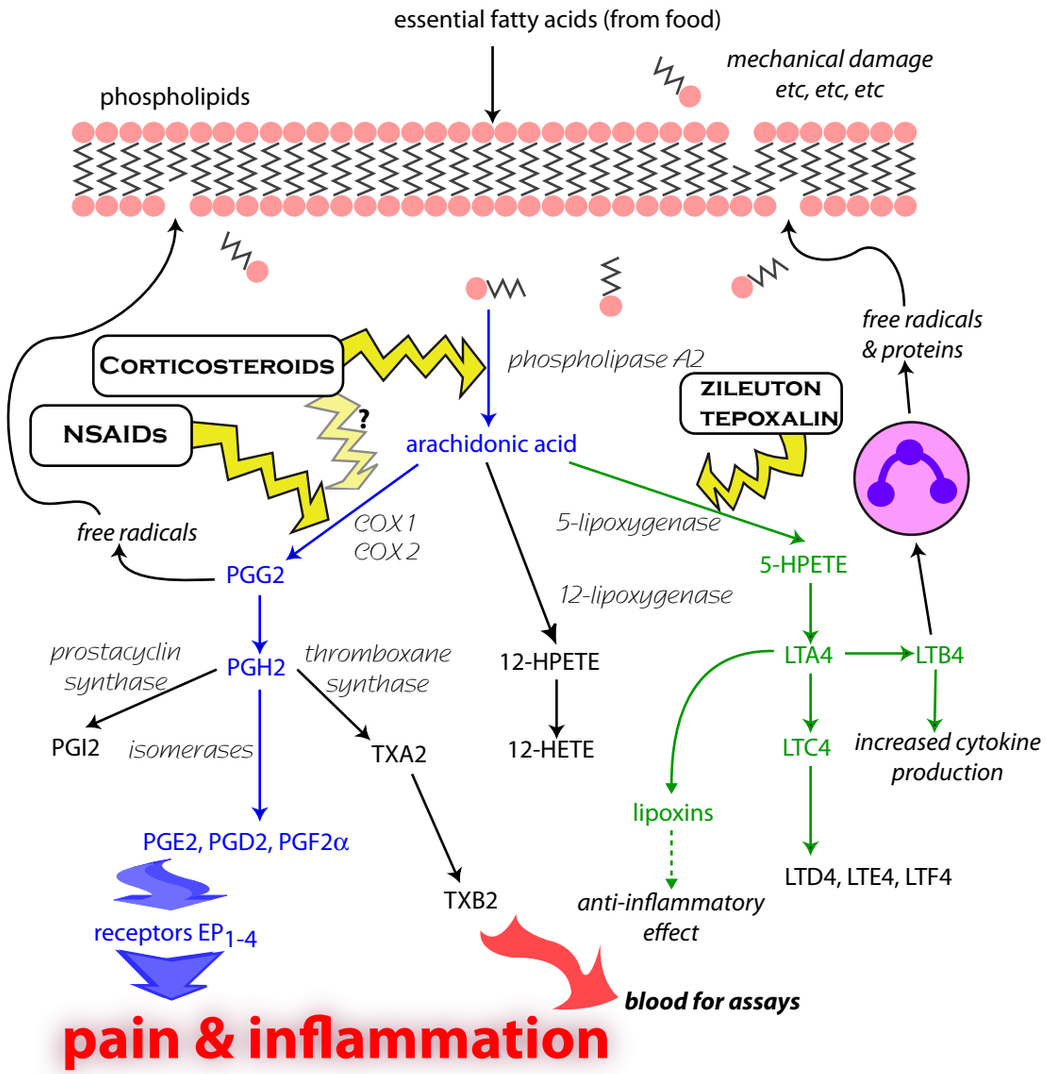
- free radical scavenging
- upsetting oxidative phosphorylation
- disrupting G protein signaling
- inhibition of neutrophil activation
- inhibition of neutrophil adhesion
- inhibition of leukocyte recruitment
- inhibition of proteoglycan synthesis
- inhibition of phospholipase A2
- prostaglandin receptor antagonism

There are major differences in the efficacy of NSAIDs against the cyclo oxygenase enzymes of various species and tissues. This may be due to variable affinities for COX1 & COX2 (this also varies between species).

> Etodolac may be selective for COX2 in horses.

Differences in efficacy may also be caused by difference in predominant end product normally generated by the isomerases of different cells e.g. platelets & throm-

DIAGRAM 6.2.2 NSAIDs mechanism



Mechanism of action of NSAIDs and related drugs.

TABLE 6.2.1 COX selectivity of NSAIDs

Drug	COX2:COX1
carprofen	129
fenamates	15
meloxicam	3
phenylbutazone	2.6
flunixin	0.6
ketoprofen	0.2
aspirin	<0.3

Selectivity for COX2 in the dog (although these figures are contentious)

boxane or neutrophils & PGE2 and PGI2; variable penetration to the site of action or different microenvironments which affect drug enzyme affinity. This can be of clinical importance: COX 2 inhibitors increase the risk of thromboembolism by blocking PGI2 but not TXA2.

Some drugs also block the lipoxygenase pathway.

Acetyl salicylate (aspirin) irreversibly inactivates the cyclo oxygenase of platelets (COX 1) by acetylating it. Most other NSAIDs in most cell types bind reversibly and competitively to cyclo-oxygenase.

Anti-inflammatory actions

Inflammation is part of the body's defensive response to injury. However, there can be therapeutic and management advantages in partially controlling this response and its associated clinical signs. NSAIDs are thought mainly to affect acute inflammatory processes through inhibiting the generation of the eicosanoids (thromboxane, prostacyclin, and the prostaglandins). They are not thought to dramatically affect the progression of chronic inflammatory processes which are mediated by other mechanisms (many different cytokines are involved). However, chronic inflammation is often associated with intermittent episodes of acute inflammation and some degree of relief from the clinical signs associated with these episodes can be gained with the use of NSAIDs.

NSAIDs are not as effective as anti-inflammatory agents as corticosteroids. They do not delay healing in the way that steroids do.

Analgesic actions

Although pain is one of the cardinal signs of inflammation, and reducing inflammation will thus reduce pain, NSAIDs seem to have a direct analgesic effect as well. See CNS notes for more.

Anti thrombotic actions

NSAIDs bind to the cyclo oxygenase enzyme in platelets inhibiting their production of thromboxane A2 (TXA2). Low doses of aspirin can preferentially inhibit the production of TXA2 relative to PGI2 by irreversibly acetylating the platelet cyclo oxygenase and can thus be used therapeutically to decrease the likelihood of development or growth of a thrombus e.g. cats with ileal thrombosis, dogs with heartworm disease. Low dose aspirin is used therapeutically for this purpose since it covalently acetylates cyclooxygenase. Platelets have no nucleus and thus no protein synthesis machinery so thromboxane production is inhibited for the life of the platelet (about 7 days), whereas cyclooxygenase in other cell types can be replaced.

Although TXA2 generation is only part of the clotting process, the increase in blood clotting times may have affect aspirin's use in post trauma situations where internal haemorrhage is a consideration. The other NSAIDs are less effective anti-thrombotics and do not prolong bleeding time significantly.

Antipyretic actions

The use of NSAIDs will not affect normal body temperature (except in cases of toxicity) nor will they affect exertionally induced hyperthermia. They will reduce pyrexia associated with pyrogens circulating in the plasma. Bacterial endotoxins can cause the release of interleukin 1 which stimulates the generation of PGE2 in the endothelium of the hypothalamic vasculature, which is thought to be the mechanism responsible for changing the bodies normal thermostatic control setting.

Anti-endotoxic actions?

Bacterial endotoxins (lipopolysaccharides) are thought to produce some of their effects through prostaglandin production. There is no good evidence that NSAIDs are beneficial, although they are often used.

Clinical Uses

Arthritis

Useful in acute joint inflammation to reduce pain and inflammation and allow use of joint. Care must be exercised if their use encourages overuse of structurally compromised joints.

The progression of chronic cases of arthritis is probably not affected by the use of NSAIDs. However most chronic joint conditions have acute inflammation associated with them to varying extents and it is the acute inflammatory processes responsible for much of the associated pain.

High concentrations of NSAID will suppress synthesis of cartilage matrix but it is unlikely that the concentrations necessary for this suppression are achieved in most clinical situations. Prostaglandins appear to be involved in the activation of chondrocyte mediated degradation of cartilage matrix and it is more likely in the short to medium term situation that most NSAIDs are potentially chondroprotective when therapeutic concentrations are achieved. However, the possibility exists that some NSAIDs could result in a significant suppression of matrix synthesis if used at high concentrations for extended time periods.

In people, chronic use of most NSAIDs reduces blood flow to the joints, which is thought to accelerate cartilage degeneration.

Soft tissue inflammation

Used to reduce the acute inflammatory response and to leave the animal more comfortable while natural healing of the tissue injury occurs. The efficacy of NSAIDs is not 100%, therefore the inflammatory process necessary for healing is unlikely to be greatly retarded. Evidence that NSAID use improves outcomes exists for few diseases, e.g. bovine shipping fever

Analgesia

(see CNS notes)

Endotoxaemic syndromes

NSAID use in endotoxic shock is controversial. NSAID toxicity is significantly increased by a compromised circulation. Combining NSAIDs with high doses of corticosteroids further increases potential for toxicity. NSAIDs have been used for treatment of acute bovine coliform mastitis, colitis X syndrome in horses, agalactia/ hypogalactia syndrome in sows and parvoviral diarrhoea in puppies.

Colic

Some NSAIDs offer profound visceral pain relief in the horse. Flunixin will give analgesia for 4 - 6 hours and ketoprofen will give similar analgesia for 2 - 3 hours (depending on the degree of pain). NSAIDs also relax smooth muscle in the gut; flunixin appears to be most potent. There is a certain amount of evidence that suggests lower dose rates may offer some therapeutic benefit without affecting diagnosis. There have been some cases where the analgesia provided by flunixin was potent enough to hide severe ischaemic damage to the gut which should have been treated surgically. It is probably best to use shorter acting analgesics (pethidine, xylazine - last about 15 - 20 mins) until you have decided that the colic is definitely medical or surgical. Remember the potential for toxicity when large doses are being repeated frequently.

Pharmacokinetics

The desired site of action is usually the peripheral tissues rather than the plasma. Penetration into and clearance from inflamed tissues where the circulation is compromised shows kinetics markedly different from those of plasma. This means that duration of action and plasma concentrations show practically no correlation.

Absorption

Bioavailability is generally good in all species. Absorption after oral administration is usually rapid. Phenylbutazone binds to hay and this reduces its absorption and presents more phenylbutazone to the large intestine and may alter the pattern of gut effects.

Distribution

Inflammation inhibits NSAID distribution to peripheral tissues, but then delays their clearance from these tissues. This is especially true where the proximity of the microcirculation is reduced such as in areas of bruising, necrosis and edema.

The NSAIDs are extensively protein bound so total plasma concentration does not reflect the concentration of free drug at the site of action, binding variability may influence CNS penetration and they can be displaced by other protein bound organic acids administered at the same time, leading to toxicity. They also bind to muscle leading to long witholding times in food animals.

They are all anionic and subject to ion trapping in areas of inflammation which are usually acidic. However, they do not cross into milk to any great extent.

Metabolism

Most are extensively metabolized by both Phase I and Phase II enzyme systems. The particular CP450 used varies between NSAID chemical classes. Species differences in metabolism are responsible for many of the inter species variations in rate of elimination.

Elimination

Plasma half lives can vary enormously. You cannot extrapolate dose rates and intervals from one species to another! The plasma half life of aspirin is very short (minutes) and most of its other anti inflammatory effects are due to its metabolite salicylate.

Selection Of Appropriate Drugs

There are lots of drugs on the market but none are perfect. They are widely used for arthritis in people and most drug companies produce drugs for this very lucrative market.

There are huge individual, species and age variations in both efficacy and toxicity for all NSAIDs. Some of the newer drugs claim to have a much higher potencies. However, it is their potency relative to the incidence and severity of side effects which is important. To date, all studies examining NSAIDs in dogs have shown gut pathology after a single dose at the recommended rate, except perhaps carprofen.

Aspirin (acetylsalicylate) has been around for a long time in the form of willow bark. It is deacetylated as soon as it gets into the plasma and most of the anti-inflammatory effects are caused by **salicylate**. Since aspirin is not very soluble, injectable forms are usually the sodium or copper salt of salicylate. Cheap, not very potent but good at producing ulcers. Cats metabolise it very slowly - it is probably best not to give more than one dose to a cat.

The pyrazolones, **phenylbutazone**, **dipyrone** and **isopyrin** have been around since the 1950s. They are no longer used in people since they very occasionally cause fatal blood dycrasias (possible in dogs too), but are still widely used in horses. Phenylbutazone has the reputation of being less analgesic and more anti-inflammatory than the others (dipyrone is the other way around), but the main reason for using them is that they are cheap. Isopyrin is only available mixed with phenylbutazone in Tomanol (they inhibit each other's metabolism and so prolong the anti-inflammatory effect). Phenylbutazone has an unexpectedly long half life in cattle.

Flunixin is very widely used. It is a very potent analgesic, anti-inflammatory and ulcerogenic drug.

A variety of propionic acids are used in human and veterinary practice. **Ketoprofen** is used in man and animals, and is similar to, but perhaps less potent than flunixin. **Carprofen** has been used in most species, it is a good analgesic but not so good an anti-inflammatory. **Ibuprofen** and **naproxen** are widely used in people. Naproxen has a very long half life in the dog and has killed several; ibuprofen is much better at producing ulcers in dogs than in people.

The fenamates have been used in man and horses for many years. Amongst others they include **mefenamate**, **meclofenamate** and more recently **tolfenamate**. They may have some prostaglandin receptor antagonist activity as well as inhibiting cyclo-oxygenase. Clinically similar to ketoprofen.

The oxicams, **meloxicam**, **piroxicam** and **tenoxicam**, are widely used in people and dogs for arthritis.

There are lots of other drugs used in man but not commonly in animals. **Indomethacin** was for years the most potent cyclo-oxygenase inhibitor available so you may see it mentioned in papers. It is rarely used. The quinolines, **cinchophen**, **quinine** and **chloroquine** are sometimes used in animals because they are cheap - there is no other reason for using them.

Paracetamol (acetaminophen USAN) is sometimes seen as a cause of poisoning, particularly in cats (see below). Do not use in cats.

Specific COX2 inhibitors such as **celecoxib** and **rofecoxib** have recently come on the human market, although rofecoxib has since been withdrawn as there is an increased risk of heart attacks with long term use. **Valdecoxib** and **parecoxib** are also available in NZ. Metabolism in dogs varies markedly with breed with celecoxib, so these drugs may be difficult to use clinically. They may also impair bone healing.

Lots of coxibs which have been rejected from human clinical trials are appearing for use in dogs and cats. **Deracoxib** was developed as a specific COX2 inhibitor for use in dogs. It can provide good analgesia at high doses. **Firocoxib** is probably the most COX2 specific drug currently used in dogs, but it can still cause gut ulceration. Giving with food delays but does not reduce absorption: bioavailability is about 40%. **Mavacoxib** is very long acting - about two weeks in most dogs but up to four weeks in some. **Rofenacoxib** is registered for cats in te USA, but has not made it this far yet.

Dual COX and LOX inhibitors such as **tepoxalin** and pure LOX inhibitors such as **zileuton** are starting to be used overseas in people.

Contraindications

- glucocorticoid therapy
- anti coagulant therapy or poisoning
- severe renal disease
- severe hypotension

Precautions

Anything which causes ulcers or kidney disease: mild renal disease, hepatic impairment, hypoproteinemia, late pregnancy, gastro intestinal ulceration, dehydration

Adverse Effects And Toxicity

Toxic doses and effective doses usually overlap. Major side effects include **gut ulceration** which is common but rarely serious - at any rate in animals. Dogs seem to be more prone to the gut side effects of NSAIDs than most species, possibly because many of the NSAIDs undergo entero hepatic recycling in the dog, but death from gut ulceration following NSAIDs is almost unknown in dogs (1200 people a year die from this in the UK - no figures for NZ). There is anecdotal evidence for serious gut ulceration with some NSAIDs in cattle.

TABLE 6.2.2 NSAID half lives in different species.

Drug	Dog	Cat	Horse	Cattle	Pig	Sheep	Man
salicylate (aspirin)	9	**22-38**	3	0.5	6		3
carprofen	8 (4.5-18)	19	17 - 43	44 - 65		30	12
deracoxib	3						
dipyrone	6						7
etodolac	10 - 15		3				6 - 8
firocoxib	8	9-12	30-40				
flunixin	2.5-4	0.7-3	1.5 - 3	6		2.5	
ibuprofen	4						3
ketoprofen	2 - 5	3-5	0.8 - 1.5	0.4			1.8
ketorolac	4 - 5					0.25	3 - 7
meclofenamate			1				3
meloxicam	24	21	3-8	13	3.4		20
naproxen	**74-92**		5-8		5		14-24
paracetamol	2		2-2.5				2
phenylbutazone	4		6	**40 - 55**	4	18	72
rofecoxib	4						17
tolfenamate	6.5		4.2 - 6	2.5 - 13.5			2.1
vedaprofen	13		6-8				

Do not extrapolate pharmacokinetics between species! There are lots of human drugs which will cause problems in animals.

The other major side effect is **kidney failure**. Inhibition of prostaglandin synthesis in the kidney of a healthy, well hydrated animal is of little consequence, and some predisposing factors (hypovolaemia, pre-existing renal insufficiency, old age, urinary tract obstruction, sodium retention eg congestive heart disease) has to be present.

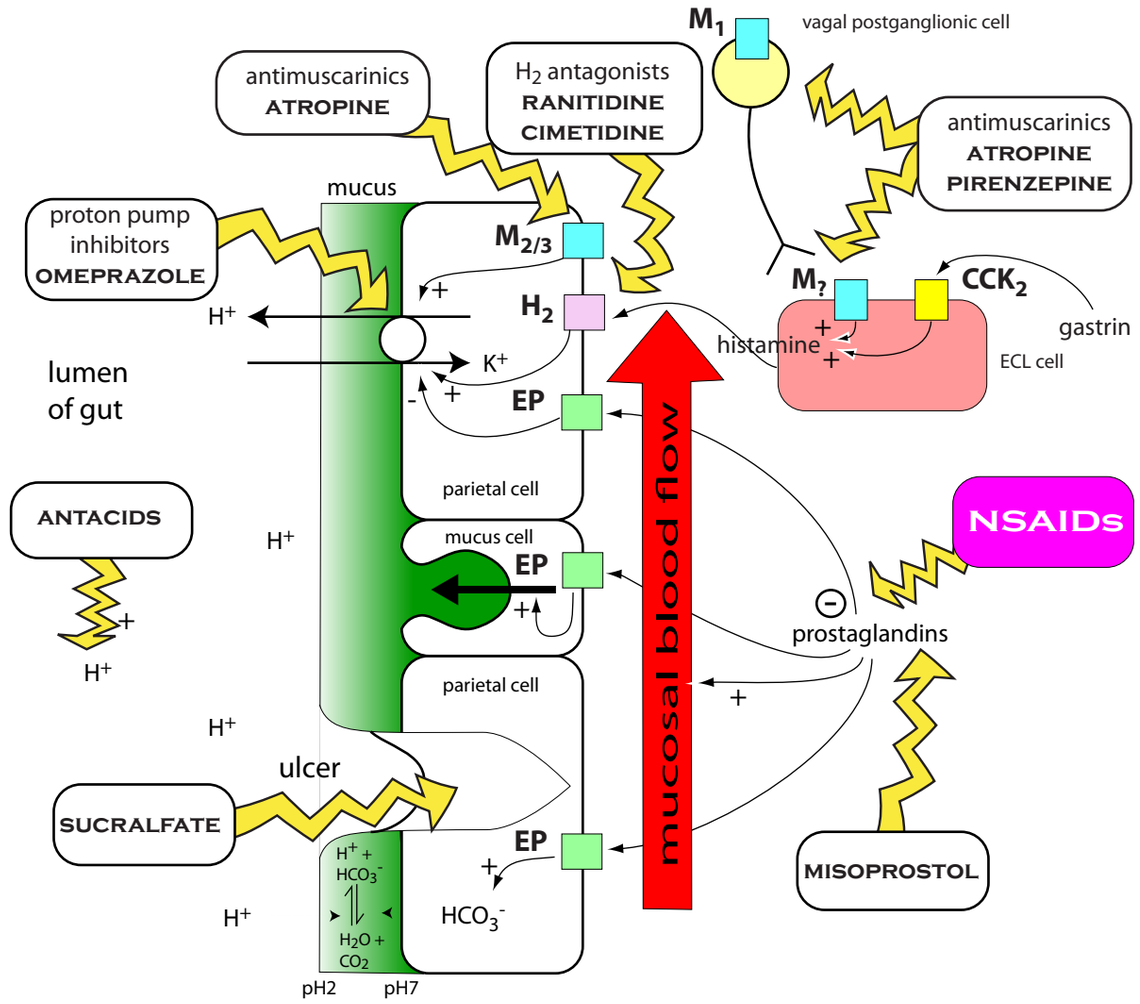
(see cardiovascular pharmacology notes).

Although some drugs have specific hepatotoxic effects, idiosyncratic reactions also sometimes take this form in dogs. This is probably an immune mediated problem, but is too rare to have been studied properly in dogs. Carprofen has been implicated in some cases of liver failure in dogs in the USA (5.2 cases / 10,000 doses). Naproxen (a human drug rarely given to dogs) has also caused problems.

Paracetamol produces specific hepatotoxic metabolites, particularly in cats. These toxic metabolites are usually mopped up by glutathione, but liver glutathione reserves can be quickly used up and liver damage results. Acetylcysteine can be given as a source of glutathione but prevention is better than cure - paracetamol is best avoided in both cats and dogs.

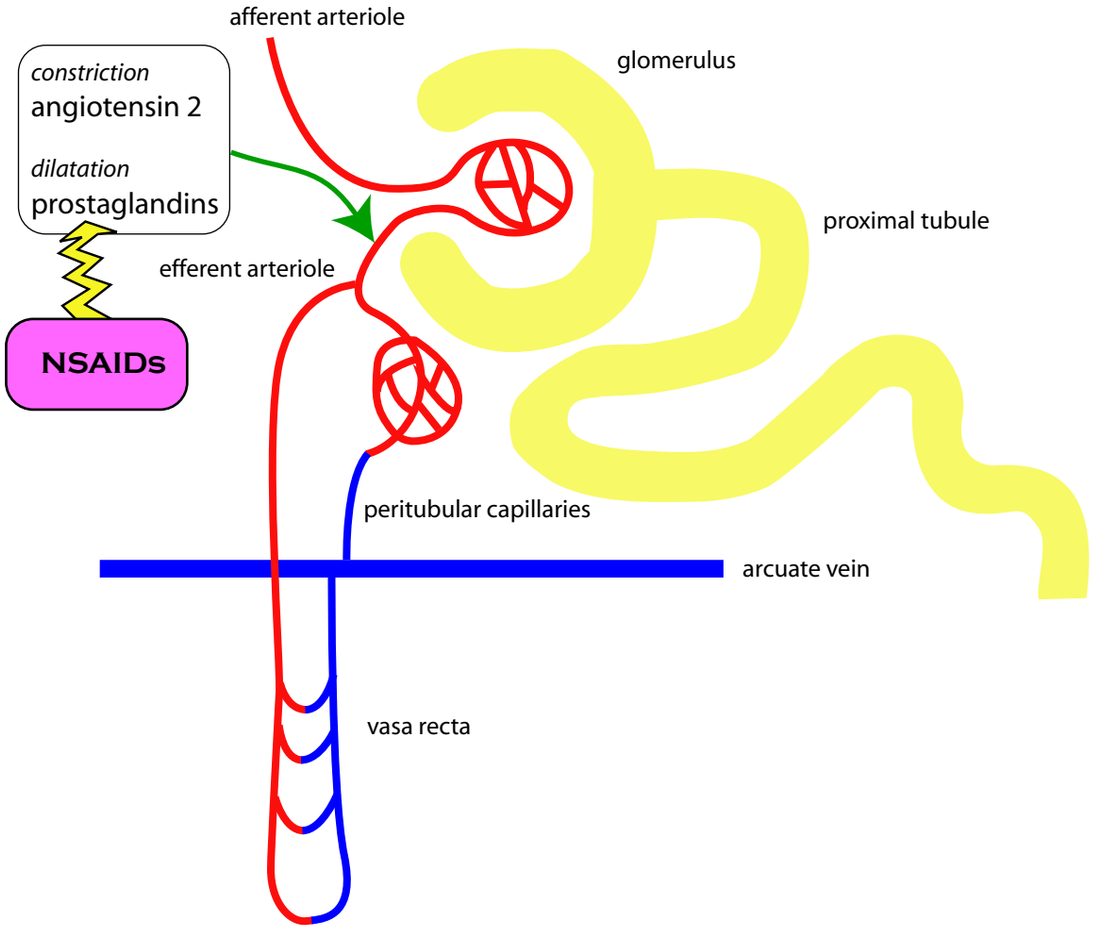
For minor side effects see NSAIDs section of CNS notes.

DIAGRAM 6.2.3 Gastric ulceration



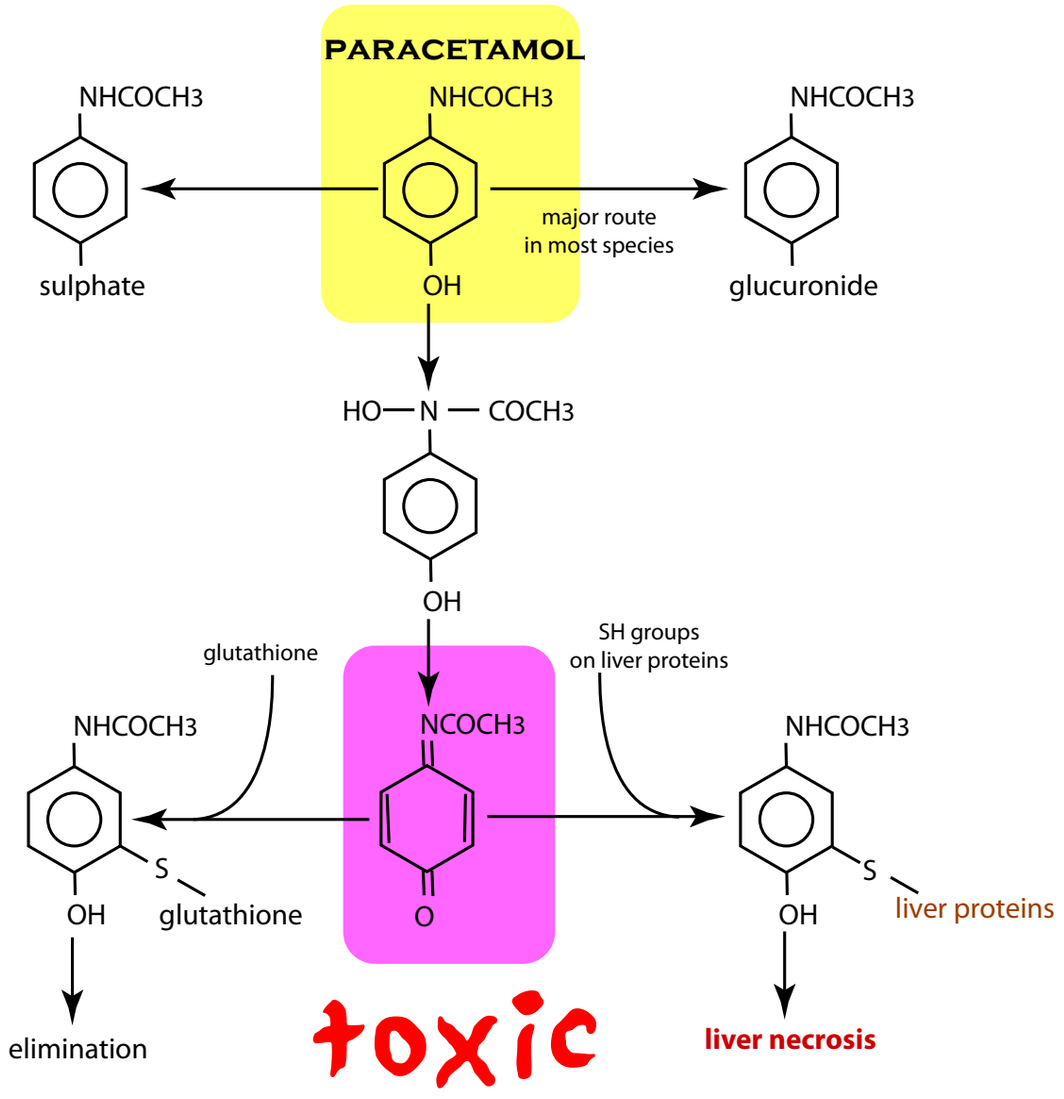
Mechanism of NSAID effects on the gut.

DIAGRAM 6.2.4 NSAID effects on the kidney.



Prostaglandins are used for emergency vasodilatation in the efferent arteriole, NSAIDs block this.

DIAGRAM 6.2.5 Paracetamol toxicity



Paracetamol overdose causes liver failure, especially in cats.

Drug interactions

NSAIDs are highly protein bound and can displace other drugs from plasma proteins, eg warfarin, other NSAIDs and anaesthetics eg thiopentone. Frusemide inhibits some NSAID excretion; some NSAIDs inhibit digoxin excretion.

The future??

Prostaglandin receptor antagonists are likely to be important in the long term, but the physiology is complex and not well understood at the moment.

Several new human NSAIDs have been designed as non acidic prodrugs. This reduces the severity of gastric ulceration but does not eliminate the problem. Another strategy is to combine NSAIDs with anti-ulcer drugs such as mifepristone.

There is lots of money going into research on COX 2 inhibitors and this will probably throw up some useful drugs in the near future. These may get round the major side effects, although so far the COX2 inhibitors are not dramatically better than the older drugs.

Cases to Think About

Cow

A high yielding cow has developed coliform mastitis. You have given her cefquinome. Would a NSAID help too?

Dog

You are treating a nine year old dog with degenerative joint disease of the stifles using phenylbutazone 10 mg/kg twice daily, but the dog has not responded after three days of therapy. What are the possible reasons for this lack of response? What is your plan to deal with this therapeutic failure?

Cat

An owner thought her cat had a sore leg and gave the cat a 500mg paracetamol tablet. The cat is now depressed. What do you do?

Horse

You choose to refer a thoroughbred filly with acute, severe colic to an equine surgeon 3 hours driving from your practice. How would you choose a NSAID for analgesia (NB: you could also consider α2 adrenergic agonists such as xylazine or opioids such as butorphanol for this purpose).

Antiarthritis drugs

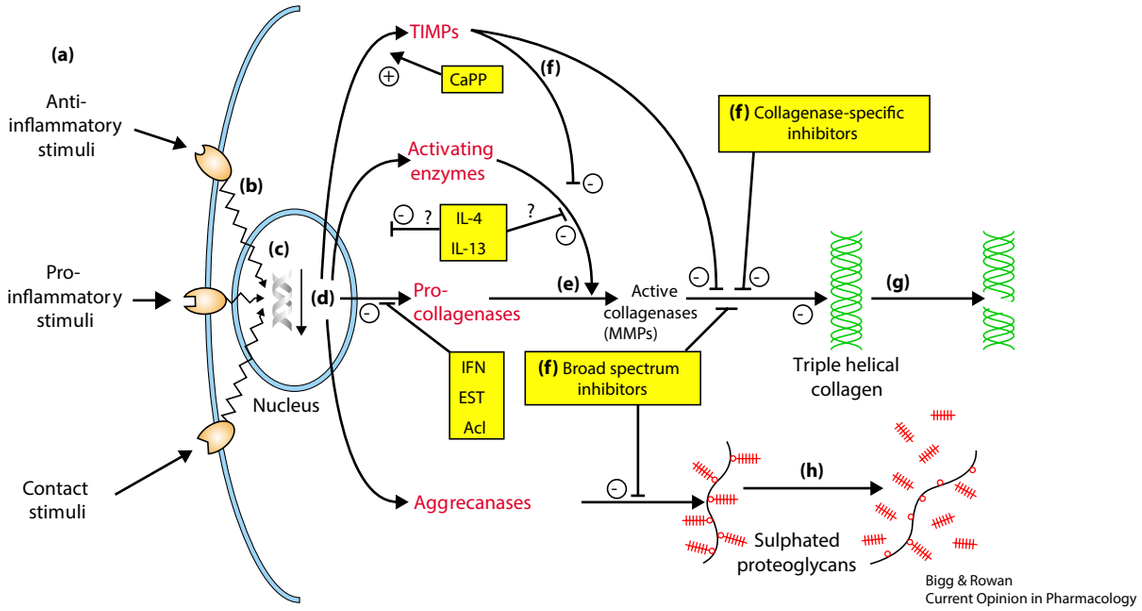
commonly used drugs

none

Antiarthritis drugs

- most of these drugs have only a small effect and are used as dietary supplements for arthritis in dogs and horses
- horses - PSGAGs for sprains
- dogs - many drugs used for immune mediated disease to supplement steroids and allow reduction in dose, EFAs for skin disease

DIAGRAM 6.3.1 Cartilage breakdown



(a) Chondrocytes and synovial cells are stimulated by anti-inflammatory and pro-inflammatory cytokines, mechanical stress and cell–cell and cell–matrix contacts through a variety of cell-surface receptors. (b) These stimuli are transferred to the nucleus via intracellular signalling and mechanotransduction pathways and (c) result in activation of gene transcription. (d) Synthesis and secretion of enzymes and inhibitors that modulate matrix turnover then occur. (e) Activation of pro-collagenases to the active forms is mediated through activating enzymes that may themselves require activation. (f) Inhibition of active collagenases and other metalloproteinases by TIMPs and synthetic inhibitors prevents matrix degradation. An excess of active enzymes compared with inhibitors results in the destruction of triple helical collagen (g) and sulphated proteoglycans (h). Points of intervention where potential therapeutic agents either promote (+) or inhibit (–) biological processes are indicated in yellow boxes. Possible points of intervention are denoted '?'. Acl, aceclofenac; CaPP, calcium pentosan polysulphate; EST, esculetin.

Articular cartilage is made up of large aggregating proteoglycans held together by strings of type 11 collagen with the odd chondrocyte here and there. The chondrocytes are continuously breaking down and synthesising the matrix. Arthritis pushes this dynamic equilibrium towards degradation. Proteoglycans are easily lost and rapidly replaced, collagen loss is slower and probably irreversible.

Matrix metalloproteinases (MMPs) break down the matrix; they are usually in balance with tissue inhibitors of metalloproteinases (TIMPs), which irreversibly block MMPs. Although MMPs can break down proteoglycans, aggrecanases are thought

to be mainly responsible. Control of these systems is only starting to be elucidated and offers lots of scope for new drugs as well as understanding how some old ones work (see diagram).

Glycosaminoglycans

A variety of high molecular weight, long chain mucopolysaccharides which mimic normal components of cartilage are used to treat arthritis in dogs and horses. Most of these are polysulphated glycosaminoglycans. They include various chondroitin sulphates (eg “Adequan”, not available in NZ), pentosan polysulphate (not strictly a polysulphated glycosaminoglycan but very similar- it is a semisynthetic pentasaccharide derived from beech wood shavings and present in many grains) and hyaluronic acid (a normal constituent of synovial fluid and cartilage matrix). Heparin is very similar, and most of the synthetic drugs started life as heparin - type anticoagulants in the 1950s.

All these drugs have a wide range of effects and it is not clear at the moment which effects are most important. For instance, pentosan given icv is the only drug shown to affect the course of variant Creuzfelt Jacob disease in people. The effects in arthritis also appear to be dose related. All work best in mild, early joint disease without destructive changes, although good clinical trials of these drugs are lacking.

Mechanism Of Action

- Limit cartilage degradation by inhibiting enzymes causing proteoglycan degradation
- Support cartilage matrix synthesis by increasing proteoglycans synthesis
- Improve the quality of synovial fluid by stimulating the synthesis of hyaluronic acid and has an anti-prostaglandin effect
- Improve circulation to the tissues of the joint because of anticoagulant activity
- Inhibit fibroblast growth factor and other cytokines. Fibroblast growth factor is required for neovascularisation and for growth of some types of tumour; pentosan is undergoing clinical trials as an anticancer drug in people at the moment.
- Hyaluronic acid may also increase the viscoelasticity of synovial fluid.
- Probably indirectly affect many aspects of proteoglycan turnover via cytokines

Indications

- adjunct therapy to correct the cause of osteoarthritis (cruciate or intra articular fracture)
- chronic osteoarthritis
- primary osteoarthritis
- degenerative joint disease

Duration of soundness after treatment increases with the molecular weight of the product from about 50 days to about 160 days.

They are usually given intra-articularly, although they may work after im injection too. They are broken down in the gut, so are not much use orally (see below).

Contraindications

- infection
- animals with clotting defects or traumatic haemorrhage
- liver or kidney disease

Side Effects

Local reaction post-injection when given intra-articularly

Extreme care must be taken to avoid introducing infection when making repeated intra-articular injections.

Heparin like clotting problems and immune mediated hypersensitivity have occurred in people.

These drugs are not cheap.

Glucosamine

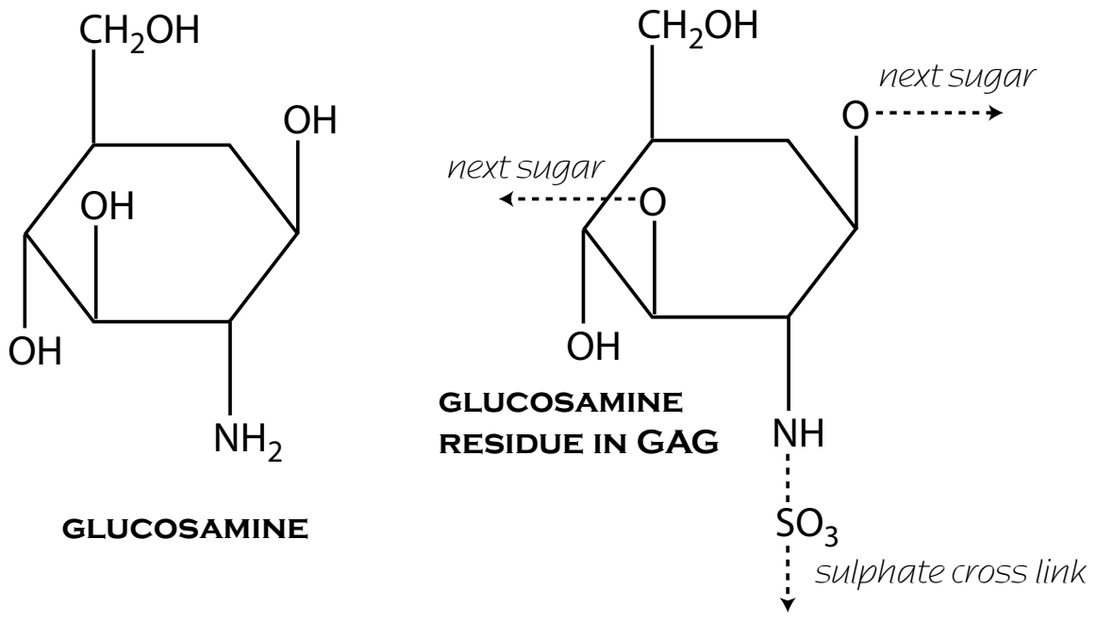
Glucosamine is the basic building block of GAGs. It is normally made from glucose by chondrocytes, but is preferentially taken up if available, and stimulates the production of GAGs (glucosamine availability is the rate limiting step).

Glucosamine is completely bioavailable from the gut and is practially non toxic, so is sometimes included in horse food.

It has a wide range of useful effects in vitro, and appears to have a small beneficial effect in osteoarthritis in rats and people. It modifies the progress of the disease rather than providing analgesia, so it takes several months for improvements to be seen in people. There are no clinical trials in dogs or horses, but as it probably has a beneficial effect and is unlikely to cause harm, it is becoming more widely used.

Glucosamine is currently being investigated for vCJD in people.

DIAGRAM 6.3.2 Glucosamine



Other drugs

Extracts of green lipped mussels (*Perna canaliculus*) have some anti-inflammatory effects. This is probably produced by a large glycoprotein similar to the other anti-arthritis drugs, but it may also be caused by the copper in the mussel's blood. Many organic copper compounds have a mild anti-inflammatory effect, probably because copper is an essential part of the enzyme superoxide dismutase, which mops up superoxide ions before they can damage tissue. Copper has been a traditional treatment for arthritis in people and is now being sold for use in dogs. Published evidence of efficacy is lacking.

A wide variety of other drugs are used in people to treat rheumatoid arthritis and are sometimes tried in dogs. These include penicillamine, chloroquine (also used as an antimalarial), sulphasalazine (see gut notes) and gold compounds (see immunosuppressive drugs). Tetracyclines (especially doxycycline) and nicotinamide are sometimes used as immunosupressants / anti-inflammatories in dogs. Their mechanism is unknown.

Phosphodiesterase 4 is involved in inflammation, and its inhibitors can have a useful anti-inflammatory effect, but they also cause vomiting. They are being investigated for asthma in people. A variety of non specific PDE inhibitors are used in animals, which may have some anti-inflammatory effect. The most widely used non specific PDE4 inhibitor used in people is oxpentifylline (pentoxifylline USAN) and it is occasionally used in animals.

There are many μ opioid receptors on macrophages in inflammatory lesions for some reason, and opioids have an anti-inflammatory effect in these sites. Morphine is occasionally injected into joints after surgery as an analgesic and anti-inflammatory.

Suramin, used to treat sleeping sickness in people, is an effective inhibitor of fibroblast growth factor, and has been used in people for this effect. It is a nasty drug and best avoided.

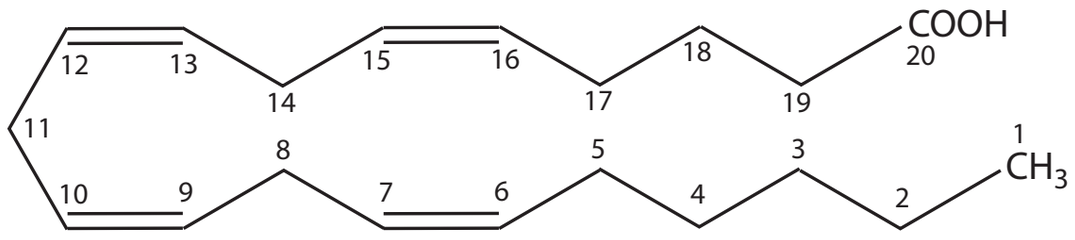
Antioxidants

Various free radicals, often superoxide ions, are released in inflammation. These are very effective at damaging cell membranes, releasing phospholipids and activating the arachidonic acid cascade. A variety of substances act as antioxidants, vitamin E and glutathione are common examples. Many plants produce compounds to mop up free radicals (they are produced during photosynthesis but also damage plant cells) so many herbal medicines have a mild antioxidant effect. Many also have NSAID compounds present which add to the effect. Plants also produce corticosteroids, and many "antioxidant" herbal medicines produce their anti-inflammatory effect through steroids, either natural or added during adulteration.

Essential fatty acids

A variety of polyunsaturated fatty acids derived from plants and sea fish have been used as dietary supplements. γ-linolenic acid from evening primrose oil or borage oil is popular in dogs, as is oil from cold water fish (eicosapentaenoic acid and docosahexaenoic acid) in people. These have an anti-inflammatory effect by being converted to abnormal prostaglandins and leukotrienes, which do not have such a pro-

DIAGRAM 6.3.3 Fatty acids

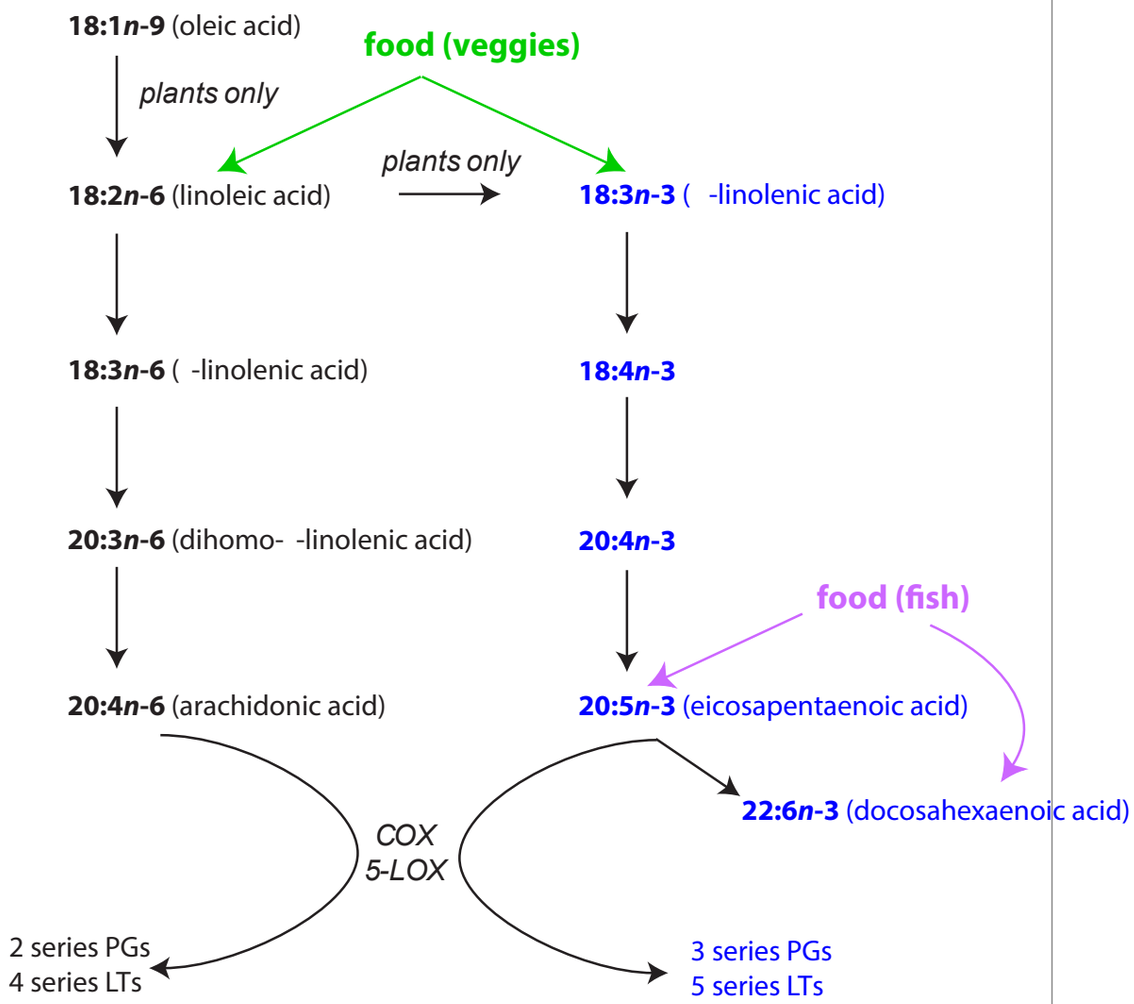


The nomenclature of fatty acids is confusing. This structure is usually known as arachidonic acid (eicosatetraenoic acid, 20:4n-6). It has 20 carbon atoms and 4 double bonds which start from carbon 6.

inflammatory effect. There are a large number of products of COX and 5-LOX which affect inflammation (and many other processes), and the optimal mix of fatty acids is not known.

The effect of polyunsaturated fatty acids is small, but can be clinically important, for instance in skin disease in dogs.

DIAGRAM 6.3.4 Fatty acid synthesis



Immunomodulator drugs

commonly used drugs

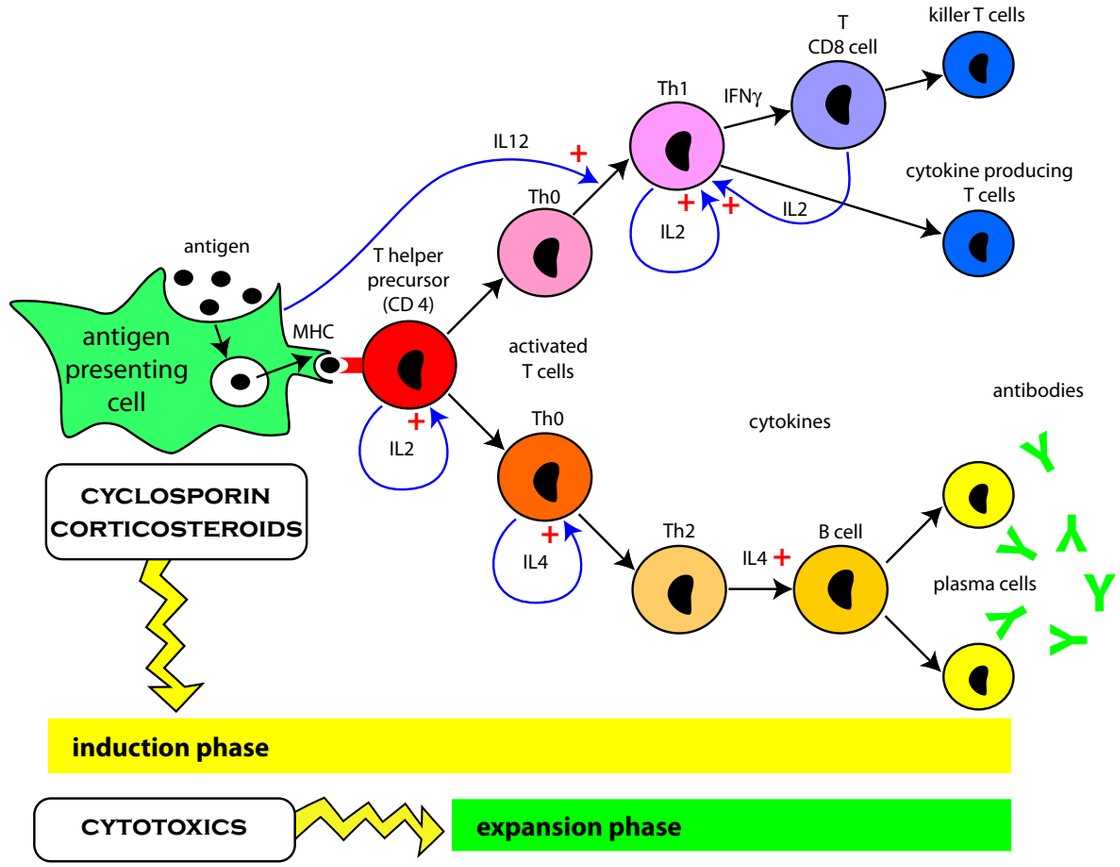
prednisolone / prednisone

azathioprine

Immunomodulator drugs

- ☑ glucocorticoids are most effective suppressants
- ☑ cytotoxics are sometimes added
- ☑ use as small a dose as possible
- ☑ taper off
- ☑ a variety of other drugs have been used but no clear indications yet

DIAGRAM 6.4.1 Immunosuppressant drugs



Sites of action of immunosuppressant drugs.

Immunosuppressive drugs suppress function of the cells of the immune system. The same drugs are used for the treatment of most immune-mediated diseases but there are certain types/patterns of drug use that maximize therapeutic success and minimize side-effects in the different immune mediated conditions. These drugs suppress the signs of immune mediated disease, they do not cure it. This means that they usually have to be given for life so chronic side effects are important.

Collectively, immune-mediated diseases are common - particularly in small animal practice. They affect all body systems. The most common immune-mediated diseases are allergic conditions (eg atopy, flea allergic derinatitis, food allergy), autoimmune skin diseases (eg pemphigus foliaceous), gastrointestinal hypersensitivities (eg inflammatory bowel disease), haematopoietic diseases (eg autoimmune haemolytic anaemia, autoimmune thrombocytopaenia), glomerulonephritis, and respiratory diseases such as bronchitis and allergic rhinitis.

The four types of immune response are:

- anaphylaxis
- antibody dependent
- complex mediated
- cell mediated

The drugs used in veterinary practice to treat immune-mediated diseases in order of importance are glucocorticoids, antihistamines, azathioprine, and miscellaneous others (see anticancer drug notes).

Glucocorticoids

Very commonly used in small and large animal veterinary practice as immunosuppressives at higher doses than used for anti-inflammatory effects (nb, there is still a small immunosuppressant effect at low doses). Duration of action varies greatly. Prednisone, prednisolone (probably the most commonly used immunosuppressants) and triamcinolone are of medium duration of action whereas dexamethasone and betamethasone are long acting. The duration of action of these drugs is further influenced by the chemical form of the glucocorticoid in the preparation. (see corticosteroid notes). Generally, prednisolone (or prednisone) is used for twice daily dosing (at about five times the anti-inflammatory dose), or dexamethasone for daily / alternate day dosing. The dose is tapered down to what works in that individual.

Immunosuppressive properties include:

- depression of antibody production especially of new antibodies or inappropriate (eg autoimmune) antibodies
- depression of migration of immune cells
- depression of cytokine release
- may be lympholytic in high doses
- decreased uptake of antigen by reticuloendothelial cells
- at massive doses glucocorticoids inhibit mitosis by stopping cell cycle in M phase

Side-effects

(see corticosteroid notes)

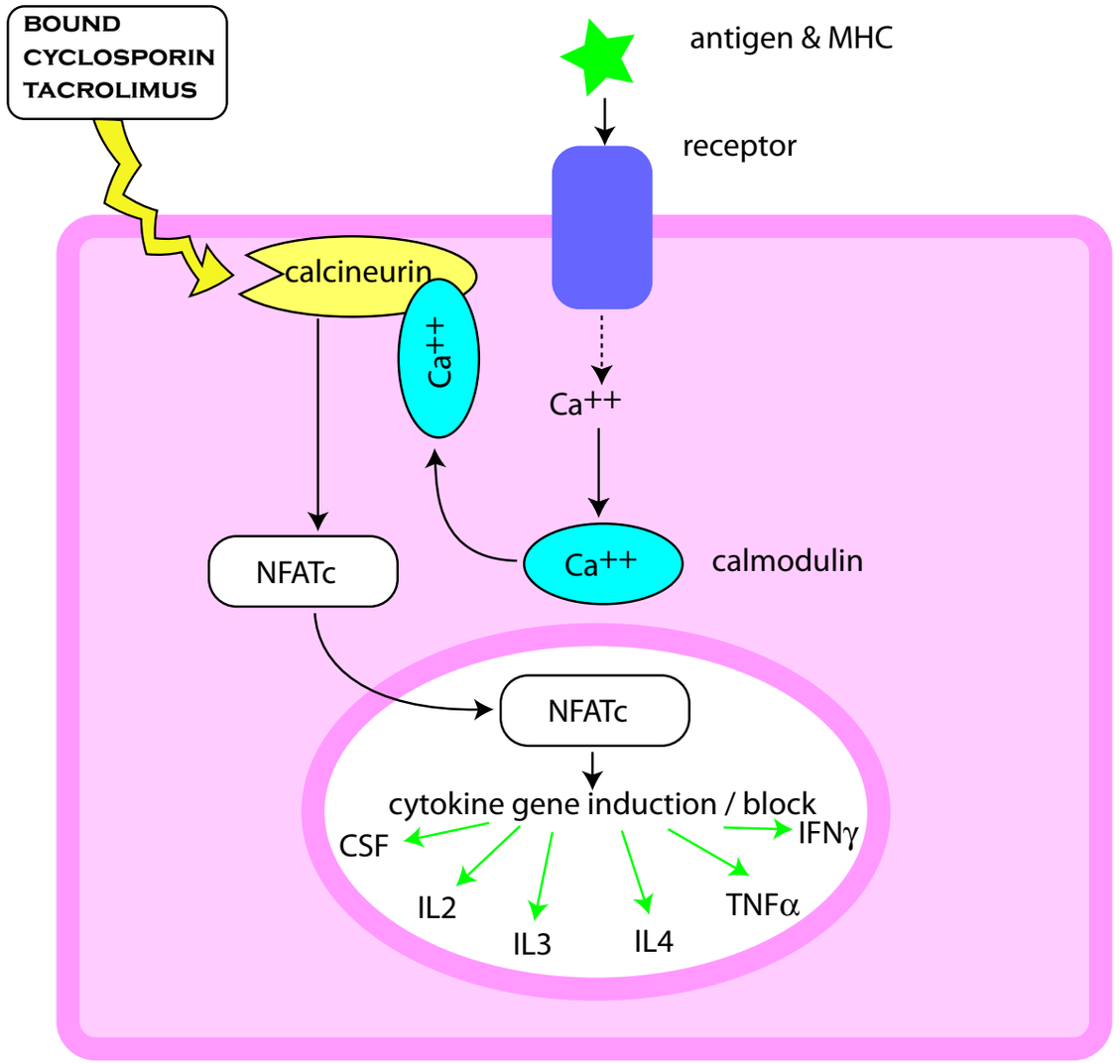
Effects On Laboratory Values

- stress leukogram (neutrophilia without left shift, lymphopaenia, eosinopaenia)
- elevated serum alkaline phosphatase (SAP) (dogs only)
- elevated ALT
- lipaemia
- increased blood albumin

Other drugs

Antihistamines are mainly used for management of allergic conditions (H1 -blockers) of the skin. They are most commonly used as glucocorticoid-sparing agents as they are not usually effective by themselves in the species we deal with. Most modern antihistamines are designed to be non sedative (in people) but sedation is often useful in dogs so older drugs, mostly phenothiazines such as acepromazine, promethazine and trimeprazine, tend to be used. Second generation drugs such as

DIAGRAM 6.4.2 Cyclosporin action



Cyclosporin switches on genes affecting many aspects of inflammation.

chlorpheniramine are also useful in dogs. There are dozens of more modern drugs, most of which have not been assessed in dogs and cats.

The only licensed drug in NZ is **tripelennamine** but it is not recommended as an antihistamine. When given iv to ruminants, it appears to block H3 receptors in the CNS increasing arousal / making them convulse. Has been used to get downer cows up but not recommended!

Cyclosporin (cyclosporine USAN, ciclosporin INN) is a potent inhibitor of T lymphocyte activation halting the immune response. Its main use has been to prevent graft rejection (in man); its main use in vet medicine is topical treatment of keratoconjunctivitis sicca as an eye drop, but it is also used for anal furunculosis and atopic skin disease.

It is too expensive for routine use in other immune-mediated diseases, and therapeutic drug monitoring is advisable if it is used systemically. Kidney toxicity is a problem in people, but does not seem to occur in dogs and cats. It has been given with P450 inhibitors such as ketoconazole to reduce metabolism, and thus dose and cost.

Newer, homologues such as **tacrolimus** are starting to come onto the human market. Both bind to numerous receptors in the brain as well as interfering with steroid receptor binding. Tacrolimus crosses intact skin better than cyclosporin and ahs been used for anal furunculosis in dogs.

Gold, as an organic salt, eg aurothioglucose; aurothiomaleate (= aurothiosuccinate USAN) is sometimes used by intramuscular injection in the dog and cat. Its mechanism of action is not known but appears to "normalize" immune function and decrease phagocytic activity. Its main use in veterinary medicine is chronic arthritis and feline idiopathic gingivitis-pharyngitis. Gold's most common side-effect is thrombocytopaenia. It is expensive.

Many parasites modulate their hosts' immune systems for their own benefit. A protein from hookworm saliva, AIP-2, has been shown to be effective in the treatment of asthma and inflammatory bowel disease in people. Research into drugs which mimic this action is underway.

Cytotoxic drugs

A variety of cancer chemotherapeutic drugs are used when potent immunosuppression is required. **Azathioprine** (Imuran) is the least toxic and most commonly used in dogs (often in combination with steroids). It is a prodrug for mercaptopurine, a synthetic purine which interferes with DNA and RNA formation, resulting in inhibition of antigen-induced lymphocyte transformation and a slow decline in antibody levels

Azathioprine is mainly used in dogs when long term, moderately potent immunosuppression is needed, but is often used when long term prednisone is resulting in unacceptable side effects. The addition of azathioprine to the treatment regimen usually allows the prednisone dose to be at least halved and sometimes eliminated.

