2 Basics

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

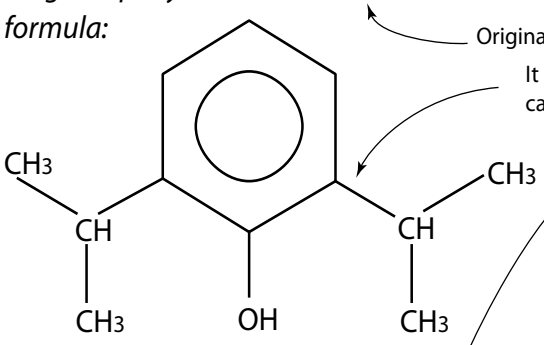
This is a constant source of confusion since every drug may have several different names.

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

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

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.

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

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).

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.

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 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!

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 pharmacokinetcs. Phase 2 is testing in patients with the disease to be treated to establish efficacy and dose. Phase 3 is similar but much larger multicentre studies of the final fomrulation. 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

To produce an effect, drugs must get from the site of administration to the site of action (covered in pharmacokinetics lectures) 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 drug receptors work

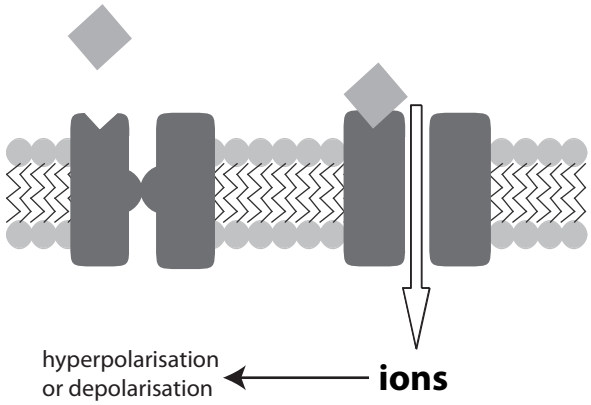
Receptors

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 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.

Ionotropic receptors

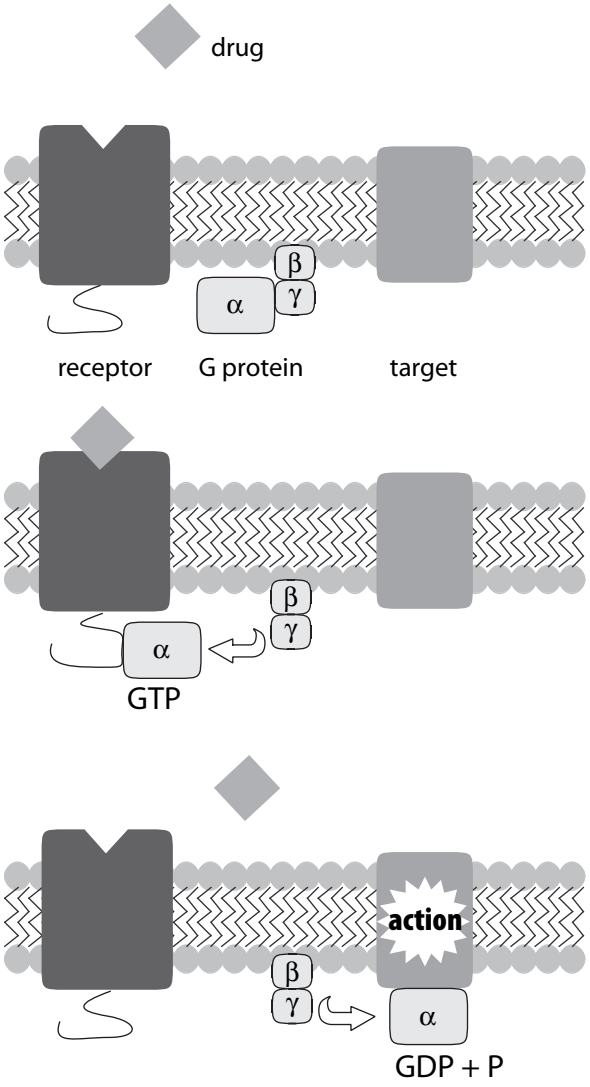
These are a group of four or five proteins embedded in the cell membrane forming a pore. When the drug binds to

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.