A lag effect of several weeks (4 months in people) should be expected before the beneficial effects of azathioprine become apparent.

The most important side effect is bone marrow suppression. Mild suppression is common with this drug and of little concern. Severe depression is rare, is most often seen early in the treatment protocol, is more common in cats than in dogs, and is usually reversible on discontinuation of therapy. A complete blood count should be performed every 10- 14 days for the first 2-3 months of therapy and should be repeated at monthly to bimonthly intervals thereafter. Treatment with azathioprine should stop if marked neutropaenia or thrombocytopaenia develop.

If more potent immunosuppression is required, other anticancer drugs are used, eg. cyclophosphamide, chlorambucil (see below for more detail). Newer drugs such as **mycophenolate** are being used in people as immunosuppressives because they are relatively specific for T and B cells, but there is no information on their use in animals yet. IL2 receptor antagonists such as basiliximab and daclizimab are occasionally used in people but are mind-bogglingly expensive.

Immunostimulants

These are very rarely used. Levamisole may have some effect. particularly on T cells. Colony stimulating factors, interleukins 3 & 6 and ampligen (interferon inducer) are occasionally used in people but all are extremely expensive.

BCG (TB vaccine) is occasionally used in horses to try to provoke an immune reaction to sarcoids. It is cheap and nasty - particularly if it gets into your eyes.

Remember that TB testing with intradermal tuberculin requires a normal immune system.

Anticancer drugs

commonly used drugs

none

Anticancer drugs

- ☑ seek advice before using and check latest protocol
- ☑ remember the aim is to prolong **useful** life
- ☑ handle drugs with great care

The options for treatment of cancer in veterinary practice are fairly limited:

- euthanasia
- palliative treatment then euthanasia
- surgery (then euthanasia)
- radiotherapy
  - X rays
  - γ rays
  - electrons
  - microwaves
  - light
- chemotherapy

None of these options is ideal, and the last three are not cheap. Current anticancer drugs are some of the nastiest drugs available and are not to be used lightly. For this reason, this chapter aims to give you an overview of the subject rather than specific instructions on how to use these drugs. Newer, safer drugs are starting to be used, but we do not know enough about them yet.

Treatment Philosophy

Treatment of cancer is appropriate provided the animal's quality of life can be preserved during treatment. Cure is often not the goal - rather extension of useful life (cure requires the removal of every single cancer cell). Provided quality of life is preserved, extending life of the patient by as little as a few months may be very worthwhile. This allows the owner to come to terms with their pet's impending death (quality time is quality time even though it is destined to be short). For some tumours, particularly those maintained by sex hormones, or thyroid tumours, response to treatment can be dramatic.

If quality of life is not preserved, treatment of cancer is inappropriate. Oncology is not about prolonging a pet's dying. Thus judgement of quality of life is of paramount importance. It requires both vet's and owner's assessment but some simple rules help: if the pet is not eating, is inactive and is not responsive to its owner, its quality of life is unsatisfactory; if the animal is in pain its quality of life is poor (painful cancers - bone tumours; bone metastases; rapidly expanding organ masses, spinal tumours, some peripheral nerve tumours).

Chemotherapy protocols used in veterinary medicine are purposefully not aggressive to minimize side effects and preserve quality of life during treatment. Veterinarians cannot sit down with their patients and explain that short term pain will

provide long term gain. Unfortunately, the trade off of less aggressive protocols is shorter remission times.

Owner Concerns

Is the pet suffering as a result of the cancer?

Owners assume all animals (and people) with cancer are in excruciating pain. They must be reassured that this need not be the case and that if the animal appears to be suffering you would recommend euthanasia. It is very important for you to convey this point to the owner least they think the animal's well being is not paramount in your mind. Otherwise the client may become suspicious your recommendation to treat is based on your wish to earn money or "experiment" on the pet.

Will the pet suffer as a result of the treatment?

Most owners believe chemotherapy will cause their pet to become very ill and lose its fur. They need to be reassured that the chemotherapy protocols used in veterinary medicine are purposefully designed to minimize such complications. Be careful of some drugs, however. For instance, many dogs vomit after methotrexate and cisplatin. Also, dog breeds with wire-haired, curly or "woolly" coats (such as Old English sheepdogs, poodles, Afghans and some terriers) may lose their hair.

How long will the animal live?

Median survival time for the particular tumour type can be quoted but it is very important to emphasize and reemphasize that some animals will live for shorter and some longer than the median time. That way, if a pet comes out of remission much earlier than expected there is no recrimination. Moreover, the fact that a small number of patients will survive a long time following treatment for tumours such as lymphoma seems to be the incentive many owner's need to elect to treat.

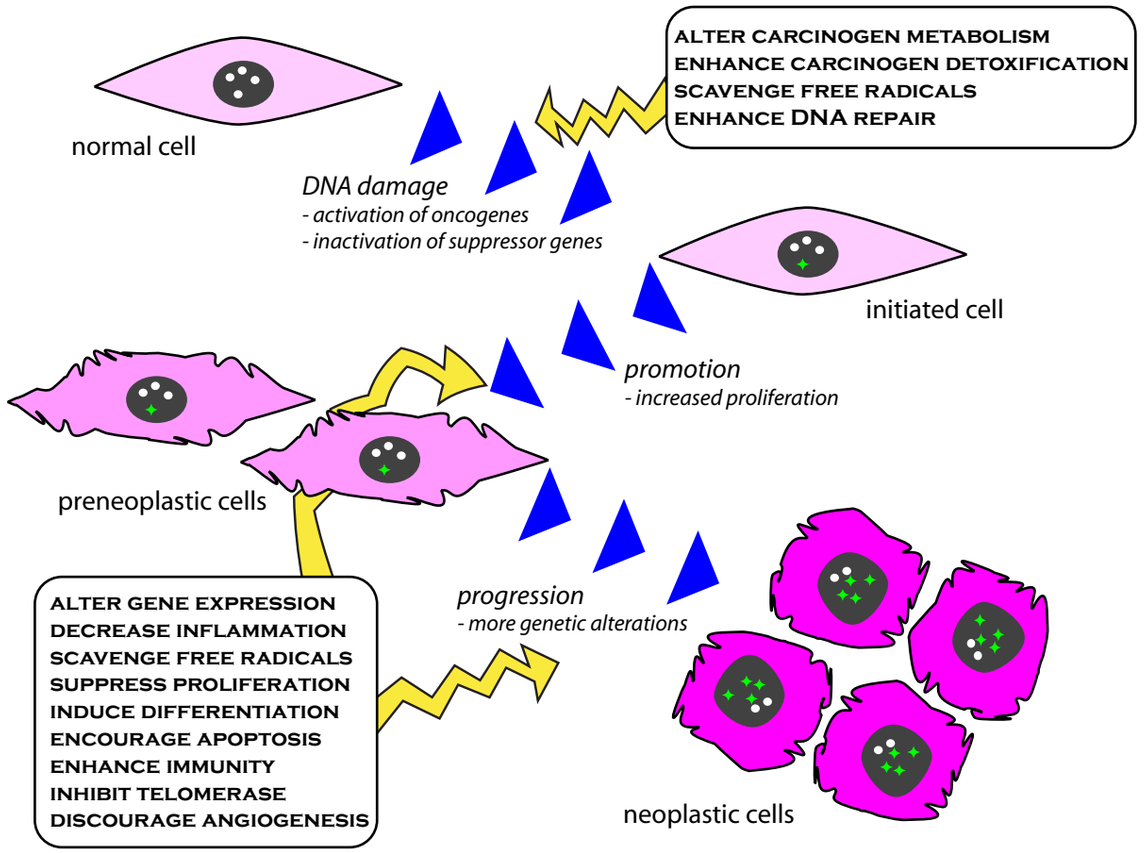
How much will it cost?

Have an estimate ready for the first 3, 6 or 12 months of treatment including all anticipated costs (chemotherapy agents, administration costs, blood work, hospitalization). For example, treatment of a dog for lymphoma for a year at Massey University costs approximately $2000. Providing an "all up" estimate like this better allows the client to budget and avoids unexpected charges arising from such things as blood work.

Formulating a treatment plan

Incisional or excisional biopsies are essential before treatment can be considered. Biopsy is necessary for diagnosis of the tumour and greatly assists prognosis (the pathologist should grade the malignancy of the tumour). Following excision of a

DIAGRAM 6.5.1 Cancer



General strategies for treating cancer.

mass, biopsy is necessary to determine if the tissue sample is free of tumour (clean margins). (See surgical oncology notes)

If the tumour can be removed in its entirety or "debulked" then surgery is usually indicated. Many publications in recent years have dealt with successful aggressive surgical techniques for removal of tumours (eg mandibulectomy for oral tumours and hemipelvectomy for pelvic tumours). The primary aim of the surgery is to remove as much of the tumour mass as possible. Complete removal offers the chance of a cure. Debulking of tumour is valuable because it reduces the number of cells resistant to chemotherapy and may stimulate dormant cells into cycling (and hence chemosensitivity). Surgery is also used for pain relief (eg osteosarcoma).

Adjuvant radiation therapy is indicated if not all visible tumour was removed at the time of surgery or if histopathology reveals dirty surgical margins or a type of tumour with a high rate of local recurrence (eg fibrosarcoma). For instance, adjuvant radiation therapy is often required for cutaneous mast cell tumours. Radiation ther-

apy is rarely justified if systemic spread of the cancer can be demonstrated. Some of the most radioresponsive tumours in dogs and cats include lymphoma, mast cell tumours, and acanthomatous epulides. Adjuvant chemotherapy may also be helpful if clean margins are not obtained.

If the cancer is multicentric or has metastasized, systemic treatment is required. The primary systemic therapy is chemotherapy.

Chemotherapy

The main problem with using drugs to kill cancer cells is that cancer cells are not much different from normal cells and most of the drugs kill lots of normal cells as well as the diseased ones. Some important cancers are dependent on sex hormones (and are usually treated by removing the hormones - castration or spaying) but the only distinguishing feature of most cancer cells is that they grow more rapidly than most normal cells. Most anticancer drugs aim to disrupt cell division in some way. They usually kill all rapidly dividing cells, hopefully including the cancer cells.

Anticancer drugs are usually divided into several different groups:

- antimetabolites
- alkylating agents
- anticancer antibiotics
- microtubule inhibitors
- odds & sods
- hormones

Indications

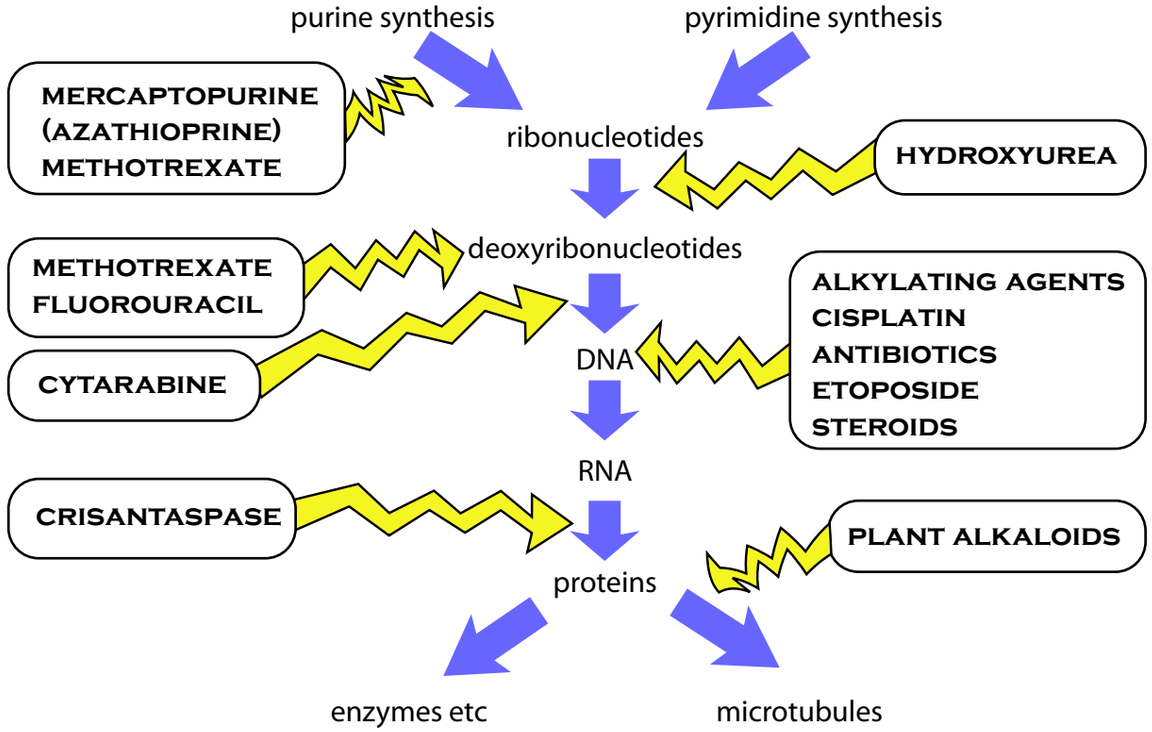
Chemotherapeutic drugs are primarily used for the treatment of cancers that have metastasized to distant sites in the body or are localized but non-resectable. They are also used when potent immunosuppression is required for immune-mediated diseases (see immunosuppressives notes).

Specifically, chemotherapy is indicated in the following circumstances:

- Palliative therapy for a non-resectable or disseminated tumour
- Adjuvant to radiotherapy and/or surgery for local control
- Delay/prevent development of metastatic disease
- "Rescue" of relapses following radiation or surgical failure

Chemotherapeutic drugs selectively kill rapidly dividing cells because they interfere with protein or DNA synthesis which is more rapid in such cells. The cells most susceptible to chemotherapeutic drugs are therefore cancer cells, cells of the

DIAGRAM 6.5.2 Cytotoxic drugs



Sites of action of cytotoxic drugs.

haematopoietic and lymphopoietic systems and gastrointestinal mucosal cells. Fortunately, normal cells have a more rapid recovery from chemotherapeutic drug injury than neoplastic cells. Obtaining a fine balance between kill rate of host cells (toxicity) and recovery rate of tumour cells (failed therapy) is the daily challenge for vets administering chemotherapeutic drugs.

Side Effects

- gut upset (vomiting, diarrhoea, colitis)
- bone marrow depression (especially thrombocytopaenia and neutropaenia)
- alopecia (especially woolly coated breeds)
- slow wound healing / infection

and miscellaneous other toxicities more specific to each drug

Dosages

Doses of chemotherapeutic drugs are usually based on body surface area because they are so toxic that the minimum effective dose must be given (metabolic rate and therefore drug pharmacokinetics and toxicity are more closely related to body surface area than body weight - see pharmacokinetics notes). You will still find

some chemotherapy doses for cats listed on a per kg basis. This is acceptable because the bodyweight range (and therefore body surface area) is very small in cats in comparison to dogs. Body surface area is usually calculated from tables or use the formula:

body surface area (m^2) = wt in $kg^{0.67}/10$

Chemotherapeutic Protocols

The same pharmacological principles apply to treatment of all neoplastic diseases, however, there are certain patterns (protocols) of drug use that maximize therapeutic success and minimize side-effects in the different neoplastic conditions. A variety of standard protocols exist for the treatment of small animal cancers. A typical protocol for the treatment of canine and feline lymphoma is included below. Intermittent dosing is preferred to continuous dosing to allow normal cells to recover.

Standard chemotherapy protocols may not suit an individual animal for a variety of reasons such as cost, idiosyncratic drug reactions, side effects, impractical administration etc. For this reason, you may have to individualise a chemotherapy protocol for an animal. Therefore you need to have some grasp of the reasoning behind chemotherapy drug protocols.

Single drug protocols are not in fashion because of resistance and efficacy with the exception of doxorubicin. It is used in cats for convenience and seems quite effective for lymphoma

Multiple drug protocols are more effective because they decrease the chance of a drug-resistant or partially resistant clone of tumour cells escaping the chemotherapy. The drugs chosen should have activity against the particular tumour (preferably proven in previously reported single-drug trials) and preferably affect cells at different stages of the cell cycle or be non-cell cycle specific (ie affect cells in all stages of the cell cycle) eg. combination of two drugs affecting the cell only during mitosis is likely to be less effective than combination of a drug that affects the cell at mitosis and a drug that strikes during DNA synthesis.

They should also have a different mode of action, not have overlapping toxicities eg. adding two markedly bone marrow suppressive drugs into the same protocol is undesirable (but sometimes necessary)and should not interact.

Another consideration is the likelihood of tumour cross-resistance. For instance, if a tumour is resistant to cyclophosphamide it will also often be resistant to chlorambucil, a closely related alkylating agent

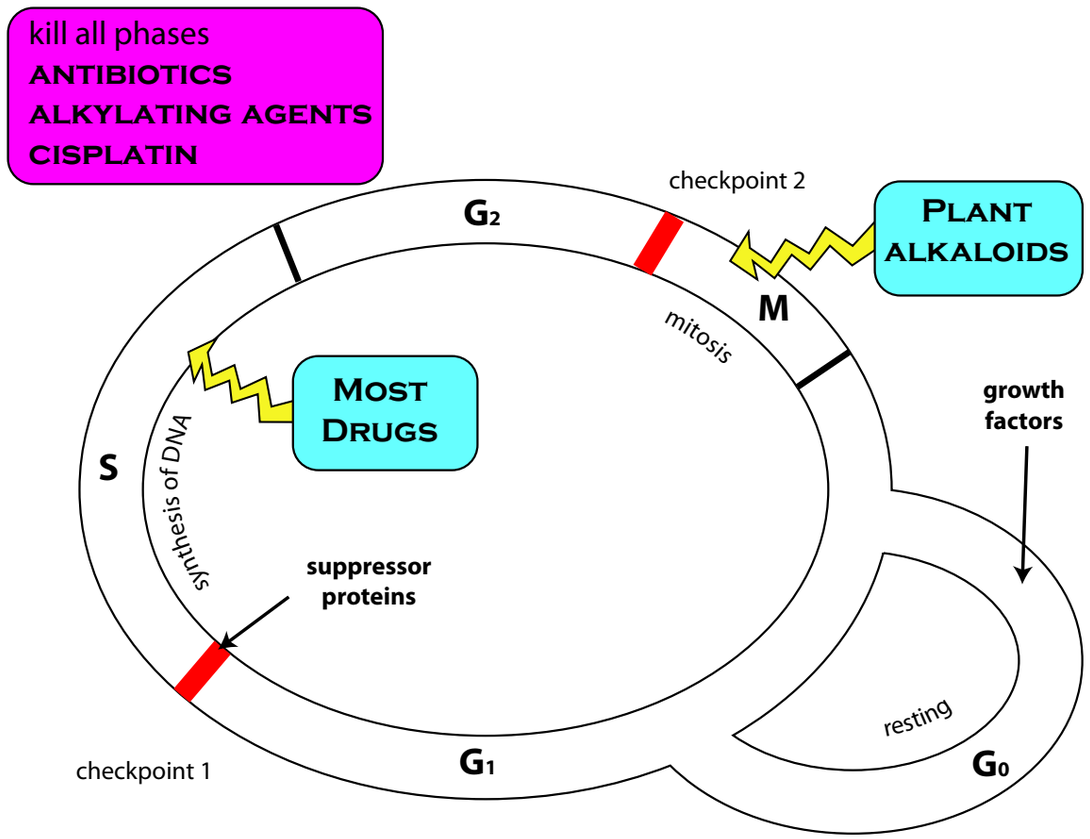
Multiple drug resistance

Rapidly dividing cells exposed to anticancer drugs are under a lot of selection pressure. The main mechanism of resistance is to express P (permeability) glycoprotein on the cell surface. This actively pumps drugs out of the cell (it is a major component of the blood brain barrier) before they can cause damage. Cross resistance to the various classes of drugs occurs. Ivermectin is one of the most potent inhibitors of P glycoprotein and is undergoing trials to reverse multidrug resistance in people.

Supportive treatment

- Analgesia - usually NSAIDs, especially for bone pain
- Bone marrow stimulants - anabolic steroids
- Appetite stimulants - benzodiazepines or steroids
- Nutritional support - gastrostomy tubes

DIAGRAM 6.5.3 Cell cycle



Stages of the cell cycle at which anticancer drugs act.

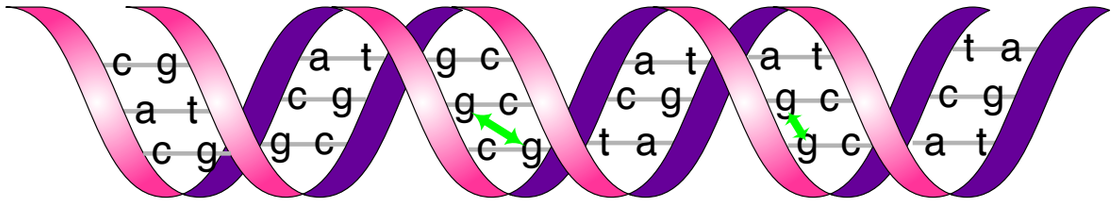
Choosing drugs

The range of tumours which animals can get is vast; most of the few which are treated, are treated empirically. Protocols (based on human protocols, which are mostly also empirical but of which there is much more experience) have been established for some tumours (particularly white cell tumours), but often it is a matter of trying drugs or protocols which have been reported to work in a small number of cases and tailoring the treatment to the response. Pharmacogenetics is starting to make a difference in people, but not yet in animals.

Alkylating agents

These are probably the most commonly used group of drugs in small animals. They include **cyclophosphamide** - a prodrug for one of the nitrogen mustards. These are closely related to the sulphur mustard gases used for chemical warfare in WW1. Cyclophosphamide is not a pleasant drug. Although it is cheaper than some of the

DIAGRAM 6.5.4 Alkylating agents



Cross linking of guanine residues is the mode of action of the alkylating agents and platinum compounds. Dactinomycin is thought to work in a similar way. The DNA damage triggers apoptosis.

other drugs and works well in some lymphomas and leukaemias, a metabolite can cause haemorrhagic cystitis (as well as all the general side effects of cytotoxic drugs). A similar drug without this effect is **chlorambucil** (similar indications). Both drugs are sometimes used as potent immunosuppressives. The other alkylating drug occasionally used is **melphalan**. **Cisplatin**, and its less toxic analogue **carboplatin**, act in a similar way to the alkylating agents and are used for a variety of solid tumours. Cisplatin in particular is nephrotoxic and should not be used in cats (carboplatin can be used in cats).

Antimetabolites

The main antimetabolites used are **methotrexate** (used for lymphoma) and **cytarabine** (= cytosine arabinoside) (used for lymphoma, leukaemia and myeloproliferative disease). Resistance develops quickly to cytarabine. There are several new antimetabolites on the way. One, **rabacfosadine**, has recently come on the market in the USA for canine lymphoma. Azathioprine (converted to **mercaptopurine**) can also act as an antimetabolite, but has numerous other mechanisms to inhibit leucocytes. Mainly used for lymphoma and autoimmune disease. Cats and horses are very sensitive to the effects.

Antibiotics

A number of antibiotics are in human use but the only one much used in animals is **doxorubicin** (Adriamycin). This is effective in a broad range of cancers and is used for carinomas and sarcomas as well as lymphoma and leukaemias. It has a broad spectrum of side effects too, including cardiotoxicity, allergic reactions and nephrotoxicity (cats). It is also very irritant when injected perivascularly.

Plant alkaloids

These are a growth area for human drugs but the only ones in veterinary use are **vincristine** and **vinblastine** (from the periwinkle, *Vinca rosea*). Vincristine in particular is not as myelosuppressive as most drugs, although it does produce some unique side effects such as peripheral neuropathies. Both are used in combinations (usually with doxorubicin and cyclophosphamide) for lymphmomas and some sarcomas and are very irritant perivascularly. Taxanes such as **paclitaxel** (Taxol) are effective in people but are too expensive for use in animals at the moment.

Tyrosine kinase receptor inhibitors

A fairly recent development is use of cytokine tyrosine kinase receptor inhibitors. Inhibition of the cKit receptor is effective in mast cell tumours in dogs, which are aggressive and were previously difficult to treat. These drugs are used for a variety of other tumours in people. **Imatinib** was the original human drug, although there are lots of new ones. **Masitinib** and **toceranib** are used in dogs overseas. They are likely to get here soon. A large number of similar dugs are in clinical trials for people.

Sex hormones

Many tumours are started or maintained by sex hormones. In veterinary practice, these are usually treated by castration (prostate cancer, anal adenoma) or spaying (mammary tumours). In people, and rarely in animals, drugs are used. **Tamoxifen** is an antioestrogen used for breast cancer in women which is also effective in dogs but too expensive to use. **Anastrozole** blocks oestrogen production and is more effective in women. **Delmadinone** is a progestagen which acts as an antiandrogen and is sometimes used in dogs. **Stilboestrol** used to be used as an

Typical lymphoma treatment (COP) protocol (dogs and cats)

This protocol is included here to give some idea of the complexity of treatment - check on the latest recommendations before treating any animals!

Induction therapy

Vincristine 0.7mg/m^2 iv on day 1
Cyclophosphamide 50mg/m^2 po on days 1,2 3, & 4
Prednisone 1mg/kg po twice daily
Repeat induction therapy for 8 weeks. Precede each vincristine injection with a WBC and platelet count.

Skip a week's treatment if WBC count is below 3x10^9/L, neutrophil count is below 2x10^9/Lor platelet count is below 100x10^9/L. Start prophylactic trimethoprim / sulphonamide if neutrophil count is below 1x10^9/L.

Maintenance therapy

Vincristine 0.7mg/m^2 iv every 3 weeks
Chlorambucil 2 - 4mg/m^2 po on days 1,2,3 & 4 every week
Prednisone 1mg/kg po every second day
Continues until the 52nd week of treatment or until the lymphoma comes out of remission.

Rescue or late intensification therapy

When the animal comes out of remission (usually due to tumour resistance) a change of drugs is required to regain remission. The second period of remission is usually shorter than the first period. The treatment required to obtain a second remission is usually more expensive. An alternative approach is to use late intensification of therapy after sucessful induction but before tumour recrudescence. Late intensification has some theoretical support as an effective strategy. It is also practical in veterinary medicine because by the time the owner is asked to consider more expensive and potentially more toxic drugs, much of their fear of chemotherapy has evaporated. Consider the following drugs for rescue or late intensification. Doxorubicin is the most effective rescue drug.

Doxorubicin 30mg/m^2 iv every 3 weeks for 3 - 6 treatments (max 8 treatments) or cytarabine 100mg/m^2 iv on days 1,2,3 & 4 repeated every 3 weeks for 2 - 3 treatments or vinblastine 2.5mg/m^2 iv every week for 6 treatments

Given with or without asparaginase 400iu/kg sc or ip weeky for 1 - 3 treatments

antiandrogen, but is no longer available.

Odds and sods

Miscellaneous cytotoxic drugs include **crisantaspase** and **colaspase** - types of asparaginase. Some tumour cells require exogenous asparagine, asparaginase breaks this down and stops the tumour cells making protein. It is used for lymphoma but can cause anaphylaxis and is expensive. Interest is reviving as asparaginases have been shown to prevent metastasis of human breast cancer cells.

Risks To People

Paradoxically, repeated exposure of people to low doses of chemotherapeutic drugs can predispose them to neoplasia. In addition, chemotherapeutic drugs are teratogenic and toxic. Exposure can occur via absorption through skin or mucous membranes, inhalation of vapours or ingestion through contamination of food or cigarettes.

Common situations in which exposure occurs:

- aerosol formation when reconstituting or removing liquid drugs from a pressurized vial
- expulsion of air from drug-filled syringes
- spills during transfer of drug between containers
- leakage of catheters, iv lines or bags
- self-inoculation when recapping needles
- crushing or breaking tablets
- handling urine or faeces from treated animals

Precautions required:

- wear latex gloves; +/-protective eyewear and a disposable gown when administering drugs or handling waste
- pet owners should be instructed to wear gloves when administering tablets.
- prepare drugs in a low-traffic, draught-free but well ventilated area
- if possible wear a respirator or dust mask when preparing drugs (often more practical to buy the drugs reconstituted from a local hospital or supplier)
- A spill kit must be available where cytotoxic drugs are prepared
- **do not** recap needles or pressurise vials
- wrap an alcohol-dampened swab around needles before withdrawing them from vials
- evacuate air bubbles from drug-filled syringes into alcohol-dampened gauze

- use disposable plastic-backed table covers to minimize contamination of tables with spilled drug
- never eat or drink in areas where cytotoxics are used
- consider altering oral drug dosing frequency to allow use of whole tablets rather than tablet fragments
- never allow pregnant women (including owners) to handle drugs or handle excreta from treated animals
- think very carefully (and discuss with the owner) before sending an animal home to a household with a pregnant woman or children
- be familiar with routes of excretion so that contaminated urine or faeces are safely disposed of. This is particularly important with the urine from cisplatin-treated dogs.
- if skin contact occurs, wash hands thoroughly with soap and water
- all materials used in the injection of a chemotherapeutic should be placed in a plastic bag, sealed and then placed in a clearly labelled, leak-proof container for disposal by incineration.

Protocol to follow if a vesicating drug is injected outside the vein

1. Do not remove needle but aspirate forcefully while needle remains in place.
2. If doxorubicin has been extravasated immediately flood area with 5 mL of 8.4% sodium bicarbonate.
3. Aspirate the area with a 25 SWG needle.
4. Infiltrate affected area with small volumes of normal saline and repeat aspiration (use 3-5 mL with vincristine and 15-30 mL with doxorubicin).
5. Infuse dexamethasone 4mg.
6. Cold pack for 15 minutes
7. Use a DMSO roll-on three times daily for 5 days.

Prevention is better than cure - **use a catheter**.

Large animals

The only tumours treated medically are sarcoids in horses. When these grow around the eyes it is difficult to resect them or use cryosurgery, so cisplatin in oil is sometimes injected into the tumours. It requires high pressure to inject oil into a solid tumour, so use Luer lock syringes and wear goggles.

The future??

The unsatisfactory state of chemotherapy (in people) has prompted a huge amount of research. This has taken several directions: new drugs are the most obvious.

Lots of plants and sedentary animals such as sponges make toxins to stop themselves being completely eaten, so the jungles and seabeds are being scoured for suitable drug candidates. (Sponges are handy because they will grow in a stream of sea water - the drug just needs to be extracted at the other end of the pipe.) Expect some new drugs soon.

Another approach has been to target the cancer cells more directly, rather than zap all dividing cells. One way is to use some drug which is preferentially taken up by the cancer cells but requires activation by / sensitises the cells to radiotherapy (ideally relatively innocuous radiotherapy such as laser light). This approach is already in use in people.

Another way is to use biochemical markers which are more specific for cancer cells (usually specific types of cancers) and attach the drug (either cytotoxic or activator) to antibodies for these markers. These markers are being well characterised for human cancers, but do not expect much useful work in animals.

Yet another way is to interfere with the tumour's blood supply and starve it to death. A rapidly growing tumour needs a rapidly growing blood supply - new vessels are under the control of various growth factors which can be blocked by drugs such as the anti-arthritis drug pentosan. Thalidomide is also being tried - it is a TNFa inhibitor which may be important in tumours which are initiated by chronic inflammation. It will never be used in animals, but newer, safer analogues are also available. The tumour's blood supply often does not keep up with demand and the tumour becomes hypoxic. Injecting anaerobic bacteria into such tumours to kill the hypoxic cells has shown some success.

New drugs are currently coming onto the market (overseas) at the rate of about one every six weeks, so do not regard this study guide as the last word on cancer chemotherapy!!!

Further down the line, insertion of tumour suppression genes looks hopeful if problems with the viral vectors are sorted out. New Zealanders will probably have to go overseas for this. A number of genes have been identified in people which predispose to cancer.

Cancer is the number one killer of humans, so there is plenty of incentive to find the definitive cure, quickly!

The Thyroid

commonly used drugs

hypothyroidism - thyroxine

hyperthyroidism - carbimazole, methimazole

The Thyroid

- ☑ dogs - hypothyroidism
  1. give thyroxin
- ☑ cats - hyperthyroidism
  1. surgery
  2. carbimazole / methimazole
  3. radioactive iodine

Disorders of thyroid function are common in small animals; usually hyp**o**thyroidism in dogs and hyp**er**thyroidism in cats. In large animals, the problems are usually external, either iodine deficiency or plant toxins which interfere with iodine utilisation (particularly plants of the cabbage family - see toxicology notes).

Thyroid Physiology

The hypothalamus releases thyrotropin releasing hormone in response to environmental stessors such as cold or trauma. Thyrotropin releasing hormone acts on the anterior pituitary to increase the release of thyrotropin. This in turn stimulates the thyroid to produce thyroid hormones. Several of these steps can be manipulated with drugs but this is not done clinically.

Thyroid hormone production

see diagram.

The thyroid gland makes four times as much thyroxine (T4, levothyroxin INN) as liothyronine (T3, triiodothyronine) but T3 is four times as active as T4 in the tissue. T4 has more control over thyrotropin releasing hormone secretion.

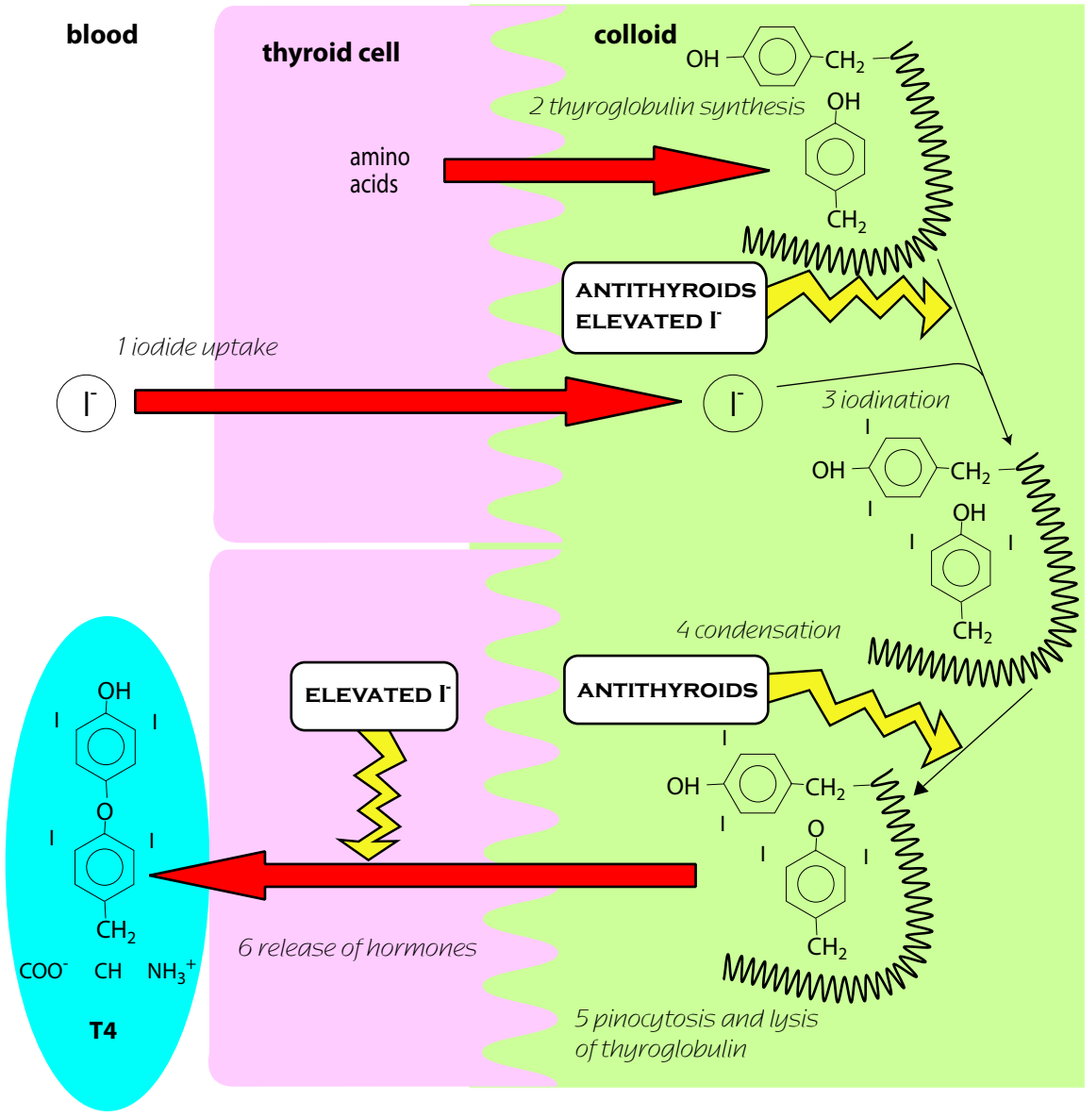
Thyroid hormones are highly protein bound in circulation. Free T4 makes up 0.1 - 0.3% of the total T4. Thyroxine-binding globulin is the major transport protein for both thyroid hormones.

T4 has a half life of approximately 10-16 hours in the dog (nb the half life in man is much longer - about 6 days - beware if reading the human literature). It is converted to T3 or reverse T3 (rT3) by deiodinase enzymes. There are two types of enzyme - type 1 found in the liver, kidney, skin and muscle (highest activity in the liver and kidney) and type 2 found in the CNS and brown adipose tissue. T3 is quickly deiodinated, then broken down in the liver and excreted in the faeces (predominantly) or urine.

Actions Of Thyroid Hormones

T4 is converted to the active T3 in cells. T3 binds to a specific receptor similar to the steroid receptor. The T3/receptor complex activates transcription of a variety of proteins (the unbound receptor will reduce transcription). These proteins result in an increase in metabolic rate and oxygen consumption, and thus temperature, mainly by an increase in gluconeogenesis and glycogenolysis. Effects on the heart are most obvious - tachycardia and possibly arrhythmias. Thyroid hormones are also necessary for growth and maturity.

DIAGRAM 6.6.1 Thyroid



Hypothyroidism

This is the most common endocrinopathy in dogs; occuring in middle aged dogs of medium to large breeds, particularly Dobermanns. It is uncommonly diagnosed in cats - most often secondary to treatment for hyperthyroidism.

Causes

primary hypothyroidism - destruction of the thyroid gland by lymphocytic thyroiditis

- idiopathic follicular atrophy
- congenital - dyshormonogenesis, Iodine deficiency, thyroid dysgenesis
- iodine deficiency/excess
- destruction of gland by tumour / infection
- secondary hypothyroidism -eg pituitary tumour

Clinical Signs Of Hypothyroidism

large range may be seen, including:

- cold and exercise intolerance
- bradycardia
- hypothermia
- depression / lethargy
- symmetrical alopecia, hyperpigmentation, lightening of the coat colour, "rat tail', but sometimes increased thickness of the coat, recurrent pyoderma
- polyneuropathy
- polymyopathy
- anaemia
- reproductive failure

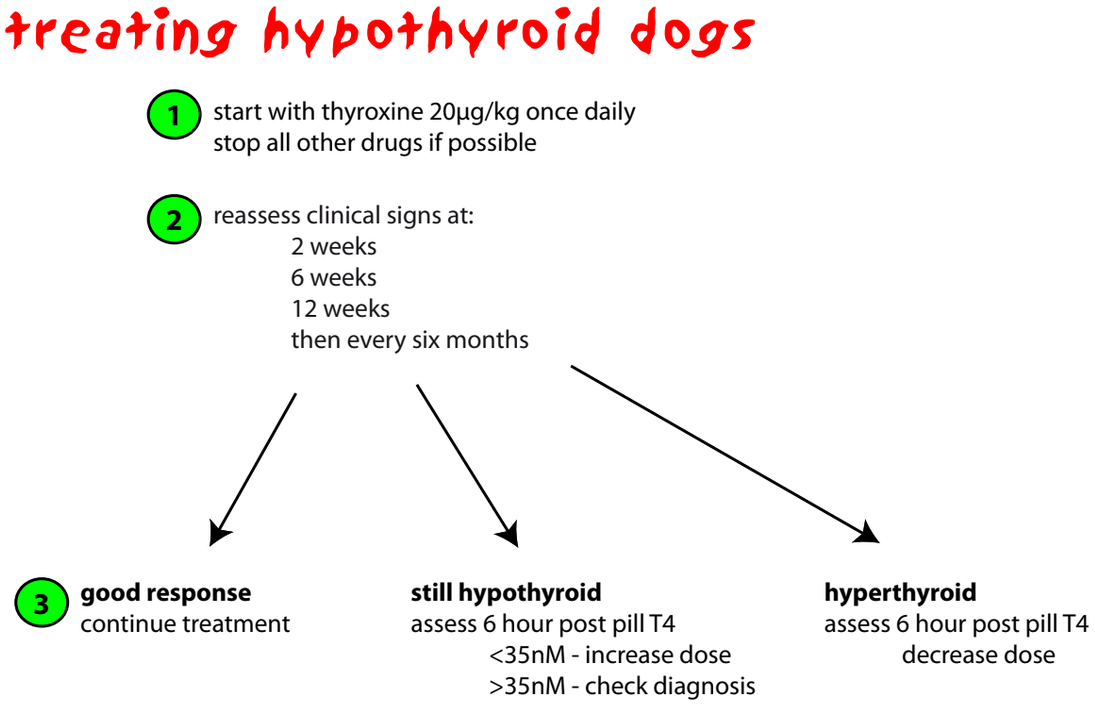
Drugs

The aim of treatment is to approximate the secretion of thyroid hormones in a normal dog. **Levothyroxine** is the treatment of choice as it mimics the normal physiological situation. It is rapidly converted to T3 and has a half life of 10-16 hours, but the biological effect lasts longer than this - it is usually given once daily. The peak plasma concentration is reached in 4-12 hours. It is cheap.

Synthetic **liothyronine** is also available. It has a short half life (5 - 6 hours) so needs to be administered every 8 hours, so is not often used. It is only given if a T4 to T3 conversion defect is diagnosed or if thyroxine is poorly absorbed, but neither of these conditions has been reported in dogs. Some tissues rely on circulating T3 for their source of intracellular T3, so when T3 is given you can get hyperthyroid signs in the heart, but the brain may be euthyroid or hypothyroid. Peak plasma levels occur 2-5 hours after administration.

Dessicated thyroid is now obselete.

DIAGRAM 6.6.2 Hypothyroid treatment



Dose

Start with a low dose, particularly if there is cardiac disease, diabetes mellitus or hypoadrenocorticism. It was usual to start with a moderate dose for three months and then decrease, but recent work shows that this is unnecessary. Hypoadrenocorticoid animals will need supplementary cortisol due to increased metabolic demands by the increased T4.

Reduce dose in liver or renal failure.

Higher doses more often are necessary in dogs than humans, as the bioavailability of T4 is low due to poor absorption and the first pass effect.

Monitoring

Resolution of clinical signs: mental state/alertness should improve in 1-3 weeks; skin and weight improve in weeks to months.

Absorption and pharmacokinetics vary between animals so therapeutic drug monitoring may be necessary. Routine post pill testing may not be necessary if clinical response is good, and there are no thyrotoxic signs.

Monitor plasma concentration if response is poor after 6-8 weeks of T4 supplementation or if thyrotoxic signs develop - tachycardia, polyuria ± polydipsia, weight loss, diarrhoea, pyrexia, pruritus, anxiety. Take a 4-8 hour post-pill serum for total T4 measurement - it should be high normal. If the T4 is high, but there are no signs of hyperthyroidism, it is not necessary to lower the dose. T3 concentrations are not helpful in monitoring T4 therapy. If the T4 appears adequate but there has been no clinical improvement consider: wrong diagnosis or antibodies to thyroid hormones.

Drug interactions

Corticosteroids, phenytoin, salicylates, frusemide and androgens enhance the elimination of T4 by decreasing protein binding. T4 increases the actions of catecholamines, ketamine will cause tachycardia and hypertension when used in patients receiving T4 and the therapeutic effect of digoxin may be reduced by T4. Phenobarbitone increase metabolism of levothyroxine and may require a higher dose to be given. Levothyroxine enhances the effects of warfarin type anticoagulants.

Avoid giving thyroid hormones with other drugs.

Hyperthyroidism

Is a common problem in middle aged to old cats and is usually a benign hyperplasia of the thyroid, although about 2-3% of cases are malignant. It rarely occurs in dogs - associated with thyroid carcinoma.

It has only become common in cats in the last 30 years and may be associated with environmental chemicals (Hill KE, Shaw IC, Does exposure to thyroxine-mimics cause feline thyroid hyperplasia? Veterinary Record, 2014 175 (9), 228-9).

Clinical Signs

- polyuria and polydipsia
- weight loss
- polyphagia
- vomiting
- alopecia/overgrooming
- heart murmur, tachycardia, gallop rhythm

Treatment Options

- surgery - thyroidectomy
- radioactive iodine
- antithyroid drugs - carbimazole
- low iodine food

Radioiodine (radioactive ^{131}I)

A single iv or sc injection (or even an oral dose) is effective in 90-95% of cases - first time failures usually respond to a second dose. No immediate adverse side effects have been reported, although occasionally cats may become hypothyroid. They may show clinical signs of lethargy, bradycardia, thick coat. Supplement T4 for life.

Disadvantages - radiation hazard and need for hospitalisation. A licence is required to posess radioactive materials. Before using, read the Code of safe practice for the treatment of cats for thyroid disorders with iodine-131, issued by: The National Radiation Laboratory, PO Box 25-099, Victoria Street, Christchurch

Recommended reading

Radioiodine treatment of hyperthyroid cats. BR Jones, J Cayzer, EA Dillon, KP Smidt (1991) NZVJ 99 71-74 .

Antithyroid drugs

Mechanism of action: block incorporation of iodine into thyroglobulin, prevent coupling of mono- and di-iodotyrosine into T4 and T3 and direct interaction with thyroglobulin molecule. They do not interfere with the ability of the thyroid to trap inorganic iodide and do not block the release of stored thyroid hormone into the circulation.

Methimazole (thiamazole INN) (only available as a transdermal formulation in NZ) and its prodrug **carbimazole** (tablets), which is rapidly converted to methimazole in the body, are most commonly used. Most side effects, vomiting, anorexia and depression, occur in the first two weeks and are mild and transient. Stopping treatment is usually not required. Other uncommon side effects may include hepatopathy, thrombocytopaenia and leukopaenia: monitor the white cell and platelet count every 2 weeks for 3 months. There is usually an improvement in about two weeks, when the dose is reduced (and ideally titrated against T4 levels). **Remember that treating the hyperthyroidism may unmask other problems such as kidney failure and myocardial hypertrophy**.

Propylthiouracil is no longer recommended due to high incidence of anorexia, vomiting, lethargy, immune mediated haemolytic anaemia and thrombocytopaenia. It has been used (illegally) to promote growth in cattle.

Low iodine food

This has shown to be effective but expensive.

Pancreas

commonly used drugs

insulin (in various forms)

Pancreas

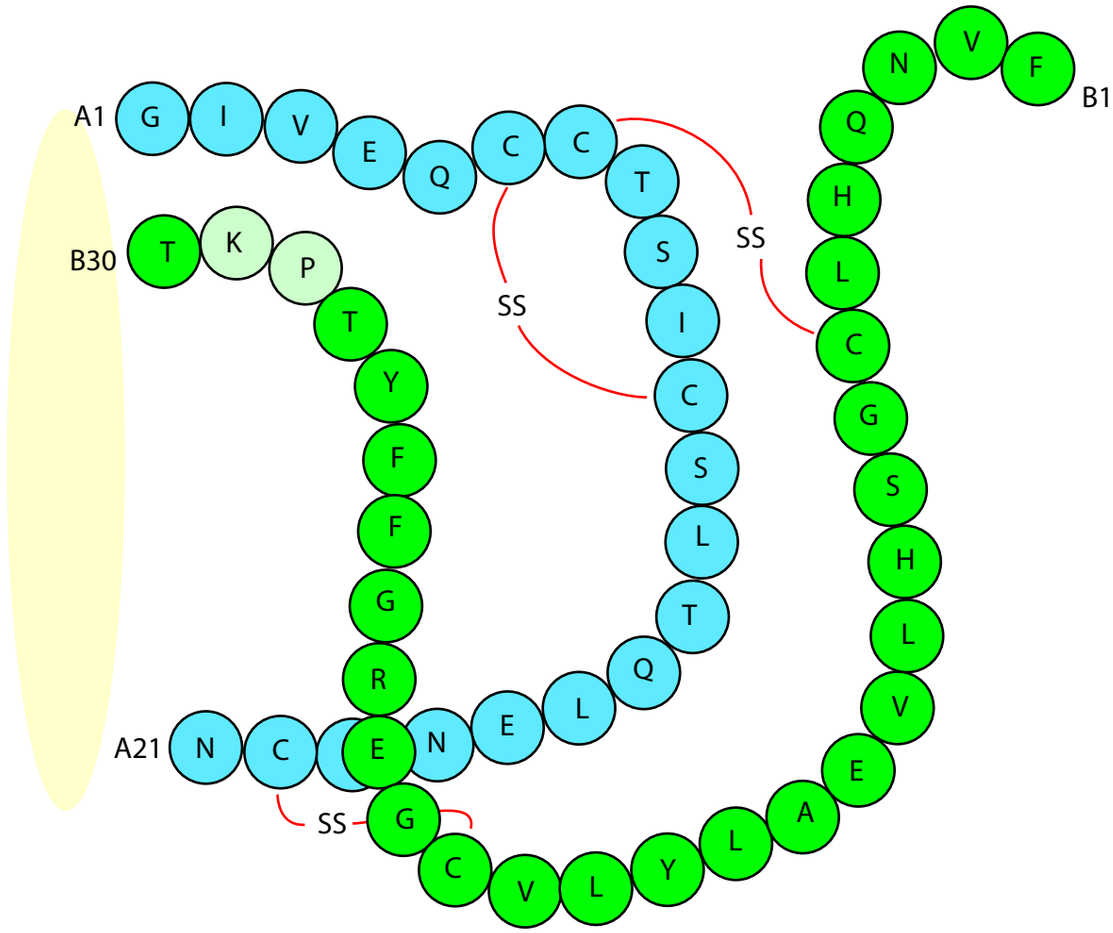
- ☑ dogs - type 1
  1. give insulin
- ☑ cats type 2 / 1
  1. give glargine insulin
  2. oral hypoglycaemics if in the early stages

Diabetes mellitus (usually just called diabetes) is common in dogs and cats (and people). Diabetes insipidus is rare.

Physiology

Insulin is a complex protein made and stored in the B cells of the islets of Langerhans in the pancreas. The amino acid sequence of the protein differs slightly between species. Insulin is produced initially in the form of preproinsulin, a single chain precursor. This is converted to proinsulin, and then insulin and is packaged in granules ready for release by exocytosis. Increased blood glucose increases insulin secretion via increased ATP in the B cells which blocks ATP-sensitive K+ channels and depolarises the cells. This causes Ca++ influx and exocytosis of insulin.

DIAGRAM 6.7.1 Insulin



Substitution of various amino acids in the B chain alters the pharmacokinetics.

Other stimuli for insulin release include gastrin, secretin, cholecystokinin and glucagon-like peptide - all released by eating. Vagal stimulation will do the same. α2 adrenoreceptor agonists (including adrenaline and noradrenaline) reduce, and antagonists increase insulin release, probably by an action at the imidazoline I3 receptor.

Insulin is degraded in the liver, kidney and muscles.

Insulin stimulates the uptake and metabolism of glucose, amino acids and fatty acids in fat and muscle. It inhibits hepatic glycogenolysis and gluconeogenesis, and the catabolism of protein and fat. It is also anabolic, especially in the foetus.

Treatment strategies

Treatment involves a combination of dietary and exercise management, and either oral hypoglycaemics or insulin.

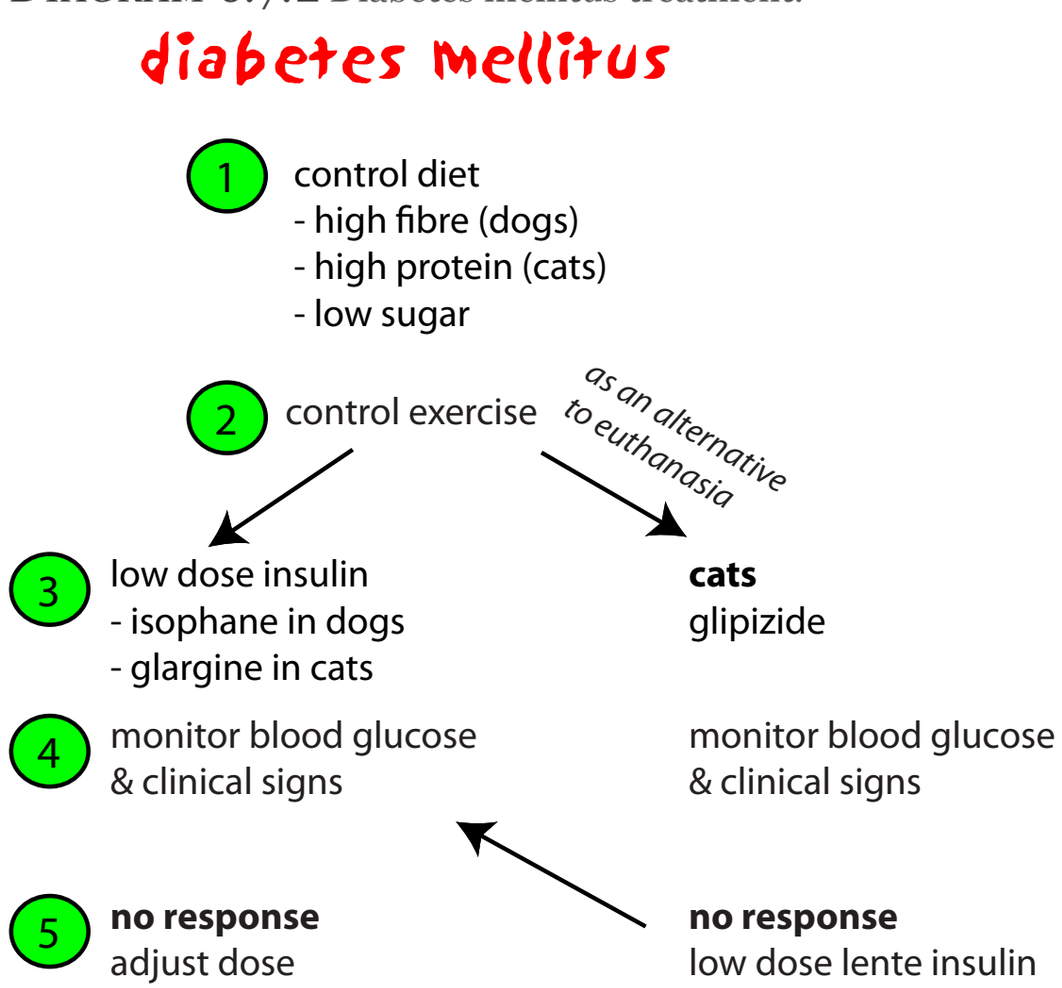
A high fibre, high complex carbohydrate diet is desirable in dogs. Avoid foods containing simple sugars, which will be rapidly absorbed from the gastrointestinal tract and elevate blood glucose. Acarbose is sometimes used in diabetic people to slow sugar absortion. Fibre slows carbohydrate absorption and dampens the post prandial rise in blood glucose.

Cats should be given a high protein diet. Slow weight loss is needed in obese cats. At least two meals a day is advisable.

Diabetic patients classically present with polydipsia, polyuria, polyphagia and weight loss. There are several different situations you will have to manage:

- the fat diabetic cat - diet & insulin, or, if owner unable to give injections, diet & oral hypoglycaemics
- the thin, sometimes ketotic, diabetic cat - diet & insulin
- diabetic dogs - diet & insulin
- insulin resistant cases - ?
- diabetic ketoacidosis - soluble insulin iv infusion
- diabetic coma - soluble insulin by iv infusion
- insulin overdose - hypoglycaemic seizures/coma - iv glucose

DIAGRAM 6.7.2 Diabetes mellitus treatment.



One approach to treatment.

Oral Hypoglycaemics

These drugs are not often effective in dogs but sometimes are in cats. The two main groups of drugs are the sulphonylureas (glipizide (best in cats), glibenclamide, gliclazide, chlorpropamide (rarely used now) and tolbutamide (most widely used in vet medicine)) and biguanides (metformin). A promising new group of drugs (glitazones) includes rosiglitazone, pioglitazone, ciglitazone and troglitazone (since withdrawn - worked in diabetes but caused liver failure), which are thought to decrease insulin resistance.

Sulphonylureas work by direct stimulation of insulin secretion by the B cells by binding to the ATP-sensitive K+ channels and blocking them. In the longer term,

they also cause increased tissue sensitivity to circulating insulin by an unknown mechanism.

Biguanides do not require functioning B cells. Their exact mechanism of action is unknown but they cause inhibition of hepatic glycogenolysis and increased peripheral glucose utilisation.

Indications

Non insulin dependent diabetes

Approximately 25% of cats will respond to these drugs, so insulin may not be required.

Side effects

•hypoglycaemia

•vomiting shortly after administration - usually subsides with time

•increased hepatic enzymes (but clinical liver disease has not been reported)

Sulphonylureas may contribute to the progression of type 2 diabetes. The response isusually slow, and in the meantime, hyperglycaemia can cause B cell death. Glipizide can also cause cats to deposit more amylin (co-released with insulin) in their pancreas, also resulting in B cell death.

In people side effects reported include cytopaenias, nausea and vomiting, cholestasis and hypersensitivity. Sulphonylureas can promote weight gain.

Insulin

Most animals with diabetes mellitus will require insulin.

Types of insulin

A confusing variety of insulin formulations are available in NZ but all except one are human recombinant insulin. The other is pig insulin marketed for dogs - nb, it is 40iu/mL as opposed to the standard human 100iu/mL.

Insulin has traditionally been conjugated with a number of adjuvants to alter its solubility and thus speed of onset and duration of action. A newer approach is to alter the protein itself to change its duration of action. Beware; the nomenclature is confusing!

insulin lispro is an insulin analogue in which a lysine and a proline residue have been swopped. It is the most rapid and shortest acting. **Insulin aspar**t is similar. These are relatively new and there is not much information on effects in animals.

soluble insulin (crystalline / neutral / regular insulin) is rapid acting, short duration and is used iv in emergencies, onset of action - minutes, maximum effect 30 mins - 2 hours, duration 1 - 4 hours (prolonged to 4 - 10 hr if given sc)

isophane insulin (NPH insulin) (complexed with protamine) is intermediate acting, only given sc - onset 30 min - 3 hr, duration 4 - 24 hr depending on preparation

insulin zinc suspension is a mixture of soluble and amorphous crystals complexed with zinc chloride. Small lumps / crystals are absorbed slowly (lente insulin), big lumps / crystals are absorbed more slowly (ultra lente insulin). These are only given sc and last about 24 hours.

Mixtures of these are also sold to get a fast onset and long duration. The insulin in these preparations is the same; the formulation is merely adjusted to alter its rate of release.

insulin glargine is another longer acting analogue (24 hours in people). It also has rearranged amino acids. It has become the drug of choice in cats.

The price of insulin is approximately $50 for 10 mls of a 100 IU/ml suspension. Insulin must be given parenterally as it is inactivated by proteolytic enzymes.

An animal's requirement for insulin will vary throughout the day, depending on feeding and exercise. Once the animal has stabilised on insulin (usually about a week) it is usual to measure blood glucose every 1 - 2 hours and plot a glucose curve for 24 hours to reasess the dose. A single blood glucose can be misleading.

Insulin resistant cases

Insulin resistance is defined as persistent hyperglycemia, glucosuria and clinical signs, despite receiving more than 2.2 iu of insulin/kg per injection. Possible causes include the Somogyi overswing, problems with insulin administration/ storage/mixing of different insulins, concurrent disease such as hyperadrenocorticism, acromegaly and urinary tract infections, the development of antibodies to insulin. The first step is to evaluate the glucose curve and assess the owner's technique (see medicine notes).