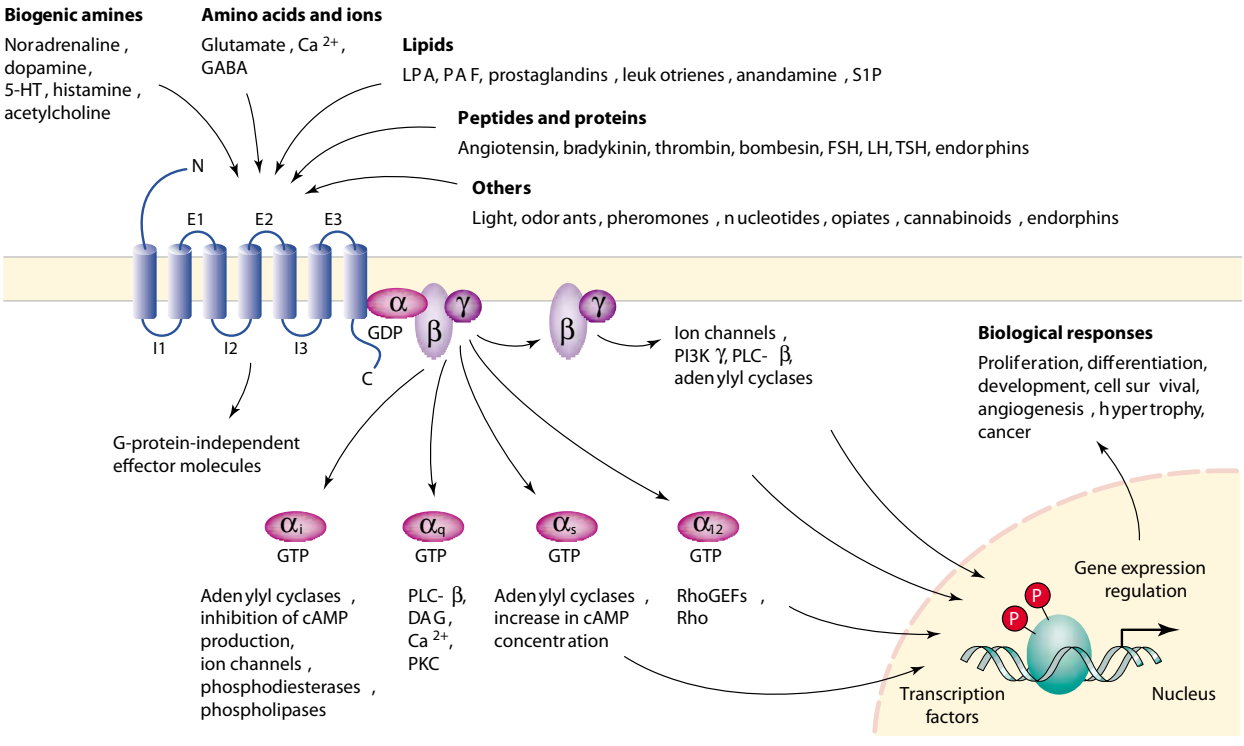
G PROTEIN COUPLED RECEPTORS

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, G_i inhibit and G_s stimulate the enzyme adenylate cyclase, which produces the second messenger cAMP; G_q 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 α_2 receptors, but have some different effects in cattle. This may be cased by different G protein coupling.

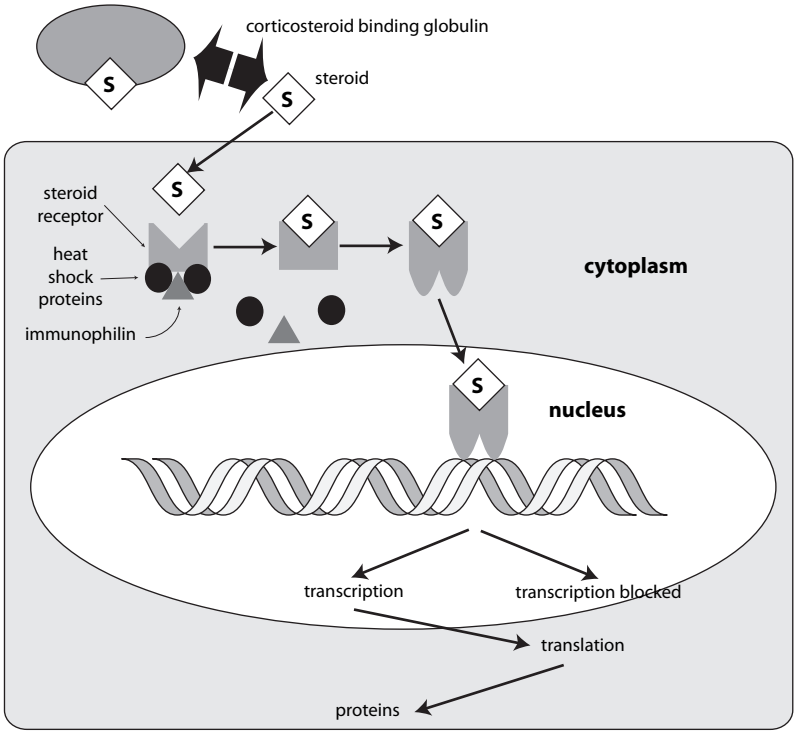
A number of toxins (pertussis toxin, cholera toxin, various wasp venoms) interact with the G proteins but there are no useful drugs yet which do so, although some drugs intract with G proteins as a side effect, eg suramin (used to kill trypanosomes) and benzalkonium (an antiseptic).