Diabetic Ketoacidosis

These animals are always dehydrated and usually have intercurrent disease. Glucose spilling over into the urine causes an osmotic diuresis and consequent sodium and potassium depletion, so these animals have hyperosmolality, hypovolaemia, metabolic acidosis and prerenal azotaemia.

Correct fluid and electrolyte deficits (0.9% NaCl with added potassium (40mmol/L)) and monitor ECG. Give soluble insulin (0.1iu/kg/h in fluids) to reduce the ketone bodies, avoiding a rapid decline in blood glucose. Check blood glucose every hour and give iv gluccose if necessary. Then correct acid base imbalance (give bicarbonate) if pH is low. Phosphate supplementations may also be necessary (potassium phosphate iv), but this can cause hypocalcaemia.

Diabetic Coma

Depression and coma result from intracellular dehydration of neurones due to increased osmolality. A vicious cycle is set up as depression leads to reduced water intake, further hypovolaemia and hyperosmolality. Treatment is as for ketoacidosis but the animal should be given lots of fluid first as insulin will result in potassium and water moving into the cells.

Treat circulatory collapse with fluids as an emergency. Replace sodium and fluid deficits with 0.45% NaCl plus potassium. Slowly correct the glucose as above - start after 6 hours fluid therapy. Once the animal has improved (blood glucose 10mM), begin stabilisation with isophane insulin.

Hypoglycaemic seizures / coma

These can occur with insulin overdose or unusually strenuous exercise. In these situations, severe hypoglycaemia may occur.

If the animal is at home get the owner to rub or pour sugar syrup onto the gums. Once the animal regains conscious a small meal should be fed and the pet should be taken to the vet clinic. 50% dextrose should be administered iv slowly to effect (2-15 mLs), preferably added to an infusion, and the animal should respond in approximately 2 minutes. If inappetance is a problem the animal should be maintained on a 5% dextrose iv drip.

The future?

A lot of work is going into ways to deliver insulin orally, but there is nothing nearing commercial release yet. Insulin sprays for inhalation or absorption across nasal or buccal membranes are in clinical trials in people. These would be difficult to use in animals. Transdermal delivery is another possibility.

An artificial pancreas is still some way off - present implantable glucose detectors are not reliable enough.

Some zinc complexes mimic the effects of insulin and are being investigated.

An islet neogenesis gene associated protein has been found which makes islet cells regrow. This has possibilities in the distant future.

Exocrine pancreatic insufficiency

This occurs mainly in German Shepherds. It is usually treated by providing a highly digestible diet (low fat and fibre) and giving pancreatin, which contains a mixture of protease, lipase and amylase enzymes. The most effective form is a powder or granules which are sprinkled on the food. It may be necessary to give a H2 blocker such as cimetidine to stop acid breakdown of the enzymes in the stomach.

Hormonal growth promoters

commonly used drugs

none

Hormonal growth promoters

- ☑ mainly used in cattle
- ☑ Banned in EU - export meat
- ☑ lots of red tape involved with use - check the latest requirements before use
- ☑ some use in sick dogs, cats and horses

There are a variety of ways of making animals grow faster using drugs; the two commonest classes of drugs used for this are hormonal growth promoters and antibiotics (fed continuously at a low level (euphemistically called "production enhancers") - see antibiotic notes).

Hormonal growth promoters, also known as anabolic steroids, are only widely used in cattle, although several preparations are sold for horses and dogs. They are all derivatives or analogues of sex hormones, usually testosterone.

The use of growth promoting agents in food producing animals is a political hot potato. They were banned in Europe in the late 1980s after (illegally used) stilboestrol was found in veal flavoured baby food in Italy. (There is still an enormous black market for them in Europe, particularly Belgium and Italy.) Europe has refused to accept any imports of meat produced using anabolic steroids since then, although there is more complete toxicity data for this class of drugs than for any others used in food animals. Recently, the USA has taken Europe to the World Trade Organisation and won its case that Europe's restrictions on imports are a barrier to trade that is not justified on scientific grounds. Europe has appealed but is likely to lose. As far as NZ is concerned, any animals treated with anabolic steroids must be clearly marked, and records kept, so that there is no chance of them getting into a consignment of beef to Europe. (For details of the red tape involved, check the NZVA website http://www.vets.org.nz/)

Advantages of anabolic steroids include increased growth rate, food conversion efficiency and carcase quality; disadvantages include potential animal welfare problems and the attention of the food scare industry.

Anabolic steroids are also occasionally used in small animals, particularly old animals recovering from surgery and those with chronic kidney failure, with or without bone marrow depression and anaemia. There are several preparations licensed for use in horses; **they should not be administered to competition horses**.

The anabolic steroids abused by human athletes are often veterinary preparations (particularly nandrolone), and vets have been struck off for supplying the human black market. Think hard before supplying these drugs to **anyone**.

Anabolic steroids are usually androgens. However, in cattle, the highest growth rates are achieved when there is a balance of androgens and oestrogens (including those produced by the animal).

In the USA, recombinant growth hormone (somatotropin, BST) is sometimes used as a growth promoter in cattle, usually in combination with anabolic steroids since their effects seem to be additive. BST also increases milk yield, which is its main use there. It is banned in NZ. Equine recombinant somatotropin has recently been approved here. It will probably be abused in racing animals but may be useful to promote tendon repair. Porcine somatotropin is also used to promote growth

Clenbuterol, and occasionally other adrenergic β2 agonists, are sometimes used illegally as "partitioning agents". They do not seem to promote growth but ensure that any growth is of muscle rather than fat.

Thyreostatics have been used as growth promoters but they make animals fat rather than promoting muscle growth. They are now illegal.

It is important to realise that animals will not grow without an adequate supply of good food. Anabolic steroids are not a substitute for good feeding.

Mechanism of action

Most of the hormonal growth promoters appear to increase nitrogen retention in muscle cells and reduce catabolism; muscle cells grow faster than fat cells. Exactly how the drugs do this is not clear.

Androgens have a direct effect on muscle cells, block corticosteroid catabolism and enhance thyroxin's effects. Nandrolone, ethylestrenol, stanozolol and methandriol are used in dogs, horses (and man); testosterone and trenbolone are used in cattle.

Oestrogens cause increased growth hormone release from the pituitary, enhance the effects of insulin (or insulin like growth factor?) and thyroxin. Recently, oestrogen receptor subtypes have been found which may shed more light on the mechanism of action. Oestrogen is only used in cattle. Oestradiol (natural oestrogen precursor) and zeranol (not strictly a steroid but binds to oestrogen receptors) are used. Zeranol is derived (via zearalenone) from a fungus (various Fusarium spp) which grows on clover, residues are frequently found in cattle in NZ, presumably from eating mouldy clover (see toxicology notes for details). Caterillars can concentrate the zearalenone to an extent that can cause serious problems if they are eaten by grazing animals: this caused an epizootic of abortions in mares in Kentucky in 2001. Stilbenes such as stilboestrol are banned as they may cause cancer when given in high doses (as may the endogenous oestrogens).

Progestagens' main effects are probably to increase appetite and reduce bulling behaviour leaving more time for eating. They may also bind to testosterone receptors and elevate oestrogen levels. Progesterone is the only progestagen used in NZ, melengestrol is used in America.

Useful effects

Most drugs will increase the rate at which cattle gain weight by 10 - 15% and the cattle are bigger at slaughter. Under some circumstances, some drugs (especially androgens) will increase food conversion efficiency. The effects on carcase quality are more controversial. While the muscles are usually bigger, they contain less fat (which may or may not be a good thing, depending on the market) and are usually tougher.

Horses and small animals are usually given anabolic steroids in an attempt to speed recovery from debilitating diseases, or in chronic renal failure. The aim is to reduce protein breakdown, which means that protein is converted to muscle and the kidney has less work to do excreting urea. Since they stimulate erythropoiesis, they are sometimes used in anaemia (see cardiovascular pharmacology notes).

Side effects

Inappropriate administration of sex hormones will interfere with breeding. Since none of the drugs promote growth in bulls, they should not be used. Bull calves given anabolic steroids are unlikely to be of any use for breeding. In heifers destined for breeding, anabolic steroids will increase their size (and possibly pelvic size) at the first oestrus, but reduce the chances of pregnancy. Oestrus cycles will be irregular. If given to pregnant heifers, everything from abortion to reduced milk yield is possible. In all animals behavioural changes will be seen, especially an increase in mounting behaviour, this often leads to injury. Other effects are rectal and vaginal prolapses, ventral oedema, teat and udder development (oestrogens).

Practical use

Cattle seem to grow best with the testosterone levels of a bull and the oestrogen levels of a young cow, however, none of the drugs have much effect on growth rates of bulls. Bulls generally grow about 10% faster than steers, this is about the same increase as anabolic steroids produce, so you may as well leave them with their testosterone producing implants.

There is only consistent evidence of a beneficial effect in steers and prepubertal calves, but nearly all the published work relates to cattle fed on grain; there is very little information on the usefulness of these drugs in a New Zealand situation. The drugs are most effective when the animals are growing quickly.

Current use in NZ

Steers

The main group in which these drugs are used: oestradiol then oestradiol + trenbolone usually gives a 5 - 30% (typically 10 -12%) increase in weight gain over controls.

Bulls

Do not use if the bulls are for breeding, zeranol may have some effect on others and may also be useful to control behaviour.

Breeding Heifers

do not use

Store Heifers

oestradiol / oestradiol + progesterone at weaning then oestradiol + testosterone
Gains are less impressive than with steers.

Most animals are implanted at a young age to take advantage of the longer growth period, then re-implanted with the same or a shorter acting product for finishing. Re-implanting with trenbolone is not recommended as carcase quality suffers.

Remember that growth promoters are not a substitute for good husbandry and feeding.

Administration

Most anabolic steroids come in the form of a silicone rubber implant (to provide a depot with very slow release). Some preparations are in the form of pellets; care is needed not to crush these which could result in a faster than expected release of drug. These implants are deposited between skin and cartilage on the outside of the middle third of the ear using specially designed applicators like large syringes. The ear is used as it will be discarded when the animal is slaughtered and there is no danger of anyone eating a depot of drug.

A good implanting technique is important. The animal must be restrained in a head bail. The ear must be pulled straight, and with the bevel of the applicator needle a nick is made in the skin cranial to the dorsal ridge of the ear. This entry point should be quite close to the tip of the ear. With a fast action, the entire length of the needle is pushed forward under the skin towards the base of the ear, making sure to stay clear of the dorsal ridge (in this area, the skin is firmly attached to the cartilage and there is an artery). It is important not to penetrate the cartilage of the ear.

When properly inserted, the implant can be clearly seen or felt just before the area of loose skin at the base of the ear. The implant is then secured in place by the thumb and the needle withdrawn. Check that only one implant is delivered. The animal must receive a specially designed ear tag at the same time. After administration, the hormone is released from the implant in a controlled manner over a certain number of days, which varies depending on the product used.

To reduce the possibility of infection, and thus the potential loss of the implant, hygienic and antiseptic procedures must be followed during implantation. The ear must be clean and dry When ears are wet or contaminated with soil, urine or faeces, the skin must be cleaned with an antiseptic soap and dried prior to implanting.

The needle of the applicator must be kept sharp and clean. To reduce possible transmission of disease or local infection, the needle must be disinfected before each implantation (between animals).

Controls On The Use Of Anabolic Steroids

Controls on the sale and use of these drugs are mandatory for access to European markets (at the moment, anyway). Basically, Brussels wants to know that we have a system to clearly separate the animals which have been implanted so that they do not get to Europe.

The use of “hormonally active substances for the purpose of promoting growth” is restricted to veterinary surgeons. They can only be administered by a vet or a trained technician under veterinary supervision after a consultation. It is illegal for vets to sell hormonal growth promoters to farmers. They are for use in cattle only. Every implanted animal must be identified with a special ear tag, as well as two other identifying ear tags (MAF do not seem to realise that cattle only have two ears). Auditable records on special forms must be kept in triplicate of all cattle implanted and of supplies of drugs kept. One copy of these forms has to be sent to MAF within 10 days after implantation. Records must be retained for at least five years. There are huge fines for failure to comply with these regulations. Before implanting any cattle, check the latest regulations at
http://www.maf.govt.nz/animalproducts

MAF routinely audit the compliance of veterinarians and their clients with the above conditions of use of HGPS. Identified "flagrant" non-compliances, abuses, or missuses will result in consideration of either a formal complaint being laid before the veterinary council or prosecution as appropriate. Veterinary delegations from the EU also make random checks on HGP product licensees, wholesalers and retail-

ers, as well as random on-farm inspections of treated cattle to see that those using HGPs have indeed complied with the requirements for the use of HGPs in cattle.

Animal Welfare

Problems can arise from:

The method of administration (implants). When done properly, implanting HGPs under the skin of the ear of cattle restrained in a head bail does not appear to cause much distress to the animal. After release, animals do not shake their head and often start grazing straight away. It is important to use the correct technique and to work quietly and quickly.

The purpose of use. Growth promoters are no substitute for inadequate feeding.

The occurrence of side effects. Behaviour problems such as excessive bulling and fighting, which are occasionally seen after implantation, must be managed properly. They may be associated with increased absorption from a damaged implant - remove the implant. Cases of rectal and vaginal prolapse or distressed ridden animals must receive veterinary attention.

Human safety

Residues in the meat

Anabolic steroid implants are designed to release very small amounts of drug slowly. For instance, “Compudose 200” contains 24mg oestradiol designed to be released over 100 - 200 days; a cow in late pregnancy produces several hundred mg oestradiol per day! The concentrations reached in meat are much lower than those of endogenous hormones. This, combined with the depot of drug being in an inedible part of the animal, mean that there is no witholding time for these drugs. There were initial concerns about persistence of the synthetic compounds zeranol and trenbolone, but these have been shown to be groundless. This assumes that the drugs have been used correctly; implantation into muscle could result in serious residues (common practice in the European black market - no detectable pellet in ear). The risk to people eating meat is further reduced as most steroids are rapidly broken down in the stomach or on first pass through the liver.

Carcinogenic potential

Oestrogen can both start and maintain tumours. However, many women in developed countries eat oestrogen containing contraceptive tablets every day without obvious problems. The EU has argued that oestrogen has not been shown to be safe in prepubertal girls, but it has not been shown to cause problems either. Many plants contain phytoestrogens, to which we are all exposed anyway. Sex hormones in laboratory animals can turn on a number of oncogenic viruses which can go on to cause various cancers. It is theoretically possible that anabolic steroids could turn on such viruses in farm animals and that these viruses could be transmitted to people. Another potential food scare? Alterations in sex hormone concentrations in people have been statistically correlated with altered incidence of a variety of tumours - in most cases the alteration in incidence after therapeutic (large) doses is small. Prostate cancer in men has been associated with increases in IGF 1.

Contamination of pasture and soil over the long-term.

Administration of exogenous substances to animals may result in their passage into the environment via faeces and urine. In theory, this could lead to accumulation of these substances or their metabolites in plants or drinking water subsequently consumed by humans. Oestrogens are excreted by the animal in faeces and urine, but are degraded by soil bacteria into biologically inactive compounds and are then lost into the ground. Contamination from implants is infinitesimally smaller than from industrial pollution with oestrogenic compounds such as polychlorinated biphenols; or endogenous phytoestrogens common in clovers and beans. Most of our rivers receive sewage high in oestrogens from the urine of women on the pill. Don’t drink water from the Manawatu!

Human abuse

There is a black market for anabolic steroids for use in human athletes. Only androgens work in people, it is usually the drugs marketed for horses such as nandrolone, stanozolol and ethylestrenol which are abused. Keep them somewhere secure.

The future?

Very heavily muscled cattle, such as Belgian Blues, have a defect in the gene responsible for making the protein myostatin. It appears that myostatin normally regulates (stops) muscle growth; if an antagonist for myostatin could be found it would be a potential winner as a growth promoter. Anabolic steroids tend to increase the size of muscle fibres, which usually makes the meat tougher, Belgian Blues have bigger muscles because they have a bigger number of muscle fibres, so the meat is more tender. Work on this is going on at Ruakura, ERMA permitting.

Further reading

MacColl D. (1994) Growth promotion for beef cattle - HGPs and rumen modifiers. Proceedings of the Sheep and Beef Cattle Society of the New Zealand Veterinary Association Veterinary Continuing Education Publication No. 159, 132-156.

Reynolds I.P. (1980) Correct use of anabolic agents in ruminants. Veterinary Record, 107, 367-369.

Growth promoters may be starting to get a better press...

BMJ 2001;322:203 (27 January)

Science commentary

Insulin-like growth factor and cognitive function

Insulin-like growth factors (IGFs) are peptides that regulate the growth, metabolism, survival, and differentiation of cells and are regulated by growth hormone. Both IGF-I and IGF-II consist of small peptides that share about 50% homology with proinsulin and are produced chiefly by the liver. IGF-I is an important cell growth regulator, but the role of IGF-II is less clear. IGF-II acts mainly via IGF-I receptors; IGF-II receptors do exist, but their role is believed simply to mop up IGF-II, rather than act as signalling receptors.

In contrast with other peptide growth factors, there is considerable evidence indicating that the IGFs play a critical role in determining overall (somatic) body growth in addition to contributing to local tissue regulation. A great deal of associative data show that IGF and IGF receptors, and growth hormone and growth hormone receptors, are located in the parts of the brain that are responsible for learning and memory (such as the hippocampus). It is feasible that early in life, IGFs and growth hormone play a role in the development of these areas of the brain, which could then explain associations between body size and subsequent measures of cognitive functions.

There has also been much speculation that relative IGF-I or growth hormone deficiency could contribute to the deterioration of cognitive functions observed in elderly people. Several studies in the United States have shown that giving growth hormone to elderly people reduces their body fat and increases lean body mass, but these same studies have produced equivocal data about memory function, and the methodology of the studies has been much criticised. Other studies have shown that giving growth hormone to adults with growth hormone deficiency does improve memory and is also associated with greater levels of circulating IGF-I, but controversy remains about what happens to cognitive function when growth hormone is given to children with growth hormone deficiency.(1)

On the basis on these observations, it has been suggested that circulating levels of IGF are related to cognitive function and that the administration of growth hormone may promote better cognitive function. But although IGFs may play a role in brain development early in life, it is much more difficult to come up with a mechanism that could explain how circulating IGF-I and cognitive function are connected in later life.

Abi Berger, science editor.

References

1. Van Dam PS, Aleman A, de Vries WR, Deijen JB, van der Veen EA, de Haan EH, et al. Growth hormone, insulin-like growth factor I and cognitive function in adults. Growth Horm IGF Res

Sex hormones

commonly used drugs

progesterone

prostaglandin F2α

Sex hormones

- ☑ manipulated to control breeding in food animals
- ☑ many drugs banned in food animals
- ☑ oestrogens are potentially carcinogenic
- ☑ beware effects on people

Human health risks

Most drugs with reproductive effects have the same actions in people. For example, prostaglandins will lyse corpora lutea, cause uterine contractions and therefore have the potential to cause abortion in pregnant women. Progestagens can cause cessation of cyclicity in women.

Some drugs have potentially life threatening effects in people. A prime example is prostaglandin F2α and analogues. Prostaglandins have a more severe effect on the respiratory tract in people than in many animals, causing bronchoconstriction and respiratory distress. People with respiratory disease (including asthma) need to be particularly careful. These drugs can be absorbed across intact skin in large enough quantities to cause major problems.

You need to know the physiology of reproduction in order to make sense of what these drugs do.

Sex steroids

Oestrogens

Oestradiol 17-β is the natural hormone; oestradiol esters such as the cypionate or benzoate are often injected. Oestradiol is rapidly metabolised when given by mouth, so ethinyloestradiol is used orally. Stilboestrol (diethylstilboestrol, DES) is no longer available in NZ.

Natural sources are ovarian follicle and corpus luteum, testes, placenta, adrenal gland.

Therapeutic uses

- behavioural receptivity
- embryotoxic effects
- anabolic effects (ruminants, but now banned in NZ)
- feedback effects on gonadotropin release
- increased resistance of the female genital tract to infection
- mammary gland development
- abortion
- maintenance of normal urethral muscle tone in small animals
- epidermal effects - sex hormone responsive dermatoses in small animals

Adverse effects

- feminization

- behavioural receptivity
- mammary gland development
- abortion
- negative feedback effects on gonadotropins (ovarian cysts, cessation of cyclicity)
- increased uterine gland activity (CEH)
- bone marrow suppression and aplastic anaemia
- carcinogenic and teratogenic

Antioestorgens such as tamoxifen and oestrogen production inhibitors such as letrozole and anastrozole are sometimes used in women but are expensive.

Progestagens

Progesterone is the natural hormone; there are numerous synthetic progestagens: altrenogest (allyltrenbolone), megestrol, proligestone, medroxyprogesterone, hydroxyprogesterone, flugestone and norgestomet

Natural sources are the ovary and corpus luteum, placenta in some species, adrenal gland.

Therapeutic uses

- feedback effects on gonadotropins (largely negative)
- inhibits expression of oestrus behaviour
- pregnancy maintenance
- mammary gland development (together with oestrogens)
- CNS calming effect
- Thermogenic (body temp drop used as a predictor of impending parturition)

Adverse effects

- increased risk of CEH and pyometra in bitch and queen, especially when coupled with increased oestrogens.
- increased appetite and weight gain
- decreased activity
- personality changes
- mammary gland enlargement, milk production and neoplasia
- increased growth hormone secretion - acromegaly, protein synthesis and growth; insulin resistance, increased blood glucose levels, pancreatic exhaustion and eventually diabetes mellitus.
- adrenocortical suppression: mainly seen in cats on progestagens with adrenal atrophy and Addison's syndrome which may occur within 1-2 weeks of beginning therapy in cats.

Androgens

Testosterone is the natural hormone. It is used in as various esters. Other androgens (usually described as anabolic steroids) include: boldenone, stanozolol, nandrolone, methandriol, ethylestrenol, etc

Natural sources are: gonads - testes primarily, ovaries (mainly as a precursor to oestrogens), placenta and adrenal gland.

Therapeutic uses

- male sexual behaviour
- negative feedback on gonadotropins
- anabolic effects - appetite stimulant, RBC production, nitrogen retention etc
- epidermal effects - sex hormone responsive dermatoses in small animals
- urinary bladder urethral muscle maintenance in male castrates
- Adverse effects
- Masculinization and aggressive behaviour
- negative feedback on gonadotopins (cessation of cyclicity and of spermatogenesis)

Chronic use of high doses and different drugsin people has been associated with severe effects on general health including cardiovacular disease, mental disorders, neolpasia etc.

Delmadinone is a progestogen which is used as an antiandrogen.

Gonadotrophins

Follicle Stimulating Hormone

Natural source is the anterior pituitary gland.

Currently made by extracting hormone from anterior pituitary glands mostly from sheep or pigs (oFSH = ovine, pFSH = porcine). All products are contaminated to some extent with other hormones such as LH. Newer techniques have resulted in greater purity. LH contamination is generally considered to be undesirable since it makes the response of the ovary more unpredictable. Synthetic FSH products are being developed. Biological half life is about 6 hours and therefore twice daily injections required to achieve results.

Therapeutic uses

stimulation of follicle growth and development for oestrus induction and superovulation.

Adverse effects

excessive stimulation of follicle production resulting in ovarian cysts, endometrial hyperplasia, hyper-oestrogenism.

Luteinizing Hormone

Natural source is the anterior pituitary gland. LH products are also made from pituitary extracts and are generally available only for research purposes. Other products are used commercially for their LH like actions (hCG and GnRH).

Therapeutic uses

Induction of ovulation

Equine Chorionic Gonadotropin (eCG)

Formerly known as Pregnant Mare Serum Gonadotropin (PMSG) and still marketed under this name in some regions. The natural source is endometrial cups in pregnant mares between days 40-120 of pregnancy. Produced commercially by extracting eCG from serum of pregnant mares or ponies.

Therapeutic uses

In the mare, eCG has a primarily LH like action. It binds to LH receptors and results in resurgence of the primary CL of pregnancy and formation of secondary CLs. It has no application in equine reproduction because such massive doses appear to be required to have any effect at all in mares. In other species, eCH binds to both LH and FSH receptors and has a long half life and therefore has become useful in stimulating the development of follicles and ovulation. It is widely used in domestic species other than the mare (sheep, cow, pig) to stimulate development of multiple follicles (superovulation) and to induce oestrus and ovulation in non-cycling animals (pigs).

Long half life (72 hours) and therefore used as a single injection.

Adverse effects

eCG has a long duration of action and therefore even a single dose can result in excessive stimulation of ovarian follicular development, resulting in cystic follicles, poor superovulatory response, hyperoestrogenism. Recently researchers have developed an anti-eCG antibody and have administered it 2 days after eCG to stop the adverse effects associated with its prolonged activity. This appears to make the product more effective as a superovulatory drug for domestic species.

Human Chorionic Gonadotropin (hCG)

Comes from human early blastocyst and placenta - appears in early pregnancy. Commercial product made from the urine of pregnant women.

Actions

LH like effect primarily and involved in women in CL support and pregnancy maintenance. In other species it is used for its LH effect primarily, for example ovulation induction, challenge testing, treatment of cryptorchidism.

hCG is a relatively large molecule and is capable of inducing an antigenic response in animals since it represents foreign protein.

Gonadotropin Releasing Hormone (GnRH)

Comes from the hypothalamus. GnRH is a very small molecule (decapeptide) which is easily synthesized and numerous synthetic formulations are available. There is no risk of antibody stimulation and therefore very safe to use. It appears to be replacing hCG in most applications for these reasons.

Actions

- Stimulation of LH and FSH release and therefore stimulation of ovarian and testicular activity.

induction of cyclicity and ovulation (cystic ovaries in cows, ovulation in all species)

- increased spermatogenesis ?

- increased libido?
- challenge or diagnostic testing.

Injectable products have been available for years. Recently a biodegradable implant was released for use in horses to cause ovulation.

Prostaglandins

ProstaglandinF2α (dinoprost - not to be confused with dinoprostone = PGE2) is produced by all tissues. Numerous synthetic analogues, such as cloprostenol, luprostiol (= prostianol) and etiproston are used as well as the natural compound.

Therapeutic uses

- corpus luteum regression - oestrus synchronization, abortion, induced parturition
- smooth muscle contraction - uterus
- cervical relaxation

Adverse effects

- corpus luteum regression as above (abortion)
- Smooth muscle contraction - vasoconstriction, bronchoconstriction, salivation, sweating, vomiting, diarrhoea, abdominal pain, micturition, pruritis, erythema, ataxia, increased vocalization, tail movement, tachycardia, fever, anxiety, pupillary dilation or constriction.

Signs in horses are mainly sweating and abdominal pain.

Side effects in animals generally appear within minutes of administration of drug and last for 15-30 minutes. Animals become accustomed to the drugs with repeated usage and side effects tend to diminish in intensity and range.

People: women of child bearing age, pregnant women, people with asthma or other respiratory complaints must use extreme caution when handling PGF2α. Prostaglandin analogues are readily absorbed through the skin (wear gloves) or as a vapour via the respiratory tract (be careful not to spray it around).

Case examples

Progesterone assays for timing of breeding in the bitch

Average bitch has pro-oestrus lasting 7-9 days and oestrus lasting 7-9 days and ovulates on about the 3rd or 4th day of standing oestrus. A traditional recommendation from breeders is to breed an oestral bitch on the 13th day after the beginning of pro-oestrus.

However, there is tremendous variation in both the length of pro-oestrus and oestrus and the timing of ovulation in bitches of normal fertility. Behaviour and vaginal cytology are not very accurate at determining when a bitch will ovulate. The bitch appears to be unique amongst domestic animals in that peripheral blood progesterone concentration rises prior to ovulation. It can therefore be measured and used as a predictor of impending ovulation. In all other species of domestic animals, progesterone does not rise until after ovulation.

In addition, the bitch ovulates a primary oocyte which takes about 2 days after ovulation to mature and become ready for fertilization (different to other species as well).

Event	Progesterone conc
pro-oestrus & early oestrus	very low (<3nmol/l)
time of LH surge	6-9nM (2-3 ng/ml)
day of ovulation	12-25nM (4-8ng/ml)
optimal time of breeding	28-80nM (9-25ng/ml)

The optimal time to breed a normal bitch is about 2 days after ovulation.

A suggested protocol is take a blood sample at about the 3rd to 4th day of pro-oestrus and measure progesterone concentration. If very low, take a second sample 2-4 days later. Continue sampling until an increase is seen. Then:

If you have identified a change from <3 to 6-9 nmol/l, consider breeding the bitch 1-2 days later and again 1-2 days after the first breeding. Consider measuring progesterone at the time of the second breeding to document the rise, confirm ovulation and determine whether further testing is necessary.

May wish to continue taking daily samples until you reach about 25 nmol/l and then breed the bitch. This approach is more commonly followed if using frozen semen.

Diagnosis of ovarian remnant syndrome in the bitch

ORS describes the bitch who has a history of being speyed and who now is showing signs consistent with oestrus. Signs include vulval swelling, serosanguineous vulval discharge, attraction to males, mammary gland development. Signs are suggestive of oestrogenism.

Primary differentials for oestrogenism are oestrogen secreting neoplasia, adrenal gland activity and a remaining remnant of ovarian tissue. Other differentials should be included for vulval discharge: urinary tract disease, vaginitis, uterine stump infection etc).

Diagnostic workup: complete physical, vaginal cytology, urinalysis, vaginoscopy, abdominal ultrasound/radiography.

Challenge testing: take a pretreatment blood sample for oestradiol and progesterone concentration. Admininster hCG (100-500 iu by im or iv injection) or GnRH (25-100 ug). 2-3 weeks later, repeat physical examination and blood testing. Look for changes consistent with ovulation and formation of luteal tissue. If changes are consistent with the presence of ovarian tissue, schedule surgery. If not continue diagnostics eg adrenal gland suppression testing.

Diagnosis of cryptorchidism in horses

Animals with a history of castration but which are now showing signs of male behaviour. A cryptorchid testicle can be retained within the abdomen or just outside the abdomen in the inguinal region. A detailed physical examination including palpation/ultrasound of the inguinal and scrotal regions and transrectal palpation/ultrasound should be performed.

Challenge testing should be considered for equivocal cases. Take a baseline blood sample and then administer hCG (2500 to 5000 iu iv). Take follow up blood samples. There is considerable debate about the best time to take follow up samples. Some labs suggest a second sample 2 hours after the injection. I prefer to wait longer and take follow up samples at 6-12 hours and occasionally at 24 hours. Look for a 2-fold increase in testosterone concentration. If this does occur it is highly likely there is testicular tissue present.

it is also possible to measure oestrone sulphate concentration in blood. In animals older than 3 years of age, oestrone sulphate concentration in a single sample (no challenge) is often sufficient to diagnose a cryptorchid (levels are low in geldings and very high in cryptorchids and stallions).

Challenge testing for cryptorchidism may also be performed in dogs and other species.

Medical treatment for pyometra in the bitch

Case selection: younger than 6 years of age, with a primary breeding function.

Stabilise systemic signs of illness associated with the disease eg fluid therapy

Once stable begin prostaglandin F2α treatment: older recommendations used high doses: 250µg/kg sc twice daily, more recently, lower doses are suggested, down to as low as 20µg/kg sc three times daily

It is best to begin at a reasonably low dose(100-150µg/kg sc twice daily) and work up to a dose of 250µg/kg sc twice daily.

Beware: side effects do occur, success rate is not 100%, pyometra tends to recur and treatment is expensive.

Duration of treatment is variable and depends on response. Older recommendations suggested 5-8 days of prostaglandin therapy. Newer approaches suggest that the bitch be monitored by ultrasound and treatment continued until at least 1 day after the uterus is observed to be free of luminal fluid on ultrasound (can take 10-14 days).

Breed on the next heat period. Consider treating the bitch with systemic antibiotic during oestrus and spey the animal as soon as her breeding function is finished (as soon as the desired number of pups are achieved).

Misalliance in the bitch

There are two drug choices: antiprogesterones and oestrogens. Aglepristone (antiprogesterone) has taken over from oestrogens as it is safer and more effective. In early pregnancy, it prevents changes in the uterus required for implantationof the egg, while in later pregnancy it antagonises the effects of progesterone necessary for maintenance of pregnancy. This causes expulsion of the foeti.

Oestradiol benzoate injection is registered for mismating. However, oestrogens have potentially serious side effects in the bitch:

i) bone marrow suppression: life threatening aplastic anaemia. Very difficult to treat successfully. Fortunately this is a rare side effect unless large doses or very long acting analogues are used.

ii) cystic endometrial hyperplasia (CEH): CEH appears to be a common side effect of oestrogen therapy and is often followed by pyometra. Oestrogens potentiate the effect of progesterone on the uterus and together the two hormones increase the risk of CEH. The presence of CEH, progesterone dominance (luteal phase of the cycle) and contaminating bacteria is highly likely to result in pyometra.

The risk of pyometra appears to be highest when oestrogens are administered to a bitch in early dioestrus (high progesterone).

No dose of oestrogen has been shown to be both effective and safe.

Suggested protocol when presented with a bitch with a history of misalliance:

Physical examination: is the bitch in oestrus?

Vaginal cytology: is she in oestrus, can you see sperm?

Options:

1) do nothing and let the bitch whelp if she is in fact pregnant

2) ovariohysterectomy

3) do nothing initially and pregnancy test the animal at about 25-30 days and consider aborting the bitch using PGF2α injections ± dopamine agonists at this stage (preferred option). Mifepristone would be better but is not available in NZ.

4) aglepristone

5) oestrogen as a last resort. Counsel the owner that treatment will make the bitch receptive to males for a further period of time (7-10 days), it is not 100% successful and may have serious side effects.

Treatment regimes

Aglepristone 10mg/kg sc as two injections 24 hours apart up to day 45 of pregnancy. Massage injection site to prevent pain and inflammation.

Oestrogen 0.3 mg/kg up to maximum of 10 mg, as a single im or sc injection, given 1-4 days after mating. Should only be administered if the bitch is still in oestrus as determined by vaginal cytology.

10µg/kg on days 3, 5 and 7 after mating. Does use a lower dose and is reported to be less likely to prolong behavioural receptivity or lead to bone marrow suppression but is more likely to result in elevated oestrogen concentrations in early dioestrus.

Inhibition and prevention of signs of oestrus in the bitch

In NZ, progestagens are the primary drug used for controlling the oestrous cycle of the bitch. An alternative drug which appears to be safer (mibolerone - an androgen) is available overseas.

suppression: means treatment initiated in early pro-oestrus to inhibit signs of behavioural receptivity. Generally requires higher levels of progestagen and is also associated with higher risk of side effects since it means using higher levels of progestagen on top of elevated levels of oestrogen.

postponement: means beginning treatment in late anoestrus to postpone the next pro-oestrus. This is considered to be safer, since it avoids any association with elevated oestrogen and usually allows the use of lower doses of progestagen.

General cautions for progestagens in bitches:

Use with caution in animals with a primary breeding future

Read the manufacturer's recommendations, particularly contra-indications

Advise the owner of possible side effects.

Abide by the manufacturer's recommendations for treatment protocols.

In decreasing order of safety, the progestagens available in NZ for oestrous control are: proligestone, megestrol, medroxyprogesterone (MPA)

Medroxyprogesterone acetate was withdrawn from the small animal market for oestrous control in the USA by a voluntary deal from the manufacturer in 1966 due to the high incidence of uterine abnormalities in treated bitches. In an Australian study (AVJ 70:249-250, 1993) 45% of treated bitches were found to have uterine lesions at subsequent spay compared to 0.05% of control bitches. As a result it is suggested that you avoid using MPA for oestrous control in bitches where ever possible since safer alternatives are available.

Greyhounds are a special case. Progestagens are associated with side effects which are undesirable for performance animals: weight gain, lethargy, reduced athletic

ability. Most greyhound owners and trainers prefer to have racing bitches on some form of oestrus suppression but they usually use anabolic steroids .

Oestrus synchronization in heifers using progestagens

Usually combined with other drugs such as oestrogens, PGF2alpha and PMSG (eCG).

There are currently two main products available in NZ for delivering progestagens to cattle. One is the CIDR-B (vaginal implant impregnated with progesterone) and the other is an ear implant impregnated with a synthetic analogue (Crestar implants which contain norgestomet).

There are many different treatment programmes with the variations mostly in how long the devices are left in place (ie, duration of progestagen therapy) and when to administer other drugs. Continued advances are being made each year in the design of these programmes. Therefore it is best to contact prodct manufacturers for the latest regime when you are in practice. Recommendations will vary depending on the type of cattle you are treating eg heifers versus cows, beef cattle versus dairy.

i) Early recommendations were to treat with progestagen only for a length of time equal to the normal CL lifespan (15-17 days). This ensured adequate time for any endogenous CLs to have regressed during treatment. Synchronization of oestrus was quite good but fertility was poor and it was subsequently found that longer durations of progestagen therapy reduced fertility.

ii) Next step was to shorten the duration of progestagen treatment and add PGF2α treatments to lyse any CLs which were present. Regimes came down to about 7-10 days of progestagen with PGF added close to the end of the progestagen treatment. Oestrogens were also administered at the beginning of treatment and helped to lyse CLs as well as having a synergistic effect with progesterone inhibiting gonadotropin release and follicle development during treatment, which helps to produce better synchrony when treatment ends.

iii) The latest development has been the addition of a low dose of oestradiol given 1-2 days after cessation of progestagen treatment. This helps to stimulate overt displays of oestrus behaviour for oestrus detection and also helps to trigger the LH surge to induce ovulation.

Examples of two standard programmes for heifers:

Ensure all animals are in fact cycling prior to treatment.

- Insert ear implant norgestromet (Crestar)
- Inject with oestrogen at the time of insertion
- Inject with PGF2α on day 7-8
- Remove ear implant on day 9-10
- Inject with PMSG at time of implant removal .
- Breed heifers based on oestrus detection or by timed breeding (48 hours after implant removal).

or

- Insert CIDR-B and CIDIROL capsule (capsule contains oestrogen and fits into a slot in the CIDR-B) into the vagina.
- Remove CIDR-B on day 7.
- Inject with PGF2α at time of CIDR removal.
- Inject with oestradiol benzoate (1 mg) 24-48 hours after implant removal.
- Breed based on oestrus detection.

Oestrus synchronization in heifers using prostaglandin F2α

The bovine corpus luteum is not susceptible to exogenous PGF until five days or more after ovulation. You should ensure all animals are cycling prior to beginning the programme. Generally do this by tail painting animals and watching for activity.

Again there are several different programmes:

1. Treat all animals with a single injection of PGF. Inseminate based on oestrus detection. Animals which respond will come into oestrus about 2-3 days later.

2. Palpate heifers and only administer PGF to those heifers which have a palpable CL on rectal palpation. Inseminate based on oestrus detection.

3. For the first 6 days of the programme, perform daily oestrus detection and breed animals based on oestrus detection. Then on day 6, inject all animals which have not been bred with PGF and continue oestrus detection and breeding.

4. Administer 2 injections of PGF separated by 11 days. At the time of the second injection, almost all animals should be responsive to PGF. May inseminate on oestrus detection or by timed insemination (heifers bred about 60-70 hours after second injection).

Reproductive toxicities

Isocupressic acid (ICA)

Sources

Cypress *Cupressus* spp - Macrocarpa (*Cupressus macrocarpa*) and other related trees

Pine *Pinus radiata* (and other related trees such as *Pinus ponderosa*) – anecdotal reports of abortions after ingesting radiata pine needles. The amount of ICA in radiata is so variable that it is conceivable that some trees may contain enough to cause abortions.

Toxic principle

Isocupressic acid was identified in Ponderosa pine in 1994. Macrocarpa was shown to contain ICA in 1995.

Cupressus species and *Pinus ponderosa* contain quite variable quantities of isocupressic acid and abietane diterpene acids.

IMAGE 6.1 *Cupressus macrocarpa* leaves

The mechanism of action is unknown.

Clinical Signs

Malaise and abortion in cattle during last trimester. Retained foetal membranes.

Severe depression/illness may lead to death.

Treatment

No specific treatment, use of antihistamines reported to be beneficial if given early.

Prevention

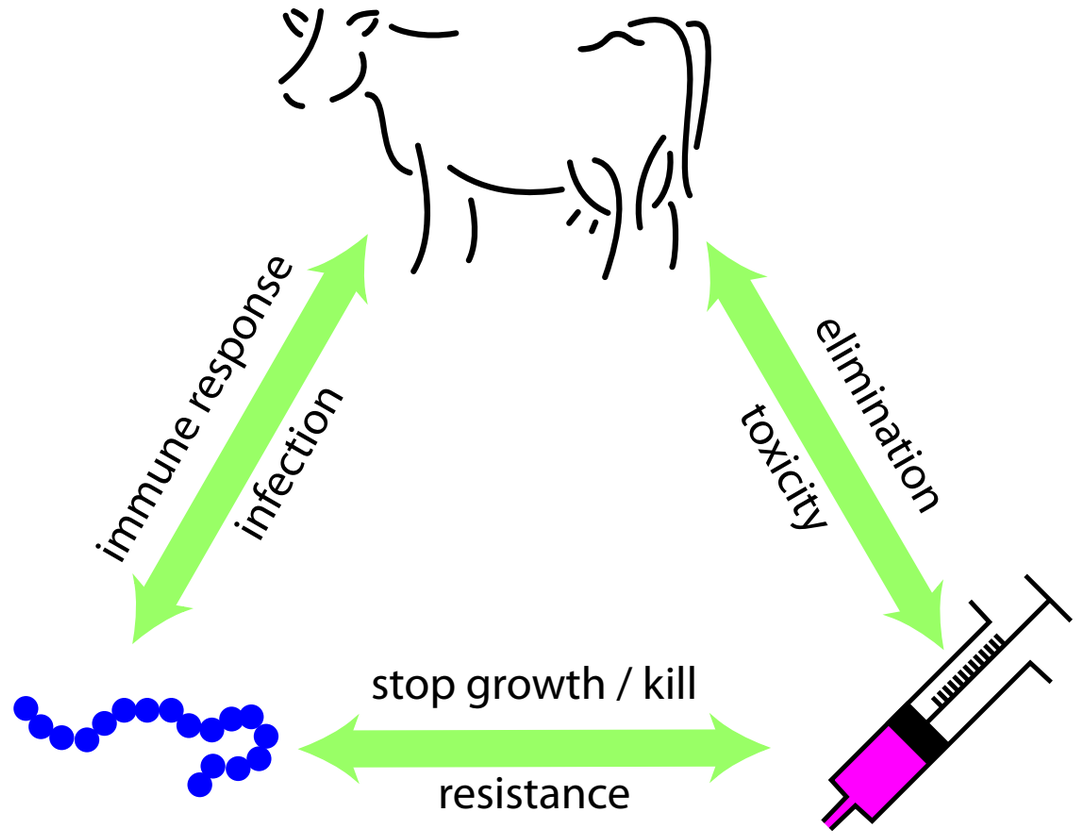
Clear up fallen trees or move cattle. Do not throw clippings into paddocks.

Cases

A farmer has a herd of pregnant dairy heifers. While on a call to the farm you recognise a stand of macrocarpa next to the pasture where the heifers are grazing. What are the potential problem(s) of this situation?

Chapter 7

Antibiotics



This part covers antibacterial, antifungal and antiviral drugs, with some hints on how to use them properly.

Antibiotics - introduction

Antibiotics - introduction

- ☑ Antibiotics can be classified by: spectrum of activity, bactericidal or bacteriostatic, mechanism of action, chemical family or toxicity
- ☑ Mechanism of action is most useful from a clinical point of view

The term antibiotic is used in this chapter to cover all antibacterial drugs or antimicrobial drugs given systemically or topically except antiseptics.

Classification Of Antibiotics

There is an enormous range of antibacterial drugs available. In order to make sensible decisions about their use, it is helpful to divide them up into groups of similar drugs. Antimicrobial drugs can be classified in different ways, each of which is useful clinically for different reasons:

- spectrum of activity
- bactericidal or bacteriostatic
- mechanism of action
- chemical family
- toxicity

Spectrum of activity

Many antibiotics act at bacterial cell walls or cell membranes. This means that the spectrum of activity often corresponds with Gram staining. This approach to classification is not always applicable, however, since there are organisms which are not easily classified by their Gram staining characteristics.

The antimicrobial drug may have a broad spectrum of activity (i.e. is active against a wide range of different bacteria) or narrow spectrum (i.e. is active against only a few bacteria or one or two families of bacteria). Usually, drugs are classified as broad spectrum if they are active against both Gram positive and Grain negative bacteria.

examples:

broad spectrum - tetracyclines, some cephalosporins, potentiated sulphonamides, fluoroquinolones, some semi-synthetic penicillins e.g. amoxycillin, ampicillin

narrow spectrum, Gram positive - macrolides, lincosamides, older penicillins e.g. benzylpenicillin,

narrow spectrum, Gram negative - aminoglycosides

You must know an antibiotic's spectrum of action in order to treat animals rationally. This is rote learning you just have to do. Bear in mind that as resistance develops, the spectrum will change!

Bactericidal or Bacteriostatic

Bactericidal drugs kill bacteria; bacteriostatic drugs stop them growing and rely on the animal's immune system to get rid of them. However, in reality, the differentiation is not very useful since all you can realistically expect is to influence the competition between the animal and the bacteria in favour of the animal.

Bactericidal drugs can be defined as those for which the reasonably achievable tissue concentration ("break point") is greater than the minimum bactericidal concentration (MBC) for the great majority of susceptible pathogens. They can be (but are not always) bacteriostatic at lower concentrations or against other pathogens.

Bacteriostatic drugs are those for which the minimum inhibitory concentration (MIC) is less than the break point. Nominally, these drugs merely inhibit bacterial cell growth or replication. At very high doses they may be bactericidal. The rational use of bacteriostatic drugs requires the animal to have a competent immune system.

Mechanism of antibacterial action

The main usefulness of knowing the mechanism of action of an antibiotic is that is helps to predict the spectrum of activity and the likelihood of inducing toxicity with many of the drugs. It is of major importance if combinations of drugs are to be used.

Inhibition of cell wall synthesis

To be effective, these drugs require the bacteria to be actively dividing since the cell walls don't do much the rest of the time. Therefore, combination with protein synthesis inhibiting drugs tends to antagonise the action of the cell wall synthesis inhibitors.

Because mammalian cells do not synthesise cell walls, these drugs tend to be non-toxic. Bacitracin is an exception to this, and is extremely nephrotoxic. It is only used topically or orally - it is not absorbed from the gut.

Some examples include: penicillins, cephalosporins, vancomycin, bacitracin

Disruption of cell membranes

Since these drugs lead to the rupture of the bacterial cell, they tend to be rapidly bactericidal. They are not dependent on bacterial replication or growth, and can therefore be combined with other drugs to broaden a spectrum of antimicrobial therapy.

Because mammalian cells have a cell membrane which is similar to that of the bacteria, these drugs tend to have either a narrow therapeutic safety margin, or are too toxic to use other than topically.

eg: polymixin B, colistin, novobiocin, nystatin, amphotericin B

Most antiseptics / disinfectants / detergents also disrupt cell membranes.

Inhibition of protein synthesis

These drugs are selective for bacteria because bacterial ribosomes (where the proteins are made) are different from mammalian ribosomes. Most of these drugs are bacteriostatic.

eg: aminoglycosides, tetracyclines, macrolides, lincomycin, chloramphenicol

Inhibition of DNA synthesis / function

For these drugs their toxicity tends not to be related to their mechanism of action, and varies with each individual drug. Drugs which interfere with mammalian DNA are potentially carcinogenic.

eg: sulphonamides ± trimethoprim, fluoroquinolones, nitrofurans, nitroimidazoles, griseofulvin

Interference with fatty acids

Many antifungals work this way, so does triclosan (not commonly used in veterinary medicine).

Chemical structure

Drugs of the same chemical family usually (but not always) have the same mechanism of action, so there are only subtle differences between this classification and that of mechanism of action. Classifying drugs by chemical family is most useful to the drug manufacturer and medicinal chemists. This method is marginally useful to clinicians, since bacterial resistance to an antimicrobial drug is often shared with other drugs of the same chemical family.

Toxicity

Nephrotoxicity is common to many antibacterial drugs. Those which cause damage to the renal tubular epithelial cells include aminoglycosides, polymixins, tetracyclines and some of the older cephalosporins. Damage to the collecting ducts and

more distal tubular structures can be caused by sulphonamide crystalluria. Sick animals drink less, which makes the problem worse.

Liver damage can be caused by tetracyclines, erythromycin and possibly potentiated sulphonamides.

Aminoglycosides, polymixins and tetracyclines can result in neuromuscular blockade, especially when anaesthetics are present. Of more clinical significance, however, is the ototoxicity of aminoglycosides, which can cause both deafness and/or vestibulocochlear injury. CNS excitement can be associated with the use of procaine salts of penicillins. This is due primarily to the procaine.

Gut problems are commonly caused in the horse and guinea pig by ampicillin, lincomycin and clindamycin upsetting the normal balance of gut flora. This manifests as pseudomembranous colitis or diarrhoea which is potentially fatal.

Bone marrow toxicity is a feature of chloramphenicol, sulphonamide and trimethoprim toxicity. In dogs this results in an anaemia or panleucopaenia which is reversible by withdrawal of therapy.

Drug interactions are a feature of giving antibiotics. Drugs which inhibit hepatic mixed function oxidase enzymes can significantly reduce the elimination of chloramphenicol and tetracyclines, resulting in toxicity. Some diuretics, especially frusemide, significantly increase the chances of inducing nephrotoxicity with aminoglycosides or some obsolete cephalosporins.

Acute hypersensitivity reactions are possible with many antibiotics. Penicillins can cause anaphylaxis, and the horse seems to be a species particularly prone to hypersensitivities, although most reactions to procaine penicillin are probably to the procaine. Care should always be taken with intravenous injections of antibiotics - monitor the animal for potential hypersensitivity reactions.

And finally...

In these notes, the antibiotics have been grouped by their mechanism of action: ie, the bacterial processes with which they interfere.

The use of particular drugs for any given disease in animals is largely empirical rather than being based on good evidence of efficacy and safety. “Commonly used” drugs will change their status according to the latest fashion! The most appropriate drug for the animal under your care may not be the commonly used drug in the UK or USA!

Resistance

Reducing resistance

- ☑ Wash your hands / gumboots!
- ☑ Isolate the patient.
- ☑ Use antiseptics / disinfectants where possible.
- ☑ Choose a drug on resistance testing, where practicable.
- ☑ Use narrow spectrum antimicrobials whenever possible.
- ☑ Use the full effective dose for as short a period as possible.
- ☑ Use antibacterials not prone to producing resistance.
- ☑ Restrict the prophylactic use of antimicrobials to high risk patients only.
- ☑ In chronic care patients, regularly (but not frequently) change antimicrobial drugs.
- ☑ With aminoglycosides, use the longest effective dosage interval.

Antibiotic resistance is a natural phenomenon. Most antibiotics are derivatives of things produced by slimy organisms for chemical warfare against other slimy life forms. This is not a great evolutionary strategy unless the organism producing the antibiotic has some means of avoiding being killed by it. Similarly, if the target organism has been exposed to the antibiotic since the year dot, it must have developed some resistance mechanisms to have survived.

useless factoid

This means that every time an antibiotic is given by a vet or a medic, there is pressure on the exposed bacterial population to select for resistance. There may be very few resistant bacteria present, but if most of the sensitive ones are killed, the resistant ones can grow to fill the space. Resistance is important, both from the point of view of treating the animal (and contact animals), and from passing resistance on to human pathogens, in either the animal's owner or the general public. Bacterial resistance in people is increasing, probably as a result of poor prescribing practices by GPs, but about half the antibiotics used in NZ are given to animals, so **responsible use of antibiotics by vets is essential**.

Antibiotic resistance is a relative term. It is a situation where a bacterium is not inhibited or killed by concentrations of antibiotic that would normally be lethal to that bacterium. By common usage, resistance relates to antibiotic concentrations achievable in the animal or person being treated for infection. (The breakpoints used to define resistance are derived from consensus of opinion, rather than science.) Sometimes the dose can just be increased, but most drugs are too toxic for this.

Bacteria can be resistant because:

- **the drug does not reach its target**, eg
  - reduced permeability of the cell membrane - reduced porins in Enterobacteria
  - active efflux of macrolides, tetracyclines and streptogramins
- **the drug is inactivated**
  - ß-lactamase enzymes which inactivate penicillins and cephalosporins
  - chloramphenicol acetyltransferase acetylates and inactivates the drug
  - modification of aminoglycosides such as streptomycin and gentamicin
- **the target is changed or protected**

- changes to the ribosome which prevent the binding of macrolides such as tylosin and erythromycin
- changes to the penicillin binding protein which stops methicillin killing some Staph aureus
- changes to the bacterial DNA gyrase, preventing the binding of quinolones

Depending on the specificity of the target or efflux mechanism, resistance may be to a single drug or a whole class, or classes of drug.

Antibiotic resistance in bacteria may be intrinsic or acquired. Intrinsic resistance occurs when a bacterium normally does not possess the particular target structure of the antibiotic, or does not possess the sort of cell wall which allows the drug in. Examples include the resistance of Gram negative organisms to penicillin. Acquired resistance occurs when a bacterial strain that is normally susceptible becomes resistant. A single bacterial strain will often be resistant to several different antibiotics via different mechanisms of resistance. These may be acquired either in single or multiple steps.

Bacteria can acquire resistance by mutation of their own DNA or, more importantly, by acquiring some DNA from another bacterium.

More - Blair et al, Molecular mechanisms of antibiotic resistance. *Nature Reviews of Microbiology* (2014) doi:10.1038/nrmicro3380

Chromosomal mutation

Mutation occurs all the time, and most mutations are of no use or detrimental to the bacterium. This type of resistance tends to develop slowly in small steps, but there are exceptions. The importance varies with different antibiotics - most important for streptomycin, erythromycin and rifampicin. This type of resistance is probably favoured by intermittent use of low doses of antibiotic.

Transferable drug resistance

Bacteria share DNA readily, both within and across species, including non-pathogenic species. This may occur by several different processes:

Conjugation is probably most important. A donor bacterium conjugates with a recipient and passes across DNA, including plasmids, which may contain resistance genes. This may occur between species, mainly in Gram - bacteria and enterococci. The plasmids may carry genes for resistance to a single or many antibiotics. The composition of plasmids is continually being changed by the insertion of transposons, many of which carry antibiotic resistance genes.

DNA can also be transferred by transduction, where a bacteriophage takes DNA from one bacterium and puts it into another. This seems particularly important in Staph aureus where plasmids carrying resistance genes for penicillins, erythromycin, tetracyclines or chloramphenicol can be transferred. It is also important in Streps for the transfer of genes for toxins.

The simplest method, transformation, is where bacteria pick up free DNA lying around. The importance of this is unknown, but it is certainly possible in the gut. It probably only occurs with Gram positive bacteria. Sources of free DNA could include dead bacteria, either gut inhabitants or the bacteria used to produce growth promoters, which are present in the crude extracts used for this purpose. (These bacteria must, by definition, be resistant to the antibiotic they produce.) Less importantly (?), many transgenic crops used for animal feed overseas (soya beans and maize) contain antibiotic (usually ampicillin) resistance marker genes.

For an animation of these processes, look at this video produced by the FDA.

Resistance is usually only measured in pathogens, but commensals can act as a reservoir of resistance genes. The importance of this is unknown but is likely to be large. Giving antibiotics selects for resistance among commensals too! This has been highlighted by the development of multi-resistant ubiquitous bacteria such as enterococci, which, although not normally regarded as pathogenic, can kill severely immunocompromised patients in intensive care units in hospitals.

Bacteria carrying resistance genes are ubiquitous on and in animals, including people, and in the environment. Use of antibiotics will select for these, so the benefits of use must be balanced against the chances of clinically significant resistance developing.

Reducing resistance

There are three main principles:

- **prevent disease** - good husbandry, vaccination, biosecurity etc
- **reduce antibiotic use** - only use where definitely indicated, treat underlying condition, etc
- **use antibiotics appropriately** - use the right drugs, right dose, right duration

Control of resistance depends on responsible use (see later), but is mainly a matter of common sense and only using antibiotics where absolutely necessary. Relying

TABLE 7.2.1 Antibiotic classification systems

WHO		EU		Aus	
critically important	nearly everything!	**category 3** These substances may only be used by way of exception and only in companion animals (including horses that are not intended for food consumption).	carbapenems some cephalosporins glycopeptides glycylcyclines lipopeptides monobactams oxazolidines some penicillins antimycobacterials	**high** These are essential antibiotics for treatment of human infections where there are few or no alternatives for many infections. Also have been called “critical”, “last-resort” or “last-line” antibiotics.	3&4G cephalosporins carbapenems monobactams glycylcyclines glycopeptides amikacin oxazolidines streptogramins fluoroquinolones antimycobacterials rifamycins polymixins nitrofurans lipopeptides
highly important	some penicillins 1&2G cephalosporins lincosamides amphenicols streptogramins tetracyclines	**category 2** These reserved antimicrobials should be used only when there are no alternative antimicrobials authorized for the respective target species and indication.	3&4G cephalosporins fluoroquinolones aminoglycosides co-amoxiclav	**medium** There are other alternatives available but less than for those classified as Low.	cloxacillin co-amoxiclav 1&2G cephalosporins gentamicin potentiated sulphonamides lincosamides nitroimidazoles
important	aminocyclitols bacitracin nitrofurans nitroimidazoles	**category 1** Antimicrobials used in veterinary medicine where the risk for public health is currently estimated low or limited.	macrolides, narrow spectrum penicillins polymixins rifamycins tetracyclines	**low** There are a reasonable number of alternative agents in different classes are available to treat most infections even if antibiotic resistance develops.	narrow spectrum penicillins amoxycillin tetracyclines streptomycin sulphonamides macrolides bacitracin amphenicols

on new drugs coming along is not an option - bacteria move much faster than the drug companies or regulators. Most human hospitals have a policy of reserving some antibiotics (eg, fluoroquinolones, glycopeptides and modern cephalosporins) for life threatening diseases, to prevent the development of resistance to them. This should happen in veterinary practice too.

Some drugs are of more concern than others, and various regulators have put out lists of drugs which should only be used in exceptional circumstances. Unfortunately, these lists do not always (or even usually) agree, although of the drugs commonly used in animals, cephalosporins and fluoroquinolones are most commonly featured.

Problem bacteria in people

There are several areas of concern about resistance in human medicine, many of which are relevant to us (remember One Health and all that). Increasingly, plasmids, or other transmissible bits of DNA encoding resistance, are at least as important as species of bacteria since movement of DNA between species seems to be common.

The WHO has recently listed the bacteria they are most worried about:

critical priority:

- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
- *Acinetobacter baumannii*, carbapenem-resistant

high priority:

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- several species of *Campylobacter*, fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

medium priority:

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- several species of *Shigella*, fluoroquinolone-resistant

Food poisoning caused by resistant Gram negative bacteria (*E coli* O157, *Salmonella* Typhimurium, especially DT104, and *Campylobacter* spp.) are probably zoonoses in many cases and are common overseas. In the UK, 4.7% of cattle and 1.7% of sheep carry *E. coli* O157 (no figures for NZ, but almost certainly not as high as the UK). Antibiotic resistant *Campylobacter* are common in NZ, most of the others are probably rare imports. Extended spectrum ß-lactamase (ESBL) producing coliforms (ie, resistant to cephalosporins) are causing concern here. These are often *Klebsiella* spp. These emerged in Hawke's Bay but S. Auckland is now the place to catch them. Some of these, particularly in the USA, are resistant to just about everything. Carbapenemase producing coliforms (mainly from India) took off here in 2015.