G protein coupled receptor. The βγ subunit may also bind an effector.



G protein coupled receptor signal transduction. It can get complicated!!!

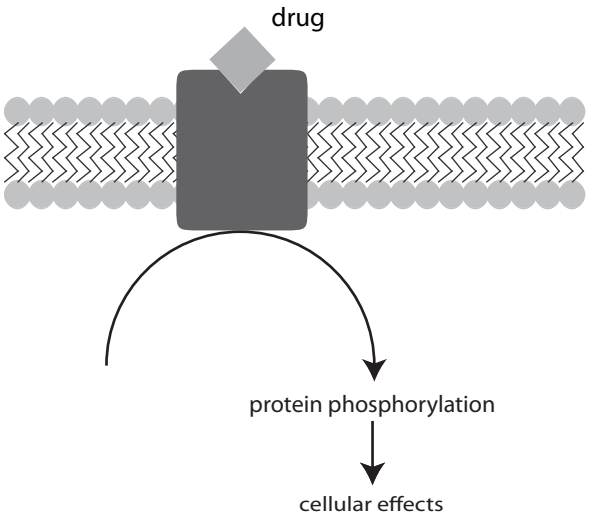


Receptor for corticosteroids. The transcription of a wide variety of proteins may be stimulated or inhibited, leading to a slow but widespread effect.

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 receptor, eg, insulin receptor.

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

Guanylate cyclase linked receptors are very similar.

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.

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 α_1 α_2 β_1 and β_2 receptors. These can be further subdivided, eg α_{2A} α_{2B} α_{2C} α_{2D} etc. However, α_{2A} receptors in humans are identical to α_{2D} receptors in the rat, and there are several more α_2 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 α_{2A} 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

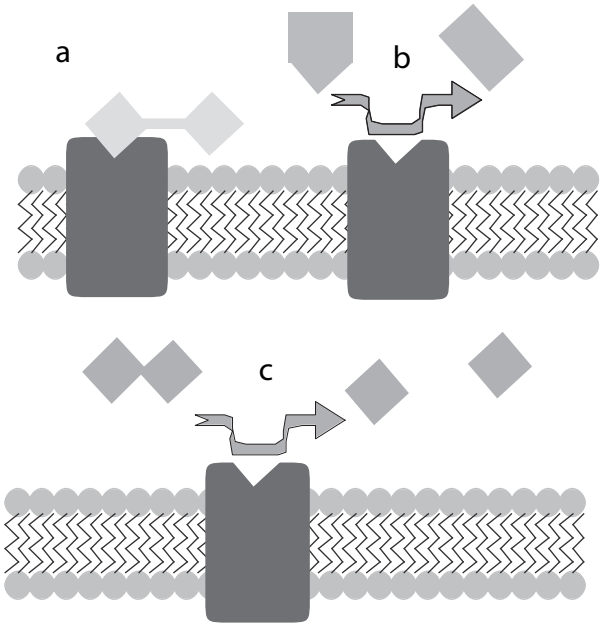
Ion channels

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.



Drugs acting on enzymes: a - enzyme blocker, b - false substrate, c - prodrug.

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 molecule 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 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.

Drugs (diamond shape) can block the channel pore, eg ketamine in the NMDA receptor, or can exert their effect from inside the channel, eg local anaesthetics in sodium channels.

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.