Gram positive pathogens, particularly methicillin resistant *Staph aureus* (MRSA) and vancomycin resistant enterococci (VRE), can be virtually untreatable. It is possible that resistant enterococci from animals pass on resistance genes to human enterococci which pass them on to MRSA. This has been shown *in vitro*, but not (yet) *in vivo*. Vancomycin intermediate *Staph aureus* (VISA) is becoming a problem in Japan and Europe. It is very bad news. Low level MRSA is fairly common in Pacific Islanders, but high level MRSA (epidemic MRSA type 15 (EMRSA-15), imported from the UK) is also important in NZ, comprising 7% of *Staph. aureus* isolates in 2001 (up from 4% in 2000) (cf UK - almost 50% in 2001). (the incidence of new EMRSA infections has since leveled off.) This particularly nasty bug has been traced back to a patient with eczema in Guildford (near London) in 1960. It has since spread around the world, mutating as it goes and acquiring extra resistance genes. There are no figures for NZ, but MRSA kills 5,000 people a year in the UK, and is involved in the deaths of 15,000 more. MRSA has been isolated from dogs, cattle and horses in NZ.

Drugs used for *Staph aureus* in people:

- **flucloxacillin** - related to methicillin and so no use against MRSA
- **rifampicin** - resistance develops quickly and this drug is usually reserved for TB
- **vancomycin** - main MRSA drug
- **linezolid** - second line MRSA drug
- **quinupristin & dalfopristin combination** (Synercid) - drug of last resort for named patients in hospitals

Vancomycin intermediate *Staph aureus* (VISA) has been around in Japan and the USA for several years, and in July 2002 the first fully vancomycin resistant *Staph*

aureus was reported from the USA. Luckily for the patient, it was not resistant to chloramphenicol.

VRE was isolated from five people in NZ in 2001; one patient and four carriers. The patient died. By 2014, 1% of enterococci tested were vancomycin resistant. It has also been isolated from chickens in Otago (it has not been looked for anywhere else in the country). Only two strains are involved in both people and poultry.

Multiple drug resistant *Shigella dysenteriae* is a big problem in developing countries, but does not receive much attention elsewhere. Resistance probably arises from inappropriate human treatment, but can spread indirectly from animals.

Acinetobacter used to be a commensal found in hot, dry countries, although it may originally have come from northern Europe. It has recently become established in hospitals in temperate climates. The current theory is that it was brought in in contaminated wounds in soldiers serving in Iraq and Afghanistan, but it has not been studied much in animals.

Drug resistance in pneumococci and *Mycobacterium tuberculosis* is also a problem, but no way has been found for blaming this on the veterinary profession yet. Multiple drug resistant (MDR) TB is an increasing problem worldwide, and usually arrives in NZ in visitors from eastern Europe. The next stage up, extensively drug resistant (XDR) TB has not reached NZ yet, but it is probably only a matter of time. This is resistant to just about everything. Its emergence has been attributed to using second line drugs to treat uncomplicated TB - some of the drugs used for TB in people can also be used for other things in animals: they should be avoided or used with extreme care. They may include:

rifampicin - sometimes used in animals

clarithromycin / azithromycin - sometimes used in animals

ethambutol, isoniazid and pyrazinamide - not used in animals

streptomycin (only used as a last resort) - commonly misused in animals

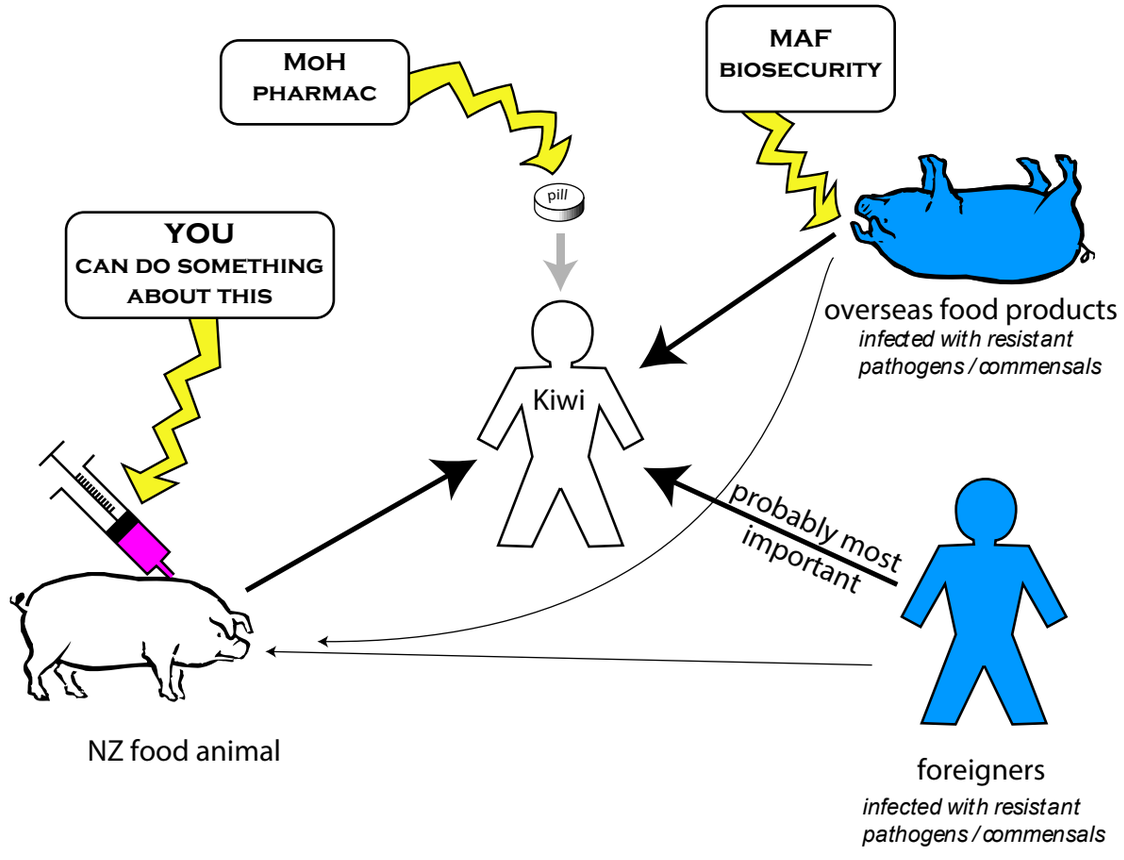
New generation fluoroquinolones and linezolid have been used and may become more popular.

Multidrug resistant TB is still rare in NZ (1.2% TB cases 2014), but is killing huge numbers of people overseas. The WHO calculates that 30% of the world population carries TB, so this is likely to become a more important issue in the future.

Problem Bacteria In Animals

Pseudomonas aeruginosa is generally regarded as an environmental organism which is an opportunistic pathogen of animals and people. It has a much larger genome than other bacteria, which means that it has lots of redundant systems it can use if one is knocked out by an antibiotic (eg, it has 12 drug efflux pump systems). In practical terms, resistance will develop rapidly, often over the course of treatment. Non-antibiotic treatments are best where possible - for instance, it does not like acid conditions and dilute vinegar can often stop it growing in dogs' ears. Transfer of antibiotic resistant *Pseudomonas* from animals to people has not yet been shown, but is a real possibility.

DIAGRAM 7.2.1 Sources of resistance genes in NZ



The killer bug and how it has developed

(Daily Telegraph 27/08/2001)

1944
Penicillin, the first antibiotic, is introduced, and proves devastatingly effective against *Staphylococcus aureus*.

1945
Doctors notice that some *Staphylococcus aureus* infections are not being killed off by penicillin. *mecA* gene for methicillin probably emerges (before methicillin!).

1945-55
New antibiotics, derivatives of penicillin, are introduced.

1955
A strain of *Staphylococcus aureus* (MSSA) has become immune to penicillin, streptomycin, tetracycline and erythromycin.

1955-60
An epidemic gathers pace of *Staphylococcus aureus* infections which resist antibiotic treatment.

1960
Methicillin invented in England by the Beecham company and is effective against the resistant strain of *Staphylococcus aureus*. The epidemic declines.

1961
The first *Staphylococcus aureus* bacterium with immunity to methicillin (MRSA) emerges in Guildford, Surrey. It is a direct descendant of the 1955 strain, but has now acquired an extra piece of DNA - the mecA gene - which makes it methicillin-resistant. A new outbreak of MRSA infections begins in the UK, and spreads to Scandinavia and the Mediterranean. In 1975 the epidemic starts to die back.

1980
A new epidemic of MRSA starts, and spreads to the US. After several years it dies back.

1986
A strain of MRSA is DNA fingerprinted in Barcelona and named "The Iberian Clone". It is another direct descendant of the 1960 strain.

1990
A third epidemic of MRSA starts, and spreads to the Far East. MRSA is now a worldwide threat.

1995-2000
Doctors report the first cases of MRSA which are also resistant to vancomycin. These, too, are descendants of the 1960 strain.

Pseudomonas (and some other bacteria) can sense when there are others around, and when a quorum forms, they cooperate to produce a slimy biofilm which is resistant to most chemicals. This can be very bad news, and cannot be prevented at present.

Food For Thought?

Although transfer of resistance from animals to people is usually blamed on the use of growth promoters in food animals, no one has looked very closely at companion animals yet. There are an increasing number of reports about transfer of resistant bacteria between companion animals and the people who handle them: this probably occurs commonly. Several recent studies have shown that a large proportion of pets and their owners have the same strains of bacteria in their gut. Development of resistant bacteria after treatment is relatively common in dogs and cats, and most owners do not practise any sort of infection control. Beware!

Situation In NZ

Antibiotic resistance in bacteria important in animals is not recorded in any systematic way, although this may change as a national surveillance system has been repeatedly promised since 1997. It is again on the ACVM Group's 2016 action plan. Anecdotal evidence suggests that we do not have the large scale problems seen overseas (14,000 people/year die in the USA from multiple drug resistant infections). Let's keep NZ free of them.

The law is in the process of changing to make it more difficult for vets to use valuable antibiotics indiscriminately (see law notes).

Antivirals And Antifungals

Resistance to these can occur as well, and is starting to emerge as a problem in people. Amantadine fed to chickens in China to prevent bird 'flu' has resulted in widespread resistance.

Further Reading

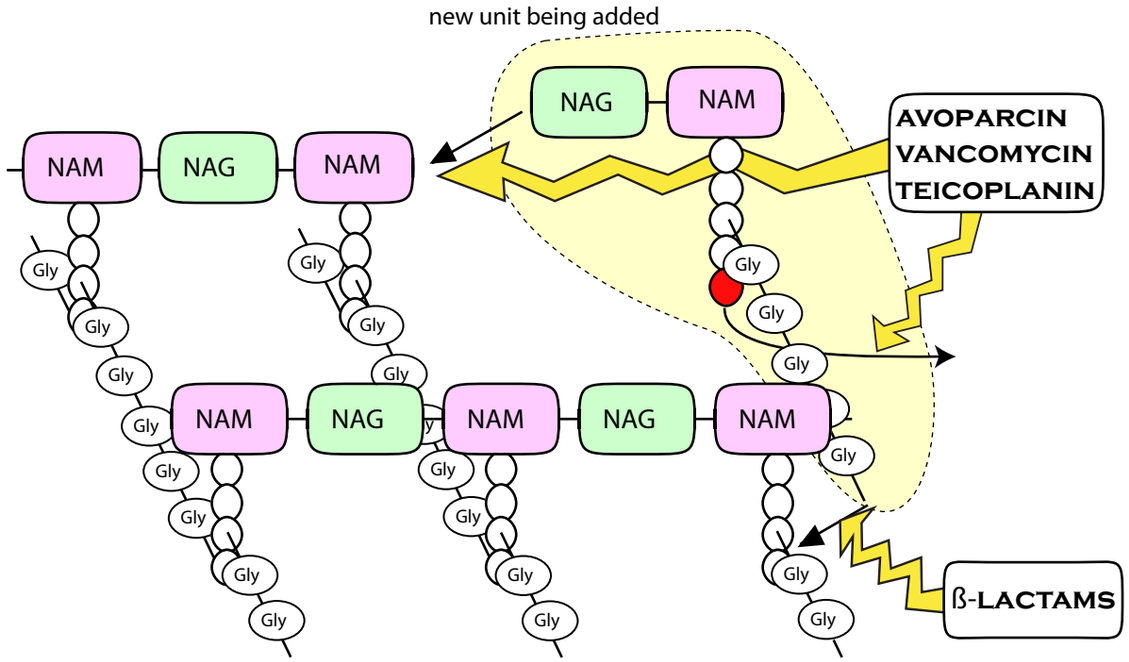
ACVIM Consensus Statement on Therapeutic Antimicrobial Use in Animals and Antimicrobial Resistance - Well worth reading!

Drugs inhibiting cell wall synthesis

Cell wall synthesis

- ☑ penicillins
- ☑ cephalosporins
- ☑ other beta lactams
- ☑ other cell wall inhibitors

DIAGRAM 7.3.1 Cell wall inhibitors



Bacterial cell wall synthesis. NAM and NAG - saccharide chains with peptide dangly bits. These are connected by cross links of five glycines.

Penicillins

commonly used drugs

benzylpenicillin (penicillin G)

amoxycillin

co-amoxyclav

cloxacillin (intramammary)

Penicillins

- ☑ very widely used in animals and people
- ☑ benzylpenicillin is narrow spectrum (G+) but resistance is common in Staphs
- ☑ the procaine salt is very widely used in large animals
- ☑ amoxycillin is braod spectrum, co-amoxyclav also kills many resistant Staphs
- ☑ limited concerns about resistance

Penicillins were the first antibiotics in clinical use (1942) and are still going strong. Benzylpenicillin (penicillin G) and its orally active analogue phenoxymethyl penicillin (penicillin V) are still used, although a wide range of semi synthetic penicillins are also on the market, eg, ampicillin, amoxycillin, cloxacillin, etc, etc.

Mechanism of action

Inhibition of bacterial cell wall synthesis. The final step in peptidoglycan synthesis in the bacterial cell wall is the transpeptidation step (see diagram). This reaction is catalysed by bacterial cell wall enzymes which differ from bacteria to bacteria and are collectively called the penicillin binding proteins. Penicillins bind covalently to these.

Failure to complete the synthesis of peptidoglycan results in weak points and holes in the cell wall of the replicating bacteria. Osmotic pressure forces the cell membrane through the holes and it ruptures.

Spectrum of activity

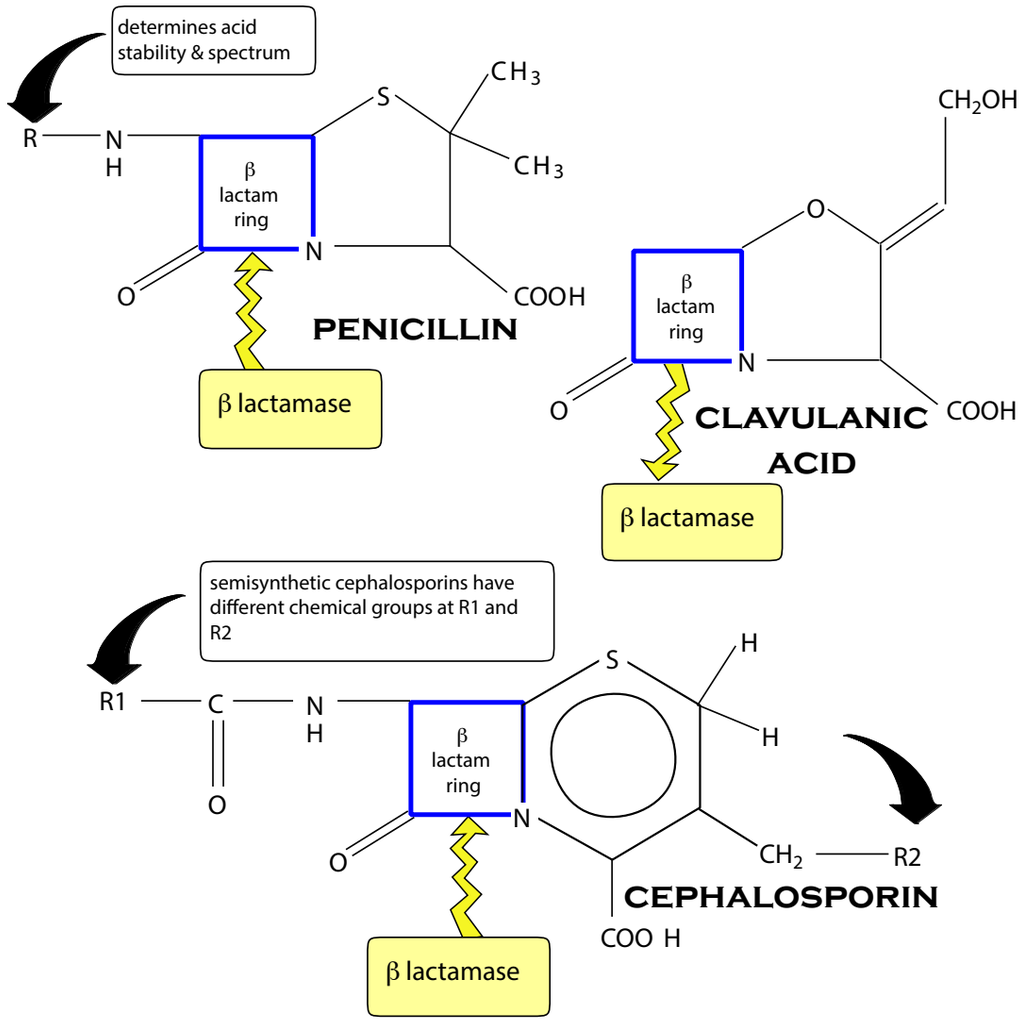
Naturally occurring penicillins (e.g. benzylpenicillin) are primarily active against Gram positive bacteria. Gram negatives are protected by their outer cell membrane.

Semi synthetic penicillins fall into several groups. Some are acid resistant and are therefore active when given orally, e.g. phenoxymethyl penicillin (penicillin V) and many of the broader spectrum semi-synthetic drugs. Some penicillins also kill Gram negative bacteria, e.g. ampicillin, hetacillin (an ampicillin pro-drug), amoxycillin, cyclacillin, pivampicillin, carbenicillin, ticarcillin, piperacillin, mezlocillin, azlocillin. Some are ß-lactamase (penicillinase) resistant, and therefore have more activity against ß-lactamase producing bacteria, e.g. oxacillin, cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin. Some are useful against *Pseudomonas* spp, eg, ticarcillin and pipercillin.

Resistance

Many bacteria produce ß-lactamase, which breaks open the ß-lactam ring and inactivates the penicillin. Gram positive organisms (especially *Staph aureus*) secrete their ß-lactamase into the intercellular fluid, where it can diffuse away. The gene for ß-lactamase is usually on a plasmid. Most Gram negative bacteria are inherently resistant because of low permeability, lack of penicillin binding protein, and a wide variety of chromosomally derived ß-lactamases in the periplasmic space. Plasmid derived ß-lactamases are also common in Gram negative bacteria. Different ß-

DIAGRAM 7.4.1 Penicillin

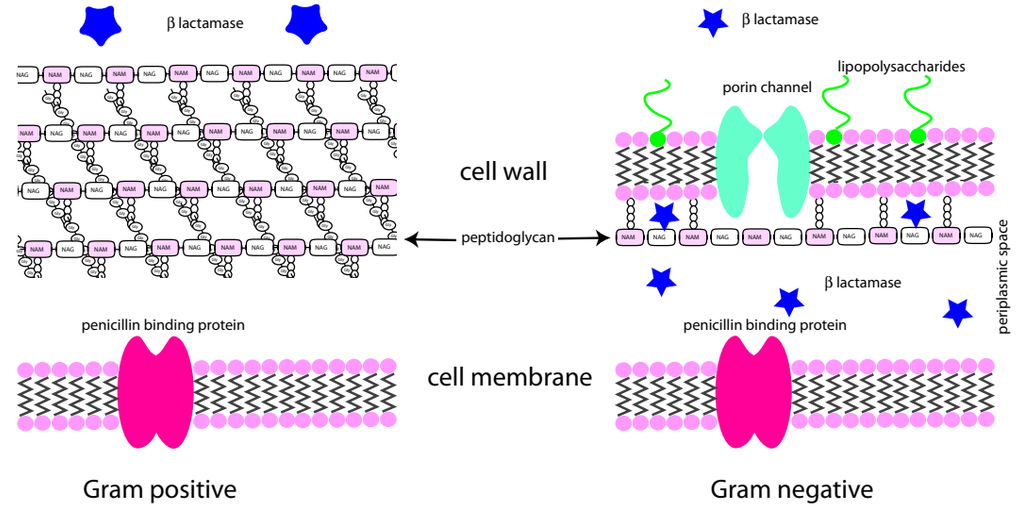


The structure of penicillins. Many bacteria are resistant because they produce β lactamase. The six sided ring on cephalosporins protects the β lactam ring to a large extent. Clavulanic acid binds to and inactivates the β lactamase

lactamases (and there are lots of them) are effective against different ß-lactam drugs.

One way around this problem is to use drugs with broad spectrum ß-lactamase inhibiting effects (but no antibiotic effects) such as clavulanic acid, sulbactam and tazobactam in combination with penicillins. Because of the location of the ß-lactamases, the antagonism of Gram negative ß-lactamase is not as reliable as it is for Gram positive ß-lactamase producing bacteria.

DIAGRAM 7.4.2 Bacterial cell walls



Different structures of G+ and G- bacterial cell walls. β-lactamases are trapped in the periplasmic space in G- bacteria where they reach a higher concentration than the equivalent enzymes secreted by G+ bacteria.

Another way around the problem is to make the antibiotic resistant to ß-lactamases. This resistance is not absolute (and getting less so) - there are hundreds of different sorts of ß-lactamase. The ß-lactamase resistant penicillins tend to remain susceptible to ß-lactamases of some Gram negative bacteria, and most *Bacteroides* spp. Extended spectrum ß-lactamases producing bacteria have been isolated in people and animals in NZ - these destroy most ß-lactam drugs.

The functional and molecular classification of ß-lactamases is complex (and there are several different systems), and not of any immediate use clinically. For more on ß-lactamases, see: http://bmj.bmjjournals.com/cgi/content/full/327/7425/1209

Streps sometimes develop resistance to penicillins by changing their penicillin binding proteins. This has been shown with *Strep pneumoniae* in man, and may be the cause of increased resistance in *Strep uberis* in cows.

MRSA have a gene, *mec-A*, which codes for a different penicillin binding protein, PBP2A. This can take over if the normal PBP is knocked out by ß-lactams, so MRSA are resistant to most ß-lactams.

Toxicity

Allergic reactions are the most common form of toxicity, particularly in horses (and people). Guinea pigs and hamsters are also sensitive to penicillins either through allergies or alterations to intestinal flora: do not use penicillins in these species.

When given intrathecally to patients with meningitis, penicillins have caused convulsions, possibly due to the procaine salts used. Procaine is also incriminated as the cause of CNS excitation and collapse in horses given procaine penicillin. This may be the result of inadvertent intravenous administration of these intramuscular preparations, but is more likely an immune mediated problem. Some brands or batches have high concentrations of free procaine, which may be absorbed rapidly from intramuscular sites.

Pharmacokinetics

Most penicillins are weak organic acids with a pKa of about 2.7. Therefore they are ionised at blood pH and are confined to the extracellular fluid. They do not cross lipid membranes well and therefore penetrate some body compartments poorly, eg eye, cerebrospinal fluid, prostate. However, in inflammation the lipid barriers are often disrupted and penicillins can be clinically useful. Esters such as penethamate, which act as produgs, are used because they cross membranes much more easily.

Penicillins are hydrolysed by strong acids and deactivated in the stomach. Some semi-synthetic penicillins have bulky side chains which sterically protect against this effect and are therefore useful when given enterally eg phenoxymethyl penicillin, ampicillin and amoxycillin.

Most penicillins are substrates for the organic anion transporters of the renal proximal tubule epithelial cells and of the choroid brush border membrane. This means that they are actively secreted into the urine and actively removed from the cerebrospinal fluid. Renal secretion is the most important mechanism for elimination from the body for most of the penicillins. Some semi synthetic penicillins are metabolised, and others (eg amoxycillin) are also concentrated in the bile sufficiently to achieve therapeutic concentration in the bile ducts and small intestine.

Other weak acids, such as aspirin and probenecid, compete for the organic anion transporters, and therefore co-administration with penicillins results in a decrease in the clearance, or an increase in the half-life of the penicillins. This has been exploited clinically in people (particularly for the more expensive new drugs) but is not well characterised for domestic animals.

Pharmaceutical considerations

Most penicillins are rapidly absorbed when given as soluble salts, so there are lots of relatively insoluble salts used to form a depot. The duration of action of intramuscular preparations of benzylpenicillin can be altered by using salts of varying solubility:

- Na or K salts = very water soluble = 2 to 6 hours
- aqueous procaine salt = suspension = 24 hours (commonest)
- procaine salt in oil = suspension = 48 hours
- benzathine salt = suspension = several days

The more slowly absorbed salts result in lower peak plasma levels, and if inadequately dosed will result in subtherapeutic plasma or tissue concentrations. There is now evidence that benethamine and benzathine salts of penicillin when used

IMAGE 7.1 Procaine penicillin

Procaine penicillin comes as a suspension of small lumps - do not give iv!

alone never result in plasma concentrations of penicillin which are likely to be effective.

Sodium and potassium salts of penicillin can be given intravenously, but **care should be taken not to give a toxic dose of potassium**. Rapid boluses will transiently depress cardiac output, presumably because of the low pH.

Penicillins will precipitate when mixed *in vitro* (i.e. in a bottle or syringe) with basic drugs, such as aminoglycosides. This can cause confusion because *in vivo* penicillins and aminoglycosides can be synergistic under some conditions. They should be administered separately unless they come as a mixture.

Drugs

Benzylpenicillin (penicillin G) is effective against most Gram positive bacteria except those producing ß-lactamase (mainly Staphs). Parenteral only: sodium and potassium salts are usually given iv, others im or sc. Frequently misused as a prophylactic antibiotic in surgery. Frequently used in combination with aminoglycosides in septicaemia, and other severe infections. Quite potent against anaerobes in addition to susceptible Gram positive bacteria. Cheap. 1 international unit (IU) = 0.6 µg Na benzylpenicillin. Phenoxymethyl penicillin (penicillin V) is very similar but can be given orally. It is underused in veterinary practice.

Cloxacillin is active against Gram positive bacteria only, including many ß-lactamase producers. Frequently used as an intramammary preparation for treatment and prevention of *Staph. aureus* mastitis in dairy cattle. Also formulated as a ointment for ophthalmic use. Flucloxacillin is very similar (but has better bioavailability after oral administration) and is used in people for Staph infections.

Ampicillin is broad spectrum and widely used orally or parenterally. Trihydrate salts for im or sc injection tend to clog needles finer than 20SWG, and tend to sting. Low toxicity. Absorption after oral administration is markedly impeded by food.

Amoxycillin (amoxicillin INN) is very similar to ampicillin. Broad spectrum. Superior in that food tends not to effect its oral absorption as much. Trihydrate salt does not clog syringes but does sting (a little) when administered sc (and presumably im).

Co-amoxyclav (amoxycillin and clavulanic acid) (Clavulox, Clavamox, Augmentin, Synulox, etc) is a combination frequently over-used in small animal medicine. It is broad spectrum and ß-lactamase resistant. Should be reserved for cases with known ß-lactamase producing bacterial infections, or for empirical therapy where these bacteria are very likely, eg skin.

Carbenicillin (obsolescent and not available in NZ), ticarcillin (± clavulanic acid) and piperacillin (± tazobactam) should be reserved for treating *Pseudomonas* and *Proteus* infections. They are parenteral only and have a very rapid clearance (short half life). Since *Pseudomonas* infections are usually iatrogenic, there should be no reason to use these in normal practice.

Use

Benzylpenicillin is the drug of choice for most Gram positive infections and is widely used in all species, except small mammals (guinea pigs and rabbits) in which it can cause a fatal enterocolitis. Where there is likely to be a mixed infection, ampicillin or amoxycillin (± clavulanic acid) are often used. Cloxacillin is very widely used to treat or prevent *Staph aureus* mastitis in cows, since the Staphs often produce ß-lactamase.

Human use

Co-amoxyclav is the most widely used broad spectrum general purpose antibiotic by a long way, but all the penicillins are extensively used. Resistant *Strep pneumoniae* can be a problem, as can allergic reactions to penicillins as a group (macrolides are usually used instead).

Cephalosporins

commonly used drugs

far too many!

Cephalosporins

- ☑ work in a similar way to penicillins
- ☑ not broken down by simple β lactamases
- ☑ extended spectrum beta lactamases are common in NZ and will break down cephalosporins
- ☑ do not use a cephalosporin where a penicillin is likely to work

Cephalosporins are also ß-lactams. They should be reserved for cases where culture and sensitivity indicates that they are the most appropriate choice. The use of cephalosporins in empirical therapy cannot be justified (but is often done in practice).

Names

Cephalosporins discovered before 1974 have traditionally been spelt with a ph, while more recent drugs use an f. The current INNs all use an f and incorporate other spelling changes as well such as t instead of th. To reduce confusion, names here are BAN / USAN.

Mechanism of action

Same as penicillins.

Spectrum of activity

There are many different cephalosporins (certainly far too many to memorise their names). They can be roughly divided into three (or four) broad groups (generations) but this classification breaks down with the newer drugs. For instance, the commonly used veterinary drug ceftiofur is technically a third generation cephalosporin but is clinically identical to a typical second generation cephalosporin.

First generation (or natural) cephalosporins are broader in spectrum than penicillins, somewhat comparable to ampicillin. They tend to be effective against ß-lactamase producing *Staphylococci*. eg cephalexin, cephalothin, cephazolin.

Second generation cephalosporins are more effective for Gram negative organisms, but retain their Gram positive activity, although slightly reduced in comparison to first generation. They are frequently active against anaerobic bacteria. eg cefuroxime

Third generation cephalosporins have predominantly Gram negative activity, and also have reasonable activity against anaerobic bacteria. eg ceftiofur, cefovecin, cefotaxime

There are also several drugs classified as **fourth generation**, eg cefquinome.

More rational ways of classifying cephalosporins on spectrum of activity have been proposed. The Williams system is most commonly used, and the USP uses a modified version of this. **All these classification systems are of du-**

bious value with modern drugs - each drug is different.

Resistance

Mainly by extended spectrum β–lactamases, either inherent or chromosomally transmitted (particularly *Pseudomonas*, and more recently, coliforms, especially *Klebsiella*). Plasmid mediated resistance can also occur. Reduced membrane permeability is probably less important, although this can produce cross resistance with other classes of antibiotic.

Bacteria generally resistant to cephalosporins include: MRSA and coagulase negative staphs, *Enterococcus*, *Listeria*, *Clostridium difficile*, atypical *Pseudomonas* spp and *Campylobacter* spp. Many *Klebsiella* are becoming ESBL producers in NZ.

Third and fourth generation cephalosporins should be reserved for serious infections in people, and not used in animals. Ceftiofur is technically a 3rd generation drug but behaves more like a 2nd generation caphalosporin; even so, it is overused. Although it is registered for foot rot in cattle, this use is highly irresponsible. Second generation drugs should only be used for serious infections where nothing else is likely to work. Induction of extended spectrum ß-lactamases by the indiscriminate use of generation 1 or 2 cephalosporins has been shown to confer resistance to generation 3 or 4 cephalosporins in dogs.

Cefovecin is a third generation cephalosporin which is very highly protein bound in dogs and cats. This allows it to stay above usual MICs for about a week. The plasma (and presumably tissue) concentrations then fall down to zero over the next month. This long duration exposure to subtherapeutic concentrations just about guarantees the development of resistance.

Toxicity

Allergic reactions occur, similarly to penicillins, at any rate, in people. Local tissue reactions at the site of injection also occur. Cephalosporins can lead to the development of a positive Coombs test (humans).

Some older cephalosporins caused kidney failure, particularly in combination with frusemide. These have now been withdrawn. Cephalosporins are excreted by the kidneys (see below): clearance may not be as fast in animals with kidney failure.

TABLE 7.5.1 Classification of cephalosporins by generation

Generation	Spectrum	Veterinary Drugs	Human Drugs
1 oral	good G+, moderate G-, not Pseudomonas	cephalexin, cefadroxil	cephalexin, cefadroxil, cephradine
1 parenteral	very good G+, moderate G-, not Pseudomonas	cephalothin, cephaloridine, cefapirin, cephalonium	cephazolin, cephradine
2 oral	fair G+, good G-, not Ps		cefaclor
2 parenteral	fair G+, good G-, not Ps	cefuroxime	cefuroxime, cephamandole
3	moderate G+, very good G-, some activity against Ps and Bacteroides	ceftiofur cefovecin	cefotaxime
3 antipseudomonal	moderate G+, very good G-, good Ps		ceftazidime, cefoperazone, ceftriaxone
4	very good G+, very good G-, good Ps, Bacteroides, E. faecalis	cefquinome	cefpirome, cefepime
cephamycins	moderate G+, good G-, not Ps, good Bacteroides		latamoxef, cefotetan, cefoxitin

TABLE 7.5.2 Williams classification of cephalosporins.

Group		Spectrum	Drugs
oral		good G+, moderate G-, not Pseudomonas	cephalexin, cefadroxil, cefaclor
parenteral	1	very good G+, moderate G-, not Pseudomonas	cephalothin, cephazolin cephaloridine, cefapirin
	2	fair G+, good G-, not Pseudomonas	ceftiofur, cefuroxime, cephamandole
	3	good Pseudomonas	ceftazidime, cefoperazone, ceftriaxone
cephamycins	4	moderate G+, good G-, not Ps, good Bacteroides	latamoxef, cefoxitin

Prolonged therapy with some third generation cephalosporins can cause blood clotting disorders through inhibition of vitamin K metabolism (very rare).

Super-infections of the gastrointestinal tract have been reported.

Pharmacokinetics

There are big differences between individual drugs which influence their clinical use. Cephalosporins for parenteral use are poorly absorbed orally, but those prepared for oral administration are almost completely absorbed. Hepatic biotransformation occurs with some of these drugs and is usually deacetylation to active metabolites.

Most cephalosporins are excreted unchanged by the kidney (60 - 100%). The major exception is cefoperazone, which is 80% excreted in the bile. Most cephalosporins are secreted by the organic anion transporters, and therefore probenecid or aspirin inhibits their renal secretion, similarly to penicillins. However, cephaloridine, ceftazidime and ceftriaxone are almost 100% filtered, with negligible secretion.

In general, cephalosporins (particularly the newer ones) have short half lives in domestic animals (although they have been designed to have long half lives in people), and therefore should be dosed at least 8 to 12 hourly. In contrast, ceftiofur, licensed for use in cattle, has an active metabolite with a long half life, and therefore can be dosed every 24 hours. Note that this long dose interval is only appropriate for ceftiofur when being used for bovine respiratory diseases caused by Pasteurella spp, since they are extremely sensitive to ceftiofur. If using the drug off label, for other bacterial infections or in other species, some consideration should be given to increasing the dose frequency, possibly to every 12 hours or less. Ceftiofur is sometimes used in dairy cows as it has a zero milk withholding time. (It does not get into the milk at doses suitable for Pasteurella.)

Cefovecin has an exteremely long half life in dogs and cats because it is very highly protein bound. It maintains therapeutic concentrations for about two weeks, then sub-therapeutic concentrations for about a month. This seems like an ideal way to induce resistance.

Use

Cephalosporins are grossly overused and abused in veterinary practice. A variety of oral cephalosporins are sold as broad spectrum antibiotics for small animals; ampicillin would work as well in most cases, or co-amoxyclav for the penicillinase producers. Several first generation cephalosporins are sold for intramammary use in cows with mastitis. This use is easier to justify, as *Staph. aureus* is often resistant to penicillin, but cephalosporins are no better than cloxacillin. Clinical "resistance" in *Staph. aureus* is usually caused by drugs failing to get to the bacteria, cephalosporins are no better than penicillins in this respect.

Ceftiofur is licensed to treat foot rot in cattle (not a sensible use of a valuable drug) as well as respiratory disease in cattle, pigs and horses. The cattle dose is based on treating *Pasteurella* pneumonia (rare in NZ) and is very low for other infections,

ie, likely to induce resistance. It has a nil milk withholding time because it does not get into milk - do not use it for mastitis!

Human Use

Third and fourth generation cephalosporins are reserved for life threatening infections. They are only used in hospitals after approval from an infectious diseases specialist and are not used lightly. First generation drugs are used in the same way as in veterinary practice, but attempts are being made to reduce this use to avoid selecting for extended spectrum ß-lactamase producers. These are currently causing problems in Hawke's Bay and Auckland (and in dogs in several Australian vet schools).

Abuse of third and fourth generation cephalosporins by vets could easily result in regulation to reserve these drugs for people - beware!!!

Carbapenems & monobactams

commonly used drugs

none

Carbapenems & monobactams

☑ do not use in animals!

These drugs were developed to deal with ß-lactamase producing bacteria. Some bacteria, particularly *Staphs* and *Pseudomonas* have evolved to cope with them.

Imipenem is a carbapenem (always combined with cilastin, which inhibits metabolism in the kidney). **Meropenem** is similar. They are active against most bacteria, including *Pseudomonas* and anaerobes. They are always given iv and should be reserved for serious infections caused by multiply resistant Gram negative bacteria in people. They are the last resort for ESBL producing coliforms, although resistance increased dramatically in 2015 in NZ - thought to be from hospital acquired infections in India. **Do not use in animals.**

Aztreonam is a monobactam (ie it only has a ß-lactam ring). It is only active against Gram negative aerobes (may be synergistic with aminoglycosides), particularly *Pseudomonas*. It is inactivated by extended spectrum ß-lactamases. It has a short half life, but penetrates the CNS well. Very expensive. **Do not use in animals.**

Glycopeptides

commonly used drugs

none currently (avoparcin in the past)

Glycopeptides

- ☑ Vancomycin is the drug of last resort for MRSA in people
- ☑ do not use in animals

Vancomycin is a glycopeptide with seven amino acids isolated from *Amycolatopsis (Nocardia / Streptomyces) orientalis*. **Teicoplanin** is similar. They are closely related to **avoparcin** which was used as a production enhancer and has now being withdrawn because of fears about cross resistance with vancomycin.

Acting outside the bacterial cell membrane, vancomycin blocks the transfer of the glycopeptide units from the carrier molecule to the growing polymer peptidoglycan (see penicillin diagram). It is therefore rapidly active. The molecular target of glycopeptide antibiotics is the d-alanyl-d-alanine (d-Ala-d-Ala) terminus of growing peptidoglycan. Glycopeptide-resistant organisms modify the drug's peptide target, changing it to the depsipeptide d-alanyl-d-lactate (d-Ala-d-Lac).

Almost all Gram positive bacteria are sensitive to vancomycin. It is one of the few drugs effective against methicillin resistant *Staph. aureus* which is why there have been concerns about the possibility of resistance developing. There is complete cross resistance with avoparcin. Almost all Gram negative bacteria are resistant.

High level resistance (*vanA* gene) transmitted on a transposon has been shown to pass between enterococci *in vitro*. There is a danger that these transposons could be passed to other pathogens such as *Staph. aureus*, although this has only been know to occur once in real life. The *vanC* gene, which confers low level resistance, is common in enterococcal chromosomes. A variety of soil bacteria, including some used as insecticides overseas, contain a very similar gene to *vanA*. Vancomycin intermediate *Staph. aureus* use a different mechanism - they have extra thick cell walls so that the drug does not get in easily.

Vancomycin is reserved in people as the last remaining effective treatment against MRSA (although resistance is starting to develop) and for life-threatening enterococcal infections.

Vancomycin must be given by iv infusion, teicoplanin can also be given im. They are not absorbed orally, and are only used orally in the treatment of antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile* (usually caused by inappropriate antibiotic use). Avoparcin's main use was the prevention of *Cl perfringens* necrotic enteritis in chickens and pigs - bacitracin (or avilamycin) are now used instead.

Politics

Vancomycin is the drug of last resort for MRSA in people: it should be reserved for this use and should not be used in animals. Avoparcin has been phased out as a growth promoter in NZ.

New derivatives of vancomycin are being developed (eg, oritavancin) which circumvent current resistance problems. Do not expect to use them in animals.

A high tech method of growing unknown organisms in soil has recently come up with a new antibiotic, teixobactin (Kåhrström, A new drug for resistant bugs. *Nature Reviews Microbiology* 13, 126–127 (2015) doi:10.1038/nrmicro3429). This is similar to vancomycin but binds to two lipid sites on peptidoglycan precursors, which makes it more difficult for bacteria to develop resistance.

Other drugs affecting cell walls

commonly used drugs

bacitracin

Other drugs affecting cell walls

- ☑ bacitracin is commonly fed to chickens
- ☑ kills G+ bacteria
- ☑ sometimes put in ear ointments for dogs
- ☑ no major concerns about resistance
- ☑ toxic parenterally

Bacitracin is a complex, cyclical polypeptide with 11 amino acids, isolated from *Bacillus subtilis*. There are over 15 different bacitracins, but bacitracin A is most potent. Commercial preparations tend to be a mixture of various types. It is used as a production enhancer in the USA, and to prevent necrotic enteritis in chickens in NZ but has been banned in Europe.

It binds to isoprenyl phosphate in bacteria and prevents this from synthesising the glycopeptide units (N-acetyl glucuronic acid (NAG) - N-acetyl muraminic acid (NAM) pentapeptide isoprene pyrophosphate) produced for construction of peptidoglycan. Bacitracin thereby inhibits bacterial cell wall synthesis. Divalent cations are required for activity, so bacitracin is often complexed with zinc.

Bacitracin is primarily effective against Gram positive bacteria including some *Staphylococcus* spp, *Streptococcus* spp, *Haemophilus influenzae*, *Corynebacterium* spp, *Neisseria* spp, and *Clostridium* spp. It is not clinically effective against enteric Gram negative bacilli. Its main use is to prevent necrotic enteritis in chickens.

Bacitracin has been around since 1947 and is used by the ton without major resistance developing. Individual farms have problems with resistant *Cl perfringens* (chromosomally transmitted efflux pump?) which seems to disappear when bacitracin is not used for several batches of chickens. There is a suggestion that bacitracin may cause the expression of high level resistance to vancomycin in enterococci: this is probably not relevant clinically. Politics are a different matter!

Bacitracin complexes with lipids, including those of mammalian cell membranes, and when given systemically is severely nephrotoxic. Therefore, its use is limited to oral or topical application.

Bacitracin is very poorly absorbed orally, and has been used for gastrointestinal sterilisation. There is no withholding time.

It is also used in combination with other drugs in topical preparations, especially those intended for use in ears and eyes.

Fosfomycin is an old drug which may be revived as it potentiates many other antibiotics. It is occasionally used in people in NZ to treat multiresistant urinary tract infections.

Cell membrane disruption

commonly used drugs

polymixin

Cell membrane disruption

- ☑ polymixin acts as a detergent
- ☑ Kills G- bacteria
- ☑ used topically
- ☑ toxic systemically

Polymixin B is a clinically useful member of the polymixin family of simple polypeptide antibiotics produced by Bacillus polymyxa. Colistin is a synonym for Polymixin E.

Polymixins act as cationic detergents (ie, antiseptics - see also skin pharmacology notes) which interact with the phospholipid bacterial cell membrane causing disruption. As a result, the cytoplasm leaks out and the cell dies immediately. Part of their beneficial action may be through binding of bacterial endotoxins which are also phospholipids. They are included here rather than under disinfectants only because they are produced by micro-organisms.

Polymixin B and colistin produce a rapid kill in most Gram negative bacteria excluding *Proteus* spp. Active growth of the organism is not required. Polymixins are particularly useful in treatment of otitis externa and superficial ocular infections caused by *Pseudomonas aeruginosa*. Acquired resistance is rare. There is complete cross resistance between polymixin B and colistin.

These drugs do not discriminate well between microbial and mammalian cell membranes (ie, they are typical disinfectants / antiseptics). They are concentrated in the renal tubule after systemic administration causing acute renal tubular injury. They are also neurotoxic and cause a non-competitive neuromuscular blockade. Use should thus be restricted to topical applications, although they have been used systemically in the hope that they will mop up endotoxins in equine colic.

Because the molecules are highly charged, no significant absorption occurs after oral or topical administration, even if administered in high doses to inflamed skin.

Polymixins are highly bound by other drugs, such as tetracyclines, chloramphenicol, sulphonamides and carbenicillin. Do not mix them with other drugs (except if commercially prepared). They are inactivated by divalent cations.

1 mg polymixin B = 8,500 iu, 1 mg colistin = 30,000 iu.

Politics

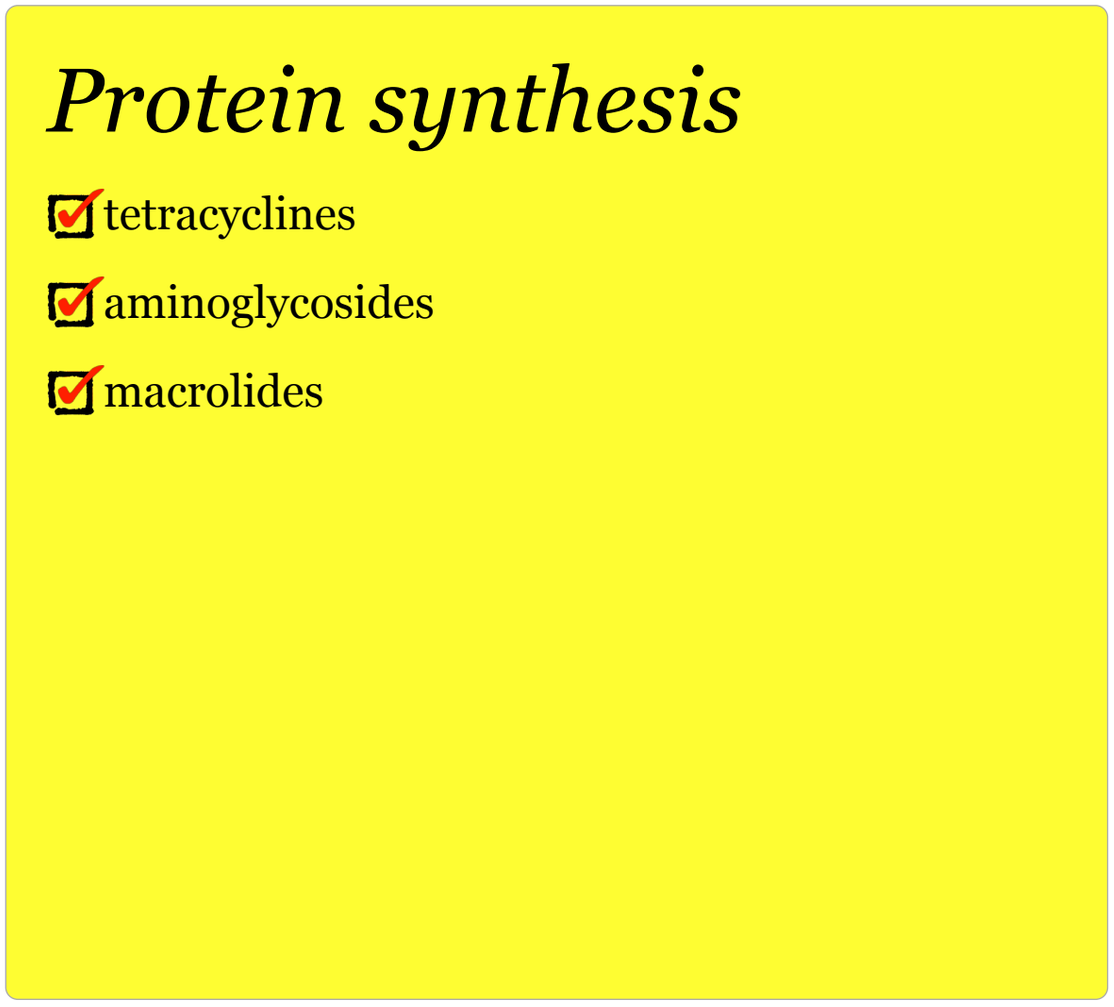
Colistin has become one of the last-resort antibiotics for multidrug-resistant *Pseudomonas*, *Klebsiella*, and *Acinetobacter*, which are almost untreatable. NDM-1 metallo-β-lactamase multidrug-resistant Enterobacteriaceae may also be susceptible. Although resistance has emerged in SE Asia, colistin is still politically hot, so be very careful about using any polymixins. In most cases in veterinary medicine, iodine solutions would work as well.

The future?

Neutrophils use a family of polypeptides called protegrins (among other things) to kill bacteria. These are being tried out for topical use in people. A synthetic animal derived protegrin, pexiganin, shows promise. No resistance so far. Iseganin is in phase 3 trials in people with cystic fibrosis. It has a broad spectrum and no resistance has been reported so far.

Protein synthesis

MOVIE 7.1 Protein synthesis



Messenger RNA, transfer RNA and ribosomal RNA are constructed on the DNA template. mRNA codes the ribosome for the amino acid sequence required for construction of a particular protein. Amino acids are then transported to the ribosome by their own particular tRNAs. The amino acid chain is then assembled by transpeptidation. Antibiotics may interfere with several of the steps in this sequence.

Tetracyclines

commonly used drugs

oxytetracycline

Tetracyclines

- ☑ oxytetracycline is very widely used in farm practice
- ☑ broad spectrum but resistance is common
- ☑ bacteriostatic
- ☑ chelates calcium - care iv in ruminants
- ☑ care in horses - suprainfection; pregnant animals - tooth staining in foetus
- ☑ newer (human) drugs are expensive

Oxytetracycline and chlortetracycline are used in food animals. Doxycycline is sometimes used in small animals: it has better penetration of tissues and binds calcium less tightly than the older drugs. Minocycline is similar. Tetracycline itself is not used in animals, although a mixture with lysine, lymecycline is available for use in people.

Mechanism of action

Tetracyclines inhibit aminoacyl-transfer-RNA from binding to the 30S ribosomal subunit-mRNA complex, thereby inhibiting peptide elongation. Tetracyclines enter Gram negative bacteria by passive diffusion through protein pores in the outer bacterial membrane, followed by active transport across the cytoplasmic membrane. This active transport is lacking in mammalian cells, so although tetracyclines inhibit mammalian protein synthesis, therapeutic concentrations are insufficient to affect the mammalian cell. Entry of tetracyclines into Gram positive bacteria is less well understood, but it is known also to involve active transport.

Tetracyclines also have anti-inflammatory effects by an unknown mechanism. Please resist the urge to use them for this effect.

Spectrum of activity

These drugs have a very broad spectrum including Gram negative and Gram positive bacteria, *Mycoplasma*, *Rickettsia*, *Chlamydia* and protozoa. (doxycycline is the drug of choice to treat *Haemobartonella felis*). Tetracyclines are moderately active against anaerobes. They are relatively poor at inhibition of growth of *Proteus* spp. and *Pseudomonas* spp. Overuse has led to resistance, and they are not as clinically useful as previously. Their main use is for *Rickettsia*, *Chlamydia* and some protozoal infections.

Oxytetracycline is cheap and commonly used as a first line broad spectrum antibiotic in large animal practice - not a good idea.

Resistance

Resistance to one tetracycline almost always crosses over to all others of this class (with the partial exception of doxycycline). Acquired resistance is common. Resistance is conferred by altered permeability / uptake and through production of drug inactivating enzymes.

Doxycycline is used in people for malaria resistant to other drugs; there may well be pressure put on vets not to use it.

Toxicity

Clinically relevant problems

All tetracyclines, but particularly doxycycline, can cause a fatal enterocolitis in horses and are contraindicated, except in cases of rickettsial disease. (They are still widely used in horses in practice though).

Tetracyclines are deposited into the calcifying areas of growing teeth, and growing bone, causing a yellow staining. They also cause temporary cessation of bone growth. Tetracyclines cross the placenta, and can have these effects in the foetus. Therefore, tetracyclines are contraindicated in young or pregnant animals.

Depression and vomiting can occur in most species as direct gastrointestinal effects. Gut disturbances associated with imbalances of the normal flora are also common, especially in ruminants. Supra infections can occur and pseudomembranous colitis has been described.

Tetracyclines are very bitter tasting, and therefore can cause profuse salivation in cats simply due to the taste (as with other bitter drugs). Warn clients that this may occur. Coated tablets are preferred and tablets should not be broken before administration to cats.

Rare problems

Photosensitisation and rashes can occur, especially with doxycycline, although it has also been recorded after oxytetracycline in sheep in NZ.

Cardiovascular collapse can occur after intravenous administration, particularly in cows, probably due to sudden chelation of the plasma ionised calcium.

Tetracyclines can induce fever: drug related fevers can cause confusion when treating infections.

Old tetracyclines beyond their use by date can cause serious renal proximal tubule mal/reabsorption disorders - Fanconi-like syndromes. This is caused by a breakdown product.

Tetracyclines can inhibit hepatic drug metabolising enzymes.

Long courses of tetracyclines can lead to vitamin B deficiencies through inhibition of gut flora. For this reason some tablet formulations are combined with supplementary vitamin B.

Tetracyclines can interfere with matrix metalloproteinases and interfere with collagen formation and contraction. Care required in foals.

They are sometimes used for their anti-inflammatory effects - avoid.

Pharmacokinetics

Tetracyclines are amphoteric, ie they have both negative and positive charges, although they usually behave as weak acids. They distribute rapidly to all tissues, with good penetration of difficult tissues such as prostate and bone. This is especially true for minocycline and doxycycline, which are highly lipid soluble and distribute to the cerebrospinal fluid quite well. Tetracyclines cross the placenta and distribute to all tissues within the foetus.

Tetracyclines are absorbed quickly but incompletely after oral dosing: most absorption is from the stomach and duodenum. Bioavailability by the oral route is approximately 0.5. They are unstable in acid (except minocycline). Intramuscular injection usually causes irritation (and pain), although this can depend on the vehicle, and absorption can be variable (but see below).

Tetracyclines are easily chelated by divalent cations, particularly calcium, making them insoluble and unavailable for absorption. Do not give iv to cattle.They should be administered at least an hour before food or antacids. Doxycycline's absorption is much less effected by foods and divalent cations.

Tetracyclines are protein bound in plasma from 60% (tetracycline) to 95% (doxycycline). They are eliminated by glomerular filtration resulting in 20 - 60% being found unchanged in the urine. They are also eliminated in the bile, and undergo enterohepatic circulation. Small intestinal secretion is the main route by which doxycycline is excreted.

Pharmaceutical considerations

The combination of tetracyclines and penicillins *in vivo* produces true antagonism. Despite this, parenteral procaine penicillin and intrauterine oxytetracycline pessaries are a traditional combination for treatment of post-dystocia uterine infections in cattle. There is clinical evidence that this combination is effective.

Tetracyclines are available in almost any formulation needed for almost all routes of administration. Because of their tendency to chelate cations, care should be exercised when choosing an intravenous fluid for administration by infusion. There are major differences in the non-active formulation ingredients from manufacturer to manufacturer. Products which use propylene glycol or ethanolamine as a vehicle tend to be irritant and cause severe muscle damage. Polyvinyl pyrrolidine (PVP) is better - much less irritant, more reliable bioavailability, less carcass damage but more expensive.

Tetracyclines gradually break down while stored, particularly in sunlight, and out of date preparations should not be used (see toxicity).

Use

Oxytetracycline is used as a cheap, broad spectrum antibiotic, particularly in food animals. It is useful for mycoplasmal diseases such as enzootic pneumonia in pigs. It does not cure bad ventilation in pig houses.

Doxyclycline is occasionally used for chlamydial or protozoal infections in dogs and cats. It may stop some oxytet resistant organisms, but is expensive. Tablets can cause oesophagitis, leading to oesophageal stricture, in cats, so wash them down with water. The injection is ridiculously expensive and is never used.

Human Use

Doxycycline is the only tetracycline used to any great extent, mainly for mixed infections where *Mycoplasma*, *Chlamydia* or certain protozoa are likely.

Demeclocycline is sometimes used to suppress anti-diuretic hormone secretion, as well as for its antibacterial effects.

The future?

Glycylcyclines - tetracycline analogues - have recently been introduced in human medicine. They have better activity, particularly against a wide range of resistant organisms. However, some *Salmonella* isolates from animals are already showing resistance. Tigecycline is available in NZ but costs $2,200 for a five day course, so it won't be widely used in animals.

Chloramphenicols

commonly used drugs

none

Chloramphenicols

- ☑ chloramphenicol banned in food animals - toxicity concerns of residues
- ☑ florfenicol safe
- ☑ broad spectrum but resistance develops quickly
- ☑ bacteriostatic
- ☑ commonly used in eye ointments in companion animals and people

Chloramphenicol has been around since 1948, and is still used despite various concerns. Thiamphenicol is very similar (including all the nasty side effects); it is still used in some European countries. **Florfenicol** is a fluorinated analogue of thiamphenicol with major advantages. It has more or less replaced chloramphenicol in most circumstances in veterinary medicine since it lacks most of the side effects. Other derivatives are under development.

Mechanism of action

Chloramphenicols bind to the 50S bacterial ribosomal subunit and inhibits peptide chain elongation by inhibition of peptidyl transferase, the enzyme responsible for peptide bond formation.

Spectrum of activity

Chloramphenicol is bacteriostatic against most Gram negative bacteria except *Pseudomonas* spp. It is also active against many Gram positives, anaerobes, the important *Rickettsia*, *Chlamydia* and some mycoplasmas.

Resistance

Resistance in Gram negative bacteria is plasmid transmitted and is caused by a specific chloramphenicol acetyltransferase which rapidly breaks the drug down. Florfenicol is reasonably resistant to this enzyme. Resistance in Gram positives is caused by a variety of plasmid transmitted acetytransferases. Decreased permeability and decreased sensitivity of ribosomes may also occur. Resistance in *E. coli* and *Salmonella* used to be widespread, but has reduced with decreased use of the drug (1999 - 4.8% of E. coli isolates from man resistant). Some bacteria, such as *Salmonella* Typhimurium DT104, show multiple resistance to a variety of antibiotics, including chloramphenicol. These resistance genes are usually passed on as a bunch.

Toxicity

In animals, chloramphenicol can occasionally cause aplastic anaemias, leukaemias and thrombocytopaenias, which are reversible after withdrawal of the drug. It can also cause gastrointestinal upset, both directly and through interference with the normal flora. In cats, vomiting, diarrhoea and anorexia are not uncommon. It has caused superinfections.

The veterinary use of chloramphenicol has been severely restricted as a result of a scare caused by anecdotal reports of a non-dose dependent, irreversible aplastic anaemia in man. This is a fatal condition which is idiosyncratic. On examining the

evidence, the WHO found that the overall incidence of chloramphenicol associated aplastic anaemia was less than 1 in 10,000,000 (WHO Technical Report 851, 1995. Evaluation of certain veterinary drug residues in food.) However, because of the scare, chloramphenicol was banned in food producing animals for any reason (although it is still used in people). It remains banned in spite of a lack of scientific evidence that it is harmful. Its use should thus probably be limited to life- or sight-saving applications in companion animals. Owners should be adequately warned to avoid exposure.

Pharmacokinetics

Chloramphenicol's outstanding lipid solubility ensures its distribution to all body compartments including cerebrospinal fluid and the eye. Brain tissue concentrations exceed plasma concentrations.

Chloramphenicol is glucuronated in the liver to an inactive conjugate, but there is no obvious first pass effect, with equivalent oral and intravenous doses achieving approximately the same maximum plasma concentrations. Maximum plasma concentration after oral dosing occurs at about 2 hours.

Approximately 90 - 95% of chloramphenicol is excreted in the urine as the water soluble glucuronic acid conjugate and the remainder as the parent drug. A small amount of the inactive conjugate may be found in the bile. Alterations to hepatic microsomal enzymes may alter the elimination rate of chloramphenicol, and result in accumulation to toxic levels. Chloramphenicol also inhibits hepatic mixed function oxidase enzymes (cytochrome P450s) and may therefore cause accumulation of other drugs being co-administered, eg, phenobarbitone, phenytoin. Elimination is very rapid in horses, slow in cats. Accumulation can occur in cats.

Florfenicol penetrates very well into the lungs reaching concentrations twice those in plasma, which persist for several days after a single injection.

Use

Dogs and cats - ointment for eye infections.

Florfenicol has the potency and spectrum of chloramphenicol, but without the toxicity (the main side effect is anorexia). It is unaffected by chloramphenicol acetyltransferase, so is active against some chloramphenicol resistant bacteria. It is sold as an injectable solution for respiratory infections in cattle, but should not be used in bulls as it causes testicular atrophy in most species (at high doses).

It was developed in the USA for *Pasteurella* (*Mannheimia*) pneumonia which had become resistant to penicillin from overuse. Its role in NZ, where this sort of pneumonia is rare, is not yet clear. It can also be used as eyedrops in horses and companion animals.

Human Use

Chloramphenicol is used as an ointment for eye infections and as an antibiotic of last resort, particularly for MRSA and VRSA.

Macrolides and similar drugs

commonly used drugs

small animals - erythromycin

pigs and chickens - tylosin, tiamulin

Macrolides and similar drugs

- ☑ narrow spectrum - mainly G+, but also *Mycoplasma*, *Pasteurella* and spirochaetes
- ☑ bacteriostatic
- ☑ erythromycin increases gut motility in dogs and cats
- ☑ can cause arrhythmias, especially if given iv

These drugs have different chemical structures but are clinically very similar in their pharmacokinetics and spectrum of action. They are all bacteriostatic.

Macrolides include erythromycin, tylosin, tilmicosin and spiramycin (less active) which are commonly used in animals; oleandomycin is sometimes used in people. Roxithromycin, clarithromycin and azithromycin are human drugs which are sometimes used in animals for their better pharmacokinetics. Kitsamycin is used in animals in Australia.

Lincosamides are chemically different but clinically identical to macrolides. Lincomycin and pirlimycin are used in animals, clindamycin in people.

Pleuromutilins are also very similar. Tiamulin is the only drug used in NZ, but valnemulin is used in Europe. Retapamulin has recently been approved in the USA and EU for *Staph* skin infections in people and there may be pressure in the future to reduce pleuromutilin use in pigs.

Mechanism of action

Diagram

Bind to the 50S bacterial ribosomal subunit and inhibit peptide chain elongation by inhibition of translocation and movement along the mRNA.

The macrolides have recently been shown to have some anti-inflammatory effect - preventing superoxide and cytokine production and stabilising macrophages and T cells. This may be a useful side effect in respiratory and skin infections.

Erythromycin acts as a prokinetic in the bowel by several mechanisms (see gut pharmacology notes). Try to avoid this use as it will encourage resistance.

Spectrum of activity

These drugs have a narrow spectrum mainly confined to Gram positive bacteria, including penicillinase producing staphs, but not enterococci. They are also active against *Pasteurella* and *Bacteroides* spp, *Mycoplasma* spp and *Rickettsia* spp. Tylosin and roxithromycin are used clinically against *Mycoplasma*, *Chlamydia* and some spirochaetes (*Treponema* and *Moraxella*). Tiamulin is effective in swine dysentery (*Brachyspira hyodysenteriae*). Most strains are now resistant to tylosin. Erythromycin is effective against *Rhodococcus equi* in foals. Macrolides (especially erythromycin) are used in people for severe *Campylobacter* infections, but resistance is high and increasing (particularly around Auckland). Roxithromycin and

azithromycin have some activity against protozoa such as *Toxoplasma gondii*. Lincosamides, particularly clindamycin, have useful activity against anaerobes.

Resistance

Chromosomal resistance occurs readily. Plasmid mediated resistance is also common. Resistance usually involves changes to the 50S ribosomal unit which prevents drug binding. This occurs very quickly with lincosamides and slowest with tiamulin.

Cross resistance amongst the macrolides, lincosamides and streptogramin Bs is common but not complete.

Pleuromutilins bind to several different sites so resistance develops more slowly, and there is less cross resistance.

Toxicity

Macrolides are generally safe unless given rapidly iv when they can cause arrythmias. Tilmicosin is is probably worst and should not be given iv. A low incidence of arrhythmias have been reported with most of these drugs given orally in people. None of the species we deal with are as bad as people (or minor arrhythmias are just not noticed), but care is still required.

Some local reactions occur at the site of injection, especially thrombophlebitis after intravenous injection. Horses tend to get gastrointestinal disturbances due to enterohepatic circulation and the antibiotic effect on the normal flora. Tylosin is contraindicated in the horse for this reason.

Dogs and cats often get gut upsets and vomiting after erythromycin (it increases gut motility (see gut notes)).

Tiamulin in combination with coccidiostats will cause severe growth depression (mainly important in pigs).

Transient deafness has been reported in people.

Pharmacokinetics

The macrolides are organic bases. Erythromycin's pKa is 8.6 and tylosin's pKa is 7.1 so their action is favoured by higher pH.

Erythromycin is absorbed poorly after oral administration, but distributes well to many tissues, achieving higher tissue concentrations than plasma. This is especially true for bone. Macrolides are also taken up by phagocytes. They do not penetrate the intact blood brain barrier. Ion trapping ensures that macrolides achieve high concentration in normal milk, but the raised pH of mastitic milk reduces the benefit of this effect.

Macrolides are found in saliva at high concentrations. One product (Stomorgyl) is a combination of the macrolide spiramycin with the nitroimidazole metronidazole. This product is marketed strongly on the basis of saliva penetration.

Macrolides undergo extensive enterohepatic circulation. They are largely metabolised and only small amounts can be found in the urine or the faeces.

Lincosamides are rapidly and almost completely absorbed after oral administration with peak plasma levels occurring within 2 hours. Clindamycin is better absorbed than lincomycin.

Clindamycin is 90 -95% plasma protein bound. It is distributed widely, but is not concentrated in any particular tissue. It does cross inflamed meninges and passes into bone, achieving about 40% of plasma concentration in these tissues (humans). Liver metabolism produces active and inactive metabolites. Most drug is eliminated by the liver, with only 8 - 20 % being excreted in the urine.

Azithromycin has a very long half life (35h) in cats so is usually given as a single dose. It is extensively bound in tissues.

Tulathromycin is highly concentrated in the lungs - useful for pneumonia in cattle.

Pharmaceutical considerations

Erythromycin is acid labile and must therefore be administered as enteric coated tablets, or parenterally. Estolate and stearate salts are used to enhance absorption. Newer macrolides such as roxithromycin have been designed to overcome this problem.

Tylosin is available as a powder for mixing with drinking water. This is used especially in the poultry industry. Tylosin is also available as parenteral preparations in some countries. It has been banned in Europe as a growth promoter.

Use

cattle - *Pasteurella* pneumonia (rare in NZ although almost ubiquitous in feedlots in the USA)

pigs - treating and preventing respiratory infections (pleuropneumonia and enzootic pneumonia) and dysentery (especially tiamulin).

chickens - chronic respiratory disease caused by *Mycoplasma*

small animals - skin infections, osteomyelitis, anaerobic infections, (toxoplasmosis)

horses - *Rhodococcus* pneumonia in foals (azithromycin), otherwise best avoided

Human Use

Erythromycin has traditionally been used as a subtitute for penicillin in people who are allergic to penicillin. It was also used to treat *Campylobacter*, but overuse as part of a protocol for *Helicobacter* means that many strains of *Campylobacter* in NZ are now resistant.

Azithromycin is usually reserved for chlamydial infections, but has been used in antimalarial combinations with chloroquine. Clarithromycin has some effect against TB, and is included in some protocols for multiresistant TB.

The future?

The 3-ketolides are a new related group of drugs which look promising. Telithromycin has been licensed for human use overseas and appears effective against erythromycin resistant *Strep pneumoniae*. However, there have been a few cases of liver disease attributed to it, so this may discourage its use.

Streptogramins

commonly used drugs

none

Streptogramins

- ☑ complete cross resistance with quinupristin & dalfopristin (Synercid) used in people for MRSA
- ☑ avoid using in animals

Virginiamycin was used as a production enhancer in animals; it is now only licensed for treating necrotic enteritis in chickens where nothing else is likely to work, and for preventing laminitis in horses. (It is supposed to alter gut flora, which results in less of whatever causes laminitis circulating to the feet.) Pristinomycin has been in human use in France for many years. It has to be given orally as it is not water soluble enough for parenteral use. **Quinupristin & dalfopristin** (RP59500, "Synercid") is a new drug used against methicillin resistant Staph aureus in people (not in general use in NZ yet).

The nomenclature of this class of drugs is confusing ahey are all synergistic mixtures of at least two different compounds. Thus virginiamycin is 75% virginiamycin M1 (a streptogramin A) and 5% virginiamycin S1 (a streptogramin B). The two drugs are structurally unrelated (streptogramin Bs are macrolides), bind to distinct sites of the 50 S ribosomal subunit, but cooperate to inhibit protein synthesis. The mechanism of inhibition is different for each component, however binding of Type A leads to a conformational change in the 50S subunit which potentiates the action of Type B streptogramin. Individually the molecules are only bacteriostatic, but together they act synergistically and are bactericidal.

Spectrum

Bactericidal against Gram positives, including MRSA.

Resistance

A single gene confers cross resistance among the macrolides, lincosamides and streptogramin Bs, but the streptogramins as a combination are not usually affected. There is complete cross resistance between virginiamycin and quinupristin & dalfopristin.

Toxicity

Bacterial overgrowth leading to haemorrhagic diarrhoea has been reported. Rarely, lung oedema has been associated with virginiamycin.

Pharmaceutical considerations

Virginiamycin is practically insoluble and so is only given orally for its effect on gut flora, pristinomycin is available in injectable form. Virginiamycin has recently been banned in Europe.

Indications

Virginiamycin is licensed in NZ for prevention of laminitis in horses and necrotic enteritis in chickens where nothing else is likely to work. In view of the cross resistance with a drug of last resort in people, this is ethically dubious. The other streptogramins should not be used in animals, and should be reserved for MRSA in people.

Aminoglycosides

commonly used drugs

streptomycin

neomycin

gentamicin

Aminoglycosides

- ☑ bactericidal
- ☑ G- and some G+ (Staphs)
- ☑ some resistance present in NZ
- ☑ beware toxicity - ears and kidneys
- ☑ water soluble - poor penetration

Streptomycin, dihydrostreptomycin, neomycin (a mixture of neomycin A, B and C), gentamicin and Framycetin (neomycin B) are used in animals. Amikacin, tobramycin, and netilmicin are used in people. Kanamycin and sisomicin are obsolescent human drugs. Paromomycin is occasionaly used to treat *Cryptosporidia*.

nb. Gentamicin and netilmicin are spelt differently from the others because they are derived from different fungi (*Micromonospora* rather than *Streptomyces*).

The related antibiotics, spectinomycin and apramycin are usually classified as aminocyclitols. They are similar in most respects to aminoglycosides.

Mechanism of action

Diagram

Aminoglycosides bind tightly to the 30S ribosomal subunit, and block peptide synthesis by preventing tRNA attachment, blocking normal initiation, and distorting the codon arm to cause mismatching of the codon-anticodon couples. This latter action results in the production of so-called “nonsense peptides”. Penetration of the cell (and thus activity) is greatly aided by drugs which interfere with cell wall synthesis such as ß-lactams.

Spectrum of activity

Aminoglycosides are rapidly bactericidal against Gram negative aerobic bacteria, and have some useful activity against Gram positive aerobic bacteria such as Staphs. Streptomycin is also active against *Mycobacterium bovis* and tuberculosis in people. Gentamicin, tobramycin and the newer aminoglycosides are usually effective against *Pseudomonas* spp.

Aminoglycosides are ineffective against anaerobic bacteria because uptake requires oxygen dependent transport processes.

Synergism with penicillins and cephalosporins can occur in some circumstances, and is probably due to damage to cell walls allowing penetration of the aminoglycoside. This is especially useful to extend the spectrum of activity of aminoglycosides to include Gram positive bacteria. However, they are usually chemically incompatible, so do not use home made mixtures. Synergy is difficult to demonstrate in many circumstances and most commercial mixtures have been withdrawn.

Resistance

Resistance to aminoglycosides develops relatively quickly, either by chromosomal mutation or by acquisition of plasmids. Resistance is caused by enzymes which degrade the antibiotic, alterations to the ribosomal binding protein, or of bacterial permeability to the antibiotic. Some bacteria have broad spectrum resistance to the aminoglycosides, others are specific for an individual drug. Gentamicin is most likely to develop resistance; amikacin is least likely. Thus cross resistance is likely but difficult to predict. Adaptive resistance has been demonstrated with the aminoglycosides. *Pseudomonas* develops resistance relatively quickly, staphs more slowly and coliforms very slowly.

Toxicity

Two toxic syndromes are clinically important:

kidneys - renal proximal tubule epithelial cell injury resulting in acute renal failure (This is the major limiting factor on their use in veterinary practice.)

ears - vestibular and / or cochlear injury resulting in cranial nerve VIII signs.

All aminoglycosides can cause renal damage, especially if pre-existing renal disease exists, or if the animal is dehydrated, or if aminoglycosides are given with frusemide. Serial monitoring of serum creatinine is recommended. Therapeutic drug monitoring is valuable. Care should be taken to allow plasma drug levels to fall to troughs less than 2 mg/ml for several hours each day. Toxicity is associated with high trough drug levels more than with high peak drug levels. In practice, once a day dosing with its peaks and troughs is safer and just as effective as maintaining steady plasma levels by more frequent dosing - peak concentration is what counts for killing bacteria rather than time above MIC.

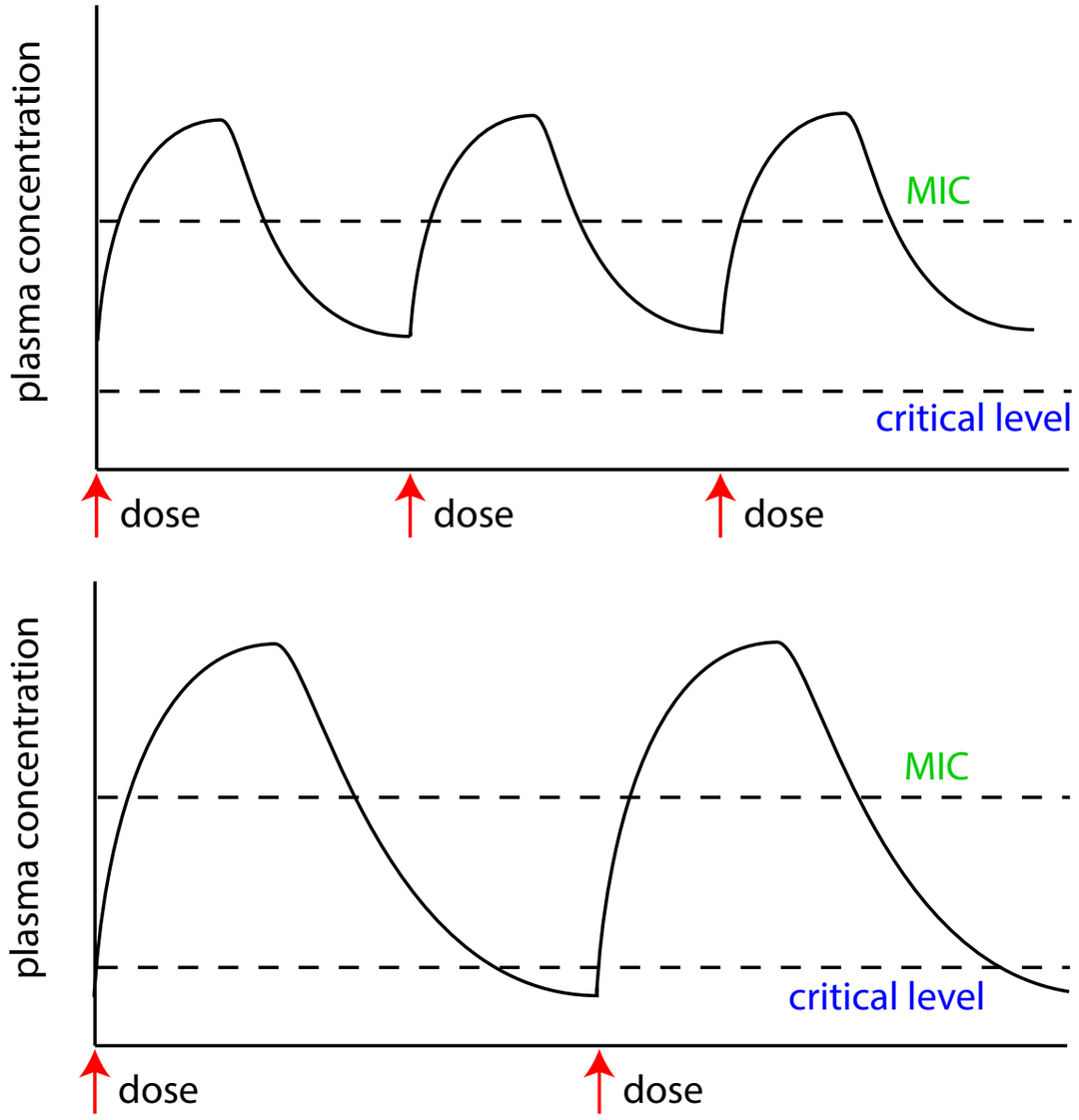
Deafness may be irreversible. Dihydrostreptomycin and amikacin are most likely to cause ototoxicity.

Aminoglycosides can also cause competitive neuromuscular blockade, especially when given with anaesthetics or other NMJ blockers.

Pharmacokinetics

Aminoglycosides are organic bases and are more active at higher pH. They are very polar at plasma pH and are therefore distributed only to body water. They do not penetrate cell membranes and are not absorbed to any great extent after oral administration.

FIGURE 7.1 Aminoglycoside pharmacokinetics



Less frequent dosing with a bigger dose allows a higher peak concentration and also allows the plasma concentration to fall below the critical level for accumulation in the kidney and ears.

Parenteral administration results in rapid absorption and distribution. Aminoglycosides are cleared from the plasma rapidly by glomerular filtration, but are accumulated by the renal proximal convoluted tubule cells, and may persist in the kidneys for months after a single injection - residues!

Since antibacterial efficacy depends on peak concentration reached and kidney damage depends on the time allowed for elimination between doses, it is now usual to give gentamicin in a high dose once daily rather than a small dose three times daily as used to be recommended.

Pharmaceutical considerations

Neomycin is too toxic for parenteral use (although available in NZ!), and is only used in topical preparations or orally for gastrointestinal “sterilisation”.

Sulphate salts improve solubility, but solutions tend to be quite acidic, so may sting when administered im or sc and when given iv must be diluted and given slowly.

Use

Aminoglycosides are falling out of favour because of residues (food animals) or toxicity (companion animals). Gentamicin is still widely used in horses. Although its spectrum of activity is mainly Gram negative, gentamicin is sometimes useful for ß-lactamse producing staph infections. It is also the drug of choice to treat *Pseudomonas* infections.

Aminoglycosides are widely abused in young food animals to treat diarrhoea. Calves and piglets with diarrhoea need fluids, not antibiotics.

Lots of streptomycin is sprayed on apple trees and tomatoes in NZ to treat fireblight and bacterial wilt, although this practice is on the decline since it was banned in Europe. It is the one registered treatment for PSA in kiwifruit, so lots has been used recently.

Human Use

A variety of the newer aminoglycosides are important in treating serious Gram negative infections. Streptomycin went out of fashion because it made people deaf, but is becoming important again as part of a multiresistant TB combination.

Other protein synthesis inhibitors

commonly used drugs

none

Other protein synthesis inhibitors

- ☑ avilamycin
- ☑ fusidate - reserved for MRSA in people
- ☑ mupirocin
- ☑ linezolid - **do not use in animals!**

Avilamycin

Avilamycin is only used to prevent necrotic enteritis in chickens. Avilamycins are oligosaccharides and are usually classified as orthosomycins. There are many closely related orthosomycins, such as the everninimicins, flambamycin, curamycin and sporosuracins, none of which are used clinically in humans or animals in NZ at the moment.

Avilamycin binds to the bacterial 30S ribosomal subunit and inhibits the attachment of tRNA, in a similar manner to aminoglycosides. The avilamycins are only active against Gram positive bacteria.

SCH27988 (Ziracin), an everninomicin which is very similar to avilamycin, looked promising at one time for Gram positive nosocomial infections in people. It was active against a wide range of multi resistant staphylococci, enterococci and streptococci, but has now been dropped for safety reasons. Similar drugs are likely to be developed in future for MRSA.

Avilamycin is used as a growth promoter in pigs and chickens overseas. Avilamycin is useful against *Cl. perfringens* (necrotic enteritis) which is resistant to bacitracin.

There appears to be complete cross resistance between avilamycin and everninomycins in enterococci isolated from broiler chickens and pigs. Resistance appears to develop slowly, both *in vitro* and in the field.

Avilamycin is the only growth promoter left for chickens in Europe, where it is now used by the thousands of tons. Any problems should show up quickly there (none so far). It is not used much in NZ - at the moment.

Fusidic acid

Fusidic acid is a lipophilic steroid antibiotic derived from the fungus *Fusidum coccineum*. It inhibits binding of aminoacyl tRNA to the ribosome so inhibiting protein synthesis. It may be bacteriostatic or bacteriocidal. It is usually used as the sodium salt (sodium fusidate).

It causes liver toxicity when given parenterally, so is usually given orally or topically. Oral fusidate is well absorbed and tends to be concentrated in bone. Effective against Gram positives, mainly staphs (including MRSA). *Streps* and enterococci are not susceptible. Also has some antiprotozoal and antiviral properties and immunosuppressant actions. It is often impregnated into wound dressings.

Resistance develops rapidly *in vitro*, but has recently been reported to be escalating rapidly among *Staphs* from people in NZ.

Although it has been used for trivial infections in the past, it is starting to be reserved for MRSA in human medicine - vets beware.

Mupirocin

Mupirocin inhibits bacterial protein synthesis by binding to isoleucyl tRNA synthetase. It is bacteriostatic at low concentrations and bacteriocidal at high concentrations.

It is only used topically as it is rapidly metabolised if absorbed.

It is mainly used against staphs (particularly MRSA) and streps, but also has activity against Candida.

In NZ, it was reserved for treating MRSA until recently, when widespread resistance has made it almost useless.

Oxazolidines

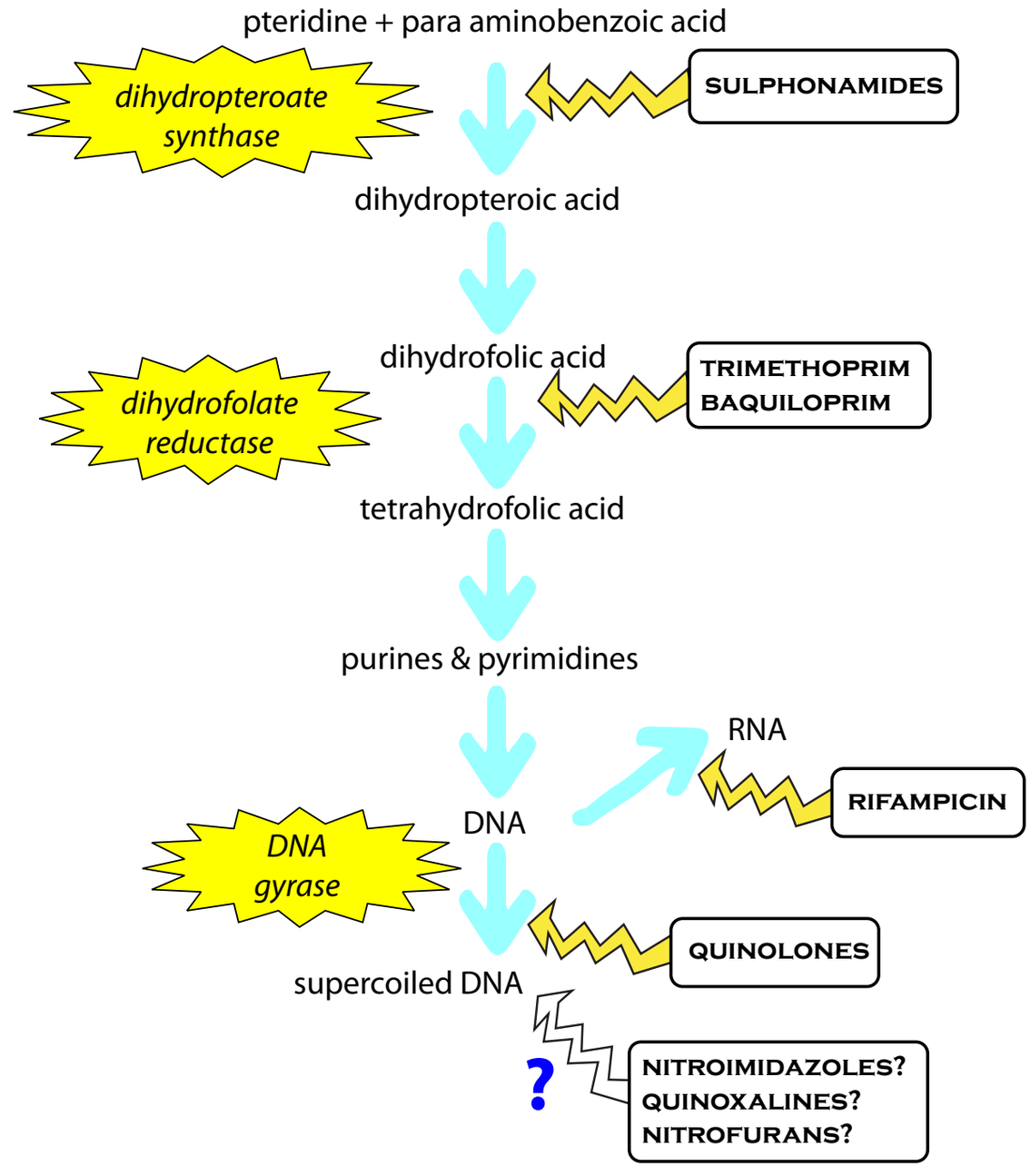
The oxazolidines are a completely new class of antibiotic - the first for many years. Linezolid has recently been approved in NZ for people. It is effective against Gram positive organisms with only rare resistance reported so far. It is reserved in people for MRSA and VRE infections (its current use in NZ) and possibly multiresistant TB. **Do not use in animals**.

Nucleic acid synthesis

Nucleic acid synthesis

- ☑ sulphonamides and potentiate sulphonamides
- ☑ fluoroquinolones
- ☑ nitroimidazoles

FIGURE 7.2 Bacterial nucleic acid synthesis inhibitors



Sulphonamides

commonly used drugs

co-trimoxazole

Sulphonamides

- ☑ usually given with a dihydrofolate reductase inhibitor
- ☑ combination is broad spectrum & cheap
- ☑ side effects common - usually immune mediated

Sulphonamides

The sulphonamides were the first group of completely synthetic antimicrobial drugs (ie, strictly speaking they are antibacterials rather than antibiotics). They are rarely used alone these days because of resistance. Sulphadiazine and sulphamethoxole are often mixed with trimethoprim (dihydrofolate reductase inhibitor, see next section) to form co-trimazine and co-trimoxazole. Mixtures with baquiloprim are sometimes also used. There is not much difference between sulphonamides except in solubility and pharmacokinetics.

Mechanism of action

Diagram

The pyrimidine thymine is a necessary precursor for DNA synthesis. In the absence of thymine or thymidine in the media, bacteria are able to synthesise pyrimidines from the precursor para-aminobenzoic acid (PABA), through the folic acid cycle. In the absence of thymidine, inhibition of its synthesis results in inhibition of cell replication, growth, and DNA repair. (Mammalian cells get their folate as a vitamin from food.)

Sulphonamides act by competitively inhibiting the incorporation of PABA into folate. Since it is a competitive inhibition, the presence of large amounts of the substrate PABA reduces the efficacy of these antimicrobial drugs. nb, the obsolete local anaesthetic procaine is metabolised to PABA. Also, if the bacterial media contains thymine, or thymidine, these can be used for DNA synthesis directly and sulphonamides will have little effect.

Spectrum of activity

These are broad spectrum antimicrobial drugs, but the spectrum has been compromised by widespread resistance. They are primarily bacteriostatic against Gram positive bacteria, excluding *Staphs*. Sulphonamides are also effective against many types of protozoa such as coccidia. The combination with trimethoprim or baquiloprim is bactericidal.

Sulphonamides may be effective in treatment of infections by *Streptococcus* spp., *Salmonella* spp., *E. coli*, *Pasteurella* spp., *Shigella* spp., *Actinomyces*, *Nocardia*, *Chlamydia*, *Toxoplasma*, and *Plasmodium* (in people) but the effect is not reliable because of resistance (see below).

Resistance

Chromosomal resistance develops slowly, but rapidly induced plasmid mediated resistance is commoner. Possible mechanisms: reduced drug penetration, increased production of PABA or reduced sensitivity of dihydropteroate reductase.

Resistance is widespread and severely limits the use of sulphonamides - they must be potentiated with dihydrofolate reductase inhibitors in most cases to be effective. There is complete cross resistance among sulphonamides.

Sulphonamides are inactivated in pus, which can lead to a lack of clinical efficacy.

Toxicity

Older forms of sulphonamide were less soluble and often crystallised out in the urine. With newer drugs this is less of a problem. Nevertheless, patients must be adequately hydrated to ensure dilute urine.

Sulphonamides often cause hypersensitivity reactions. Sulphonamides or potentiated sulphonamides are the main cause of adverse drug reaction in people in NZ. Their use in people is rare now for this reason. Photosensitisation or rashes, blood dyscrasias and hepatopathies occur, but are usually reversible by stopping the drug. These probably occur in animals too but are not noticed.

Sulphonamides can cause keratoconjunctivitis sicca in dogs after prolonged administration (mechanism unknown but probably immune mediated). Immune mediated polyarthritis has been reported in Dobermanns. Other immune mediated reactions are likely.

Sulphonamides in ruminants can cause suppression of ruminal flora. Prolonged treatment in any species can reduce vitamin K production leading to haemorrhage (especially in poultry).

Sulphonamides can also cause thyroid supression (cf propylthiouracil - a sulphonamide). Reduced thyroid hormone production causes increased TSH secretion which can cause thyroid tumours.

Combination with dihydrofolate reductase inhibitors mean that much smaller doses need to be given, which reduces the incidence of all but hypersensitivity side effects.

Since sulphonamides are given in large quantities and are often highly protein bound, they can displace other drugs from plasma proteins.

Pharmacokinetics

With the exception of some drugs which were synthesised particularly for use in the lumen of the gastrointestinal tract (and are thus not absorbed, e.g. sulphasalazine, sulphaguanidine, phthalysulphathiazole) sulphonamides are absorbed well and rapidly after oral administration.

Sulphonamides are distributed rapidly to all tissues, including the eye and the cerebrospinal fluid. There are differences in distribution between drugs, and sulphadiazine is best distributed to the CNS.

Sulphonamides are weak acids, and are therefore more active in acidic environments.

Free sulphonamides and hepatic metabolites (acetylated derivatives) are eliminated by both glomerular filtration and tubular secretion. Longer acting forms achieve their lower clearance by being more highly protein bound and by being reabsorbed by the renal tubule.

Acetylation of sulphonamides increases the chances of crystalluria. The extent of acetylation is greatest in man > ruminants > horse > cat. The dog does not acetylate sulphonamides. Of the two most commonly used sulphonamides (in preparations with diaminopyrimidines; see below) in those species which acetylate sulphonamides, sulphamethoxazole is more likely to cause crystalluria than sulphadiazine.

Sulphonamides are often classified on the basis of the pharmacokinetics, specifically half life:

Short acting

- sulphanilamide
- sulphacetanide
- sulphadiazine
- sulphadimidine (=sulphamethazine)
- sulphafurazole (=sulfisoxazole)
- sulphachlorpyridazine

Medium acting

- sulphamethoxazole

Long acting

- sulphamethoxypyridazine
- sulphadimethoxine

Ultra long acting

- sulphadoxine

This classification must be kept flexible because of species differences.

Sulphamethoxazole is the most commonly used these days.

Sulphasalazine is sulphapyridine complexed with salicylic acid. It is sometimes used in chronic large bowel disease where bacteria break down the complex. It is thought that the salicylic acid probably produces all the useful effects.

Pharmaceutical considerations

Sulphonamides are often formulated as sodium salts to increase their solubility. Monosodium salts are very irritant to tissues, and must be given iv only. Disodium salts can be given im, ip etc.

The “law of independent solubility" means that the presence of one drug in solution does not affect the solubility of another drug. However, the antimicrobial action of the different sulphonamides is additive. Therefore, combination of several sulphonamides together can reduce the dose of each, thereby reducing the potential for toxicity, without compromising the antibacterial efficacy.

Drug interactions

B vitamins and their precursors (and related amino acids such as methionine) antagonise sulphonamides. Some drugs such as procaine have PABA as a major metabolite and will do the same.

Use

Sulphonamides on their own are really only (ab)used to treat scours in calves and piglets. Potentiated sulphonamides are still amongst the most commonly used broad spectrum antibiotics in veterinary medicine - they are cheap!

Human Use

Not used much any more because of side effects (mainly minor things like skin rashes). Even so, sulphonamides and trimethoprim account for over half of all drug adverse reactions in NZ.

Similar Drugs

Other sulpha-like drugs include sulphones, e.g. dapsone, sulphoxone. These are bacteriostatic or bactericidal to Mycobacteria spp. They are used in people for leprosy, but have been used in cows for mastitis and have the same spectrum of activity as sulphonamides. Concerns about residues mean that they should not be used in food animals (dapsone is potentially carcinogenic).

Sulphamylon has been used topically to prevent infections of burns.

Dihydrofolate reductase inhibitors

Trimethoprim is a diaminopyrimidine analogue of para aminobenzoic acid. A very similar drug, **baquiloprim**, is also used in cattle and pigs because trimethoprim has a short half life in these species. They are nearly always used in combination with sulphonamides as potentiated sulphonamides.

Mechanism of action

Diagram

Trimethoprim acts by inhibiting the enzyme dihydrofolate reductase. This results in failure to reduce dihydrofolate to tetrahydrofolate, thereby blocking pyrimidine synthesis and potentiating the effects of sulphonamides.

Spectrum of activity

Trimethoprim has a similar spectrum of activity as sulphonamides. They are probably synergistic in most circumstances. Trimethoprim is used alone in urinary infections in people, where it appears that sulphonamides do not contribute to its effect.

Resistance

Plasmids encoding trimethoprim resistant dihydrofolate reductases can be passed on and become incorporated in the chromosomal DNA. Some bacteria just overproduce dihydrofolate reductase. Cell wall permeability to trimethoprim may also reduce and some bacteria have learned to rely on exogenous thymine and thymidine as mammals do.

Clinically, resistance exists but is not a huge problem.

Toxicity

Blood dyscrasias (anaemia) occur rarely and are usually reversible by stopping trimethoprim or giving folate. Trimethoprim may cause an increase in serum creatinine through inhibition of renal secretion. Several cases of hypersensitivity in Dobermanns and Great Danes have occurred with polyarthritis, pyrexia, anorexia and depression. This was probably caused by the sulphonamide component of the mixture.

All the side effects of sulphonamides can occur with potentiated sulphonamides as well.

Pharmacokinetics

Trimethoprim is usually administered with sulphamethoxazole (co-trimoxazole) or sulphadiazine (co-trimazine) at a fixed dose ratio of 1:5. The pharmacokinetics of trimethoprim and sulphamethoxazole are closely matched when given independently in most species. However, trimethoprim tends to slow the absorption of sulphamethoxazole. These kinetic interactions vary between species. High levels are areached in the urine and CNS.

Trimethoprim is more slowly eliminated than short acting sulphonamides in most species. Therefore the combination with sulphamethoxazole seems more rational, especially in the dog where acetylation of sulphamethoxazole is not a problem. The half life of trimethoprim in cattle is about 30 min, so baquiloprim, with a half life of 10 hours, seems a more rational choice.

Human use

Mainly as a first line drug for cystitis in women.

Similar Drugs

A variety of dihydrofolate reductase inhibitors are used against protozoa. **Pyrimethamine** is more specific for protozoal dihydrofolate reductase and was commonly used for malaria in man, and occasionally for *Toxoplasma* or similar organisms in animals. **Methotrexate** is more specific for mammalian dihydrofolate reductase and is used as an anticancer drug (qv).

Current research is concentrating on dihydrofolate reductase inhibitors which are more specific for Gram positives, specifically MRSA. There are a number of promising drugs coming along.

Fluoroquinolones

commonly misused drug

enrofloxacin

Fluoroquinolones

- ☑ drugs used in vet medicine are mainly active against G- bacteria
- ☑ Staphs develop resistance quickly
- ☑ important drugs in human medicine
- ☑ toxic effects - eye damage in cats, cartilage damage in all young animals

Fluoroquinolones are derived from nalidixic acid, which itself has fallen from use because of neurotoxicity problems. The fluoroquinolones are one of the newest groups of antibiotics (at least in veterinary medicine) and therefore subject to most market hype. Enrofloxacin, marbofloxacin, orbifloxacin, sarafloxacin and danofloxacin are registered for veterinary use in NZ. Norfloxacin and enrofloxacin's main metabolite ciprofloxacin are in human use in NZ. The newer generation fluoroquinolones (8-methoxyfluoroquinolones), such as levofloxacin, moxifloxacin and gatifloxacin, have recently reached NZ for human use. They have greater Gram positive activity (particularly for *Streps*) and kill many resistant bacteria. However, fluoroquinolones are one of the two main groups of drugs for Gram negative infections in people and there will be pressure from the medical profession to reduce their use in animals to slow the development of resistance.

Mechanism of action

Bacterial DNA normally forms superhelical twists under the influence of the enzyme DNA-gyrase (topoisomerase II) (most important in Gram negatives) and to-

MOVIE 7.2 DNA gyrase

Fluoroquinolones inhibit supercoiling by blocking DNA gyrase.

poisomerase IV (most important in Gram positives). DNA gyrase and topoisomerase IV are composed of four subunits; two each of GyrA and GyrB, and ParC and ParE respectively. The enzymes bind to the DNA, cut it, then allow a stand to pass through and join the DNA again (see diagram). This process of winding and unwinding is necessary for protein binding to DNA such as occurs in DNA transcription and DNA repair. Fluoroquinolones inhibit DNA-gyrase and topoisomerase IV (the balance of effects being different with individual drugs), resulting in failure of DNA super helix formation and management. This happens in two stages - the fluoroquinolone binds to the enzyme - DNA complex (bacteriostatic) then causes the release of unjoined DNA (bacteriocidal). Other mechanisms may also be involved in the bactericidal action. This may partly account for high concentrations of quinolones having less bactericidal activity (in vitro).

Fluoroquinolones have been shown to cause a marked post-antibiotic effect, ie, a continued bacterial growth inhibition in those bacteria surviving after the removal of the drug from the bacterial media. Nevertheless, the rate of bactericidal action is proportional to the length of time above MIC, so efficacy might be improved by increasing dose frequency above that recommended.

Spectrum of activity

Ciprofloxacin and enrofloxacin are mainly active against aerobic Gram negative organisms, but are not very active against Gram positive aerobes (except for reasonable activity against Staphs) or anaerobic organisms. They are reasonably active against Mycoplasma. Some activity is reported against Pseudomonas, Rickettsia, Chlamydia, and Mycobacteria. Newer drugs (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin, and trovafloxacin) have more activity against Gram positives, especially Streps.

Resistance

Fluoroquinolone resistant isolates usually contain one or more mutations in a small section of GyrA or ParC; mutation in GyrB and ParE is rare, but getting commoner. In Gram negative bacteria, where mutations have given rise to a resistant DNA gyrase (low level resistant), mutations then occur in the topoisomerase IV genes (and vice versa for Gram positive bacteria) to give a highly resistant bacterium. Newer drugs which inhibit both enzymes give rise to less resistance.

In addition, there are genes that influence the uptake of the drug into the bacterial cell and efflux pumps that can be over expressed to enhance excretion of quinolones from the cell. This enhanced efflux in turn causes increased MICs of several drugs, including fluoroquinolones, tetracycline, chloramphenicol, and ampicillin. It has been suggested that mutations enhancing efflux occur as a first step, allowing the bacteria to survive so that mutations can accumulate in genes encoding the target proteins. Plasmid mediated, transferable fluoroquinolone resistance has recently been described; its mechanism of resistance is by coding for a protein that binds the drug and inactivates it.

Clinically significant resistance occurs in *Pseudomonas*, *Staph aureus* and *Campylobacter*. Resistance in *Pseudomonas* and *Staph aureus* is likely to develop over a course of treatment. The resistance in *E. coli* isolated from dogs in NZ is rising at a much faster rate than that in *E. coli* isolated from people here.

Toxicity

Mammals do not super coil their DNA so these drugs are relatively safe. Injury to growing articular cartilage in young animals (dogs are most sensitive) occurs - usually at high doses. Use in children has shown reversible joint pain in 1.5% of cases, but there is *in vitro* evidence of chondrocyte damage in adults. There is a small risk of tendonitis in old people, especially when combined with steroids. Avoid use in young animals if possible. Nausea, vomiting and diarrhoea are the commonest side effects in people.

Very high doses may cause embryonic losses in some species and ocular damage in dogs, although intravitreous injections have been used in people. Retinal damage has been reported in cats at clinical doses of enrofloxacin and it is now recommended to **avoid enrofloxacin in cats** and certainly do not give more than 5mg/kg. Orbifloxacin does not appear to cause this problem, but experience is limited.

Fluoroquinolones can block $GABA_A$ receptors (although some drugs are worse than others - norfloxacin worst, ofloxacin best), and this effect is potentiated by NSAIDs. Enrofloxacin can induce hallucinations and rarely convulsions in humans (ofloxacin is used instead). Fluoroquinolones should probably not be given to animals with a history of seizures.

Photosensitivity (potentiation of the effects of UVA) and tachyarrhythmias have been recorded in people.

Pharmacokinetics

Fluoroquinolones exhibit variable gastrointestinal absorption in most species, with food inhibiting absorption. Concomitant administration of antacids containing magnesium or aluminium, or of sucralfate almost completely prevents oral absorption.

Oral bioavailability of enrofloxacin in foals appears to be good, but chondrotoxicity prevents its use.

Norfloxacin is inactivated at pH < 6.8 and may cause crystalluria in alkaline urine.

Fluoroquinolones are partially metabolised in the liver and are excreted as both active and inactive metabolites (ciprofloxacin is the major active metabolite of enrofloxacin), and as parent drug. They may be found in both the bile and urine at 20 times the plasma concentration.

Fluoroquinolones are rapidly and widely distributed to many tissues including prostate, testes, urinary bladder wall, renal parenchyma, uterus, gall bladder, and to the CSF across healthy or inflamed meninges. They are actively concentrated in neutrophils, which may carry the drugs to the site of infection. Topical norfloxacin can penetrate all chambers of the eye to concentrations above MIC for most pathogens.

Doses of fluoroquinolones should be reduced in renal failure.

Pharmaceutical considerations

Drugs which inhibit protein synthesis, eg rifampicin and chloramphenicol, are antagonistic to the fluoroquinolones.

Politics

Fluoroquinolones and group 4 cephalosporins are the main drugs used to treat serious Gram negative infections in people. The medical profession is not happy about their use in animals - **use them only for serious infections where nothing else is likely to work**, preferably after a culture and sensitivity test. This is a legal requirement for some products in food animals.

The future?

After a rush of new 8-methoxyfluoroquinolones onto the market, development of new drugs has paused, possibly because some of the newer drugs have caused serious cardiovascular side effects in people. Don't hold your breath for new veterinary drugs.

Other antibacterials

commonly used drugs

none

Other antibacterials

- ☑ hexamine is occasionally used when all else fails in urinary tract infections

Hexamine (methenamine USAN) does not fit into any classification system so it is stuck in here at the end. It is sometimes called a urinary antiseptic. It is a complex amine which is excreted into the urine and broken down in acid urine to formalin, which kills any bacteria present. There is no resistance as such, but bacteria which alkalinise the urine stop the formation of the formalin. Still available in NZ (for people) but not used much (as an antibiotic at any rate - it is used as a fuel for camping stoves and in a wide range of industrial applications).

Triclosan is an old drug traditionally used as an antiseptic mouthwash. It has recently been discovered to act specifically against bacterial fatty acid synthesis and is being reinvestigated. It is effective against most Gram positive and Gram negative bacteria except *Pseudomonas*. It is also active against some fungi and protozoa. It is being investigated for malaria in man.

Quinoxalines such as carbadox (still used here) and olaquindox (no longer licensed) are mainly G- drugs previously used for growth promotion in pigs, now used to treat scours and prevent swine dysentery. These have been in use since before science was involved in drug licensing and very little is known about them except that they are potentially carcinogenic and neurotoxic.

Heavy metals have antibacterial properties. Silver is the only one used therapeutically (usually in combination with sulphadiazine), copper and arsenic are used as growth promoters (qv). Oral colloidal silver was used as an antibacterial before antibiotics were discovered, but is not very effective in any infection. It has recently enjoyed a resurgence of popularity as a “natural” medicine. Overdose can irreversibly turn people's skin a blue gray colour - no information in animals.

Ionophores

commonly used drugs

monensin

Ionophores

- ☑ coccidiostatic - not antibacterial
- ☑ vets not usually involved in use
- ☑ potentially toxic to horses and dogs

Ionophores are another family of antibiotics produced by various species of *Streptomyces*. They are highly lipophilic monocarboxylic acids that are toxic to many protozoa, fungi - and higher organisms. There are a number of ionophores licensed for use in NZ (lasalocid, maduramicin, monensin, narasin, salinomycin, semduramicin). These are mostly fed in large quantities to chickens - vets are usually not involved.

nb - although these are antibiotics, they are not antibacterial, and are sometimes included or excluded from discussion on antibiotics for political reasons.

Mechanism

The exterior of their molecules are hydrophobic, and the interior hydrophilic, being able to bind one (uniporters) or more (antiporters) cations. Their lipophilic nature allows them to readily penetrate cell membranes and act as a pore, allowing uncontrolled influx and/or efflux of selected ions, such as potassium and sodium. This uncontrolled ion flow interferes with the osmotic control mechanisms in cells, often leading to cell death.

The different drugs transport different ions across the cell membrane: monensin - mainly Na^{+}; lasalocid - Ca^{++} and Mg^{++}, and to a lesser extent, K^{+}; salinomycin and narasin - mainly K^{+}.

Spectrum

Protozoa, mainly *Eimeria* spp.in animals, but also *Plasmodium* (malaria).

The susceptibility of Gram positive bacteria to ionophores varies according to bacterial cell wall structure. The structure of the cell envelope of Gram negative bacteria appears to influence susceptibility to ionophores through differences in ionophore binding and permeability. They have some effect against Gram positives, importantly Cl perfringens, and Mycoplasma, but most Gram negatives are resistant (ionophores do not reach their cell membranes).

B hyodysenteriae and *Lawsonia intracellularis* in pigs can be controlled clinically with ionophores. Monensin has been effecitive against an *Enterococcus*-like organism in trout.

The polyene antifungals nysatin and amphoteracin B are also ionophores.

Resistance

Organisms which produce ionophores have efflux pumps to get rid of the drugs, but the mechanism of resistance in pathogens is unknown.

Increased resistance to ionophores has been reported for *Staphs* in pigs and cattle and for enterococci in chickens and pigs. It has also been reported in the rumen bacterium, *Prevotella (Bacteroides) ruminicola* M384, which appeared to have arisen from chromosomal mutation not plasmid transfer, possibly resulting in decreased porosity of the outer membrane.

There appears to be no development of resistance in *Clostridia*.

The effects of the drugs are markedly influenced by the growth media, which adds uncertainty to reports of resistance.

Cross-resistance to other ionophores can occur, but resistance is not complete. Anecdotal evidence of resistance in chickens in NZ is emerging.

Toxicity

Monensin, and probably the other ionophores, is very toxic in low concentration for horses and dogs and in high concentration for cattle (myocardial degeneration). They are also very toxic to people and are not used in this species.

LD_{50}s mg/kg

- cattle 22 - 80
- horses 1 - 2
- sheep 12
- pigs 16
- dog 10 - 20 (bitches lower)
- chicken 200

Turkeys, Guinea fowl and Japanese quail are more susceptible than chickens.

Use

Monensin is by far the most widely used, mainly as a coccidiostat. Ionophores are primarily used in broilers, but also in layer replacements, goats, sheep and cattle for prophylactic control of coccidiosis caused by Eimeria spp. They may also have the useful side effect of preventing necrotic enteritis (Cl perfringens). They are also used to control swine dysentry and proliferative enteropathy in pigs. Salinomycin is also licensed as a growth promoter for pigs and beef cattle. Monensin is licensed for controlling bloat and ketosis as well as improving food conversion efficiency in cattle.

The improved feed efficiency effects in ruminants is due in part to a increase in the proportion of Gram negative to Gram positive bacteria. However, ionophores also appear to affect Gram negative bacteria, which may either be sensitive at concentrations likely in vivo and subsequently become resistant, or they may be able to grow but the presence of the ionophore causes altered metabolism. The net result is an increase in the proportion of propionate to acetate, and decrease in rumen ammonia, probably as a result of reduced hydrolysis of peptides, along with less proteolysis and deamination of amino acids in the rumen.

Bloat is a major health issue for grazing cattle, and coccidiosis of major concern to monogastric animals and neonatal ruminants. The effects of coccidiosis are debilitating and can be fatal, either directly or through increased susceptibility to other diseases such as necrotic enteritis, caused by Clostridium perfringens, in poultry.

Other anti-bloat treatments are available, however, none are suitable for extensively grazed animals. The effect of monensin of reducing methane production and emission by ruminants, a major contributor to the greenhouse effect, could be considered beneficial to the environment.

Interactions

Monensin reduces the uptake of macrolides into macrophages in vitro. Ionophores and tiamulin interact to severely retard growth in pigs.

Human Use

Not used in people because of toxicity, but antimalarial use is a possibility in the future.

Politics

Ionophores are used by the ton and are technically antibiotics, so are sometimes included in the animal antibiotic use figures by people trying to overemphasise the misuse of antibiotics in animals. If you want to use a smaller number for the quantity of clinically important drugs used in animals, talk about antibacterials.

The future?

The future?

- ☑ antibiotics are expensive to develop
- ☑ no new groups near clinical use yet
- ☑ there will be pressure to avoid use in animals

The WHO has prioritised some pathogens for antibiotic development: top of the list is extensively drug resistant TB, with carbapenem resistant *Acinetobacter*, *Pseudomonas* and *Enterobacteriacae* critical; vancomycin resistant *Enterococcus faecium* and *Staph. aureus*, clarithromycin resistant *Helicobacter*, fluoroquinolone resistant *Salmonella* and *Campylobacter* and cephalosporin / fluoroquinolone resistant *Neisseria* high priority. Many of these are also relevant to veterinary practice.

Most effort in new antibiotic discovery is currently (2017) going into new drugs in existing classes and new ß lactamase inhibitors / combinations. However, there are five drugs in clinical trials in people with new mechanisms of action.

There is also some promising research on getting old drugs into bacteria more efficiently, eg cephalosporins attached to siderophores to target Gram - bacteria.

Bacterial fatty acid synthesis is starting to be targeted (Fabl inhibitors) although several old drugs such as triclosan and isoniazid have recently been shown to act by this mechanism. Mammals get their fatty acids from food so should not be affected by these drugs.

Some new pleuromutilins are in the pipeline - these drugs are not used yet in people but are widely given to pigs.

The genome of many major pathogens is in the process of being sequenced. This is likely to lead to a variety of new approaches to killing bacteria or stopping them from infecting animals. Genes which code for resistance will be high on the hit list, or even the processes which allow bacteria to mutate happily without killing themselves in the process. We still do not know much about all the slimy things which live in soil, so people are still growing these and looking for antibacterial effects.

Expect plenty of new antibiotics and other drugs targeted specifically at processes which only occur in pathogens. Also expect heavy pressure to prevent their use in animals. On a more optimistic note, many of the drugs which interfere with DNA transcription will be potential carcinogens; if they are rejected from human medicine for this reason, they may make it into veterinary medicine, although probably only for small animals.

Further reading

Walsh, C. 2003, Where will new antibiotics come from? Nature Reviews: Microbiology, 1, 65 - 70

TABLE 7.22.1 Summary of antibiotics

Group	Drugs	Spectrum
penicillins	benzylpenicillin	G+, anaer, (G-)
	ampicillin, amoxycillin	G+, G-, anaer,
	co-amoxyclav	ß-l Staphs, G+, G-, anaer
	cloxacillin	ß-l Staphs, G+, anaer
cephalosporins	G1 - cephalexin	ß-l Staphs, G+, anaer, (G-)
	G2 - cefuroxime	G- (G+)
	G3 - ceftiofur	G-
bacitracin		G+, ß-l Staphs
polymixins		
tetracyclines	oxytetracycline, doxyclycline	all - but variable resistance
chloramphenicols	chloramphenicol, florfenicol	all - but variable resistance
macrolides & similar drugs	erythromycin, tylosin, licomycin, tiamulin	G+, ß-l Staphs, mycoplasma, spirochaetes
aminoglycosides	streptomycin, neomycin, gentamicin	G-
sulphonamides	sulphadiazine	G+, G-
potentiated sulphonamides	co-trimazine, co-trimoxazole	ß-l Staphs, G+, G-, anaer
fluoroquinolones	enrofloxacin	G-, (ß-l Staphs, some G+)
nitrofurans	nitrofurantoin	
nitroimidazoles	metronidazole	anaer
rifamycins	rifampicin	G+, ß-l Staphs
odds and sods	novobiocin	ß-l Staphs

Drugs and particularly spectrum will change!!!

Therapeutic principles

Therapeutic principles

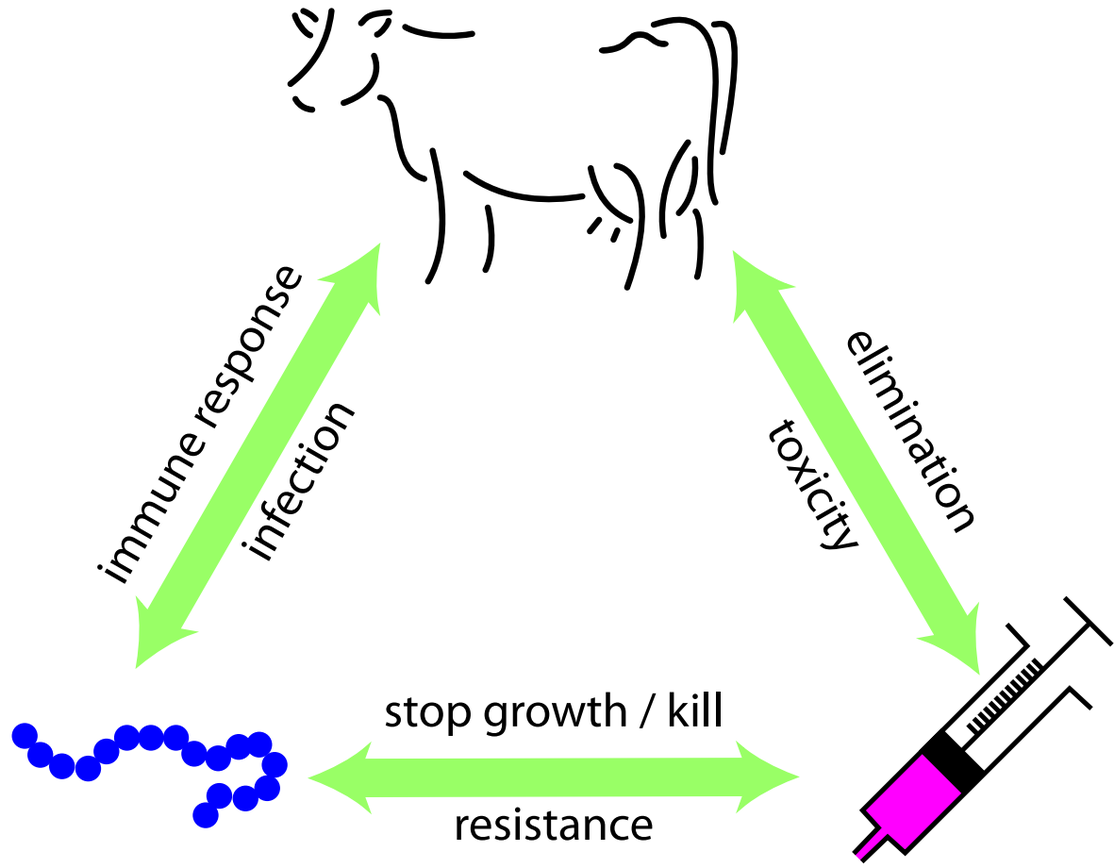
☑ does the antibiotic kill the bacteria?

☑ does it get to where the bacteria are?

☑ is clinically significant resistance likely to develop:

1. in the animal?
2. in contact animals?
3. in the owner?

FIGURE 7.3 The chemotherapeutic triangle



The chemotherapeutic triangle

When antimicrobial drugs are administered to an animal (the host) infected with a pathogenic micro-organism, there is a triangular interaction between the the host, the micro-organism and the antimicrobial drug. These interactions must be considered when formulating a rational protocol for antibiotic use.

Host responses to antibiotics include:

- no effect
- allergic responses
- tissue drug residue deposition
- toxicity
- drug interactions with other therapy
- Bacterial responses to antibiotics include:

- death of the micro-organism
- slowing or stopping of bacterial replication
- development of resistance
- super-infection

Success of antimicrobial therapy depends on achieving one of the two desirable responses while keeping undesirable effects to a minimum. Remember, the underlying principle of all drug use which was initially stated by Hippocrates (460-377 BC): “Primum non nocare.” You must balance the risk of undesirable effects against the probability of benefits.

Drug selection process

For any antibiotic to work, the bacteria must be susceptible to the drug, and the drug must get to where the bacteria are. You should also consider the chances of clinically significant resistance developing, either in the animal(s) or environment / owner. There are also a number of other desirable factors. Follow the process below.

1. Make a diagnosis. Any treatment in the absence of a diagnosis is irrational. Therefore, before selecting an antimicrobial drug as (part of) a treatment, an attempt must be made to confirm that an infection exists. Giving an antibiotic in the absence of a susceptible infection will only lead to the development of resistance.

2. Identify the (class of) bacterium causing, or likely to be causing the infection. A sample, smear and Gram stain is useful to help with this. In the practical clinical situation, it is not always possible to sample, smear, identify and culture the causative bacterium. You may have to rely on knowledge of the incidence of bacterial disease in your practice, and on the patterns of disease caused by commonly pathogens. This allows an empirical choice of antimicrobial. (A word of warning: charts which are to be found in text books showing incidence of bacterial diseases should be used as a guide only. Major differences occur in host species and between countries.) It is best to isolate, culture and test the resistance of the infective organism to available drugs. The infective microorganism must be sensitive to the drug chosen.

3. Consider pharmacokinetics. The drug must come into contact with the bacteria, ie, it must be adequately distributed to the infected tissue and it must be soluble in the milieu of the infected tissue matrix. The drug must be able to reach high enough concentrations at the site of the infection to affect the bacteria, ie, the drug must achieve a concentration greater than the MIC for the causative bacteria at the site of the infection (ideally 4 - 5 times the MIC should be achieved in the plasma). The drug must be present for sufficient length of time at the site of the infection but must not reside in tissues excessively (especially in food producing animals). To achieve all this, the correct dose and frequency must be chosen.

4. Consider resistance. It is better to choose a drug for which resistance is slower or less likely to develop. A narrow spectrum drug will exert less selection pressure on non target organisms. Use drugs which are less likely to produce clinically significant resistance in the animal, owner or environment; eg, if a penicillin is likely to work as well as a cephalosporin, use the penicillin.