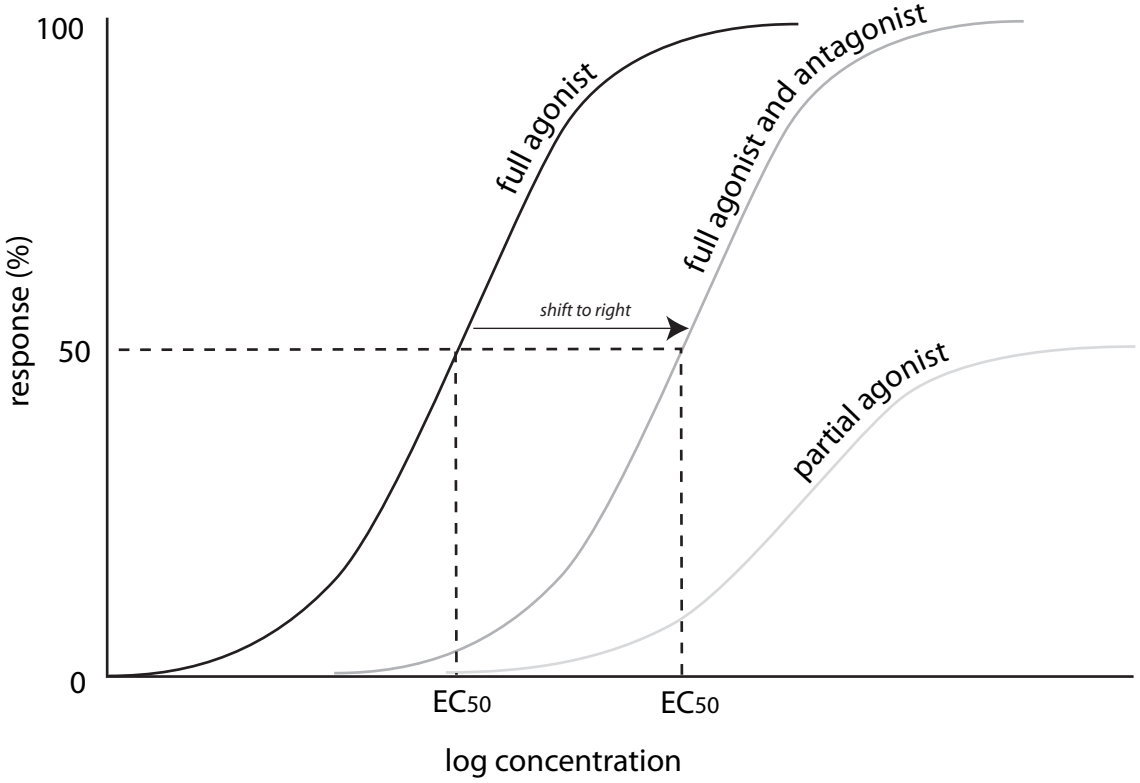
If a full agonist can produce a maximal response in a tissue without occupying all the receptors, the tissue possesses spare receptors or a receptor reserve. This often happens with smooth muscle, and appears to be a way of economising on endogenous ligand. Changes in the amount of endogenous ligand (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:

•**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 ef-



Concentration response curves for a full agonist, a full agonist in the presence of a competetive antagonist, and a partial agonist.

fects 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).

•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.)

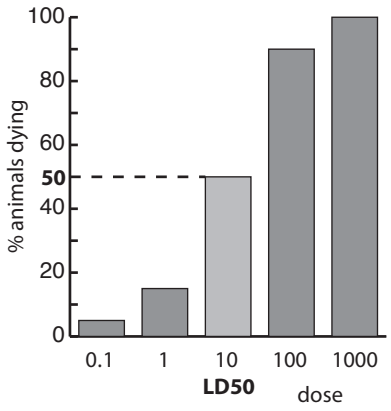
The ED50 is the **dose** at which a drug produces a quantal response in 50% of animals; eg. the minimal alveolar concentration of an anaesthetic is the dose (despite the name) which stops 50% of animals responding to a supramaximal stimulus (often skin inciscion).

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.



The LD50 - the most extreme form of ED50. In this case, a dose of 10 kills 50% of animals to which it is given.

Measurement

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.

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 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.

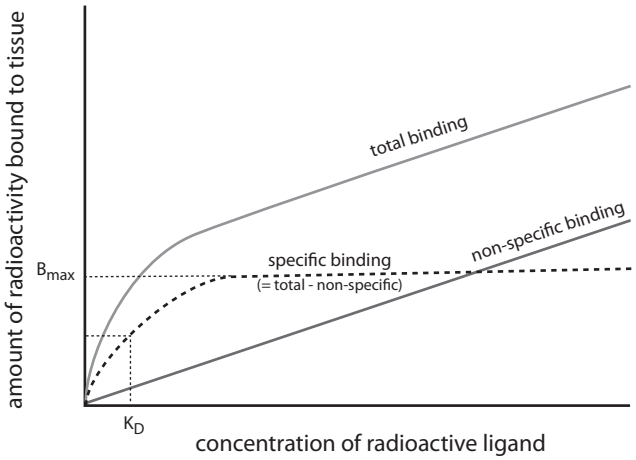
These sort of experiments show the B_{max} which gives an indication of the number of receptors in the tissue, and the dissociation constant, K_D, which is the concentration of drug which occupies 50% of the receptors.