5. Consider host factors

- Species: what drugs are registered?
- Is this a food producing animal? - withholding times!
- Are there any other restrictions (racing animals)?
- What routes of administration are practical and are there appropriate formulations?
- Is the animal pregnant / lactating?
- Age: are there special toxicity or dose rate considerations?
- Body weight: are there special toxicity or practical dosing considerations?
- Is the animal adequately hydrated and do the animal’s kidneys work?
- Is there evidence of biliary obstruction?
- Is the animal immunocompetant?

6. Consider the mechanism of action of the antimicrobial drug of choice. Until recently it was thought better to choose a drug which is nominally bactericidal over one which is merely bacteriostatic. However, it is now clear that little information exists as to whether a particular antimicrobial drug is bactericidal or bacteriostatic against a particular infective organism at the concentration reached at the site of infection. It is more important to consider whether or not the drug is likely to penetrate well to the site of infection, and whether it will be active in that environment. The distinction between bacteriostatic and bactericidal drugs is probably only important in immunocompromised animals.

7. The probable toxic effects of the chosen drug should be considered. The frequency of immune mediated reactions to the antimicrobial drug formulation should be considered.

8. Interactions between the chosen drug and any other present or potential medications should be anticipated.

9 The propensity for the drug to initiate super-infections should be considered, especially in some species (eg, the horse, guinea pig).

10. The ease of administration, and the pain and / or stress caused by the administration of the chosen drug should be considered. These factors are important both from client compliance and animal ethical view points. The pain caused by deep intramuscular injections of certain antibiotic preparations is probably overlooked as a major cause of continuing debilitation.

11. The cost of the chosen drug should be considered.

12. Supportive treatment may make a big difference to the outcome.

Finally, assess the risk / benefit ratio! (but see also the guidelines below).

13. Monitor the effects of the drug - reduction in fever, etc - to check that your selection was suitable. Be prepared to go back to step 1!

Common problems

Factors under control of the veterinarian:

The most common reason for misuse of antibiotics is a failure to make a diagnosis. This often derives from an invalid assumption that an elevated temperature or fever means an infection. The diagnosis “fever of unknown origin” is not in itself sufficient justification for administration of antimicrobial drugs.

Another common error is to fail to identify the infective organism, even empirically. This leads to the frequent prescription of broad spectrum antibiotics. Broad spectrum antibiotics are more likely than those with a narrower spectrum to induce super-infection and bacterial resistance. From the legal point of view, the medical record should indicate the reason for the choice of drug. Habitual use of a broad spectrum antimicrobial drug indicates a low (and unacceptable) standard of diagnosis.

Isolation of the wrong organism occurs frequently. Therefore, laboratory reports should be considered carefully, not blindly acted upon. It is necessary to reconsider the method of sampling (aerobic vs anaerobic), and the suspected agent (bacteria, mycoplasma, viruses).

Inappropriate choice of antimicrobial drug is a leading cause of failure of therapy. Assuming an organism has been identified, there really is no excuse for this. Often this error occurs because of a lack of knowledge. Does the drug of choice cross the blood/brain barrier? Does it have access to the prostate? Is it excreted in an active form in the urine? etc...

Inappropriate dose schedules (too little, too infrequently, not for long enough), and failure of client compliance in dosing are frequent causes for failure of antimicrobial therapy.

Failure will often result from not providing adequate ancillary therapy, eg, drainage for an abscess.

Factors not (necessarily) under control of the veterinary surgeon

Bacterial resistance to the chosen antimicrobial drug occurs frequently in some clinical settings. In general, resistance patterns cannot be predicted. Bacterial resistance to the chosen antimicrobial drug can also develop during the course of therapy.

Mixed infections can result in disease in which it is difficult to adequately identify all active bacteria.

Lack of correlation between in vitro tests and in vivo sensitivity occurs frequently. A knowledge of pharmacokinetics and pathology should allow this to be predicted in most cases.

Occasionally, treatment has to be stopped because of side effects.

“Antimicrobial sensitivity” testing

Samples for isolation and culture of bacteria from infected tissues can be very useful in selection of appropriate drugs since different bacterial species have different patterns of antimicrobial sensitivity. However, not all resistance patterns can be predicted. Therefore, testing the sensitivity of bacterial isolates to available drugs should be carried out where practicable.

If an organism is resistant to an antimicrobial drug in vitro, then it will almost certainly be resistant to the same drug in vivo (assuming it has been properly cultured on the correct medium). However, if an antimicrobial drug is effective in vitro, it is

not necessarily effective in vivo. Hence, laboratory testing is really resistance testing and not sensitivity testing.

The results of Kirby-Bauer sensitivity tests can be misleading. The diffusion of the drug through the culture media may be impeded or enhanced relative to other drugs, leading to altered expectations of its efficacy. The media may contain factors which allow the bacteria to avoid toxicity, e.g. para-aminobenzoic (PABA) will antagonise the effect of sulphonamide antimicrobials. Different labs use different techniques, although the American NCCLS protocols are probably commonest. MIC data is much more useful than merely “R” or “S”.

The presence of antibiotic in samples taken from animals already treated with an antibiotic may prevent bacterial growth in vitro, despite their failure to do so in vivo. So take the samples for culture and sensitivity testing before you give the drug. If empirical therapy has been started and has failed, then all antimicrobial drugs should be withdrawn 2 to 3 days before samples are taken for culture.

From the practical point of view, it is important to request the testing for sensitivity to drugs which are available for use by the route necessary to reach the site of infection.

Prophylaxis

Rational use of antimicrobial drugs for prevention of infectious disease is limited to very few applications: either where there is a predictable high risk of infection which cannot be reduced in any other way, eg, immunocompromised patients, or a few sick animals in a herd which cannot be separated; or where the consequences of infection would be disastrous, eg, some orthopaedic implants.

In small animal medicine, prophylactic antimicrobial therapy is only rational for severely immunocompromised patients, such as those with diabetes mellitus, those with myelogenous leukaemia, or those on immunosuppressive chemotherapy. In procedures such as catheter placement there is no justification for the use of antimicrobial drugs. Aseptic technique when placing and regular replacement of intravenous catheters should be sufficient to prevent infections.

In food animal medicine, antibiotics are frequently overused to prevent infections. They are not a susbtitute for good hygiene. See guidelines below.

The use of antibiotics in surgical procedures should be limited to cases where bacteraemia is likely to be produced **and** the animal is immunocompromised **or** has an implant of some sort (eg, an orthopaedic plate). Antibiotics are not a substitute for aseptic technique!

Guidelines for antimicrobial prophylaxis in surgery

Use penicillins or cephalosporins, iv if possible. They are bactericidal, achieve peak tissue levels rapidly (approximately 20 - 40 mins, so give the drug half an hour before surgery), and are relatively non toxic. The more strongly protein bound drugs in these classes (oxacillin, nafcillin) do not penetrate fibrin as well as the less strongly protein bound (ampicillin, penicillin). Use intermittent bolus dosing at half the normal dosing intervals (about every 2 hours for iv ß-lactams). This regime produces approximately 2 - 4 times higher tissue concentrations than does iv infusion. Continue therapy throughout surgery but there is no value in prophylactic treatment afterwards.

Cephazolin sodium 20mg/kg iv every 2 hours gives broad spectrum cover.

Review - Moore, A.H. 1996 Rational use of antibiotics in surgery. The Veterinary Annual, 36, 57 - 66

Before using antibiotics, ask:

Does it kill the bacteria?

Does it get to where the bacteria are?

Is clinically significant resistance likely to develop?

- in the animal?
- in contact animals?
- in the owner?

Stewardship

Stewardship

- ☑ Antibiotics will become less useful if they are used inappropriately
- ☑ Follow the guidelines - any guidelines!
- ☑ the more important an antibiotic is in human medicine, the more care, thought and documentation must go into its veterinary use

There is a plethora of guidelines on prudent use of antibiotics. The guidelines below were produced by the BVA and published in the Veterinary Record of 14th November 1998, pp565 - 566. The NZVA basically endorses the BVA guidelines, although the resistance situation is much better here (so far). Each Special Interest Branch of the NZVA is working on guidelines for their species - check the website http://www.vets.org.nz

These guidelines are good general principles. Following guidelines such as these is a good way of making sure that you are using these drugs responsibly. The section on regulatory concerns is not directly relevant to NZ, but gives some idea of the shape of things to come!

BVA Guidelines

These guidelines are intended to act as an adjunct to clinical judgment. It may not be possible for every consideration to be observed in every case, but they should always form part of an automatic checklist when deciding on an antimicrobial use regime

Introduction

(1) The use of antimicrobial agents provides an effective method for the control and treatment of infectious or contagious diseases caused by bacteria and certain other micro-organisms. Their application in veterinary.practice since the 1950s has assisted in ensuring the health of livestock and companion animals. Antimicrobial use has also enabled the production of meat and milk products which are unlikely to present disease problems for the consumer or those concerned with their production. Antimicrobial use is also justifiable on animal welfare grounds ('freedom' to receive treatment for disease is incorporated in the Welfare Codes).

(2) It must be remembered at all times that widespread use of antimicrobials is not a substitute for efficient management or good husbandry practice.

Principles of antimicrobial use

(3) The appropriate selection of antimicrobials in practice is a critical decision and should be based on:

(a) accurate diagnosis;

(b) known or predictable sensitivities (sensitivity testing);

(c) known pharmacokinetics/tissue distribution to ensure the selected therapeutic reaches the site of infection;

(d) known status of immunocompetence.

Routine considerations

(4) Antimicrobial agents should only be used when it is known or suspected that an infectious agent is present which will be susceptible to such therapy.

(5) When antimicrobial agents are used, every effort should be made to determine the origin of the problem and to ascertain the most effective treatment.

(6) While therapy may need to be initiated before the results of diagnostic or sensitivity tests are known, it will need to be reassessed as test results become available. In such circumstances, before the results are known, decisions as to the choice of antimicrobial will need to be made:

(a) in the light of what has previously been effective in similar types of problems;

and

(b) on any knowledge of previous antimicrobial efficacy on the premises.

(7) Infectious disease should be treated with the antimicrobial found, on appropriate testing, to be most efficacious and also based on the previous history of effective antimicrobial use on the premises.

(8) Careful calculation of dose is always important, but in particular if an extra-label use of a product is being considered. In such cases, caution needs to be exercised regarding meat and milk withholding periods.

(9) The efficacy of all disease treatments should be monitored and, if part of the treatment regime was undertaken by the livestock or pet owner, a check should be made to ensure that they have understood fully the instructions on dosage and duration of any antimicrobial use. Quantities of antimicrobials left with the animal owner should correctly reflect the needs, to avoid an over-supply.

(10) Antimicrobial usage should always be part of, and not a replacement for, an integrated disease control programme. Such a programme is likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination, etc.

(11) Continued antimicrobial use in such control programmes should be regularly assessed as to effectiveness and whether their use can be reduced or stopped.

(12) Protocols should be agreed between the veterinary surgeon and the client as to when veterinary involvement is required in on-going disease conditions. These protocols must be regularly and frequently reviewed and updated.

(13) Protocols should be agreed and docu-mented for treatment of all endemic conditions on the farm or other livestock-rearing or production premises. These protocols must be regularly reviewed and updated.

Dosage strategy recommendations

(14) In order to minimise the likelihood of broad antimicrobial resistance developing, it is recommended that where an appropriate narrow spectrum agent is made available it should be selected in preference to a broad spectrum agent, which will exert a greater selection pressure on commensal bacteria.

(15) It is recommended that optimal therapeutic dosage strategies be used and that all efforts be made to avoid administration of sub therapeutic dosages, which can lead to a lack of efficacy (and, in some specific cases, such as fluoroquinolones and erythromycin, has been shown to induce resistance). Dosage recommendations as laid down in the relevant data sheet should always be followed.

(16) Should there be recurrence of disease following successful treatment (and control) of an outbreak, it will need to be investigated thoroughly to ascertain why this has occurred and the most suitable therapy to be used.

(17) Use of antimicrobials for the prevention of disease can only be justified where it can be shown that a particular disease is present on the premises, or is likely to become so, and that strategic antimicrobial use will prevent clinical outbreaks of that disease.

(18) Antimicrobials need to be used with care to maintain their efficacy. If possible, look for alternative methods of disease control (vaccination) to reduce antimicrobial use.

Regulatory concerns

(19) Any use of antimicrobials outside normal data sheet recommendations (in accordance with the prescribing ‘cascade’) should be carefully justified and documented.

(20) Note must be made, and documented, of any adverse reactions which may be observed or a decline in efficacy of a previously effective antimicrobial.

(21) All antimicrobials in use must be used and stored correctly in the manner outlined in the BVA Code of Practice on Medicines. In accordance with statutory requirements, full records must be kept of all products used.

(22) Consideration must always be given to the health of the person administering the products. Any necessary warnings should be issued.

Stick to the guidelines!

If that's too difficult, there are several simplified versions over the page. BEVA also have a good but longer version here.

FIGURE 7.4 BVA responsible use poster

Are you PROTECTing your antibacterials?

PROTECT

P ractice policy

- A practice policy for empirical prescribing (whilst awaiting cultures) can optimize therapy, and minimize inappropriate use of antibacterials

R educe prophylaxis

- Antibacterials are **not** a substitute for surgical asepsis
- Prophylactic antibacterials are only appropriate in a few medical cases (e.g. immunocompromised patients)

O ther options

- Reduce inappropriate antibacterial prescribing (e.g. due to client pressure, in uncomplicated viral infections or self-limiting disease) by providing symptomatic relief (e.g. analgesia, cough suppressants)
- Use cytology and culture to diagnose bacterial infection correctly
- Effective lavage and debridement of infected material reduces the need for antibacterials
- Using topical preparations reduces selection pressure on resistant intestinal flora

T ypes of bacteria and drugs

- Consider which bacteria are likely to be involved, e.g. anaerobic/aerobic, Gram +ve *versus* Gram -ve
- Consider the distribution and penetration of the drug
- Consider any potential side effects

E mploy narrow spectrum

- It is better to use narrow-spectrum antibacterials as they limit effects on commensal bacteria
- Avoid using certain antibacterials as first line agents; only use when other agents are ineffective (ideally determined by culture and sensitivity testing)

C ulture and sensitivity

- Culture promptly when prolonged courses are likely to be needed (e.g. pyoderma, otitis externa, deep/surgical wound infection) or when empirical dosing has failed

T reat effectively

- Treat long enough and at a sufficient dose – **and then stop**
- Avoid underdosing
- Repeat culture after long courses

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Updated March 2012

Write your practice policy on empirical antibacterial use in the boxes below

Periodontal disease

amoxicillin OR amoxicillin/clavulanate OR ampicillin OR clindamycin OR metronidazole + spiramycin. With or without chlorhexidine mouthwash.

Practice Policy:

Respiratory infections

Bacterial pneumonia (including aspiration):
- cats: amoxicillin/clavulanate OR doxycycline.
- dogs: aminoglycoside* + metronidazole* OR amoxicillin + fluoroquinolone OR amoxicillin + metronidazole* OR doxycycline OR oxytetracycline.

Practice Policy:

Bacterial rhinitis, chronic rhinitis and sinusitis: amoxicillin/clavulanate

Practice Policy:

Kennel cough: no antibacterials in mild cases; more severe: amoxicillin/clavulanate OR doxycycline OR oxytetracycline.

Practice Policy:

Suspected ***Mycoplasma*:**
- cats: azithromycin* OR doxycycline.
- dogs: azithromycin* OR doxycycline OR oxytetracycline.

Practice Policy:

Pyothorax:
- cats: amoxicillin/clavulanate
- dogs: ampicillin + fluoroquinolone OR clindamycin + fluoroquinolone OR metronidazole* + fluoroquinolone.

Practice Policy:

Gastrointestinal infections

Acute diarrhoea with complications: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Anal sacculitis: lavage plus topical installation (saline or chlorhexidine); amoxicillin/clavulanate.

Practice Policy:

Confirmed ***Campylobacter* (if clinically significant):** enrofloxacin OR erythromycin*.

Practice Policy:

Cholangitis/cholangiohepatitis: amoxicillin OR amoxicillin/clavulanate OR ampicillin OR cefalexin. Metronidazole* may be added in dogs.

Practice Policy:

Gastrointestinal bleeding or bacterial translocation: metronidazole* + amoxicillin/clavulanate OR metronidazole* + 1st generation cephalosporin. Add fluoroquinolones or aminoglycosides* to improve Gram -ve cover.

Practice Policy:

Suspected ***Helicobacter*:** amoxicillin + metronidazole* OR azithromycin* + tindizole OR clarithromycin* + metronidazole*. In combination with bismuth *(caution in cats)* OR famotidine OR omeprazole OR ranitidine.

Practice Policy:

Genitourinary infections

Cystitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine. Many *cats* with cystitis do not have bacterial infections – routine antibacterials not required.

Practice Policy:

Endometritis/Pyometra: amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Suspected ***Leptospira*:** ampicillin OR pencillin G; doxycycline for carriers. Aminopenicillins treat bacteraemia but do not address carrier state.

Practice Policy:

Prostatitis (acute): fluoroquinolones OR trimethoprim/sulfadiazine. Culture required in chronic cases.

Practice Policy:

Pyelonephritis (acute): trimethoprim/sulfadiazine. Culture required in chronic cases.

Practice Policy:

Struvite urolithasis (dog): amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Orthopaedic infections

Discospondylitis/Osteomyelitis: amoxicillin/clavulanate OR 1st generation cephalosporin OR clindamycin. Long courses (6–8 wk) may be needed.

Practice Policy:

Septic arthritis: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Skin infections

Bite and other traumatic wounds: Lance, debride and lavage. In cat bites amoxicillin first choice; otherwise choice as for Pyoderma. Heavily infected/deeper injuries: metronidazole OR amoxicillin/clavulanate + fluoroquinolone are appropriate while awaiting culture results.

Practice Policy:

Infected traumatic wound: amoxicillin/clavulanate OR 1st generation cephalosporin.

Practice Policy:

Pyoderma:
Empirical choice of antibacterials suitable for surface and superficial pyoderma (if no resistance or treatment failure) but culture required for deep pyodermas.
- **Topical:** chlorhexidine AND/OR fusidic acid OR silver sulfadiazine*. (Antifungals for concurrent *Malassezia* often useful.)
- **Systemic:** amoxicillin/clavulanate OR cefadroxil OR cefalexin OR cefovecin (if problems expected with administration/compliance) OR clindamycin OR fluoroquinolones (if others inappropriate). Continue 1 week beyond resolution of clinical signs.

Practice Policy:

Pyoderma (idiopathic recurrent):
- **Topical therapy** important: antimicrobial shampoos/rinses, especially chlorhexidine.
- **Systemic:** Alternatives to antibacterials include immunostimulants (Staph Phage Lysate, autogenous vaccine). Last resort is pulse therapy 2–3 consecutive days/wk.

Practice Policy:

Pyoderma (confirmed MRSA/MRSP): choice based on sensitivity. If sensitivity not known, use topical chlorhexidine AND/OR fusidic acid OR systemic tetracyclines OR trimethoprim/sulfadiazine.

Practice Policy:

Pyogranuloma: as for Pyoderma but *culture essential and may need to be repeated.* Filamentous bacteria: clindamycin OR doxycycline OR trimethoprim/sulphonamide. Mycobacteria: fluoroquinolones ± doxycyline.

Practice Policy:

Ear infections

Otitis externa (erythroceruminous):
- **Topical:** fusidic acid OR framycetin OR gentamicin OR marbofloxacin OR orbifloxacin OR polymixin B/miconazole. (Antifungals to treat concurrent *Malassezia* will often be useful.) Combine with effective antibacterial ear cleaners with a low pH (chlorhexidine, chloroxylenol, isopropyl alcohol, PCMX.)
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Otitis externa (suppurative) or otitis media:
- **Topical:** Choice (including ear cleaners) as for erythroceruminous OE. Enrofloxacin, marbofloxacin, aqueous gentamicin appear to be safe in the middle ear. Multidrug-resistant infections: 1.7% ceftazidime OR 2.8% clavulanate/ticarcillin OR 0.6% enrofloxacin OR 0.2% marbofloxacin OR 0.1–0.5% silver sulfadiazine (diluted in trisEDTA).
- **Systemic:** choice as for Pyoderma.

Practice Policy:

Eye infections

Bacterial conjunctivitis:
- **Topical:** cloxacillin OR fusidic acid OR gentamicin.

Practice Policy:

Suspected ***Chlamydophila*:**
- **Systemic:** doxycycline OR enrofloxacin. Topical fusidic acid may be added if desired.

Practice Policy:

Miscellaneous

Endocarditis: amoxicillin/clavulanate + enrofloxacin OR amoxicillin/clavulanate + metronidazole*.

Practice Policy:

Mastitis: amoxicillin/clavulanate OR trimethoprim/sulfadiazine.

Practice Policy:

Suspected ***Mycoplasma haemofelis*** *(*formerly *Haemobartonella)* (feline infectious anaemia): doxycycline OR fluoroquinolone.

Practice Policy:

Neutropenia: Mild: no antibacterial required. Severe but asymptomatic: trimethoprim/sulphonamide. Severe and with clinical signs: 1st generation cephalosporin + fluoroquinolone.

Practice Policy:

Septic peritonitis: amoxicillin/clavulanate OR ampicillin + cefotaxime OR ampicillin + gentamicin* OR clindamycin + enrofloxacin OR fluoroquinolone + ampicillin. Add metronidazole* if anaerobe suspected.

Practice Policy:

Septicaemia: ampicillin + cefotaxime OR ampicillin + gentamicin* OR clindamycin + enrofloxacin OR enrofloxacin + ampicillin OR fluoroquinolone + amoxicillin/clavulanate.

Practice Policy:

For further information on individual drugs and dosages, see *BSAVA Small Animal Formulary, 7th edition.*

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Surgical prophylaxis

Prophylactic antibacterial use is not a substitute for good aseptic technique.
- Perioperative antibiosis is appropriate:
  - for prolonged surgery (>1.5 hours) or surgery involving implants
  - for debilitated or immunosuppressed patients
  - where infections would be catastrophic (e.g. in CNS)
  - where there is an obvious break in asepsis
  - for all bowel surgery
  - for dental procedures where there is periodontal disease
  - for contaminated wounds or pre-existing infection.
- In most cases:
  - intravenous amoxicillin/clavulanate OR first-generation cephalosporin.
- Where anaerobic involvement is highly likely (e.g. periodontal disease):
  - *add or substitute* metronidazole.
- For significant bowel leakage in an otherwise metabolically stable animal:
  - combination may be most appropriate, e.g. ampicillin + aminoglycoside (e.g. gentamicin)
  - if patient volume-depleted, replace aminoglycoside with fluoroquinolone.

Practice Policy:

Antibacterials not indicated unless cytology and/or culture is positive

- Cardiorespiratory
  - Chronic bronchitis/allergic airway disease
  - Aspergillosis
  - Congestive heart failure
- Urinary
  - Feline lower urinary tract disease (including struvite urolithasis)
  - Urinary incontinence
- Gastrointestinal
  - Acute vomiting (uncomplicated)
  - Acute diarrhoea (uncomplicated)
  - Chronic gastroenteritis (unless 4-week treatment trial for antibiotic-responsive diarrhoea)
  - Pancreatitis (uncomplicated)
- Surgery
  - Routine castration and ovariohysterectomy
  - Removal of uninfected skin mass not involving major reconstruction
- Metabolic
  - Polyuria, polydipsia (unless pyogenic focus suspected)
  - Weight loss
- Skin and ears
  - *Malassezia* dermatitis
  - Acute non-specific pruritus, scaling, nodules, crusts, etc.

DO NOT USE

There are very strong arguments that antibacterials with restricted use in human medicine (e.g. imipenem, linezolid, teicoplanin, vancomycin) should **not** be used in animals under any circumstances.

Second and Third Choice Antibacterials

These include: amikacin, 3rd generation and 4th generation cephalosporins (except cefovecin) and fluoroquinolones. These antibacterials should be used only when other agents are inappropriate (e.g. in penicillin-sensitive individuals) and/or ineffective, *and* culture/sensitivity testing indicates that they will be effective.

Follow the Cascade

Suggested antibacterials for dogs and cats are listed in alphabetical order. Order of selection should follow the Prescribing Cascade. The following agents (*) are not authorized as sole agents for systemic use in small animals: aminoglycosides, azithromycin, erythromycin, gentamicin, metronidazole. Metronidazole is authorized for oral use in combination with spiramycin. Oxytetracycline is not authorized for use in the cat.

FIGURE 7.6 Aussie guidelines

Veterinary use of antibiotics critical to human health

The World Health Organization, the Food and Agriculture Organization and the World Organization for Animal Health are working to protect the effectiveness of antimicrobials in the face of rapidly increasing resistance in serious and life-threatening pathogens.

Antimicrobial use in animals contributes to the selection and spread of resistance. Veterinarians must help preserve existing antibiotics and fight the serious public health threat of antimicrobial resistance. Veterinarians need to carefully consider how they prescribe antibiotics, especially those that are critical in human medicine, to help preserve these lifesaving drugs for the future.

The table on the next page outlines in a broad and general sense how veterinarians should use the antibiotics critical to human medicine identified by Australia's Antimicrobial Resistance Standing Committee. Responsible use of these antibiotics should have a limited impact on human medicine. In making a therapeutic decision, you will also need to consider other issues, for example, withholding periods and export slaughter intervals in the case of food-producing animals. Where possible, choices should be based on culture and susceptibility testing and the narrowest spectrum drugs effective against the infection.

Alternatives to antimicrobial use – such as changes in husbandry, management and infection prevention and control – should also be explored in each case. The overriding principle of antimicrobial prescribing is to use as little as possible but as much as necessary to address the infection.

Following diagnosis, consider using the **first line antimicrobials** along with alternative treatment approaches.

Second line use should be limited where possible to when susceptibility testing or clinical results have proven that first line antibiotics are not effective.

Third line antimicrobials are for use as a last resort. They should be used only when other options are unavailable and wherever possible only after susceptibility testing has been completed.

	Pigs	Poultry	Cattle	Sheep	Aquaculture (no products registered)	Horses	Dogs and Cats
First line use	Amoxicillin Erythromycin Chlortetracycline Oxytetracycline Sulphonamides Kitasamycin Tilmicosin Tylosin Penicillin Florfenicol Neomycin	Amoxicillin (not layers) Erythromycin (not layers) Neomycin Tylosin (not layers) Chlortetracycline Oxytetracycline (not layers) Zinc bacitracin	Ampicillin/ Amoxicillin Erythromycin Oxytetracycline Sulphonamides Oleandomycin Tilmicosin Tylosin Penicillin Florfenicol Framycetin Neomycin Streptomycin	Amoxicillin Erythromycin Chlortetracycline Oxytetracycline Framycetin Neomycin Penicillin	Oxytetracycline Florfenicol	Amoxicillin Bacitracin Oxytetracycline Sulphonamides Penicillin Chloramphenicol Framycetin Neomycin Streptomycin	Amoxicillin Bacitracin Chlortetracycline Doxycycline Penicillin Chloramphenicol Framycetin Neomycin Streptomycin
Second line use	Amoxicillin-clavulanate Apramycin Lincomycin Trimethoprim-Sulphonamides Tiamulin Tulathromycin Spectinomycin	Apramycin (not layers) Spectinomycin Lincomycin Tiamulin (not layers) Trimethoprim-sulphonamides (not layers)	Amoxicillin-clavulanate Cefuroxime Cloxacillin Apramycin Lincomycin Trimethoprim-sulphonamides Tulathromycin	Amoxicillin-clavulanate Cloxacillin Framycetin Trimethoprim-sulphonamide		Amoxycillin-clavulanate Cloxacillin Gentamicin Trimethoprim-sulphonamides	Amoxicillin-clavulanate Cephalexin Cephalonium Cloxacillin Clindamycin Lincomycin Gentamicin Trimethoprim-sulphonamides Spiramycin/ metranidazole
Third line use	Ceftiofur	Virginiamycin (not layers)	Ceftiofur Polymyxin B Virginiamycin	Virginiamycin Polymyxin B		Ceftiofur Fluoroquinolones (Enrofloxacin) Virginiamycin Polymyxin B Nitrofurans	Ceftiofur Cefovecin Fluoroquinolones (Enrofloxacin Marbofloxacin Orbifloxacin Bafloxacin) Nitrofurazone Polymyxin B
Use prohibited	Fluoroquinolones Gentamicin Chloramphenicol Nitrofurans	Fluoroquinolones Gentamicin Chloramphenicol Nitrofurans	Fluoroquinolones Gentamicin Chloramphenicol Nitrofurans	Fluoroquinolones Gentamicin Chloramphenicol Nitrofurans			
Critically important antimicrobials not registered for use in animals that should not be used off-label except in exceptional circumstances for individual animals	Colistin					Amikacin Rifampicin	Meropenem Vancomycin Teicoplanin Amikacin Aztreonam Tigecycline Ceftaralone Ceftriaxone Cefotaxime Linozelid Nitrofurans Fusidanes Ticarcillin-clavulanate Rifampicin

[1]Australian Commission on Safety and Quality in Healthcare. *AMRSC Importance Ratings and Summary of Antibacterial Uses in Humans in Australia*, Sydney. ACSQHC, 2014.

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November 2014

nb. different drugs are available in NZ!

Infections of systems

before using antibiotics ask:

- does it kill the bacteria?
- does it get to where the bacteria are?
- is clinically significant resistance likely to develop?
  - in the animal?
  - in the herd or contacts?
  - in the environment or people?

Empirical antimicrobial therapy is often necessary because of a client's financial restrictions and the need to begin treatment as a life-saving measure before the results of culture and sensitivity testing become available. However, if you expect the drug to work, you must try to identify the microorganism(s) involved and their likely antimicrobial resistances.

In large animal practice cost and practicality are important. Although you should help the farmer consider the benefits of antimicrobial therapy on a basis of economic returns, you also have a legal and ethical responsibility to relieve animal suffering. It can be very difficult to reconcile these two roles.

You should also bear in mind public health and the chances of significant resistance developing. This involves having a basic understanding of which drugs are important in human medicine. If you use antibiotics which might increase resistance in serious Gram negative infections in people (eg, cephalosporins or fluoroquinolones), MRSA (eg, glycopeptides) or MDR TB (eg azithromycin), you must be prepared to justify your choice. A culture and sensitivity test showing nothing else is likely to work is probably the best justification. This is already a legal requirement in some cases.

Recommended reading

Cooper, BS (ed) Antimicrobial Prescribing Guidelines for Veterinarians, 2nd ed, Postgraduate Foundation, University of Sydney. Although this book is Australian, a lot of it is just as relevant to NZ, particularly the cattle section (written by a Kiwi).

Cardiovascular system

A complete work up is necessary to try to find the original focus of infection, eg, vegetative endocarditis, unless it is obvious, eg, umbilical infection in a neonate. This is necessary to make sure that the chosen drug gets to the site of the infection. Blood cultures are often negative as bacteraemia tends to be episodic. Multiple cultures may be necessary. Bacteraemia is thought to precede fever spikes.

Treatment must begin before bacterial isolation and identification, especially as it is often difficult to isolate the causative organism. Early, aggressive, broad spectrum anaerobic and aerobic treatment at high dose rates is recommended.

TABLE 7.25.1 Antibiotics for cardiovascular infections

Animal	Disease	Bacteria	First Choice	Second Choice
dogs	septicaemia, endocarditis	Staphs, Streps, E.coli	gentamicin & amoxycillin	cephalexin
cats	infectious anaemia	Haemobartonella felis	doxycycline	azithromycin
pigs	erysipelas	Erysipelothrix	penicillin	co-trimazine
foals	septicaemia	coliforms, Pseudomonas	ceftiofur	gentamicin

Skin

Successful treatment of skin infections usually requires ancillary treatment for ectoparasites or inflammation. Many, if not most, cases of skin infection in dogs and cats are the result of atopy and antimicrobial drugs alone rarely work, particularly in the long term. This is especially true for suppurative otitis externa caused by bacteria such as *Pseudomonas* which rapidly develop resistance over the course of treatment. As the condition is likely to recurr, this makes subsequent treatment difficult. The atopy should be treated - consider prednisolone or cyclosporin. Non antibiotic treatment should be used for the otitis where possible: the ear should be cleaned and dried, and possibly acidified (with a proprietary acidic cleaning soltution or dilute vinegar) to discourage *Pseudomonas*. Remember to check if the ear drum is intact as many drugs are potentially toxic in the middle ear.

The commonest skin pathogen in dogs is *Staphylococcus pseudointermedius*, usually coagulase positive, and frequently penicillinase producing. Narrow spectrum drugs are best. Superficial infections may be better treated with antiseptic washes (chlorhexidine or povidone iodine).

Gingivitis is common in cats and dogs. Most pathogens are Gram negatives or anaerobes with normal commensals being Gram positive. Chlorhexidine mouthwashes are useful before dentistry, gingivitis involving bone loss usually needs antibiotics.

Burns can be especially difficult to treat. Contamination with bacteria is almost guaranteed as burned skin is an ideal culture medium. There is no evidence that systemic antibiotics are of any value, unless bacteria have invaded systemically. Topical therapy aims to physically obstruct access to the underlying dermis for bacteria, and to reduce bacterial numbers with a bactericidal gel.

Politics

Development of resistance always needs to be considered when treating dogs with skin infections as treatment may have to be prolonged and there is good overseas evidence that the prevalence of resistant bacteria in dogs is increasing. Clinical trials of antibiotics for skin infections typically last for three or four weeks, so resistance development is rare in these.

A recent study from Denmark has shown that 46% of owners of dogs with deep pyoderma have the same strains of antibiotic resistant *Staph. pseudointermedius* as their dogs. Think about the transfer of resistance to human staphs before treating the dog!

Methicillin resistant *Staph. pseudointermedius* (with the *mecA* gene) has been found in dogs. There has only been one reported case in NZ so far, but it is getting more common overseas.

Fluoroquinolones can be very effective for skin infection in dogs, at least in the short term, but overseas data indicates that resistance in *Staph. pseudointermedius* is developing, so fluoroquinolones are probably best reserved for cases where other drugs are unlikely to work.

Further reading

Hillier, A., Lloyd, D. H., Weese, J. S., Blondeau, J. M., Boothe, D., Breitschwerdt, E., et al. (2014). Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases). Veterinary Dermatology, 25(3), 163–75– e42–3. http://doi.org/10.1111/vde.12118

TABLE 7.25.2 Antibiotics for skin infections

Animal	Disease	Bacteria	First Choice	Second Choice
all	wounds	Staphs, Streps, E.coli, Clostridia, Pasteurella	co-amoxyclav	co-trimoxazole
cats	bites	anaerobes and Pasteurella	drain ± penicillin	co-amoxyclav
all	burns	Pseudomonas, Klebsiella, Proteus, β-haemolytic Streps, Staphs	silver sulphadiazine	polymixin/neomycin/bacitracin
dogs	pyoderma	Staph pseudointermedius	co-amoxyclav and topical treatment	clindamycin and topical treatment
dogs	otitis externa	Malassezia	clotrimazole	miconazole
dogs	otitis externa	Staphs, E. coli, Proteus	acidic cleaning solution	polymixin/neomycin/antifungal
dogs	otitis externa	Pseudomonas	flush with acidic solution	flush & silver sulphadiazine
dog & cat	gingivitis	mixed	metronidazole ± co-amoxyclav	metronidazole ± clindamycin

TABLE 7.25.3 Antiobiotic resistance in *Staph. pseudointermedius* internationally.

Drug	Australia	Spain	France	Denmark	Canada	USA	USA	USA	Hungary
year / ref	1998 / 1	1996 / 2	1996 / 3	1995 / 4	2002 / 5	2002 / 6	1998 / 7	2016 / 9	1997 / 8
penicillin	22		57 (1988)	50	25 - 40	38	36 - 41	21	
co-amoxyclav	100		99	100	50 - 90		100		98
cloxacillin (oxacillin)	96		-98		20 - 90	-100		51	50
1st G cephalosporins	98		98		82 - 100	100	78 - 93		98
tetracyclines	92	72	65	80	10 - 60	63	58 - 62	73	19
macrolides	84 - 90	44 - 72	72 - 77	76	10 - 70	73		60	58 - 62
trim / sulph	58	24	64	100	20 - 25	82	36 - 52	60	62
fluoroquinolones		71 - 97	95 - 98	100	50 - 95	100	86 - 96	77	98

Percentage of Staph intermedius *from dogs susceptible to various antibiotics in vitro. There are no published data for NZ. 1 Mueller et al., 1998, Aus Vet Practit, 28, 10 - 12; 2 Piriz et al., 1996, J Vet Pharm Ther 19, 118-23; 3 Pellerin et al., 1998, Comp Imm Micro & Inf Dis, 21, 115 - 133; 4 Pedersen & Wegener, 1995, Acta Vet Scand, 36, 335 - 342; 5 Hoekstra & Paulton, 2002, J App Micro, 93, 406–413; 6 Peterson et al., 2002, J Am Anim Hosp Assoc, 38, 407–413; 7 Cole et al., 1998, JAVMA, 212, 534 - 538; 8 Kiss et al., 1997, JSAP, 38, 51 - 56; 9 Wu et al., J. Clin. Microbiol. doi:10.1128/JCM.00270-16*

Respiratory system

The upper respiratory tract is frequently infected with viral pathogens. Elimination of normal flora by antibiotics can make the disease better or worse. Therefore, although culture and isolation is complicated by an abundant commensal population, it is very important to make a diagnosis. Purulent discharge is not pathognomonic for bacterial infection. Antibiotics are probably not indicated in the majority of upper respiratory tract infections in any species. Strangles is a special case - antibiotics can be justified if abscesses have not yet formed, but prevention of spread is much more important.

Infections of the lower respiratory tract are relatively common. Usually the bacteria concerned are aerobes and approximately two thirds are G-. Except in the case of aspiration pneumonia, pure infections are common. Therefore, culture and sensitivity testing is usually successful and valuable.

Cattle and sheep live outdoors at grass in NZ which means that they avoid most of the respiratory diseases caused by intensive husbandry systems overseas (pigs and chickens are not so lucky). In cattle, these are generally lumped together as bovine respiratory disease complex. Extensive use of antibiotics overseas has resulting in a high prevalence of resistance: this is not the case in NZ (yet?). Because these infections often occur as outbreaks in a herd, cost is a major consideration in the choice of drug. Transtracheal washings (or post mortem samples) followed by smear culture and sensitivity may be necessary to find the cheapest effective drug. Remember milk and meat residues!

Antibiotics are not a substitute for good husbandry.

TABLE 7.25.4 Antibiotics for respiratory disease.

Animal	Disease	Bacteria	First Choice	Second Choice
cattle & sheep	pneumonia / BRD	Pasteurella (Mannheimia) ± others	penicillin	oxytetracycline
horse	pneumonia	Streps	penicillin	
foal	pneumonia	Rhodococcus equii, Strep zooepidemicus	erythromycin & rifampicin	azithromycin
horse	strangles	Strep. equii	penicillin	co-trimazine
dog & cat	pneumonia	Pseudomonas, E. coli, Klebsiella	gentamicin	enrofloxacin
dog & cat	pneumonia	Streps & Staphs	ampicillin	erythromycin
dog & cat	pneumonia	unknown	co-amoxyclav	co-trimazine

Urinary tract

Firstly rehydrate the animal or encourage it to drink to produce an adequate urine output. Uncomplicated cystitis in female dogs should probably be treated for 7 days, although there should be improvement in hours and clinical resolution in 3 days. A single large dose of antibiotic may be sufficient. In male dogs the prostate is usually involved and 4 - 5 weeks of treatment may be required. If there is some predisposing factor, all that long courses of antibiotics do is to ensure that resistant bacteria develop. If there is no improvement in 3 days, the animal should be reexamined and the diagnosis confirmed. If you induce a multiresistant infection, you will have to resort to old drugs such as nitrofurantoin and hexamine, which are more likely to cause side effects.

The concentration and activity of an antibiotic in urine varies according to the pH. Although urinary pH can be altered to suit the chosen antimicrobial drug, it is more sensible to consider the activity / pH spectrum of the drugs available, and to choose a drug which is active in the conditions to be found. Remember, though, that as an infection is controlled, the pH of the urine may alter. Drugs with optimum activity in acidic urine are themselves acids or neutral: penicillins, tetracyclines, nitrofurantoin, hexamine. Drugs active in alkaline urine are themselves bases or neutral: erythromycin, aminoglycosides. Drugs relatively unaffected by pH: cephalosporins, sulphonamides, chloramphenicol, fluoroquinolones.

Many antimicrobial drugs are concentrated in the urine, particularly ß-lactams, so *in vitro* resistance does not necessarily indicate that the drug will not be effective *in vivo*. Ensure that sensitivity testing is carried out at concentrations of antimicrobial drugs relevant to urinary tract concentrations of drug *in vivo*.

Cystitis in cats is very rarely caused by bacteria: antibiotics should not be used.

Leptospiral nephritis is best prevented by vaccination. If streptomycin is used to treat it in food animals, remember that it has a very long meat withholding time.

TABLE 7.25.5 Antibiotics for urinary tract infections.

Animal	Disease	Bacteria	First Choice	Second Choice
dogs & old cats	cystitis	E.coli, Staphs, Streps, Proteus, Pseudomonas	co- amoxyclav	co-trimazine
sows	cystitis / pyelonephritis	Corynebacterium suis	penicillin	co-trimazine
cattle	pyelonephritis	Corynebacterium renale	penicillin	co-trimazine
food animals	nephritis	Leptospira	streptomycin	oxytetracycline

Central nervous system

The drug chosen must be able to cross the blood brain barrier. Large molecules and highly protein bound drugs do not have access through a normal blood brain barrier, but during inflammation most drugs get in.

Most drugs are removed from the cerebrospinal fluid by active transport and therefore do not achieve concentrations in central nervous tissue which are equivalent to plasma drug concentration - give bigger doses than usual. Lipid soluble drugs achieve high concentrations (in general) in nervous tissue: sulphonamides, trimethoprim, enrofloxacin, metronidazole, chloramphenicol.

The intrathecal route for administration of antimicrobial drugs is occasionally used, but has significant toxicity problems. Most drugs are not isotonic or body pH and cause neuronal excitation - convulsions.

Listeriosis in ruminants must be treated aggressively and early to be successful, but this is rarely economic.

TABLE 7.25.6 Antibiotics for meningitis.

Animal	Disease	Bacteria	First Choice	Second Choice
dog & cat	meningitis	Staphs, Pasteurella, Actinomyces, Nocardia	co-amoxyclav	co-trimazine
pig	meningitis	Strep suis	penicillin	oxytetracycline
ruminants	meningitis	Listeria monocytogenes	penicillin Na	amoxycillin Na

Gut

Antimicrobial therapy is NOT indicated for routine treatment of undiagnosed or non specific acute or chronic gastrointestinal disease. Fluids should be used instead. The only specific indication for antimicrobial therapy is invasive bacterial infection, secondary to mucosal damage. This applies also to diseases such as salmonellosis and coliform diarrhoea. Prevention is better than cure!

Normal flora are affected by most antimicrobial drugs. Anaerobes predominate distal to the ileum, but are difficult to culture. Broad spectrum antibiotics play particular havoc with the rumen microbial population.

With the exception of potentiated sulphonamides and certain formulations of penicillin (not available in NZ), all oral antimicrobials are contraindicated in the adult horse since they can cause diarrhoea. Potentiated sulphonamides are used nevertheless.

Coccidial diseases are better prevented than cured -monensin (toxic to horses) and many other coccidiostats are available.

Peritonitis occurs after perforation of the bowel. The primary problem must be sorted out which usually means surgery. Flushing the peritoneal cavity is essential. Vigorous antimicrobial therapy is required using a broad spectrum combination including anaerobic cover.

Mass medication in sheep has been tried in an attempt to control *Salmonella* Brandenburg: it did not prevent abortions. However, sheep and cattle continue to excrete *Salmonellae* for long periods, so there is a (weak and unproven) argument for treatment to prevent this shedding. In people, antibiotic treatment has been shown to prolong shedding of *Salmonella*. *Salmonella* infections in other species should not be treated with antibiotics unless a bacteraemia develops. Remember that *Salmonella* infections are zoonotic and potentially lethal in children and old people.

Politics

Oral antibiotics were used as growth promoters for many years (and still are in some countries). This use has been shown to lead to antibiotic resistant pathogens and commensals in the gut and has given antibiotic use in animals a bad name. Nasty pathogens such as *E. coli* O157 and *Salmonella* Typhimurium DT104 are not a problem in NZ (yet), but the situation in the UK shows what could happen. Enterococci are usually commensals, but can cause disease: vancomycin resistant Enterococci have been found in chickens and people in NZ.

Think carefully about the effects on the gut flora of any antibiotic you give!

TABLE 7.25.7 Antibiotics for gut infections.

Animal	Disease	Bacteria	First Choice	Second Choice
calves	diphtheria	F. necrophorum	penicillin	sulphonamide
most species	coccidiosis	mainly Eimeria	sulphadimidine	amprolium
pigs	swine dysentery	B. hyodysenteriae	tiamulin	tylosin
neonates	invasion of mucosa and enteritis	E. coli	co-trimazine	apramycin
chickens	necrotic enteritis	Cl. perfringens	bacitracin	avilamycin
horse	peritonitis	gut flora	penicillin & gentamicin & metronidazole	
cattle	peritonitis	gut flora	co-trimazine	oxytetracycline

Eye

Most infections are superficial and most drugs will easily get to where the bacteria are. Chloramphenicol was widely used because it has excellent ability to penetrate both chambers of the globe, but it is banned in food producing animals (florfenicol can be used instead). However, infections of the deeper structures will probably require systemic antibiotics.

Most antibiotics are applied as drops or ointments. Subconjuctival injections can be made to prolong a drug's action. These routes can lead to significant systemic absorption and thus residues in food animals - remember withholding times. Powders should never be applied to the eye.

TABLE 7.25.8 Antibiotics for eye infections.

Animal	Disease	Bacteria	First Choice	Second Choice
dogs	superficial keratitis	Staphs, Streps, coliforms	gentamicin	neomycin/polymixin/bacitracin
horses	conjunctivitis	Staphs, Streps, coliforms	gentamicin	neomycin/polymixin/bacitracin
cattle, sheep, goats	pink eye	Moraxella bovis	cloxacillin	oxytetracycline

Reproductive tract

Penetration of the drug to the site of the infection is a major problem. Normal prostatic fluid has a pH of about 6.4, so weak bases penetrate best. This is important in chronic prostatitis - in acute cases the barrier is usually broken down by inflammation. Castration or an antiandrogen such as delmadinone are usual adjuncts to antibiotics for prostatitis.

Antibiotics are used to treat both acute and chronic uterine infections in cattle. However, for acute metritis the current trend is toward inducing oestrus with prostaglandins and away from antimicrobial therapy. Chronic metritis in all species is treated by uterine infusion, or systemic antimicrobials if there is evidence of deep tissue or systemic infections. Local intrauterine infusions are used to treat acute and chronic infections, unless there is evidence of deep tissue or systemic infections. A significant amount of drug can be absorbed - remember withholding times!

In the acute phase, care must be made to differentiate simple contamination from true infections. Contamination is not treated with antimicrobial drugs.

Although still common in clinical practice, the routine use of intrauterine pessaries (usually oxytetracycline), especially as prophylactic therapy, has fallen into disfavour.

TABLE 7.25.9 Antibiotics for reproductive tract infections.

Animal	Disease	Bacteria	First Choice	Second Choice
dogs	prostatitis	E coli, Pseudomonas, Staphs, Streps, Proteus	co-trimazine	macrolide / fluoroquinolone
dogs	pyometra	sterile / ditto	surgery ± co-amoxyclav	
cattle	metritis	A. pyogenes, F. necrophorum	induce oestrus / prostaglandins	oxytetracycline iu
mare	metritis	Streps, Pseudomonas, Klebsiella, Aerobacter	penicillin ± gentamicin	

Bone and joints

Osteomyelitis requires aggressive treatment with antibiotics. Although most antibiotics should reach adequate concentrations in bone when dosed appropriately, adequate blood supply to the site is also necessary. Areas of necrotic bone or sequestra will not heal without surgery. Parenteral antibiotics are indicated if a bacteraemia or septicaemia are present, otherwise oral antibiotics for 4 - 6 weeks should be used. Cephalosporins or co-amoxyclav are usually used. Tetracyclines should not be used as they bind to calcium in the bone and their activity is reduced.

Discospondylitis usually responds readily to antibiotics. If good improvement is not seen after five days, the animal should be re-evaluated.

Infected arthritides are common in foals. They can be caused by a variety of organisms. Culture and sensitivity is necessary. Treatment usually involves arthrotomy and flushing, as well as antibiotics.

Foot rot should be prevented or treated before it gets to the stage of osteomyelitis.

TABLE 7.25.10 Antibiotics for bone infections.

Animal	Disease	Bacteria	First Choice	Second Choice
dogs	osteomyelitis	usually Staphs	co-amoxyclav	lincomycin & aminoglycoside
foals	arthritis	a variety	gentamicin	
horses	arthritis	a variety	penicillin & gentamicin	
pigs	arthritis / meningitis	Strep suis	penicillin	oxytetracycline
cattle & sheep	foot rot	F. necrophorum	penicillin	oxytetracycline

Udder

Prevention is much better than cure, as antibiotic residues are a big problem. It is rarely economically viable to treat mastitis in the most pharmacologically rational way, and a compromise between pharmacology and economics often gives the worst of both - incomplete cure **and** residues (and possibly resistant pathogens, too).

Use intramammary infusions where possible. If there are signs of systemic illness, then systemic therapy should be considered in addition to intramammary therapy. A bewildering array of preparations are available for intramammary infusion. It is usual to develop a working knowledge of the bacteria frequently causing mastitis in the herds you treat, and the antimicrobial resistances of these bacteria (by frequent cultures and sensitivity testing), although things can change from year to year.

It is necessary to decide whether to cull or to treat; or to let the infection linger sub-clinically and treat it after drying off. In many cases (about 20%) the cow is able to defeat the infection without help, although it may take longer. This is usually a matter of economics rather than pharmacology.

Before starting treatment for mastitis without systemic illness, some idea as to the causative organism is necessary. In NZ, most clinical mastitis during lactation is caused by *Strep uberis* (environmental) or *Staph aureus* (infectious). They can cause anything from a slightly raised cell count to complete destruction of the udder. Staph mastitis can be difficult to treat because it is often intracellular or in micro-abscesses and is difficult for the drug to reach. *Strep agalactiae* used to be very important but has been much reduced by good farming and penicillin. *Strep epidermidis* also commonly causes mastitis with much greater tissue pathology, fibrin clotting and inflammation. These cases are more difficult to resolve, require longer courses of antimicrobial therapy, and result in permanent loss of production potential.

Environmental pathogens (*Strep uberis* is commonest in NZ) usually occur just after calving. It is becoming commoner as the other pathogens are being reduced. There have been recent reports of resistance to cloxacillin developing - 17% of isolates in one survey. Streps often develop resistance by changing their penicillin binding proteins rather than producing ß-lactamases.

Mastitis due to *E. coli* is uncommon in NZ. American data has shown that treatment of coliform mastitis with antibiotics is not necessarily any more effective than simply stripping out all the milk from affected quarters several times per day - absorption of lipopolysaccharides from dead bacteria is what causes the problem. Treatment of cows with coliform mastitis with bactericidal antibiotics may result in increased morbidity and mortality due to antimicrobial drug induced release of endotoxins.

Staph aureus mastitis often responds to penicillins, although a significant number of isolates are resistant (about 35%) and cloxacillin (or a cephalosporin) has to be used. None of these drugs are very good at penetrating cells or abscesses to get at the bacteria:the ideal way to treat would be to give a long course of high doses or use a drug with good penetration but both treatments would result in very long withholding times. Erythromycin is a compromise which is sometimes used, pirlimycin may be better.

Sometimes the cow is dried off and the bacteria treated with dry cow intramammary preparations. These contain the same drugs but in a slow release form (usually a waxy or aluminium stearate base) and have very long withholding times (30 days). Concern has been expressed recently about dry cow therapy producing residues in bobby calves - follow the NZVA guidelines (http://www.vets.org.nz). Dry cow therapy is effective, particularly for *Staph aureus*, but is coming under increasing political pressure.

Streps are nearly always sensitive to penicillins and are easy to clear up but tend to reinfect cows.

Read the bit in the data sheet about the withholding time and tell the farmer!

TABLE 7.25.11 Antibiotics for mastitis.

Animal	Disease	Bacteria	First Choice	Second Choice
cows	mastitis	Staph aureus	cloxacillin	oxytetracycline
cows	mastitis	Strep uberis	penicillin	cloxacillin
cows	mastitis	Strep agalactiae	penicillin	erythromycin
cows	mastitis	coliforms	antibiotics do not work	
sows	mastitis / metritis / agalactia	coliforms	co-trimazine& NSAIDs	amoxycillin & NSAIDs

TABLE 7.25.12 *Staph. aureus* MICs in cattle.

Drug	World Average	NZ Heifers	NZ Cows
penicillin	0.5	4	1
ampicillin	1		1
cloxacillin / oxacillin	1	0.5	0.5
cephalothin	0.5		
ceftiofur	1	2	
cephapirin		0.5	0.25
co-amoxyclav	<0.06		0.5+0.25
novobiocin		1	
enrofloxacin	0.125	0.25	0.25
premafloxacin	<0.0078		
erythromycin	0.5	0.5	
clindamycin	1		
lincomycin	16		
pirlimycin	1	1	
neomycin	2		1
sulphamethazine	4		
cefuroxime			2

Staph aureus *MIC90s (µg/mL) for a variety of drugs. World average from Oliveiera et al., 2000, Journal of Dairy Science, 83, 855 - 862; NZ heifers from Salmon et al, 1998, Journal of Dairy Science, 81, 570 - 578, cows - McDougall, S., Hussein, H., & Petrovski, K. (2014). Antimicrobial resistance in Staphylococcus aureus, Streptococcus uberis and Streptococcus dysgalactiae from dairy cows with mastitis. New Zealand Veterinary Journal, 62(2), 68–76. http://doi.org/10.1080/00480169.2013.843135.*

Production enhancers

commonly used drugs

none

Production enhancers

- ☑ also known as antibiotic growth promoters
- ☑ currently none registered in NZ
- ☑ if you prescribe them for disease prevention, be prepared to justify yourself.

Antibiotics are not just given to sick animals, there are a number of different ways that they can be used:

Treatment - antibiotics given at full doses to kill or inhibit pathogens causing disease in individual animals.

Metaphylaxis - antibiotics given at full doses to kill or inhibit pathogens in groups of healthy animals exposed to disease. Sometimes (rarely) necessary.

Prophylaxis - antibiotics given at low doses to groups of healthy animals to prevent disease. Ethically dubious - often a substitute for good husbandry.

Growth promotion - antibiotics given at low doses to make animals grow faster / use food more efficiently / produce more milk solids etc. Justifiable if husbandry is good and the drugs have no chance of producing cross resistance with drugs used for treatment in man or animals, otherwise highly unethical.

There is political pressure to phase out every use except treatment (see below).

Antibiotic growth promoters are sometimes called production enhancers to differentiate them from hormonal growth promoters (= anabolic steroids). They are usually narrow-spectrum (usually Gram positive) antibiotics which are added to the feed in small quantities (up to 100 grams per tonne) or administered orally, sometimes in the water. They are most widely used in pig and poultry diets and increasingly in rations for intensively reared cattle, where they stimulate growth rate, improve feed conversion efficiency and reduce feed intake. They are usually not absorbed systemically.

These agents may increase live weight gain by 3-5% in poultry, pigs and young, pre-ruminant calves (similar to gnotobiotic animals), and up to 10% in ruminating cattle. The resultant increased feed conversion efficiency reduces the time and quantity of (concentrate) feed required to rear the animal. There is no obvious benefit to grass-fed animals.

There is a continuum between drugs used to promote growth and drugs used to treat disease, despite the four groups mentioned above. Drug use to prevent disease - usually caused by poor husbandry - is tricky. If the drug use is successful, the animals stay healthy. Most drugs used for prophylaxis also have a growth promoting effect in healthy animals. Unfortunately, this type of use is widespread in NZ. There are regulatory differences in that growth promoters are regarded as safe enough for farmers to give unsupervised, but drugs for prophylaxis of disease re-

quire a vet's prescription. If you prescribe these drugs, be prepared to justify yourself.

Politics

These drugs are used by the ton. In 1998 in NZ, approximately 36 tonnes of antibiotics were used for growth promotion and prophylaxis compared to a total human use of about 40 tonnes of antibiotics. This is where the veterinary drug companies make most of their money, but there is pressure from several directions to reduce their use. Consumers are becoming jumpy about eating "contaminated" meat and these drugs have been banned in Scandinavia for this reason. When these drugs first became widely used in the 1960s, it was agreed that drugs used clinically in people would not be used as production enhancers in case of resistant bacteria transferring into people. This sensible idea has lapsed a bit over the years, but as highly resistant strains of bacteria emerge in response to indiscriminate use of antibiotics by the medical profession, there is pressure for the previously obscure production enhancers to become human clinical drugs (and thus not be used as production enhancers any more). Europe has recently banned avoparcin, bacitracin, virginiamycin, tylosin and spiramycin. In NZ, except for avoparcin which is also banned here, these are mainly used in pigs and poultry, which are not exported to Europe. Growth promoters as such are being phased out in NZ.

Growth promoters are not all bad. The most complete figures are from Denmark where there is an excellent surveillance system for both animals and people. Since growth promoters were banned there in 1997, the amount of therapeutic antibiotics used in animals has almost doubled. The incidence of salmonellosis and campylobacteriosis in people has also reached a record high. Coincidence?

The NZVA has said that we will phase out the use of antibiotics for animal production by 2020. The same drugs will probably still be available for treatment and possibly prevention of disease, so you will have to have an excuse for prescribing them.

Mechanism of action

Most of these agents are active against Gram positive bacteria and appear to act on bacterial populations in the gastrointestinal system. Most drugs are not absorbed from the gut to any great extent so the plasma drug concentrations are low. They must be given daily in the concentrate part of the diet or administered orally (daily drenching or bolus form - cattle only). When incorporated into feed blocks or licks, individual animals may receive widely varying doses.

In monogastric species (including pre-ruminant calves) the mode of action is not clear, but the drugs are thought to act by suppressing harmful bacterial metabolites, suppressing potential pathogenic organisms, or suppressing the competition between intestinal organisms. They may also act by altering the metabolic activity of the bacterial population, or enhancing the ability of the host to absorb nutrients from the gut.

Antibacterial agents which act in the rumen rather than the lower gut are called "rumen modifiers" or "rumen-active anaboles". These compounds can be used once the rumen is fully functional (of no use in veal calves) and alter the pattern of rumen fermentation. Gram positive bacteria are major producers of the volatile fatty acids acetate and butyrate and methane gas. They decrease the microbial production of lactic acid and enhance the production of the gluconeogenic fatty acid propionate at the expense of acetate and butyrate. The reduction in the acetate-propionate ratio results in more available energy and substrate for glucose production by the liver. The reduced production of methane means less wastage of dietary carbon and energy through eructation. These drugs are probably more relevant to cattle fed on grain than grazing animals; in fact there is no good evidence that they are likely to work in cattle under the usual NZ conditions.

Resistance

Any use of antibiotics exerts selection pressure for resistance in bacterial populations exposed to the drug. Giving antibiotics by the ton to food animals is thus a cause for concern. There is convincing evidence from Europe and the USA that antibiotic use in animals gives rise to resistance in human pathogens for a variety of Gram negative food poisoning organisms (E coli O157, Salmonella spp, Campylobacter spp.). The evidence for such resistance in human Gram positive pathogens such as methicillin resistant Staph aureus (MRSA) and vancomycin resistant enterococci (VRE) is not very convincing at the moment, although nearly all the VRE in NZ (people and chickens) seems to be the same clone. However, in sick people, the consequence of infections with these bacteria is often death. Some in the animal feed industry in the USA have expressed the view that since these are people in intensive care units who will probably die anyway, there is no need to change animal feeding practices.

Drugs

Bacitracin

Interferes with cell wall production and has a similar spectrum of activity to penicillin. Resistance has been reported in Staphs, Streps and enterococci, but problems with breakpoints make interpretation difficult. It has been in use since the 1940s without clinically significant resistance problems, although on some farms Cl perfringens is no longer susceptible. Its main use in NZ is the prevention of necrotic enteritis (Cl perfringens) in broiler chickens. It may also have some effect against Lawsonia intracellularis in pigs. It is not used in people, and is too toxic to give parenterally. It just been reclassified as a prescription animal remedy, and is not allowed to be used for growth promotion any more. It used to be used in milk replacers and mineral/ vitamin premixes, although there was no evidence that it was effective.

Ionophores

Particularly monensin, are used as coccidiostats (poultry and cattle), growth promoters in grain fed cattle (overseas) and to prevent bloat (cattle) and dysentry (pigs). Monensin produces a higher protein content in the milk, but reduced milk fat concentration (net result is still an increase in total milk solids) - at any rate in cattle fed rubbishy Australian diets. Resistance is not a problem. Ionophores are not used as antibacterials in people and are not prescription drugs. Remember that ionophores are toxic to horses.

The other drugs are used in much smaller quantities in NZ, but pose more of a risk if animal use leads to resistance in human pathogens.

Avilamycin

An orthosomycin which blocks protein production. Mainly active against Gram positives, although also Borrelia and Legionella spp. It is active against a wide range of multi resistant staphylococci, enterococci and streptococci. Resistance has been reported in enterococci from animals and Strep pneumoniae from people. No resistance has been found in Cl perfringens. Resistance appears to develop slowly, both in vitro and in the field. Used as a growth promoter in pigs and chickens. It is also useful against necrotic enteritis in chickens. It compares favourably to vancomycin in vitro. The equivalent human drug was withdrawn from stage 3 trials and there are no drugs of this class currently in use in people. It is not a prescription drug and can still be used as a growth promoter here.

Avoparcin

Was used as a growth promoter in chickens, pigs and cattle, and to prevent necrotic enteritis in chickens. It has also been used to improve milk production in dairy cows. It is closely related to vancomycin and teicoplanin which are used for MRSA in people. There appears to be complete cross resistance. Resistance may be transferred by VREs. The medical profession was very unhappy about the use of avoparcin in animals and it is no longer manufactured, so you should not come across it.

Dimetridazole

A nitroimidazole used to prevent swine dysentery and diarrhoea in pigs, chickens and turkeys. Resistance is rare, but there is cross resistance with metronidazole which is used in people. Dimetridazole is banned in Europe and the USA because it is carcinogenic, but is still used here. It is a prescription animal remedy.

Flavophospholipol

Also known as bambermycin, moenomycin and Flavomycin, it interferes with cell wall production, mainly in Gram positives. Its spectrum is similar to benzylpenicillin, although MRSA has been shown to be susceptible. It is used as a growth promoter in broiler chickens, turkeys, pigs and calves. Its efficacy is dubious. Resistance does not seem to develop, although there is a suggestion that it can promote cross resistance to vancomycin. Most Clostridia and enterococci are intrinsically resistant, although the numbers in faeces can be reduced by flavophospholipol. There are also some reports that it can reduce shedding of E coli resistant to other drugs. There is in vitro evidence that it prevents plasmid transfer. It is not used in people and is not a prescription animal remedy.

Heavy metals

Arsenic, copper and zinc have been used as growth promoters, particularly in pigs. Disposing of the faeces creates environmental problems - pig faeces on pasture can contain enough copper to kill sheep. Resistance can develop, and there is cross resistance with some antibiotics. Some E. faecium contain a plasmid which encodes for extra copper efflux pumps - the plasmid also contains resistance genes for tylosin and avoparcin. This means that changing from an antibiotic to copper for growth promotion can still select for antibiotic resistance.

Macrolides

Tylosin and related drugs such as tiamulin, are widely used in pigs and chickens as respiratory (enzootic pneumonia) and gut disease (swine dysentry) prophylactics. Other macrolides, particularly erythromycin and some of the newer drugs, are widely used in people. There is extensive, but not complete, cross resistance. All of these drugs require a prescription, you must make sure that you have a sound reason to give them before writing a prescription.

Tetracyclines

Oxytetracycline is often misused to prevent diarrhoea in calves and piglets, and respiratory diseases in poultry. It also has a growth promoting effect. It requires a veterinary prescription. Long courses of the drug require long withholding times.

Quinoxalines

Quinoxalines, such as carbadox and olaquindox, and related compounds such as dinitro-o-toluamide and nicarbazin, are used for diarrhoea (swine dysentry) and coccidiosis prophylaxis in pigs and chickens. They are mainly effective against G -. They are probably carcinogenic and are not used much and there is little modern information about them. No prescription required.

Virginiamycin

A streptogramin closely related to the human drug dalfopristin / quinupristin (Synercid). It only kills Gram positives, including Staphs, Streps and enterococci, although some E faecium are intrinsically resistant. Resistance in enterococci develops quickly and has also been reported in Staphs. Virginiamycin was used as a growth promoter in pigs, chickens and turkeys, and is still used to prevent laminitis in horses. It can also prevent necrotic enteritis in chickens. Resistance to virginiamycin confers full resistance to dalfopristin / quinupristin, which has become the drug of last resort against MRSA and VRE in people. Virginiamycin is a prescription animal remedy which can only be used in horses, or for metaphylaxis of necrotic enteritis in chickens after culture and sensitivity indicates that nothing else would work, and MAF have been informed.

Clinical use

Unless the law changes, it is unlikely that vets will be involved in the use of growth promoters as such (but the WHO recommends that all antibiotics given to animals should be under veterinary control). MPI's current policy in NZ is to phase out most growth promoters and to only license the (same) drugs for prophylactic use under veterinary prescription.

If you are involved in advising on growth promoters, or if you prescribe antibiotics to prevent disease, it is sensible to follow the guidelines below (based on BVA guidelines since the NZVA have not got their act together yet):

Growth Promoters

(1) Antibiotic growth promoters should only be used where husbandry and feeding are optimal - they should not be used to compensate for the growth retarding effects of disease, poor nutrition or poor housing.

(2) The inclusion rates and feeding instructions must be followed.

(3) There should be periodic review of the benefits of growth promoters as prices (feed, antibiotics & products) alter, as husbandry systems (housing, disease, management, nutrition etc) improve and as new knowledge becomes available.

Prophylactics

(1) Antimicrobial usage should always be part of, and not a replacement for, an integrated disease control programme. Such a programme is likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination, etc.

(2) Continued antimicrobial use in such control programmes should be regularly assessed as to effectiveness and whether their use can be reduced or stopped.

(3) Protocols should be agreed between the veterinary surgeon and the client as to when veterinary involvement is required in on-going disease conditions. These protocols must be regularly and frequently reviewed and updated.

(4) Protocols should be agreed and documented for treatment of all endemic conditions on the farm or other livestock-rearing or production premises. These protocols must be regularly reviewed and updated.

(5) Use of antimicrobials for the prevention of disease can only be justified where it can be shown that a particular disease is present on the premises, or is likely to become so, and that strategic antimicrobial use will prevent clinical outbreaks of that disease.

(6) Antimicrobials need to be used with care to maintain their efficacy. If possible, look for alternative methods of disease control (eg, vaccination) to reduce antimicrobial use.

(7) Should there be recurrence of disease following successful control of an outbreak, it will need to be investigated thoroughly to ascertain why this has occurred and the most suitable therapy to be used.

Check if there are withholding times and tell the farmer!

IMAGE 7.2 Pigs and antibiotics

A pill in a jam sandwich is better than tons of antibiotic in the feed!

Antifungals

commonly used drugs

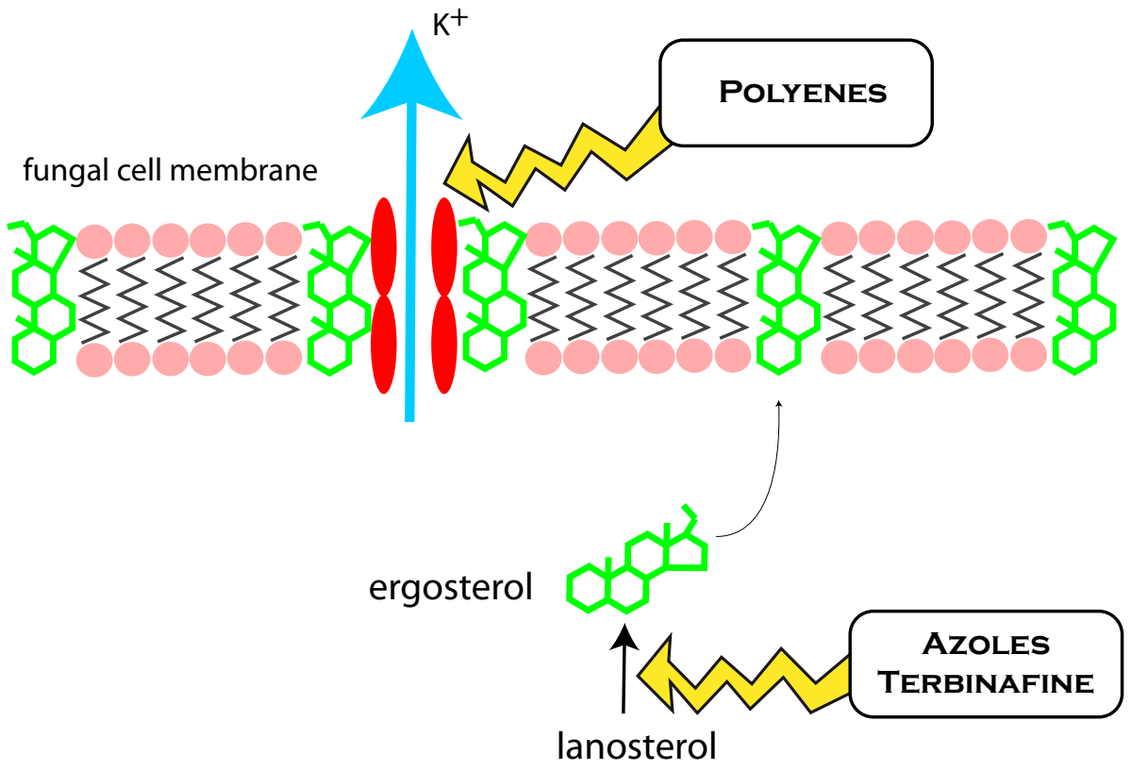
clotrimazole

itraconazole

Antifungals

- ☑ clotrimazole is used as a general antifungal, usually for topical infections
- ☑ other azoles with potential advantages are available, but expensive - extortionate
- ☑ a wide variety of drugs are used for fungal otitis in dogs
- ☑ amphotericin is used for severe systemic infections

FIGURE 7.7 Antifungals



Sites of action of antifungal drugs. The polyenes bind to ergosterol and create ion channels in the fungal cell membrane.

Fungal infections

Probably the most commonly encountered fungal disease is ringworm. This is usually caused by *Trichophyton mentagrophytes* in cattle and *Microsporum canis* in cats. It is usually self limiting but is zoonotic, so cats in contact with children are often treated to cure the children's ringworm. Environmental decontamination is important. Griseofulvin used to be widely used but is no longer easily available. Azole shampoos are used in cats, cattle are left to get over it.

Malassezia is often found in dogs' ears and in some skin infections. It is not clear if it is a true pathogen or just overgrows in skin disease, but it is usually treated anyway. Azoles as a wash or ear drops are usually used.

Nasal aspergillosis is often not diagnosed until too late to treat systemically. Surgery to debride and flush the nose, and soaking in clotrimazole are the usual treatment at this stage.

Systemic fungal infections are rare but potentially life threatening and often associated with immunosupression: modern azoles orally or amphotericin iv are used. The azoles have superseded the other drugs in human medicine but are relatively expensive since long courses of treatment are often needed for fungal infections. In human medicine, resistance is starting to emerge as a problem - this has not happened in veterinary medicine yet.

A variety of other substances can inhibit fungi to some extent, these are often seen as poisoning cases after home cures for ringworm have gone wrong!

Drugs

Azoles

These are synthetic imidazoles or triazoles, whose structure is similar to the benzimidazole anthelmintics. (Thiabendazole is used as an antifungal in the food industry.)

Miconazole and enilconazole are used in washes and shampoos; clotrimazole is used topically as ointment or lotions; itraconazole has recently come off patent and is used as a general purpose oral antifungal; ketoconazole is no longer available; fluconazole is relatively water soluble and short acting. Posaconazole, voriconazole ans isavuconazole (not in NZ yet) are newer human drugs which are broader spectrum but extortionately expensive.

Mechanism of action

The azoles inhibit the specific cytochrome P450 enzyme of the fungi which demethylates lanosterol, the precursor of ergosterol, thereby inhibiting ergosterol synthesis. Ergosterol is necessary for normal cell membrane integrity. In mammalian cells this inhibition results in suppressed cholesterol synthesis, but mammals are able to utilise dietary cholesterol, whereas fungi are obliged to synthesise their own ergosterol. Furthermore, compared to fungal sensitivity 600 x concentrations are needed to inhibit mammalian cholesterol synthesis.

Spectrum of activity

Azoles have a broad antifungal spectrum of activity. They are usually active against: *Candida* spp., *Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp. *Pityrosporum* spp. Azoles are either fungistatic or fungicidal, depending on dose. The newer drugs have a broader spectrum than the old ones.

Imidazoles (but not triazoles) also kill *Nocardia* and *Rhodococcus*.

Toxicity

Miconazole, enilconazole and clotrimazole are only used topically, where they occasionally cause local irritation.

Ketoconazole can cause anorexia, vomiting and depression. Cats are more sensitive than other species. Avoid in liver disease - hepatic enzymes may be mildly elevated. Ketoconazole inhibits cytochrome P450 enzymes, and may lead to accumulation of other co-administered drugs, through inhibition of their hepatic clearance. It was sometimes used deliberately to inhibit the metabolism of expensive drugs such as cyclosporin.

Pharmacokinetics

Almost none is absorbed after topical administration. Topical administration for fungal infections of nails is unlikely to be beneficial because of poor penetration into this tissue.

Oral absorption depends on water solubility and formulation. Fluconazole is relatively water soluble and is absorbed (and eliminated) easily, itraconazole is very lipid soluble and must be specially formulated to be absorbed at all. The newer drugs are better absorbed.

Pharmaceutical considerations

Miconazole, fluconazole and clotrimazole are available in a variety of topical preparations. Itraconazole is available as tablets for oral use. Voriconazole is available for iv infusion, as well as tablets and suspension.

Indications

Systemic mycoses (itraconazole), ringworm (miconazole, enilconazole topically, itraconazole orally), nasal aspergillosis (clotrimazole, itraconazole), severe yeast otitis (clotrimazole).

Polyenes

Amphotericin B, natamycin and nystatin are polyene antibiotics active against fungal pathogens. They bind to ergosterol, the main sterol of fungal cell membranes

(analogous to cholesterol of mammalian cells) and thereby disrupt the spatial configuration of the phospholipids, creating a hydrophilic channel through the membrane. The consequent leaking of potassium results in cell death.

Spectrum of activity

Amphotericin B is usually active against: *Candida* spp., *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Aspergillus* spp., *Mucor* spp., and *Rhizopus* spp. It may also have some antiviral effect.

Nystatin is usually active against: *Candida* spp., *Histoplasma*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces*, *Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp.

Natamycin is mainly used for *Malassezia* and *Candida* infections. It is also active against *Trichomonas*.

Toxicity

Amphotericin is a highly nephrotoxic drug, causing distal renal tubular damage resulting in loss of urine concentrating ability, hypokalaemia and hypomagnesaemia. Red and white blood cells, albumin and tubular casts appear in the urine. Plasma creatinine and K+ levels should be monitored daily. Clinical signs of poor tolerance include vomiting, diarrhoea and depression. Therapy for toxicosis includes withdrawal of treatment. Flucytosine is sometimes given with it as they are synergistic and the amphoteracin dose can be reduced.

Pharmacokinetics

Amphotericin B is highly lipophilic, and therefore has a large volume of distribution (it is not distributed to the cerebrospinal fluid - intrathecal injections are necessary to achieve therapeutic concentrations). It is slowly released from lipid membranes, and therefore has a protracted mean residence time. The elimination phase half life for this drug can exceed 15 days.

Nystatin is too toxic for parenteral use. Almost none is absorbed after topical or enteral administration. The oral route is used for treating intestinal candidiasis, which can occur after cancer chemotherapy.

Pharmaceutical considerations

Amphotericin is usually reconstituted with a special phosphate buffer solution or 5% dextrose. Once reconstituted it is only stable while refrigerated for up to 7 days. The daily dose is administered in 5% dextrose by intravenous infusion over 4 to 6 hours. Usually the drug is given every second day until a total dose is achieved. A liposome formulation is available overseas. Doses of this have to be much higher.

Indications

Amphotericin - systemic fungal infections. A nasty drug - avoid if possible

Nystatin - topical and gut (*Candida*) infections

Natamycin - fungal otitis (*Malassezia*)

Griseofulvin

Griseofulvin is microtubular toxin which inhibits mitosis. Inhibits growth rather than killing fungi, so has to be given for a long time. (nb duration of treatment needs to be longer with some species of dermatophytes eg, *Microsporum*, than others, eg, *Trichophyton*). It is deposited in keratin precursor cells and concentrated in the stratum corneum of skin, hair and nails, thus preventing fungal invasion. It is currently unavailable in NZ.

Spectrum of activity

Ringworm. It is probably toxic to many other cell types, including mammalian.

Toxicity

Teratogenic, therefore contraindicated in pregnant animals. Warn female owners about handling the drug. Diarrhoea, depression and anorexia have been reported. Sometimes damages liver.

Pharmacokinetics

Griseofulvin is variably absorbed after oral administration. Absorption is markedly enhanced by fat in the gut, so it is recommended to give griseofulvin with a fatty meal. Most absorbed drug is inactivated in the liver (first pass effect) and an inactive metabolite is excreted in the urine. Induction of mixed function oxidase enzymes increase this inactivation.

Pharmaceutical considerations

Griseofulvin itself induces hepatic mixed function oxidase enzymes, resulting in altered kinetics of other drugs.

Indications

Ringworm

Other Antifungals

Terbinafine is sometimes used in people to treat dermatophyte infections. It also inhibits fungal sterol production and may be synergistic with the azoles. It is only fungistatic against yeasts. Limited info on its use in animals.

Flucytosine is sometimes used for systemic yeast infections. Resistance develops quickly, so it is always given with amphotericin - the two are synergistic.

Lufenuron is a chitin inhibitor sold for killing fleas. Fungi also use chitin, and it has been tried in difficult fungal infections in cats with some success.

Caspofungin is a new human drug which claims to combine the efficacy of amphotericin and the safety of the azoles. May be good for *Aspergillus* infections but oo expensive to use (>$1000/dose).

Sodium **iodide** is sometimes used for actinobacillosis and actinomycosis. Its mechanism of action is unknown.

Antivirals

commonly used drugs

none

Antivirals

☑ rarely used in veterinary medicine

There are not many of these (at the moment) which are clinically useful in veterinary medicine. Many drugs work in vitro but are too toxic to use in vivo. Most drugs used in people are virostatic.

Drugs which stop transcription

Idoxyuridine is active against DNA viruses and is used in people for coldsores (herpes). Systemic use causes leukopaenia, liver damage and gut upsets.

Cytarabine is a nucleoside analogue which inhibits DNA polymerase. It is effective against herpes, pox viruses, vaccinia, rabies, cytomegaloviruses and probably hepatitis B virus in vitro, but is only used for herpes keratitis or encephalitis (and as an anti-cancer drug). Vidarabine is available as an opthalmic ointment for herpes.

Acyclovir is effective against herpes viruses and is sometimes used to treat ocular herpes in cats (Zovirax eye ointment). It, and the related gancyclovir, are also used for cytomegaolovirus infection in people.

Zidovudine (AZT) is a reverse transcriptase inhibitor which has been used to treat feline AIDS and FeLV. In combination with interferon α 2b, it appears to improve the cats' condition. It is toxic to the bone marrow - adverse effects include anaemia and granulocytopaenia. It should not be given for more than 3 weeks and blood counts checked regularly. Lamivudine is used for hepatitis B in people in NZ. Resistance has already been reported to zidovudine and lamivudine - 27% of AIDS cases in people in the UK. Nevirapine is another reverse transcriptase inhibitor available here - no experience in animals.

Interferon

Interferons are glycopeptide molecules produced by animals in response to certain infections. They must be given parenterally as they are mostly inactivated in the stomach. They are used for a variety of viral infections in people: they have also been used in cats with FeLV, usually in combination with zidovudine. Expensive!

Other drugs

Zanamivir is a neuraminidase inhibitor which inhibits the release of influenza viruses from respiratory epithelium. It is given to people as a powder for inhalation so veterinary application would be difficult. There are sveral similar drugs on their way.

Nelfinavir is an HIV protease inhibitor used in AIDS patients - no animal experience.

Amantadine is used in people for flu viruses, although resistance has already been demonstrated. This has not been helped by illegal feeding to chickens in China to prevent bird flu. Amantadine is also an effective NMDA antagonist and has become trendy in the USA as part of a balanced analgesic technique. Use amitrptylline instead for this and keep the amantadine for viruses.

Cases to think about

before using antibiotics ask:

- does it kill the bacteria?
- does it get to where the bacteria are?
- is clinically significant resistance likely to develop?
  - in the animal?
  - in the herd or contacts?
  - in the environment or people?

Standardbred foal

Description: one week old male

History: foal was normal until yesterday, other than leaking urine from umbilicus for two days after birth. Yesterday developed swelling of the left hock, and is now very lame in that leg.

Clinical Exam: The foal is lame with a fluid swelling of the tibiotarsal joint, febrile with a moist exudative umbilicus.

Q1: List the problems you can identify.

Your initial diagnosis is septic arthritis of the left tibiotarsal joint, probably secondary to umbilical infection (in this case) and bacteraemia. No other joints appear to be infected.

Q2: What bacterial samples could you take?

Q3: How would you take these, and get them to the lab?

X rays of the left hock show no lesions ofosteomyelitis. An ultrasound scan of the umbilicus shows fluid accumulation around the umbilical remnant, suggestive of umbilical abscess.

Q4: What immediate treatment would you give while waiting for results of culture and sensitivity? What problems might be anticipated with the antibiotics you choose? What precautions might you take?

Culture: Joint fluid - E coli (1), blood - E coli (2) Bacillus spp. (3), umbilical fluid - E coli (4)

Antibiotic MICs µg/mL	1,2,4	3
ampicillin	2	1
penicillin	>64	0.5
amoxycillin	2	1
co-trimazine	1	0.4
gentamicin	0.25	0.1
amikacin	0.25	0.1
erythromycin	>64	0.032

cephalothin	4	1
oxytetracycline	4	2
enrofloxacin	0.016	0.4

Q5: What antibiotic treatment would you choose for the foal? Your choice should be based on practical considerations as well as sensitivity patterns. Estimate the duration of therapy.

Scottish Terrier Snapper

Description: 10 years old entire male

History: Been treated empirically by the referring vet "on and off" for 8 months for urinary cystitis, diagnosed by history of dysuria and presence of protein in the urine. Amoxycillin, co-trimazine and enrofloxacin have each been used separately for six or seven day courses; each caused a clinical improvement followed by an interval before recurrence.

Q1: List the problems you can identify.

Clinical Exam: Bilaterally symmetrical but large prostate, bladder wall slightly thickened and dysuria. Otherwise normal.

Q2: Now list the problems you can identify.

Culture: Urine culture - E. coli (1), Proteus spp (2)

Antibiotic MICs µg/mL	1	2
amoxycillin	16	>32
carbenicillin	>32	>32
cephalothin	16	1
cefadroxil	0.5	0.5
erythromycin	1	16
gentamicin	2	>32
amikacin	1	2
co-trimoxazole	0.5	0.5
tetracycline	2	4
nitrofurantoin	>32	8
norfloxacin	0.08	0.08

Q3: What other clinical pathology test would be most likely to be beneficial to your diagnosis?

Q4: Which of the resistances reported would you have expected, and why? Are any of the reports surprising?

Q5: Choose an antibiotic or combination of antibiotics to treat Snapper and design dosage regime for him. Justify your decisions.

Q6: What are the limitations of in vitro antibiotic sensitivity testing?

NZ white rabbit

Description: pet doe about 1 yr old

History: The rabbit has been sneezing off and on for three weeks (it is summer, the weather has been hot for several weeks and more recently humid). The owner has noticed a discharge from the nose for the last day or two. The rabbit has a decreased appetite and activity.

Clinical Exam: The rabbit has a mild conjunctivitis, mucopurulent nasal discharge, appears depressed and the fur on the medial aspect of the front paws is wet and matted. There is an increase in temperature (40.5˚C).

Q1: List the problems you can identify.

Q2: What samples would you take to determine the cause of infection?

Q3: How would you take the sample(s)?

Q4: What treatment would you begin while waiting for culture results? Route of administration? What problems, if any, would you anticipate from your choice(s)? Are there any contraindications to antibiotics in the rabbit?

Culture: Pasteurella multocida

Antibiotic sensitivity

benzylpenicillin	s
amoxicillin	s
gentamicin	s

erythromycins	
tetracycline	r
enrofloxacin	s

Q5: what antibiotic therapy would you consider for this patient? This is a pet rabbit (only one in the household) and the client is somewhat concerned about cost, but is willing to do what is best for the family and the pet. What advice should you give the client concerning drug treatment, follow up care and zoonoses?

Great Dane Fergus

Description: 7 yr, female spayed

History: The dog had been normal up until a spay 4 weeks previously. 1 week after the operation, the dog developed a fever (39.9˚C), a poor appetite and reluctance to move. A 7 day course of enrofloxacin was prescribed by the referring vet but little improvement was noticed. On physical examination, the dog had injected brick red mucous membranes, was tachycardic (156 bpm), febrile (40.2˚C) and had a weak pulse. Capillary refill time was very rapid (<0.5secs). She was hyperaesthetic, unwilling to move, and had a swollen right elbow. Haematology showed a mild leucocytosis. Blood biochemistry was normal.

Q1: List the problems you can identify.

Interim Summary: In view of the major problems identified the clinician in charge suspected Fergus was septic. This decision was based on the elevated body temperature and evidence of hyperdynamic shock (brick red mucous membranes, tachycardia, brisk capillary refill time, and weak pulse). Many other conditions (eg immune-mediated disease, neoplasia, stress) can result in elevated body temperature but these are usually not associated with hyperdynamic shock. The swollen elbow was considered most likely to be due to infectious arthritis although trauma, neoplasia, or immune-mediated arthritis could not be ruled out. The plan adopted was to acquire diagnostic samples for culture and then to embark on a search for a source of the infection (via cardiac ultrasound, abdominal radiographs & ultrasound, spinal radiographs etc).

Q2: Comment on the referring veterinarian's choice of enrofloxacin for the

initial treatment of this dog.

Q3: What 3 tissues or fluid samples would you take to determine the responsible agent?

Q4: Having obtained your diagnostic samples what antibiotic(s) would you empirically choose (ie prior to the sensitivity pattern) to treat this dog's suspected septic shock and by what route would you give them?

Q5: A Staph aureus was cultured from 2 of these diagnostic samples. 5 days later, the sensitivity pattern listed below became available. By this time Fergus was starting to improve. No focus of infection was found but the suspicion remained that there may be a misplaced swab in the abdomen or an early discospondylitis lesion. What antibiotic would you use now and for how long?

Antibiotic sensitivity

ampicillin	r
co-trimazine	s
chloramphenicol	s
gentamicin	s
enrofloxacin	s
cephalexin	s
co-amoxiclav	s

Thoroughbred colt

Description: valuable yearling

History: The colt has had a nasal discharge and cough for 2 days and won't eat. “Oh, and while you're here, two of our other yearlings have just gone off their feed as well.” (There are 12 in the paddock)

Clinical Exam: The 3 affected yearlings have elevated rectal temperatures, cough, laboured respiration, and purulent nasal discharge. Two also have tense swelling of the lymph nodes around the mandible and throat region. In one of these yearlings, one lymph node is draining thick purulent material. The nine other yearlings, from a distance, seem to be unaffected.

Q1: What problems can you identify?

Q2: What further physical examination procedures will you do now (if any)?

Q3: What clinical pathology and bacteriology tests will you perform?

Three yearlings appear to require immediate treatments

Q4: What treatment will you give while waiting for results of tests?

Q5: How will you manage unaffected yearlings?

Culture: Streptococcus equii

Antibiotic sensitivity:

penicillin	s
ampicillin	s
tetracycline	s
co-trimazine	s
gentamicin	r
erythromycin	s

Q6: Choose the most appropriate treatment, including dosage and route of administration. Justify your choice.

Q7: What problems might you anticipate with the treatment you chose?

Q8: What problems are associated with administration of oral antibiotics in horses (other than foals)?

DSH cat Minnie

Description: 3 yr, female spayed

History: Minnie was presented with the primary complaint of diarrhoea. She had been vaccinated against panleucopaenia on an annual basis. The diarrhoea was acute in onset, was voluminous and contained fresh blood and mucus. Frequent straining to defaecate had been observed. On physical examination the cat was determined to be depressed, dehydrated and febrile (40.2˚C). Liquid faeces and excessive gas could be palpated throughout the intestinal tract. Haematology showed a leucopaenia but no other abnormalities.

Q1: List the problems you can identify.

Q2: Do these clinical signs point to small bowel-type diarrhoea, large bowel-type diarrhoea or both (enterocolitis)?

Q3: What are 3 potential infectious causes of these signs?

Q4: Would you place the cat on antibiotics prior to the culture results? If so, which antibiotic and by what route?

Q5: Do antibiotics have any adverse consequences on the GI tract? If so, list 2 adverse effects.

Q6: What is a pharmacokinetic property of certain antibiotics that increases the likelihood of adverse effects on the normal flora?

Q7: What antibacterial spectrum of an antibiotic (io aerobic, anaerobic, gram +ve, gram -ve) will Increase the likelihood of adverse effects on the normal flora?

Q8: How would you confirm a bacterial enterocolitis?

Interim summary: Because of the clinical signs, an infectious enteritis was suspected and a faecal culture for enteric pathogens was submitted. A Salmonella species was cultured after 3 days incubation. No sensitivity pattern was available.

Q9: Would you continue antibiotic treatment once the diagnosis of salmonellosis has been made?

Q10: What antibiotic would you use to treat Salmonella in this cat if you decided to treat?

King Charles Spaniel Charlie

Description: 10 years old, overweight, entire female

History: Charlie has a poor appetite but is bright. She has recently been on heat and there was a misalliance. She is polyuric and polydipsic and there is a discharge from her vulva.

Q1: List the problems you can identify

Clinical Exam: Charlie is panting though it is not a hot day and she is not nervous. Her abdomen is distended and hard to palpate. There is a purulent discharge from her vulva. Temperature 38.9˚C; Heart Rate 160. Your provisional diagnosis is a pyometra.

Q2: Now list the problems you can identify. What clinical pathology tests could you use? What will you treat Charlie with while you wait for the results? Why?

Haematology:		Normal Range
Hb	9.5 g/dl	12-18
PCV	0.25	0.37-0.55
RBC	4.22x1012/l	5.5-8.5
MCHC	38.0 g/dl	32-36
Total Protein	90 g/l	60-75
Fibrinogen	9 g/l	1-4
PP:F	9:1	
Reticulocytes	2.1 x 109/l	
WBC	55.3 x 109/l	6-17
Neutrophils		
- segmented	48.6(88%)	3-11(70%)
- bands	2.76(5%)	0-0.3(0.07%)
Eosinophils	0.55(1%)	0.1-1.25(2-10%)
Lymphocytes	1.66(3%)	1-4.8(12-30%)
Monocytes	1.66 (3%)	0.5-1.35(3-10%)

Q3: What do these total and differential white blood cell counts indicate? Are there any other problems here? What other routine diagnostic tests could you use to confirm your diagnosis?

Q4: What are your treatment options? What is the likelihood of success with conservative treatment?

Q5: Choose an antibiotic or combination of antibiotics with which to treat Charlie and design a dosage regime for her for each treatment option. Justify your decisions.

Friesian cow No. 267

Description: four years old, high yielder

History: Cow had a difficult calving 2 weeks ago and was down with calving paralysis for 10 days. She is now able to walk around but she is still being milked by hand in the paddock. This morning the farmer noticed that she has a hot, swollen quarter and was difficult to milk. The farmer suspects mastitis but hasn't treated her yet because he has run out of intramammary antibiotics. This cow has never had mastitis before.

Clinical Exam: Cow is in poor condition but appears bright and alert. Temperature is 39.1˚C, heart rate and respiratory rate are normal. the left-hand back quarter of the udder is hot, swollen and painful and the milk from this quarter is watery and,contains white flecks.

Q1: Given that you agree with the farmer's diagnosis of mastitis what would you do next?

Being an astute clinician you realise that acute mastitis is most commonly caused by either Streps, Staphs or rarely E.coli.

Q2: What immediate treatment would you give? Give doses, route of administration and duration of therapy. You have the following antibiotic preparations available:

Intramammary:	Parenteral:
cloxacillin & neomycin	procaine penicillin
penicillin, streptomycin	co-trimazine
ampicillin, cloxacillin	streptomycin/penicillin
co-amoxiclav, prednisolone	erythromycin
cloxacillin	oxytetracycline

Do you think it is necessary to administer parenteral antibiotics? Why?

Q3: What factors determine a drug's distribution from blood into milk?

Culture: E.coli

Antibiotic sensitivity

penicillin	r

ampicillin	s
cloxacillin	r
amoxicillin	s
streptomycin	r
neomycin	r
co-trimoxazole	s
erythromycin	r

Q4: Would you now change your initial treatment plan based on these results? If so, what would be your new treatment plan?

Q5: Apart from spectrum of activity what other important factor do you need to consider and make the farmer aware of when selecting and administering antibiotics to dairy cows?

German Shepherd dog Kaiser

Description: 6 year entire male

History: Kaiser had an acute onset of pain in his abdomen and hind legs 2 weeks ago and has been referred to you by another vet. The history is that he was presented to one vet in a practice and had a temperature of 40˚C and was treated with a non-steroidal anti-inflammatory (flunixin) and antibiotics (amoxicillin). He returned to the same clinic and saw another vet 3 days later with no improvement, was hunched when walking and resented hind limb and abdominal palpation and manipulation of the neck. A blood sample was taken and radiographs of the cervical spine and hips showed no clinical changes. Because Kaiser appeared bright and alert and was moving freely there was no further treatment and he was sent home. The blood results showed an acute inflammatory change with a slight neutrophilia and as the owners felt the dog was starting to stiffen up co-trimoxazole and a steroid(prednisolone) was dispensed 5 days after the second visit. Three days later there appeared to be no improvement, Kaiser had fallen down some steps and was in pain again.

Q1:List the problems of Kaiser that you can identify.What do you think of the referring vets pharmacological therapy. Why?

Clinical Exam: From your examination Kaiser is reluctant to stand, is hunched in the back while standing and resents any caudal hindlimb extension or pressure on his lumbar spine. There does not appear to be any abdominal pain. He takes short strides when walking and has normal neurological findings.Temperature is normal. One of your differential diagnosis is discospondylitis.

Q2: Now list the problems you can identify. What clinical pathology tests could you use? What other diagnostic aid will you use? What will you treat Kaiser with while you wait for the results? Why?

Q3: What would you expect to see in your other diagnostic aid? Why may it differ from when the dog first presented?

Q4: Choose an antibiotic or combination with which to treat Kaiser and design a dosage regime for him. Justify your decisions.

Labrador retriever Dribbles

Description: 8 yr, female,

History: You are presented with Dribbles, with a history of chronic skin infections. She has been treated by your employer over the past several months empirically, using erythromycin or chloramphenicol for an isolated penicillinase.producing Staphylococcus intermedius. The dog also has had an intractable outer ear infection, which has been treated with gentamicin ear drops twice daily for two months. Dribbles owners tell you that she seems to be depressed, and has not “moved around much lately”.

Q1 List the problems you can identify with this dog.

Q2 Defend or criticise your boss’s approach to therapy.

Clinical exam: Dribbles is overweight. She is cold to touch and has a sparse, patchy hair coat. She has large patches of exudative purulent dermatitis on her flanks and ventral abdomen. Her external ear canals are full of a green smelly purulent material: she resists them being examined. Her heart rate is 54 bpm at rest. You suspect that Dribbles may be hypothyroid. You know that hypothyroidism can cause decreased cell mediated immunity, and you suspect this might be occurring in Dribbles.

Q3 List the additional problems you can identify now.

Q4 Should you do anything diagnostically or therapeutically about the hormonal disorder at this time and why?

Q5 Should you do anything differently about the skin and ear infections at this time? If so, what and why?

Q6 Indicate your course of therapy if the owner has no money and cannot afford diagnostic tests at all, i.e. what is your recommended empirical therapy?

Culture: skin (1) Staphylococcus and ear (2) Pseudomonas.

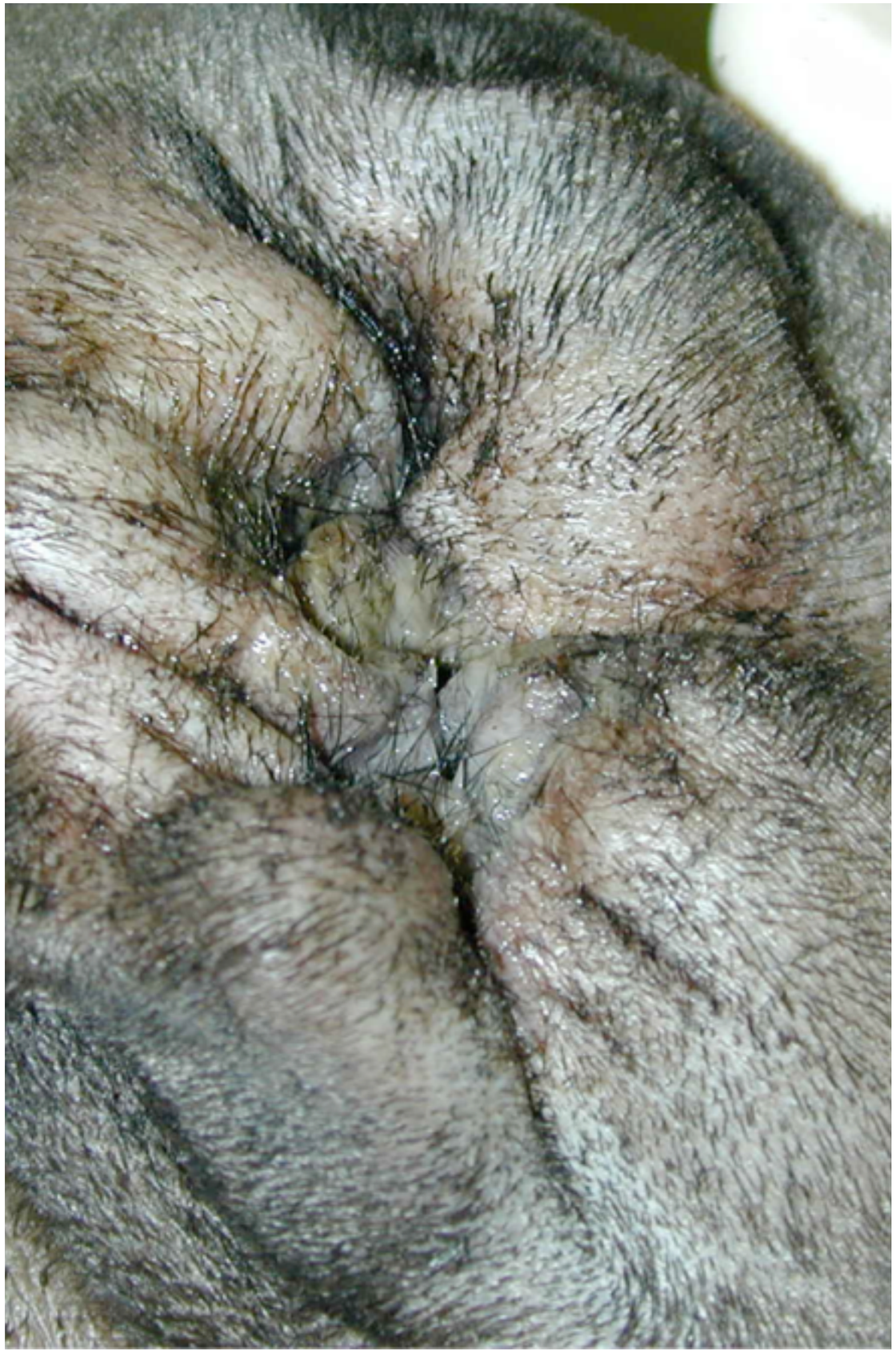
Antibiotic sensitivity	*1*	*2*
Amoxicillin	r	r
Oxacillin	s	r
Carbenicillin	r	r
Cephalothin	r	r
Cefoxitin	s	r
Erythromycin	r	r
Gentamicin	s	r
Amikacin	s	s
Co-trimoxazole	s	r
Tetracycline	s	r
Nitrofurantoin	s	s
Norfloxacin	s	s

Q7 Define your recommended therapeutic regime now.

Chapter 8

The Skin

This part covers therapeutic approaches to skin disease and a bit about drugs applied topically for systemic effect.



Pseudomonas *infection in a dog's ear*.

Topical treatment

commonly used drugs

many and varied

Topical treatment

- ☑ can be useful to get high drug concentrations at the target site, eg, otitis externa
- ☑ some drugs are formulated for absorption for systemic effects, eg, anthelmintics
- ☑ animals will lick or rub topical drugs off - oral absorption
- ☑ wear gloves! (and give some to the animal's owner)

The skin is one of the few organs to which drugs can be applied directly. This is the usual way of treating ear problems in small animals and foot problems in large animals. Many drugs which are applied to the skin have already been covered, the purpose of this chapter is to tidy up the loose ends.

Many drug formulations are available for topical use on the skin of animals. In general, surface active drugs can be classified as either mechanical or chemical in their mechanism of action. Thousands of drugs have been applied to the skin over the years; their use is largely empirical. The usual intention is for them to act locally, but to reach the deeper layers of the skin, they must penetrate the stratum corneum - many drugs carry on in and are aborbed systemically. Animals often lick drugs off the skin, again leading to systemic absorption. This can occasionally be useful - sometimes drugs are applied to the flanks of cows for them to lick off, but usually it is undesirable and can lead to toxic doses being absorbed.

To understand what happens when drugs are applied to the skin, you must know some histology and pathophysiology of the skin - absorption, and thus clinical effects, can vary enormously.

Remember that all drugs formulated to cross animal skin will affect human skin too - warn the owner to take care, or better still, give them some gloves. This is not absolute protection since drugs such as DMSO will happily diffuse through ordinary rubber gloves as well as skin, but is sufficient for most drugs.

Principles of Topical Therapy

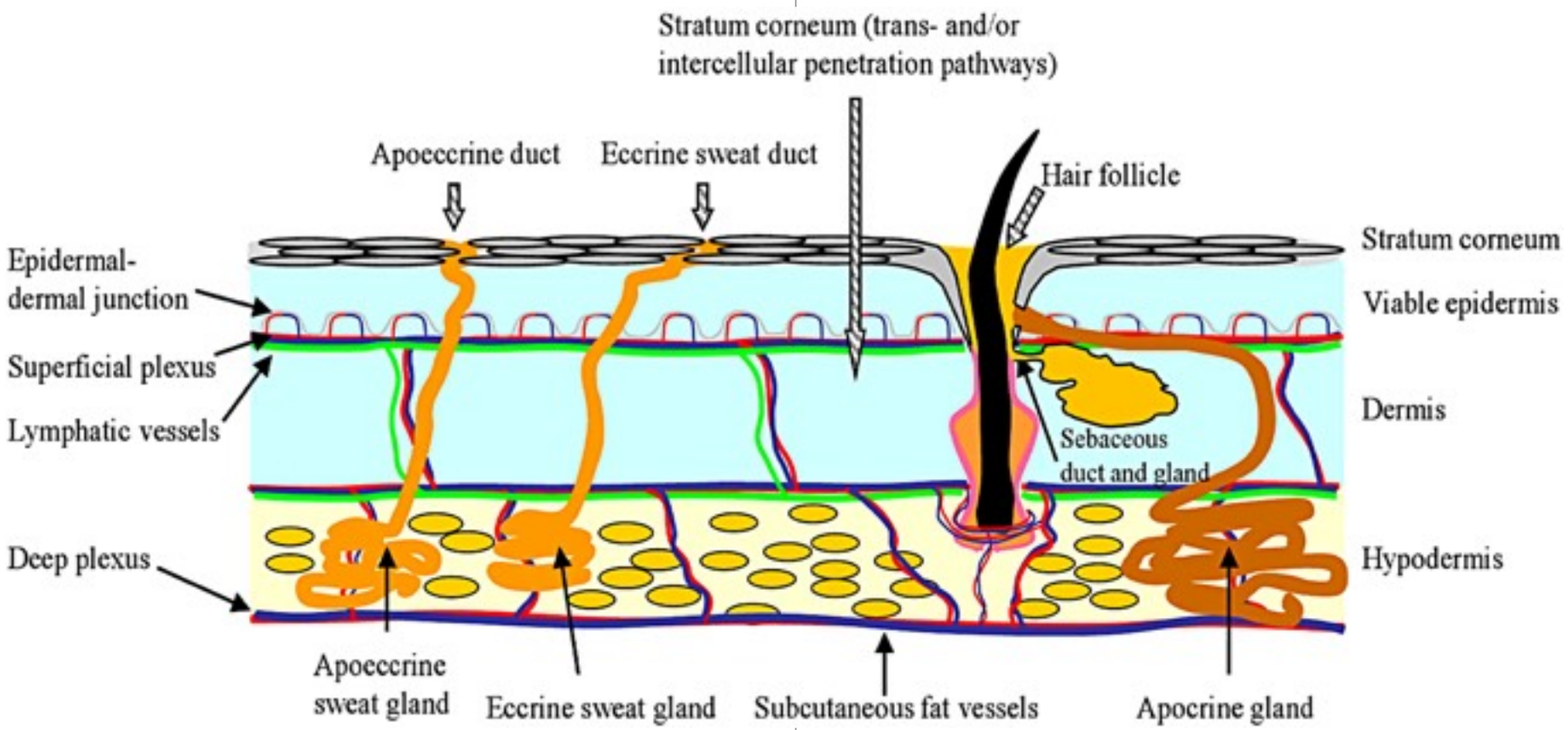
The skin is the easiest organ to examine. It is also easy to biopsy. Treatment is most likely to succeed if targeted at a specific diagnosis.

When treating skin disease first consider whether systemic treatment is more appropriate than topical then select and implement any necessary ancillary therapy. Consider the actions of both the active ingredients and the vehicles of chosen topical formulations; then apply chosen topical drug formulations. Consider ramifications of systemic absorption of either the active drug or vehicle.

A rule of thumb for topical therapy is

if it is wet, dry it

DIAGRAM 8.1.1 Routes of absorption through skin.



Topical absorption. Jepps et al., Modeling the human skin barrier — Towards a better understanding of dermal absorption. Advanced Drug Delivery Reviews 65 (2013) 152–168 doi:10.1016/j.addr.2012.04.003 All you ever wanted to know on the subject.

if it is dry, wet it

Pharmacokinetics

Drug penetration depends on:

- state of hydration of stratum corneum
- body condition
- surface area
    - hair follicles
    - number
    - density
    - type
- blood flow rate
    - exercise
    - inflammation
- skin thickness
- ambient temperature
- rainfall
- concentration of active drug molecule in the applied formulation
- solvent / carrier (vehicle)
- solubility (lipid/water partition coefficient)
- alteration to hydration state of keratinized layers

Topical formulations

A number of substances are used in topical preparations, both for their non-specific effects and as vehicles for active ingredients.

demulcents

These are water soluble ointments or creams which coat the surface, reduce dehydration, partially rehydrate and relieve irritation. They include gums, methylcellulose, hydroxymethylcellulose, etc.,glycerol (glycerin), propylene glycol, polyethylene glycol. These last two substances are very different, despite their similar names. Propylene glycol is similar to other alcohols, and can be irritant to exposed sensitive tissues, polyethylene glycol (PEG) is inert. PEG comes as a variety of different molecular weights, which range from an oily liquid (PEG200) to a waxy solid (PEG35k).

emollients

Inert oils which occlude the stratum corneum and reduce dehydration. They may be either oil in water suspensions or water in oil suspensions. They include: vegetable oils e.g. castor, animal fats e.g. lanolin, other oils e.g. liquid paraffin

protectives and adsorbents

These reduce contact exposure to irritants and allergens although they may have some direct actions to increase evaporation, block pruritus, adsorb toxins and reduce inflammation. They include: starch, especially oatmeal, talc (quite irritant to exposed tissue), zinc oxide, boric acid, gelatin, lanolin, olive and mineral oils, kaolin

astringents

Dry the skin or precipitate proteins if applied to wounds. They include: salts of Al, K, Zn, Ag, Fe, tannic acid, vegetable acids. Copper and zinc salts are sometimes used in this way for foot rot.

counterirritants

(= rubefacients, vessicants, blistering agents) These irritate the skin to induce hyperaemia and inflammation and “promote healing”. They may cause blisters. They may produce a placebo effect in people (“I can feel it burning so it must be doing some good!”) but their use in animals is obselete and unethical.

caustics

Historically used to "treat" lameness in horses and to seal open wounds (as was actual cautery, ie firing). They are likely to cause pain and suffering and should not be used. The more caustic astringents are sometimes used to stop bleeding after over enthusiastic nail clipping and to remove warts. Active ingredients silver nitrate, ferric chloride or salicylate.

keratolytics

Dissolve the intercellular cement and allow increased desquamation of keratocytes. They are used to treat hyperkeratosis. Active ingredients: benzoyl peroxide (also acts as antiseborrheic by opening the sebaceous gland pores), coal tar, zinc pyridinethione, salicylate, selenium sulphide, urea

antiseborrhoeics

Reduce excessive sebaceous gland secretions primarily by reducing inflammation. Active ingredients: selenium sulphide, coal tars (do not use on cats - they have problems metabolising phenolic compounds).

topical anti-inflammatories

topical steroids

fluocinolone, beclomethasone, hydrocortisone, triamcinolone, betamethasone. In people, these can sometimes cause an allergic reaction (to the vehicle?) so systemic steroids are usually used.

dimethyl sulphoxide (DMSO)

DMSO is widely used in veterinary medicine. It is a solvent which rapidly penetrates the skin itself and is rapidly distributed throughout the body by the blood. It enhances penetration of solutes, drugs, toxins etc. Therefore, care must be exercised in its use, including wearing butyl rubber gloves during application. It also acts as a rubefacient (increasing blood flow) and stimulates mast cell degranulation at high doses.

It has potent anti-inflammatory activity, it is a free radical scavenger, it interferes with fibroblasts and collagen production, it may be antimicrobial, it may have some muscle relaxant properties and is analgesic, probably by direct interference with C fibre afferent neurones.

It is used clinically as a gel or solution applied topically to reduce acute swelling due to trauma, and as a vehicle for other drugs. It is used iv for treating acute cranial trauma in horses - great care in dilution and dose rate is necessary.

DMSO's side effects include local burning, itching, diuresis, blockade of collagen production, teratogenicity, lenticular cataracts, haemolysis (if too rapid or too concentrated iv), convulsions and pulmonary oedema. It may also be carcinogenic - it is rapidly going out of use from fears about clients absorbing it.

"inert" vehicles

These are important since they are responsible for the absorption and many of the side effects of the active drugs. **These can cause enormous variations in clinical effect between different formulations containing the same active ingredient.** Commonly used vehicles include: aqueous creams, emulsifying ointments, hydrous ointments, white soft paraffin, starch powders, various lotions, gels and aqueous sprays. Nasty chemicals such as dimethyl formamide are sometimes used to get drugs across the skin in animals, safer products such as poloxamer lecithin organogels are starting to be used in people, and to a lesser extent, in animals. This is a big growth area for drug companies.

Since you are unlikely to be making up your own topical formulations, these will not be covered further.

Otitis

commonly used drugs

broad spectrum ear drops

dexamethasone

Otitis

- ☑ acute - rule out foreign bodies (remove under anaesthesia) then broad spectrum ear drops
- ☑ cats - include something to kill mites
- ☑ chronic - flush, appropriate antibiotics after C&S, anti-inflammatories then regular cleaning to keep canal clean and dry
- ☑ surgery is a last resort

Despite the huge volumes of drugs poured down animals' ears annually, pharmacology is not always the answer. Otitis is very common - about 20% of dogs and 5% of cats - but it can be caused by many different things. First diagnose the cause - bacteria, yeasts, mites, ear conformation, or all of these! Otitis may also be the most obvious sign of generalised skin disease (55% of dogs with atopy also have otitis). Bear in mind that chronic inflammation will alter the conformation of the ear as well, which will predispose to bacterial infection. In acute otitis, remember foreign bodies, particularly grass seeds.

The goals of treatment are usually to remove muck and wax, establish drainage, reduce inflammation and get rid of whatever is causing the inflammation. Contact animals should also be checked and treated if necessary.

Treatment may involve:

- flushing (under anaesthesia)
- systemic steroids?
- collars to stop scratching
- surgery
- as well as topical drugs

Drugs for infections

A large number of commercial preparations are sold for use in animals' ears. They are nearly all a mixture of different drugs to treat all the possible pathogens. Except in very severe otitis, drugs are always given topically.

Because the chances of recurrence are high, think carefully about resistance when giving antibiotics.

Mites

Otodectes cyanotis are involved in about 10% of otitis cases in dogs and 50% in cats (see parasitology note for further details). Commonly used drugs include pyrethroids and monosulphiram.

Yeasts

Malessezia pachydermatis (Pityrosporon canis) is a common inhabitant of dogs' earswhich is considered an opportunistic pathogen. Commonly used drugs include clotrimazole, miconazole, nystatin and natamycin.

DIAGRAM 8.2.1 Ecology of the ear

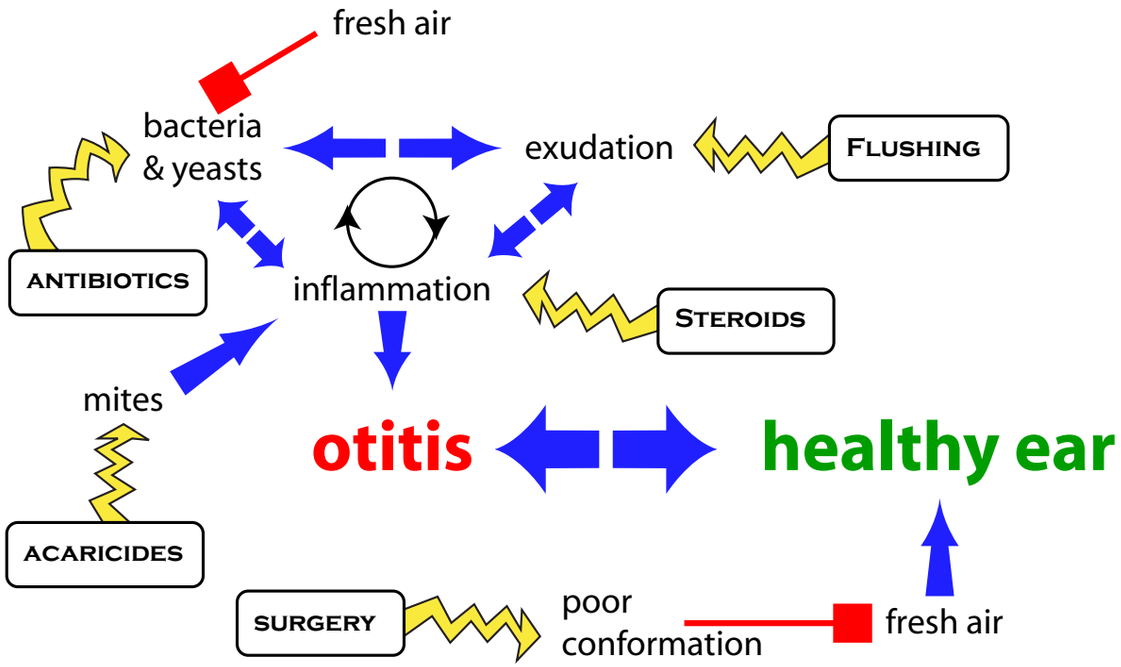
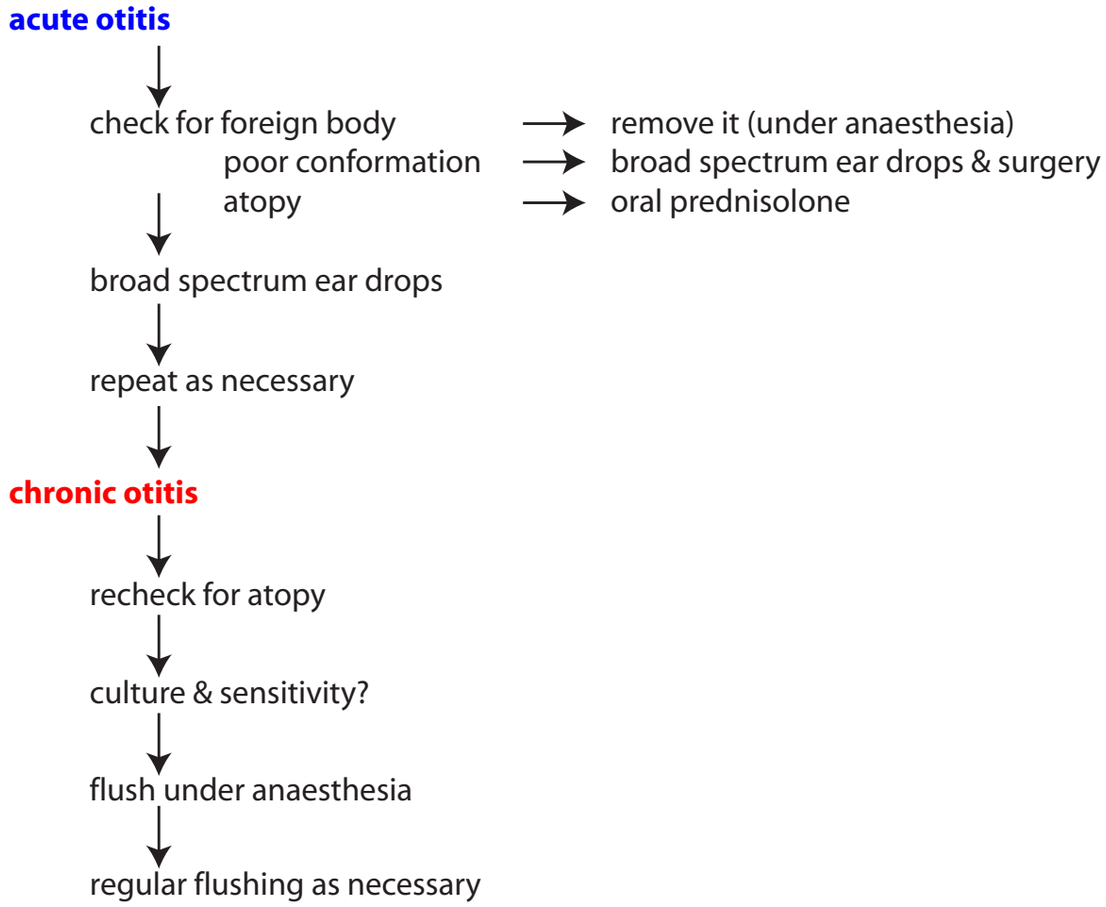


DIAGRAM 8.2.2 Otitis externa treatment



Bacteria

Staphs can be cultured from 10 - 20% of normal ears in dogs and 20 - 40% of inflamed ears. Streps can be cultured from 16% of normal ears and only 10% of inflamed ears. Proteus spp are only cultred from inflamed ears - about 11%. Pseudomonas can be cultured at very low levels from normal ears and about 20% of inflamed ears.

Staphs are usually treated with neomycin or gentamicin. These will kill most Proteus as well. Pseudomonas are more difficult. Although gentamicin or polymixin are the drugs of first choice, resistance usually develops quickly. Polymixin is inactivated by pus, so the ears must be clean before it is used. Enrofloxacin is sometimes used as a second line drug but resistance to it develops quickly as well.

Most chronically treated ears end up full of Pseudomonas resistant to most drugs. When this happens, the two approaches are to use specific antipseudomonal drugs such as amikacin, ticarcillin or cephalosporins (expensive and likely to induce resistance), or use non-antibiotic treatments (cheap and safe). Silver sulphadiazine 1% solution is effective (it is the silver which is thought to be active, not the sulphonamide). 2% acetic acid (50% vinegar) reduces the skin to pH4 which stops the bacteria growing. There are a variety of commercial preparations containing other weak acids, usually including salicylic, which softens keratin and helps to clean the ear canal. A Tris - EDTA solution can also be effective (particularly with aminoglycosides) and relatively cheap, but has to be made up (see formulary).

Anti-inflammatory drugs

Steroids (usually betamethasone) are often used to try to reduce inlammation and pruritus. They also reduce bacterial populations by making growing conditions less favourable. Local anaesthetics such as amethocaine are also used for pruritus.

Flushing solutions

Cleaning the muck out of the ear is very important to allow examination, allow the drugs to get to the tissues, stop inactivation of drugs, remove bacteria and bacterial breakdown products which may cause inflammation. The ears can be thoroughly cleaned under anaesthesia, followed by regular flushing by the owner.

If the ear drum is intact, solutions containing mild detergents designed for this purpose can be used. If the eardrum is ruptured or cannot be seen, use saline. If there is just an accumulation of wax, oils are sometimes used to soften it. Bactericidal flushing solutions (Tris EDTA) may be desirable.

Drug Administration

The pinna is held up and drugs dropped into the vertical canal. The ear is massaged for about 30 seconds. It is then a good idea to stand back, as the animal's response is usually to shake its head vigorously, when the drug plus any muck is distributed around the room.

Beware

Many drugs are toxic to the inner ear - be extremely careful if the eardrum is not intact. Drugs to avoid include: aminoglycosides, chloramphenicol, polymixin, anything containing polypropylene glycol (polyethylene glycol is OK) or a detergent and most antiseptics (especially chlorhexidine).

Having said that, a middle ear full of Pseudomonas is not good news either - you will have to weigh up the benefits and side effects.

If chronic otitis is not treated, the ear canal lining becomes so thickened that the only likely effective treatment is surgical ablation.

Further reading

Rosychuk, R.A.W., 1994, Management of otitis externa. Veterinary Clinics of North America, 24, 921

The scabby dog

commonly used drugs

prednisolone / prednisone

The scabby dog

- ☑ atopy is common
- ☑ steroids are usually used - remember side effects
- ☑ lots of adjuvant drugs are often tried to reduce steroid dose
- ☑ cyclosporin works but is expensive
- ☑ remember fleas!

Scabby dogs and cats which spend most of their time scratching are the predominant feature of small animal practice, particularly if they have diarrhoea as well. In many cases, the original cause is flea infestation (or rarely mites) which should be treated aggressively, including contact animals and the environment. However, there is a wide variety of diseases which can cause skin problems and which should be diagnosed and treated. Once all of these have been ruled out, there is a large number of dogs and a smaller number of cats which probably have atopic dermatitis. This is the development of an allergy to environmental allergens. If it is possible to avoid these allergens, the problem can also be avoided, but it is usually necessary to give anti-inflammatory / immunosuppressant drugs of some sort. The dog is likely to need treatment for life, so side effects (and cost) of drugs becomes important.

The main problem for both dogs and owners is itching. The pathophysiology of itch is not well understood, but is being targetted by drug companies - people get these problems too!

Skin reactions are a common side effect of drugs in people, but are not recognised in animals.

Monotherapy

Traditionally, corticosteroids have been the main treatment and many dogs have developed Cushing's syndrome as a result. Oral prednisolone or prednisone is still the main treatment, but the dose should be reduced as much as possible, often by using adjuvant drugs.

Cyclosporin can be used as a monotherapy with fewer side effects, but is expensive. A veterinary product has recently become available in NZ. Similar drugs, topical tacrolimus and pimecrolimus, are used in people. Oral formulations work better in dogs. These drugs usually have a slow onset.

Remember that dogs have an immune system for a good reason - long-term, high-dose immunosuppressants increase the risk of strange infections or tumours.

Oclacitinib (Apoquel) has recently been licensed in the USA. It is a Janus kinase 1 inhibitor and rapidly reduces interleukin 31 concentrations in dogs. This gives rapid relief from itching. Expensive.

Adjuvant drugs

Antihistamines

Histamine H1 blockers are useful in about 20% or less of dogs. A wide variety of drugs with antihistamine effects is available. Hydroxyzine, diphenhydramine, amitriptyline and several of the older phenothiazines such as promethazine and trimeprazine are used. It is difficult to predict which will work, so a two week treatment trial is often used.

Essential fatty acids

Omega 3 fatty acids, either as dietary supplements (pills or just vegetable oil) or prescription diets can reduce pruritus in about 40% of dogs. They take at least three months to work (see anti-arthritis drugs).

Oxpentifylline

Oxpentifylline (pentoxifylline USAN) may have some anti-inflammatory effect on its own, but also seems to potentiate corticosteroids and antihistamines. It has partial efficacy at best, but is reasonably safe (most likely side effect is vomiting).

Washing

Washing at least weekly helps to keep allergen concentration on the skin down. Shampoos containing emollients may help to prolong the effect (emollients are the main treatment in people). They may also contain things such as oatmeal which are supposed to adsorb irritant bacterial toxins. Remember that washing will remove any residual flea treatments.

Hyposensitisation

If the allergen has been specifically identified, hyposensitisation using the allergen as a “vaccine” may work. It can take up to six months to have an effect.

Disinfectants

commonly used drugs

chlorhexidine

iodine

Disinfectants

- ☑ disinfectants are used to kill bacteria, viruses and fungi on inanimate objects
- ☑ antiseptics are used on animals - dilute disinfectants or safer drugs
- ☑ all work best on clean surfaces but may be incompatible with various detergents
- ☑ where organic contamination is impossible to prevent, remember steam

Although most vets would prefer to leave disinfectants and antiseptics to their nurses, these things can have nasty effects on people (and animals) so you have to know about them.

Disinfectants are chemicals which are lethal to bacteria, bacterial spores, fungi, yeast, protozoa or viruses. Just as is the case with antibiotics, some disinfectants are broad in spectrum, whereas others are relatively confined in their spectrum to one or other of these groups of target organisms. Properties of an ideal disinfectant include:

- rapidly lethal activity against the broad spectrum of target species
- a low surface tension for ease of spread
- activity in the presence of organic matter
- low toxicity
- not corrosive
- low cost.

An antiseptic is essentially a disinfectant which can be applied to skin or mucus membranes of mammals without causing toxicity. Therefore, the properties of the ideal antiseptic are essentially similar to those of the ideal disinfectant. In addition, an antiseptic ought not be:

- irritant to the host's tissues
- allergenic
- absorbed to any significant extent across the skin
- lacking in pleasant aesthetic properties!

Frequently the only difference between a disinfectant and an antiseptic is dilution.

Both disinfectants and antiseptics can be generally classified into broad groupings based on their mechanism of action or chemical structure.

Alcohols

Ethanol and isopropyl alcohol at dilutions of 70% by weight in water are rapidly bactericidal and virucidal for some virus families. They do not kill spores. Isopropyl alcohol has a more rapid killing action against vegetative bacteria than does ethyl alcohol. Methanol is not a good disinfectant nor antiseptic and is also toxic, therefore is not a good substitute for ethyl or isopropyl alcohols.

The alcohols act by disrupting cytoplasmic membranes causing disruption of the semi-permeable membrane barrier and resulting in bacterial death through the

leakage of cytoplasmic constituents. The genera of large viruses, especially those with lipid membrane coats are also susceptible. The alcohols have no residual effect, being active only whilst in direct contact with the bacteria or virus. A contact time of between 1 and 30 minutes to aqueous dilutions of ethyl alcohol is required for the killing of most organisms. Dilutions of less than 30% of ethanol are not effective.

Topical application of the alcohols as antiseptics is unlikely to result in a serious toxicity. However, as is well known, oral toxicity of ethyl alcohol involves central nervous system depression which can be life-threatening. Isopropyl alcohol is similar but more potent. It can also cause ketosis. Ethanol and isopropyl alcohol in effective concentrations are inflammable and volatile. They should be used in well ventilated areas and kept in sealed containers somewhere safe. Remember the HSNO Act and OSH.

Aldehydes

Glutaraldehyde and formaldehyde are both potent and broad spectrum disinfectants and fumigants: they must not be used as antiseptics. They are active against most vegetative bacteria, fungi, yeast, many viruses and some bacterial spores. Glutaraldehyde is usually supplied as a 2% alkaline solution known as activated glutaraldehyde. Glutaraldehyde can also be purchased at higher concentrations or in dry form ready for dilution in water.

Both formaldehyde and glutaraldehyde react with amide groups of cellular proteins, thereby disrupting cellular protein activity. In addition, glutaraldehyde causes much general coagulation and binds to thiol groups resulting in the production of highly reactive compounds. Some vegetative bacteria are killed within minutes of exposure to glutaraldehyde, but 10-20 minutes of contact with new 2 % glutaraldehyde is necessary for broad spectrum action. As glutaraldehyde ages the contact time required for killing increases. By 28 days in use bactericidal contact times are greater than 1 to 2 hours are often necessary. Because of its pungent odour solutions of formaldehyde are rarely used as disinfectants in veterinary practice.

It is now well established that glutaraldehyde is dangerous to people inhaling it. In human hospitals exposure of patients to glutaraldehyde has been shown to slow healing. This is a possible concern for veterinary practices. Because of the volatile nature of alkaline activated glutaraldehyde, it must only be used in well ventilated areas. Care must be taken while mixing and while discarding glutaraldehyde preparations to avoid aerosol production. Contact by users to aerosols of glutaraldehyde results in upper respiratory and ocular irritation. Persistent exposure to glutaraldehyde over prolonged periods or single acute large exposures to glutaraldehyde, can cause malaise, anorexia, weakness, rashes or alterations in measurable parameters of the immune system. These parameters include the development of antinuclear antibodies, the development of antibodies to single stranded DNA and disorders of compliment and compliment components.

Glutaraldehyde should not be used unless there is no alternative. If it is deemed necessary then personal protective equipment and carefully constructed, written guidelines for it use should be available for all workers. The number of people exposed to glutaraldehyde should be minimized. The HSNO Act is likely to severely limit the use of aldehydes.

Halogens

Free chlorine in solution is an effective disinfectant, rapidly killing bacteria, many spores, fungi, algae and viruses. Chlorine acts by: direct disruption of the cytoplasmic membrane, reaction with thiol groups on enzymes disrupting their function, reaction with amine groups on cellular proteins and production of highly reactive compounds.

Chlorine is normally made available in solution by the addition to water of salts of hypochlorites. Sodium hypochlorite is the most commonly used salt, which is stable at an alkaline pH, but which at an acid pH releases chlorine. The concentration of chlorine resulting in solution is a function of the concentration of sodium hypochlorite and the pH. Label recommendations should be followed closely to produce a final solution which is an effective disinfectant.

Chlorine disinfectants are irritant to tissues and should not be used as antiseptics. Care should be taken in their preparation, use and disposal to avoid endangering the health of the people handling the disinfectant. Sodium hypochlorite loses activity on exposure to air and light. New solutions should be prepared frequently. Chlorine adheres to organic matter and becomes unavailable. Chlorine is also corrosive and bleaches textiles.

If hypochlorite solutions are mixed with acids or ammonia solutions, free chlorine or chloramine gas is produced, which is very irritant.

Municipal water supplies sometimes have chlorine added in the form of chloramine, but this seldom causes problems.

Free iodine in aqueous solution (Lugol's solution) is effective against bacteria, bacterial spores, yeast, fungi and most viruses. Iodine is also active in alcoholic solution (known as tincture of iodine). Iodine has a bactericidal action through interference with the electron transport chain and with the function of thiol groups on bacterial enzymes.

Alcoholic solutions of iodine lose their potency rapidly on exposure to air, both through evaporation of the solvent and through loss of the iodine (which is a volatile molecule). Alcoholic preparations of iodine are also drying to skin and irritant. Exposure of animals to Lugol's solution or tincture of iodine has resulted in central nervous system depression and in suppression of thyroid hormone production.

These disadvantages of iodine have been largely overcome by formulation with active carrier agents such as polyvinylpyrrolidine (povidone). Formulations of iodine with povidone and other similar polymers are collectively known as the iodophors. Povidone in aqueous solution above a critical concentration forms aggregations known as micelles. Iodine dissolves into the micelles from which it is slowly released as free iodine into the aqueous solution for activity against bacteria etc. Therefore, if povidone iodine preparations are diluted below the critical micellar concentration, the reservoir for iodine is lost and the volatile free iodine is therefore depleted. This results in rapid loss of activity.

Iodophors are popular as surgical scrub solutions and as antiseptics. They have an extremely broad spectrum of activity, low toxicity, low propensities for sensitization, stability and low likelihood of bacteria developing resistance. However, they can be absorbed in some situations, such as burn treatment. They are corrosive to metal instruments.

In comparison to chlorhexidine the iodophors have a slower bactericidal action. Therefore, the use of iodophors as surgical scrub solutions requires more care. Strict adherence to recommended duration of pre-surgical scrub procedure is necessary. An inadequate period of contact between the iodophor and the skin will result in fewer bacteria being killed. Nevertheless, the iodophors are very useful in surgical scrub solutions.

Phenols and Cresols

Phenols are rapidly bactericidal and virucidal for some germs. Their activity depends upon:

- direct action on the cell wall
- interference with action potentials
- alterations to cell membrane permeability
- general coagulation of cell constituents.

Phenols are all irritant, unless very dilute. They can also cause allergic dermatitis in people.

These disinfectants have fallen into disuse since the development of more effective and safer agents. Nevertheless many phenol-containing disinfectants are still used principally as toilet cleaners and as floor detergents. These products often have a pleasant smell and lack of contact irritation.

For most species, diluted phenols are minimally toxic. Cats are an exception. Cats are extremely sensitive to phenol induced toxicity, showing CNS signs of seizure and coma. Phenols should be used with care in areas to which cats have access - remember that cats lick their feet.

Hexachlorophene is a chlorinated phenol which is distinguished from most disinfectants by its ability to work in the presence of anionic soaps. Therefore hexachlorophene is formulated as both hard and liquid soaps. When used repeatedly over prolonged periods, hexachlorophene results in a decrease in the density of skin commensals and is sometimes used as a routine soap by surgeons. However, hexachlorophene is not recommended as a pre-surgical scrub solution. Triclosan is similar.

Pine oil is similar to the phenols in smell, uses and toxicology. It is fine for cleaning toilets, but keep it away from animals.

Quaternary Ammonium Compounds

The quaternary ammonium compounds are highly surface active agents. Their activity depends upon general coagulation of cell components. The commonly known quaternary ammonium compounds include benzalkonium chloride, cetrimide (cetavlon) and cetyl pyridium chloride.

The quaternary ammonium compounds are rapidly bactericidal against Gram positive bacteria and have some Gram negative activity. Their major drawback is that some Gram negative organisms including Pseudomonas spp., may thrive in these solutions. Quaternary ammoniums possess some fungicidal activity, but are not active against bacterial spores or viruses. The activity of this group of disinfectants is markedly inhibited by the presence of organic matter. Therefore thorough cleaning is required before their use.

These compounds have little place in modern disinfection despite their continued wide availability.

Cetrimide is frequently included at approximately 3% in formulations intended for use as antiseptics. Cetrimide in these products is included primarily for its detergent properties rather than its properties as a disinfectant. Cetrimide improves the general cleansing action. Unfortunately, cetrimide frequently causes contact sensitivities. Veterinarians with contact sensitivity to antiseptics in use in their practice should check if cetrimide and other quaternary ammoniums are part of the formulation.

High concentrations are very caustic.

Miscellaneous Disinfectants

Thiram is a powder which has action as a disinfectant when in suspension in water (it is virtually insoluble). It is fungicidal and bacteriostatic and is included in some bacteriostatic soaps. Thiram has little application in companion animal or equine practice.

“Virkon” is a mixture of oxidising agents (notably potassium monopersulphate), a surfactant (a rapidly-degraded alkyl benzene sulphonate), organic acids and an inorganic buffer system. It also contains various aldehydes. It is effective against most species of bacteria, fungi, yeast, bacterial spores and viruses including Parvovirus. It also has some effect against Cryptosporidium cysts. It is available as a powder which when mixed according to label directions provides a strong oxidising solution. Virkon has little, if any, oral or contact toxicity. It is as yet unknown whether infectious organisms are able to develop resistance to this disinfectant.

Chlorhexidine is a biguanide antiseptic with a wide spectrum of activity against both Gram positive and Gram negative vegetative bacteria. Chlorhexidine is not sporicidal, fungicidal or virucidal. The mechanisms of action of chlorhexidine are general coagulation of cell components, alteration of cell membrane permeability and inhibition of the enzyme adenosine triphosphatase.

Chlorhexidine has a rapid action. It use during surgical site preparation and hand scrubbing results in significant decrease in bacterial numbers within one or two minutes of contact time. Chlorhexidine also has residual action which results in a decreased rate of recontamination of surgical sights or hands when compared to other surgical scrub solutions.

Chlorhexidine is rarely toxic to mammals unless it gets into eyes or ears. It has been used to promote scar formation in people. Chronic or repeated exposures to chlorhexidine containing surgical scrub solutions can cause skin sensitization in people. It is probable that this is usually caused by surface active agents such as cetrimide in the scrub.

Hydrogen peroxide is occasionally used as an antiseptic. It releases oxygen on contact with tissue which kills many bacteria; the frothing action also removes muck.

Physical methods

Steam (usually produced by a hot water blaster) kills most things and is a good way of disinfecting premises. It must be kept well away from animals and people.

Ultraviolet and γ radiation kill many bacteria. γ rays penetrate packing and are used for some surgical instruments and consumables.

TABLE 8.4.1 Antiseptics and disinfectants

Group	Spectrum	Use	Drugs
alkylating agents	G+, G-, weak spores, fungi, viruses, Mycobacteria?	disinfectant - surgical equipment, feed, housing	formaldehyde, glutaraldehyde, ethylene oxide
biguanides	G+, G-, a few fungi & viruses	antiseptic & disinfectant	chlorhexidine
cationic detergents, quaternary ammonium compounds	G+, G-	antiseptic & disinfectant	cetrimide, benzalkonium chloride
halogens	G+, G-, viruses, fungi including yeasts	antiseptic & disinfectant	chlorine, sodium hypochlorite, povidone iodine
alcohols	G+, G-, most viruses, some fungi	antiseptic & disinfectant	ethyl alcohol, isopropyl alcohol
acids	bacteria (Pseudomonas), yeasts	antiseptic & disinfectant	boric acid, acetic acid, benzoic acid
oxidising agents	bacteria, especially anaerobes	antiseptic	hydrogen peroxide, benzoyl peroxide
cresols	G+, Mycobacteria, fungi (not G-)	antiseptic & disinfectant	Lysol, hexachlorophene
phenols	bacteria, fungi	disinfectant	phenol, coal tar and pine derivatives
anionic detergents	weak antibacterial activity, some fungi	antiseptic	soaps, sodium lauryl sulphate
acridines	gut and skin bacteria, protozoa, fungi	antiseptic	hydroxyquinoline, clioquinol, iodoquinol

Chapter 9

The Law

This part covers the regulation of drugs used in animals in New Zealand.

Legislation

Legislation

- ☑ The main legislation covering veterinary medicines is the ACVM Act, but the HSNO Act also applies
- ☑ human medicines can be given to animals under the Medicines Act
- ☑ The Misuse of Drugs Act regulates drugs of abuse - storage and records, etc

Introduction

There are several different levels of legislation:

•**Acts of Parliament** - must be discussed and debated before being passed by Parliament. The modern tendency is for them to contain general outlines of the legislation with the details hidden within

•**Subsidiary legislation** (usually Regulations in NZ) These have to be laid before Parliament (after they come into force) but are not subject to the same (any?) scrutiny and debate. Politicians like these because they give them control over the details of the operation of the law and minimise public debate. They are still law.

•**Codes of Conduct** such as the Vet Council Guide to professional conduct are not strictly speaking law, but if you fail to follow them, you may be stuck off and be unable to practise as a vet. Courts have used them to interpret the law. NZVA policies are not generally legally binding but are well worth following. If the worst happens and you end up in court, it is useful to be able to claim that you were doing what a consensus of the profession believed should be done. There are lots of grey areas where the law is not defined and the test of legality is likely to be what the rest of the profession consider reasonable.

Successive NZ governments have become very keen on Codes of Conduct, since these are written by the organisations being regulated and the government does not have to pay someone to write them. If they have too many unintended effects they can always be quietly abandoned without troubling Parliament. Many CoPs now have the same status as regulations, ie, they are law.

For instance, the Agricultural Compounds and Veterinary Medicines Act (1997) section 75 says that the government can make regulations to cover all aspects of veterinary medicines, the Agricultural Compounds and Veterinary Medicines Regulations (2001) say that vets can use human medicines in animals under their care provided that a suitable code of practice is followed, and the NZVA Code of Practice for the Discretionary Use of Human and Veterinary Medicines by Registered Veterinarians specifies the conditions of use of human medicines in animals.

There are lots of areas where the law is not clear, in these situations it is advisable to stick to what is considered best practice. So for instance, when writing prescriptions and labelling dispensed drugs, when the veterinary legislation is unclear, most vets will comply with the recommendations for human medicines.

Overview

The situation is confused at present. A “new” law, the Agricultural Compounds and Veterinary Medicines Act (1997) (ACVM Act) started to come into effect in July 2001, and has been tinkered with to try and make it workable ever since. This says that everything sold for use in animals must be registered (with a few exceptions) and conditions are imposed on registration, which can cover use among other things. This Act is supposed to fit in with the Hazardous Substances and New Organisms Act (1996) (HSNO Act) and the Biosecurity Act (1993) so that everything to do with agriculture is covered by these Acts. This may have sounded like a good idea over a beer in the Backbencher's Bar, but it appears that very little thought went into the details. In particular, none of the politicians seems to have realised that veterinary medicines are given to small animals as well as farm animals, and that human medicines are given to both. The Animal Products Act (1999) requires standards for foods to be contained in separate regulations, but at present, MRLs are covered by New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards (2016) made under the Food Act (2014). However, where these are different to EU MRLs, the EU MRLs are used for veterinary medicines! Everything to to with food is supposed to be administered by the NZ Food Safety Authority, which moves backwards and forwards between MPI and the Ministry of Health. The ACVM Act is administered by the NZFSA, which shows clearly where their priorities lie. Confused? So is every vet in NZ, but ignorance of the law is not a defence for breaking it (in most cases - that is not very clear either).

The ACVM Act, while full of flaws, is relatively straightforward compared to the HSNO Act. Since all veterinary medicines fit into the category of hazardous substances (human medicines do too, but they have been given an exemption), they are supposed to be registered under the HSNO Act. This involves public consultation, which can be mind-bogglingly expensive. This originally meant that very few new veterinary medicines were registered, but a threshold for HSNO regulation has now been set and the ACVM Group can approve low threshold applications. The status of the large volumes of human medicines used in animals does not appear to have been considered, but this volume is likely to increase as the price differential caused by double registration of veterinary medicines increases.

In the meantime, while people try to get to grips with the ACVM Act, vets carry on much as they did under the Animal Remedies Act (1967) (now repealed). This is similar to veterinary medicines legislation in many other countries, where everything to do with veterinary medicines is contained in one Act. The Animal Remedies Act was one of the first main pieces of animal medicines legislation in the world and had to be extensively modified over the years.

The Medicines Act (1981) only deals with human medicines, but veterinary surgeons using human medicines in animals must stick by its provisions. There was a rash of medicines legislation around the world following the thalidomide affair in the late 1950s; by waiting and basing its legislation on what was done elsewhere, NZ got it right first time. There are significant differences from the Animal Remedies and ACVM Acts.

The Misuse of Drugs Act (1975) is designed to stop people abusing addictive drugs. It contains a number of sensible provisions which increase the burden of paperwork. Most countries have similar legislation.

Both these Acts are under review as part of a harmonisation process with Australia (but don't hold your breath). There is tighter control of discretionary use of drugs in Oz, so expect the worst.

The Dairy Industry Regs (1990) made under the Dairy Industry Act (1952) require farmers to follow Product Safety Programmes to ensure that contaminated milk does not enter the supply chain. MPI Standard D105 “Milking Animal Health” requires farmers to keep records of drugs given to their animals. This information usually comes from vets, on a standard form (treatment form 2).

Animal Remedies Act (1967) (repealed)

This has been repealed, but you still need to have an idea of its provisions as most traditional practice is mistakenly based on it.

It defined an animal remedy, made it illegal to sell an unregistered animal remedy, established the Animal Remedies Board which had control of drug registration and use. Drugs had to be safe and effective to be registered, and the ARB could refuse registration or impose conditions on use to take into account public health and environmental issues.

Most vets assume that the ACVM Act must be similar, **but it is not**.

Classification of Animal Remedies

Class I prescription animal remedy (PAR): may be administered to an animal only by a

- veterinary surgeon
- under and in accordance with authority or prescription of veterinary surgeon.

Class II PAR: administered only by a

- veterinary surgeon or
- in the presence and under the direct control of a veterinary surgeon.

Class III PAR: administered only by a veterinary surgeon

(Most drugs in this category were made PAR2s.)

Other drugs can be purchased without a prescription, sometimes called over the counter drugs (OTC).

This classification was continued under the ACVM Act until 2010. The term "prescription animal remedy" was retained since the ACVM Act defines the more sensible term "veterinary medicine" in such a silly way. PARs are now called Restricted Veterinary Medicines, but who knows how long this will last.

Note that the Animal Remedies Act covered all aspects of veterinary medicines (including public health and environmental issues) in contrast to the ACVM Act, although this has recently been amended to cover some aspects of public health.

Agricultural Compounds and Veterinary Medicines Act (1997)

"Veterinary Medicine" is defined as anything used in the direct management of animals, and this wide definition has caused problems. NZFSA have gradually reduced the working definition to something sensible. Tractors and sheds are now excluded (although the position of stockmen is unclear), and the idea of registering hypodermic needles and surgical instruments has been dropped. Grass is a veterinary medicine, although it is generally recognised as safe (GRAS in ACVMspeak). To get round this problem, NZFSA are again referring to what the rest of the world knows as "veterinary medicines" as "animal remedies".

The ACVM Act is designed to manage specific risks: trade in primary produce, agricultural security and animal welfare. Domestic food standards are mentioned as an afterthought. Benefits such as efficacy are not considered (you are supposed to sue the manufacturer under consumer legislation if the drug does not work) and safety is only considered as it affects animal welfare. Inaccurate labelling (exaggerated claims) is also a matter for the Fair Trading Act (1986). The act has recently been amended to include public health (eg, antibiotic resistance). In practice, drug companies submit the same dossier of information they have compiled for overseas registration, so most drugs have evidence of efficacy and safety, however, the ACVM Group keeps all this secret, so you cannot tell for sure.

Under the ACVM Act, the Animal Remedies Board (which controlled drug registration and use) has been abolished and drug registration is now carried out by civil servants subject to political control.

It is illegal to use drugs in animals which are not registered with NZFSA or specifically exempted from registration (either with or without conditions). To comply with international treaties, nearly all drugs for use in food animals have to be registered (eg, antibiotics). Registration can involve conditions on use. Drugs which pose a low risk are exempted (eg hoof treatments, oxygen, shampoos, human over the counter medicines). Many drugs for small animals are fall into the "exempted with conditions" category, in most cases, the conditions are that a code of practice is followed, although in some cases the conditions may be related to the manufacturing process, or packaging and labelling, and do not directly affect vets. The relevant code of practice for vets will usually be the NZVA Code of Practice for the Discretionary Use of Human and Veterinary Medicines by Registered Veterinarians (more on this below).

Horses are treated as companion animals, provided a long withholding period (6 months) is observed.

The PAR classification persisted until 2010 but has been modified and remodified back again several times. Most vets still refer to PARs. Currently all drugs which used to be PARs are Restricted Veterinary medicines, roughly equivalent to PAR1. This system was imposed as conditions on registration. The ACVM Group periodically decides that this is too simple and that every individual drug will have different conditions on registration. Even the drug companies cannot keep up with this vacillation and most drugs now have something on the label like "See the ACVM website for conditions". These conditions are compulsory but are usually totally unknown to vets in practice.

The latest classification is:

- unrestricted = OTC
- restricted class A = PAR1
- restricted class B = PAR3 (no drugs in this class)

- restricted class C = a means of allowing corporate farmers to use prescription veterinary medicines without veterinary interference in their money making

How long this will last is anyone's guess.

The NZFSA has also separated prescribing from trading in veterinary medicines, which allows anyone with a trader's licence to fill prescriptions written by a vet. Vets have to register as traders, but are not subject to some of the vetting that others are.

One of the big problems with the ACVM Act is that since the Act itself contains so little useful information, the civil servants in the ACVM Group of the NZFSA have had to make up the rules as they go along. It can be very difficult to determine what is actual law and what is only ACVM Group policy. Very little of this legislation has been tested in court.

The NZVA have published their summary of the ACVM Act in their Guide to Veterinary Pharmacy and Dispensing, **which all vets should read**: http://www.vets.org.nz/Vetzone/Forms/infoforms.htm

Agricultural Compounds and Veterinary Medicines Regs (2011)

These list the "veterinary medicines" which are exempt from registration under the ACVM Act (medicines made up for use on someone's own animals, medical gases, hoof and skin preparations, etc, etc), and specify the conditions for those which are exempt with conditions (homoeopathic preparations, herbal medicines, antiseptics, human medicines and medicines compounded by vets).

The regs also include a list of banned poisonous plants, and a list of banned drugs. There are also specifications for paperwork and recordkeeping.

Schedule 8

A list of banned drugs; mostly things like DDT and strychnine, which have not been used for years. However, like the rest of this legislation, it is badly written. Many of the drugs are acronyms: it is not clear if DDD stands for "Donald Duck Drug" or is a synonym for mitotane.

Hazardous Substances and New Organisms Act (1996)

As the name suggests, this is designed to regulate hazardous substances (environmental and human effects) and new organisms (anything not already present in NZ). It established the Environmental Risk Management Agency (ERMA) now called the Environmental Protection Authority (EPA) which spent a long time bogged down in trying to regulate genetically engineered organisms. All veterinary medicines originally had to be registered under this act too, but a threshold has now been set where the EPA delegates this approval to the ACVM Group. The hazardous substances part is mind-bogglingly complicated and has been amended many times so far. On the day the Act was passed, someone realised that it would be illegal to fill a car up with petrol, so the first amendment was rushed through. This process continues.

The HSNO Act is different from other Acts by registering generic substances: thus if a company spends megabucks registering their new drug, other companies can freeload on this registration once the patent runs out. Understandably, this does not encourage registration. A sensible compromise has emerged, where EPA delegates registration of low risk compounds to more appropriate people, such as the ACVM Group.

Higher risk chemicals could only be used by "approved handlers", nearly all veterinary medicines fell into this class, but the bar has recently been raised a bit so that anyone can use most drugs.

EPA regards drugs with potential environmental effects, such as avermectins, as high risk. It is probably the environmental effects which mean that veterinary medicines are regulated at all: identical human medicines are exempt.

The hazard classification and controls in the HSNO Act and Regs are truly of mind-boggling complexity, I seriously doubt if anyone in NZ who handles chemicals understands them fully. This Act has the potential to cause complete chaos; if it was enforced as it is, all industry in NZ would stop. This does not mean it can be ignored. The NZVA has material to help guide vets through it.

Medicines Act (1981)

Medicines Regulations (1984/143)

Regulates the manufacture, supply and use of human medicines. Drugs must be approved for sale, and must meet standards for purity, safety and efficacy. Covers prescriptions, labelling and storage requirements (see below). Veterinary surgeons may prescribe and dispense drugs for animals under their care. Classifies drugs into "Prescription only medicines", "Restricted medicines" and "Pharmacy medicines", which are subject to different controls. Drugs not specifically classified are "general sales medicines". Regulates prescriptions and rules on possession etc.

Administered by Medsafe, who have an excellent web site - http://www.medsafe.govt.nz/profs.htm

Human medicine sales in NZ largely depend on Pharmac subsidies. If Pharmac does not subsidise the drug, there is unlikely to be a big enough market for a drug company to sell a drug and make a profit. To get around this problem, section 29 of the Medicines Act allows medical practitioners to procure a drug (from overseas) for a named patient. The MoH until recently interpreted "medical practitioner" to include vets, but no longer. This means that vets have to do without many common drugs, or go through a tedious and expensive process to import veterinary medicines via the ACVM Group for a named patient. This obviously does not work for emergency drugs, such as bicarbonate, but no one has come up with an answer yet.

There has been talk of a new Medicines Act for at least 20 years, so something may happen in our lifetimes.

Misuse of Drugs Act (1975)

Misuse of Drugs Regulations (1977/37)

The main legislation designed to control the use of addictive drugs. Most countries have something similar; the NZ act is based on the UK one. Classifies controlled drugs - mainly important for illegal possession. Vets are permitted to supply, prescribe and administer controlled drugs Class B or C for animals under their care. Specifies the more stringent requirements for prescriptions, labelling and storage of controlled drugs. Allows the Minister of Health to ban specific vets from prescribing controlled drugs, ensures that the Veterinary Council is informed of any convictions concerning controlled drugs so that convicts can be struck off.

Class A controlled drugs

Drugs of addiction such as LSD, heroin, cocaine, most amphetamines; drugs with no clinical use such as Spanish fly! The only drug of veterinary interest is etorphine. It is probably included here as it is highly dangerous to people. Permission from the Minister of Health is required to use Class A drugs. You should not come across these drugs in practice in NZ. Phenylpropanolamine is officially a class A drug, but this is not enforced (at present).

Class B controlled drugs:

Most opioids, including diphenoxylate (but also ecstasy and cannabis for some reason). In veterinary practice it is never necessary to prescribe or dispense Class B drugs: they should be kept in the clinic and administered to the animal as needed.

Class C controlled drugs

Codeine, barbiturates, buprenorphine, meprobamate; very dilute solutions of morphine, < 2.5mg diphenoxylate (also cannabis plant and coco leaf!). Ketamine has recently been classified as C4. Benzodiazepines, which are the class of drugs most widely abused by people, have recently been added to class C. "Designer drugs" (analogues of drugs of abuse) are in class C 7. This includes carfentanil (!?).Some drugs commonly used in small animal practice such as pseudoephedrine (used illegally to make methamphetamine) are likely to be made class C soon.

Security

Controlled Drugs from classes B and C 1 - 4 and 7 must be secured when not in use. Secured means locked in a metal or concrete cabinet bolted down to the building and keys kept elsewhere. These drugs should not be left unattended in vehicles. Remember that pentobarbitone is class C 4. Class C 5 do not need to be locked up, but it is still a good idea.

Records

Class B and C7 drugs must have records kept of their use. A Controlled Drugs Register must be kept on the premises (usually with the drugs). It must be a bound book with consecutively numbered pages with details of one form of one drug per page. Entries must be legible and indelible, and filled in within 24 hours of the use of the drug. A full audit of drugs obtained and used is to be carried out at the end of June and December. The Controlled Drug Register must be available for inspection by the police or Ministry of Health officers. Vets are notoriously bad at filling out the controlled drugs register - I have yet to see one in practice which complies with the law.

DIAGRAM 9.1.1 Controlled drugs register

CONTROLLED DRUGS REGISTER

page 1

Name and Form of Drug (One kind and one strength only to each page) *morphine 30mg/mL*

Date	Name and address of person from whom received; or Name of patient; or Name and address of person supplied; or Declaration "Physical stocktaking"	Prescription or Order Number or time	In	Out	Balance	Name of Authority	Issued, Dispensed, or Administered by	Initials of Person Making Entry or Checking Balance
16/10/02	*From Baxter's*	*order no.1234*	*10*		*10*		*A. Scuffham*	*JPC*
16/10/02	*Dog Smith*	*123456*		*1*	*9*	*Barter*	*Linda*	*JPC*

must be written out

animal's name

case no.

number of ampoules used, not mg of morphine

actual number of ampoules left in safe - not how many there should be!

name of vet who authorised use

signature of person giving drug

signature of person checking balance

Form of controlled drugs register. Different drugs and different forms of the same drug (eg morphine 30mg/mL) should be recorded on different pages.

If you thought all this was too easy...

The VCNZ also has requirements around controlled drugs, which often conflict with the legislation.

Food Act (2014)

This is mainly important because it specifies that MRLs must be published as a notice under the Act, these notices usually come out twice a year.

TABLE 9.1.1 Controlled drug classification

Class	Drugs	Restrictions
A	etorphine (heroin, cocaine, LSD methamphetamine etc)	controlled drug safe controlled drug register permission from MoH
B1	morphine	controlled drug safe controlled drug register
B2	ephedrine pseudoephedrine	controlled drug safe
B3	alfentanil fentanyl pethidine methadone	controlled drug safe controlled drug register
C2	codeine	controlled drug safe
C4	buprenorphine pentobarbitone ketamine	controlled drug safe
C5	benzodiazepines phenobarbitone	locked cupboard recommended
C6	dilute solutions/forms	none
C7	carfentanil (designer drugs)	controlled drug safe controlled drug register
not controlled at present	butorphanol nalbuphine pentazocine	locked cupboard strongly recommended

Prescribing & dispensing

Prescribing & dispensing

- ☑ prescriptions or authorisations are legal documents and must be written correctly
- ☑ prescriptions for human drugs must follow the form in the Medicines Regs, but this is a good idea for all prescriptions
- ☑ dispensed drugs must be labelled correctly
- ☑ when using veterinary medicines “off label” or human medicines, follow the NZVA CoP on discretionary use
- ☑ the law is constantly changing, so keep up!
- ☑ The VCNZ CoPC has a section on veterinary medicines - read it!

A prescription is a set of instructions to a pharmacist to make up and supply a medicine. They are usually only used in veterinary practice for infrequently used medicines. Animal owners can also ask for a prescription so that they can get it filled by another vet or a trader, if they think that this will be cheaper. The legal requirements for a prescription vary, but it is good practice to write all presriptions in the same way. Pharmacists have a legal responsibility to verify a prescription: if they don't like it they will not fill it.

Prescriptions for veterinary medicines are a grey area in the law. The requirements for presecriptions for human drugs are set out in the Medicines Regs, and vets prescribing human drugs must stick to these. It is good practice to follow the same requirements for veterinary medicines. There is an ACVM code of practice written by the NZVA for writing prescriptions, but it is not clear if it is a legal requirement. The NZFSA has issued the snappily entitled "Veterinarians Recognised (under s 62, ACVM Act) to Issue a Valid Authorisation for Purchase and Use of Restricted Veterinary Medicines Requiring Veterinary Authorisation Perfromance and Technical Standard" but it is not clear if this is actually law either. See: http://www.nzfsa.govt.nz/acvm/registers-lists/cop.htm

“Authorisation” is a term used by the ACVM Group where most people would talk about a prescription. They usually take the form of a note in the case records of an animal or farm to the effect that the client can be supplied with drugs, although the definition is constantly changing. Note that this is a different definition from other countries. Bear in mind that authorisations for veterinary medicines will probably be filled by someone who knows nothing about pharmacy.

Requirements for a prescription

A prescription must be written in ink and should include:

- Name and address of the prescriber and the veterinary practice
- Date of prescription
- Name, initials and address of the client (include animal's name or species)
- Superscription
- Name of drug(s) and strength. This is usually the approved name, in which case the pharmacist may dispense any suitable product, but you may use a tradename for a particular product. This is compulsory for veterinary medicines.
- (Directions to pharmacist - how to prepare any preparation which needs to be made up)

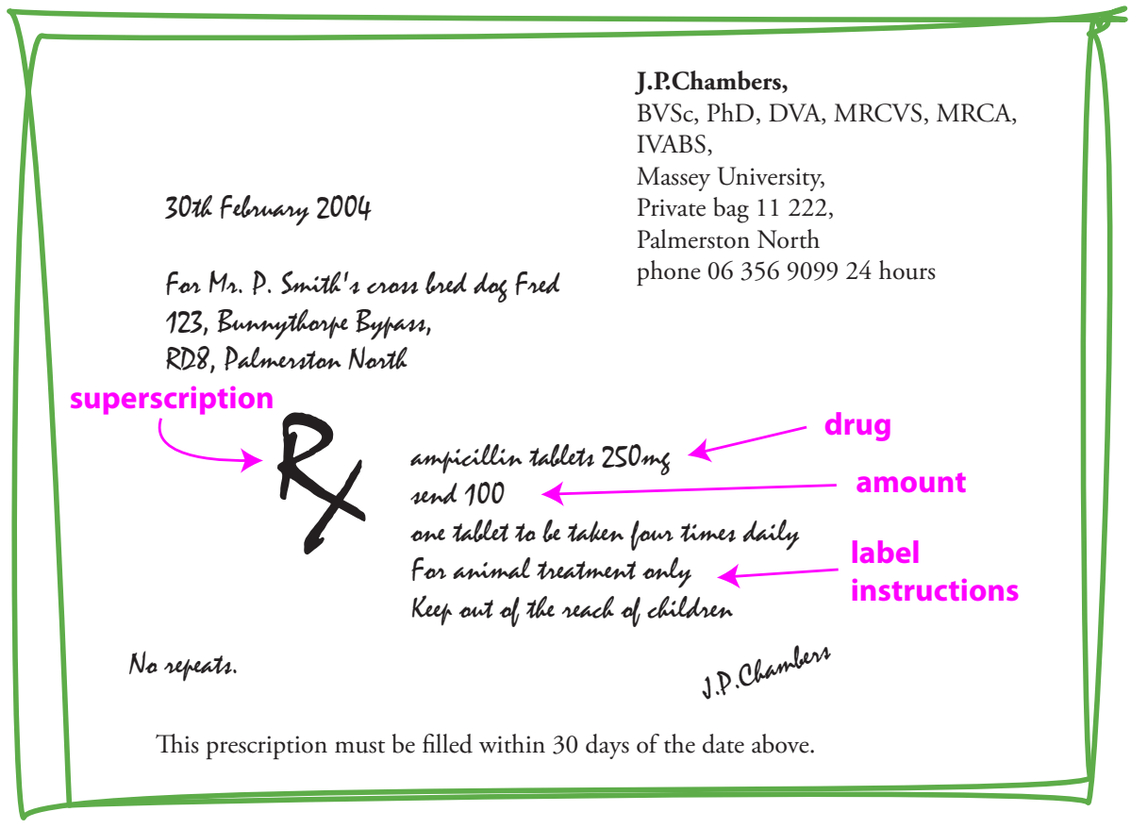
- Amount to be dispensed. For controlled drugs this must be in words and figures to stop people altering it.
- Directions you wish to appear on the label. Dose, directions for use, "for animal treatment only", “keep out of the reach of children” and any precautions or warnings
- Veterinary surgeon's signature
- Policy on repetition. If nothing is put down here the prescription cannot be repeated, but it is possible to specify one or two repeat prescriptions. This is very rarely necessary in veterinary practice.

Printed prescriptions are a grey area too. Currently, the drug, the amount and the signature should be handwritten, but the MoH are reconsidering this, and fully electronic presriptions may be allowed soon. The NZVA have prescription forms available at: http://www.vets.org.nz/Vetzone/Forms/infoforms.htm

A veterinary authorisation for a restricted veterinary medicine must:

a. be legible and indelibly printed;
b. be signed and dated personally by the authorising veterinarian or identified in a manner that allows the authorising veterinarian to recognise it as the one he or she issued;
c. carry the printed name of the authorising veterinarian, the address and name of the veterinary practice or organisation of the authorising veterinarian;
d. set out the identification and address of the owner (or person in charge) of the animal(s) to be treated;
e. show the date of the relevant veterinary consultation;
f. describe the essential identification details of the animal(s) to be treated;
g. identify clearly the registered trade name product and active ingredient(s) being authorised;
h. state the quantity of RVM authorised;
i. specify the dose and frequency of the doses if the RVM is to be administered by injection, or by insertion into any cavity of the body, or by swallowing;
j. specify the method, application rate and frequency of use if the RVM is to be applied externally;
k. specify if it is to be used for repeat supply/filling (if repeats allowed, specify the number of occasions the RVM can be supplied under the same authorisation, or the interval to elapse between each supply, or the period of treatment during which the veterinary medicine is intended to be used); and
l. state the duration of the validity of the veterinary authorisation.

DIAGRAM 9.2.1 Form of prescription



A veterinary authorisation must also:

a) allow dispensing of, or access to, only a quantity of the RVM that is necessary and sufficient to achieve the purpose of the authorisation; and

b) direct the person dispensing the RVM to provide to the person specified in the veterinary authorisation the use instructions and any additional instructions, including withholding periods, to be followed or precautions to be taken as considered necessary by the authorising veterinarian.

Abbreviations

Prescriptions used to be written in Latin, and some Latin abbreviations are still seen. However, **they should be written without abbreviation and in English these days**, particularly if you do not understand Latin! Abbreviations are illegal in prescriptions for controlled drugs.

for information only:

Veterinary - may not be recognised by pharmacists

sid - semel in die	once daily
bid - bis in die	twice daily
tid - ter in die	three times daily
qid - quater in die	four times daily
q12h - quaque 12 hora	every 12 hours
q6h - quaque 6 hora	every 6 hours
qd - quaque dies	every day
q2d - quaque 2 dies	every 2 days
qs - quantum sufficiat	as much as needed
ad lib - ad libitum	freely available

DIAGRAM 9.2.2 Superscription

Prescription writing goes back a long way. The superscription is usually taken to be an abbreviated form of the Latin recipe = take, but could also be a representation of the Eye of Horus, supposed to enlist his aid in making the drug work!

Human

ac - ante cibum	before food
bd - bis die	twice daily
od - omni die	every day (daily)
om - omni mane	in the morning
on - omni nocte	at night
pc - post cibum	after food
prn - pro re nata	when required
qds - quater die sumendus	four times daily
qqh - quarta quaque hora	every four hours
stat - statim	immediately
tds - ter die sumendus	three times daily

Directions to include drugs in feed

This is a form of prescription, and the requirements are much the same. Bear in mind that all animals to which medicated feed is given are food animals. The manufacturer is not allowed to make up the feed until he receives the written directions. Use the NZVA production animal prescription pad:
http://www.vets.org.nz/Vetzone/Forms/infoforms.htm

Things to be included:

- Name and address of veterinary practice
- Name of prescribing veterinary surgeon
- Name and address of client
- Date
- Name of drug, form and concentration
- Inclusion rate
- Final concentration of active ingredient in food
- The feed to which the drug is to be added
- The quantity of medicated feed to be supplied
- The species to be treated
- Number of repeats allowed
- Precautions, including withholding period
- Contact phone number

- Signature

Keep a record!

Labelling drugs

Every package of any sort of prescription animal remedy dispensed must be clearly labelled with the following information:

- Name and address of veterinary practice
- Contact phone number
- Emergency phone number
- Name of prescribing veterinarian
- Date dispensed
- Name and address of owner
- Name / no. and species of animal
- Name, strength and quantity of drug
- Directions for use: dose, method of administration and frequency
- Any relevant warnings (e.g. "wear gloves when handling")
- Witholding period for food animals
- In bold print "for animal treatment only"
- "Keep out of reach of children"

If the drug is in a container inside another container, eg, a tube inside a box, put the label on the container with the drug in it.

For over the counter sales of animal remedies in the manufacturer's original packaging, this label is not necessary but still a good idea.

It is difficult to fit all the necessary information on a label, even if your writing is very small. It is likely in the near future that computer printed labels will be required. They are certainly a good idea.

Storage of medicines

Drugs should not be kept anywhere that food is stored. If you want to keep vaccines and milk in the fridge, you need two fridges. It is also illegal to prepare or pack drugs in any room where food or drink is prepared or consumed. Children and unauthorised people must not have access to the drug storage area. Buildings or vehicles containing drugs must not be left unattended unless they are properly secured.

DIAGRAM 9.2.3 Labels

J.P.Chambers, MRCVS
IVABS, Massey University
phone 06 356 9099

24/1/01
for Mr. Smith's dog Fred
123, Bunnythorpe Bypass,
RD8, Palmerston North
100 tablets ampicillin 250mg
give one tablet four times daily

For animal treatment only
Keep out of the reach of children

J.P.Chambers, MRCVS
IVABS, Massey University
phone 06 356 9099

24/1/01
for Mr. Smith's weaner pigs
123, Bunnythorpe Bypass,
RD8, Palmerston North
Zaquilan 20% injection 100ml
give 2ml intramuscularly and repeat in 2 days
withholding period 28 days

For animal treatment only
Keep out of the reach of children

J.P.Chambers, MRCVS
IVABS, Massey University
phone 06 356 9099

24/1/01
for Mr. Smith's horse Jim
123, Bunnythorpe Bypass,
RD8, Palmerston North
Dr. Chambers' patent horse medicine 1 pint
rub on the affected area once a week

For external use only

Wear full protective clothing

For animal treatment only
Keep out of the reach of children

Many drugs have specific storage requirements; many must be refrigerated. Most drugs will have a longer shelf life if stored in a cool dry place out of direct sunlight. The back of a car is about the worst possible place to store drugs.

Discretionary (off label) use of drugs

All licensed animal remedies have been approved by the NZFSA for certain species, uses and at certain doses. These are written on the label. Vets may use almost any drug they consider helpful but this use is unapproved and discretionary or “off label”. If a registered veterinary medicine is used in the approved way and something goes wrong, it is the drug company’s responsibility. If it is used in an unapproved way, the prescribing veterinary surgeon is responsible. All veterinary use of human drugs is discretionary.

Under the new legislation, a vet can presribe almost any drug but it is a legal requirement to comply with the NZVA Code of Practice for the Discretionary Use of

TABLE 9.2.1 ACVM default withholding times

Animal	Meat	Milk	Eggs
ruminants	91	35	
pigs	63		
horses	180		
birds	63		10
camelids	63		
rabbits and hares	63		

Default withholding times in days used as a guide by the ACVM Group. nb. these have no basis in law (or science).

Human and Veterinary Medicines by Registered Veterinarians. This says that before using drugs in a discretionary way, a veterinary evaluation must be made, and certain requirements must be met.

A veterinary evaluation involves several consecutive steps:

The animal must be in your immediate care, and you must have sufficient information anout the animal to decide that treatment is justified. It is a good idea to clinically examine the animal and make a diagnosis.

Assess if there is a veterinary medicine available which is likely to work at the doses stated on the label. If there is, use it.

If there is a veterinary medicine available which is likely to work at doses outside those on the label, this should be used.

If no veterinary medicine is available which is likely to work, then a human medicine or a medicine made up on a one off basis can be used.

Requirements for discretionary use:

Ensure that the drug is not banned. No drugs are banned at the moment, but the ACVM Act allows the Minister of Agriculture to ban specific drugs. Some drugs have conditions on their use which mean that they cannot be used as you might want. Check before use:
http://www.nzfsa.govt.nz/acvm/registers-lists/acvm-register/index.htm

Assess the scientific information available. Have you enough information to use it safely and effectively? Information can be obtained from the drug company (the drug may be licensed overseas for your use), from the literature or from colleagues (preferably ones you can trust as the responsibility is still yours). You must be sure that the drug will not cause unnecessary pain or suffering. Remember species differences - particularly in pharmacokinetics.

Keep in contact with the owner to check for adverse reactions.

For food animals, think about the possibility of drug residues in food. You have to have a very good reason to give an unapproved drug to a food animal. You also have to calculate witholding periods, or use the defaults (see table).

Assess if there is a risk to agricultural security. This boils down to the development of resistance in pathogens.

Give the owner the following information in writing and keep a record for two years:

(i) Name of owner or owner's agent

(ii) The identity of the animal or group to be treated

(iii) The established name of the drug, the active ingredient (if compounded for discretionary use) and the concentration

(iv) The dose rate and frequency of treatment

(v) The route and method of administration

(vi) The duration of treatment

(vii) The withholding time (for food animals)

(viii) The date of treatment

(ix) The name of the prescribing veterinarian and the name, address and contact phone numbers of that veterinarian's practice.

Ensure that the following information is conveyed to the animal's owner or agent:

(i) Any special considerations in regard to operator safety;

(ii) Specific advice that adverse reactions should be reported immediately to the prescribing veterinarian or in the absence of that veterinarian to other veterinarians in the practice;

(iii) Provide the information that this use is discretionary use

This code of practice has been approved by the Minister of Agriculture under the ACVM Act. Note that there are major differences from the situation in our major trading partners. In the USA, there is a list of drugs which are banned in food animals; in Europe, it is illegal to give a drug to a food animal unless the active ingredient is licensed in some food animal species (ie, an MRL has been established). This means that there may be political pressure to change the NZVA code of practice.

Making up your own drugs

All animal remedies sold commercially must be registered with the NZFSA or exempted from registration, but you are allowed to make up your own drugs for animals under your care, ie, you must have examined the animal and have been given responsibility for its treatment by the owner. As this is an discretionary drug use, all the considerations above apply. You cannot put home made medicines on general sale without going through the registration process (which is a serious exercise in filling in forms and spending money). If you are compounding drugs, you must have a documented system.

Making up mixtures requires knowledge of the chemical compatibility and stability of drugs, and is best avoided. If it must be done, it may be better to write a prescription and get a pharmacist to do it.

If registered animal remedies are bought in bulk and repackaged, they must only be used for animals under your care. Once the seal on the original container is broken, the drug company is unlikely to take responsibility for any problems with the drug (there is usually something on the label along the lines of “use within two days of opening”). Particular attention must be paid to labelling.

Repackaging bulk drugs because you anticipate a requirement for small lots is acceptable: doing it to save money is not.

Dispensing of medicines

The exact legal requirements for packaging animal remedies are unclear, but veterinary surgeons dispensing human medicines must comply with the same regulations as medical practitioners and pharmacists. The veterinary profession cannot afford to be sloppy in this, or the right to dispense drugs may be removed. Child proof safety containers for all dispensed drugs are highly recommended. Envelopes are not acceptable.

Unopened manufacturer's packaging is usually acceptable - stick the label where it will not obscure any warnings etc.

Foil wrapped / blister packed tablets are legally regarded as childproof containers and may be dispensed in resealable plastic bags; loose tablets must be in a proper childproof rigid container.

If preloaded syringes are dispensed, the needle should be supplied separately and the syringe should be capped to prevent leakage.

All packages (no matter how small or awkwardly shaped) must be properly labelled. Most drugs given to animals will also affect people; anyone handling the drugs must be properly trained and appropriate safeguards taken. This is the responsibility of the veterinary surgeon. The HSNO Act is likely to make this more onerous.

Disposal of unwanted drugs

Do not just tip them down the sink or throw them in the bin! The veterinary surgeon is directly responsible for safe disposal of drugs - think about their possible effects on the environment. In most cases the drugs should be incinerated at high temperatures (do not just throw them in the fire either!). Talk nicely to your local chemist or hospital, or pay for them to be disposed of properly.

Adverse drug reactions

An adverse drug reaction is an undesirable, unintended or unexpected response to the clinical use of a drug, including injury, toxicity, sensitivity reaction or lack of efficacy.

possible causes of adverse reactions:

- anaphylactic / anaphylactoid reactions
- misreading instructions - double dosing, incorrect dilution, miscalculation
- use of an unlabelled product
- known side effects of a drug
- use of expired product
- interactions of one or more animal remedies
- idiosyncratic reactions

Adverse drug reactions should be reported to the ACVM Group on forms provided by them. If you do not have a form handy, collect as much information as possible at the time and organise the form later from:

http://www.foodsafety.govt.nz/elibrary/industry/Acvm_72-Chemicals_.doc

or contact MAF ACVM Group, PO Box 2526, Wellington. Fax: (04) 460 8771 phone (04) 460 8750, ACVM-AdverseEvents@mpi.govt.nz

The info you will need is likely to include at least:

- Your name and contact details
- The name, batch no., licence no. and expiry date of the product
- The animal's owner's name and contact details
- The actual dose given and the route of administration
- The number of animals treated and the number reacting
- The date and nature of the reaction
- Animal details: species / breed, age, sex, weight
- Other products given
- Immediate treatment
- Samples taken for analysis

Keep any remaining drug for analysis!

Reporting of adverse reactions is a condition of registration of all veterinary medicines, ie, compulsory, but only for the drug company. It is an ethical requirement under the Code of Professional Conduct. Reactions in people handling the drugs should also be reported to the ACVM Group.

As a matter of professional courtesy, the drug company should also be informed. Adverse reactions to off label use of drugs should also be reported.

The future?

The present fluid situation makes prediction difficult, with the only certainty that the amount of paperwork involved will inevitably increase. Every use of drugs of any sort will probably have to be recorded in an auditable way. The most up to date information on what is happening can be found at the ACVM Group's web site: http://www.nzfsa.govt.nz/acvm/

Clients are likely to want more information about drugs given to their animals: this may well be enshrined in law.

For instance, in Europe, human patients have a right to prescribing information and prescribers have a duty to explain all the relevant information in non technical language. The same thing is recommended in NZ (for people). You may have to learn some pharmacology!

Antidote

a substance that specifically counters the action of a poison. (e.g. Vitamin K1 for anticoagulant poisons).

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Chapter 1 - Basic toxicology

Antitoxin

an antibody to the toxin of a microorganism (or zootoxin or phytotoxin) that specifically binds to the toxin and neutralises it; eg. Tetanus antitoxin is derived from injecting toxin into animals and collecting the antibodies for therapeutic use that is to bind the toxin in the sick animal

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Chapter 1 - Basic toxicology

Drug

Any substance which can affect a biological system. The original definition was “dried herb”; in the USA, “drugs” are what drug addicts use, anything else tends to be a “pharmacologic agent”.

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Chapter 1 - Basic stuff

Pharmacodynamics

What the drug does to the animal.

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Pharmacokinetics

What the animal does to the drug, or strictly speaking, the movement of drugs within the body.

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Pharmacology

The study of drugs - from φαρμακον - drug, medicine or poison!

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Chapter 1 - Basic stuff

Pharmacopoeia

An official list of drug preparations, principally concerned with purity standards. You may see a drug name followed by the letters BP or USP indicating that it was made to the standards specified in the British Pharmacopoeia or the United States Pharmacopoeia.

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Chapter 1 - Basic stuff

Pharmacy

The science of the preparation and formulation of drugs.

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Chapter 1 - Basic stuff

Poison

any solid, liquid or gas that regardless of the route of exposure (oral, topical, inhaled etc) causes a harmful effect on the body

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Chapter 1 - Basic toxicology

Therapeutics

The treatment of disease. This is more of an art than a science - there is usually no single right way to treat disease in an individual animal (despite the impression you may get from some people!). There are usually plenty of wrong ways though; a knowledge of pharmacology can avoid most of these.

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Toxic effect

any noxious effect on the body – reversible or irreversible; any chemically induced tumour - benign or malignant; any mutagenic or teratogenic effect or death as a result of contact with a substance via the respiratory tract, skin, eye, mouth, injection or any other route.

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Chapter 1 - Basic toxicology

Toxicity

refers to the amount of poison necessary to have harmful effects.

All substances are potentially toxic if given in sufficient quantities. The LD50 is an expression of the amount of compound that is necessary to cause death to half the animals exposed to the compound.

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Chapter 1 - Basic toxicology

Toxicology

The study of poisons. Remember that most drugsa re poisonous in overdose!

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Chapter 1 - Basic stuff

Toxin

generally used to describe poisons that come from biological sources. For example the tetanus bacteria produces a (bio)toxin that causes lockjaw in humans and animals

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