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.

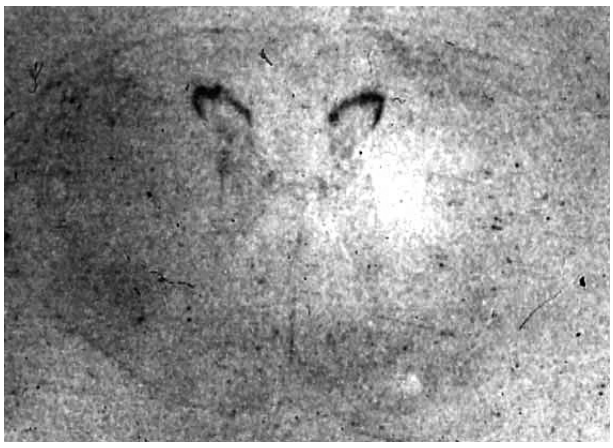
Another variation which can be used in patients is positron emisson tomography where a drug containing a positron emitting isotope is given to the patient and radioactivity is visualised by various techniques. This is particularly useful for showing how disease affects receptor numbers.

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.

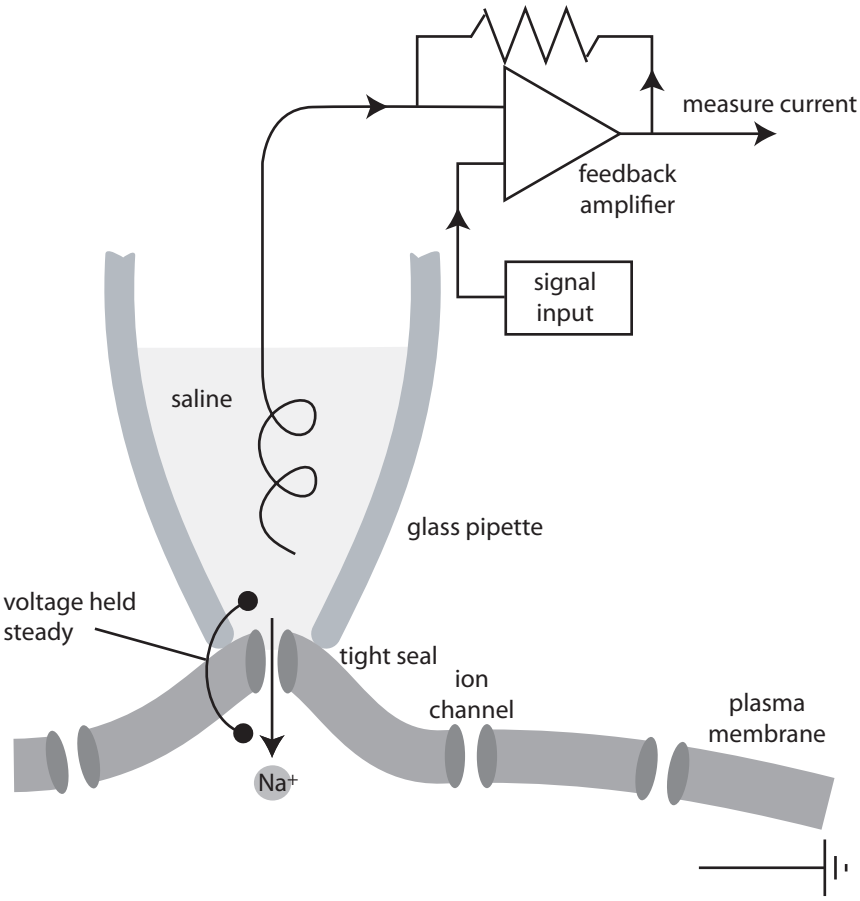
Drugs can be applied to the whole cell, or put in the



Saturation curve for a radioligand binding experiment.



Autoradiograph of a section of horse cervical spinal cord. Dark areas show increased radioactivity from ^3H clonidine binding to α_2 receptors, mainly in the substantia gelatinosa.



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.

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.

Basic toxicology

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.

Basic Toxicology
The dose makes the poison!

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

7. 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, p186

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

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

Note that 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

• 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. An anion exchange compound used to bind toxins is 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

- 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 are used

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Clinical Signs & 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

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

brackenfern - 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 α 1 stimulation but also β1

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 blink-

ing, 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 CO2 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 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 CO2 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

Emergency Poisons Kit

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

Practice exam questions

Multiple Choice Questions

1. Most drugs produce their effects by binding to
   - receptors ❑
   - lipids ❑
   - water ❑
   - ions ❑
   - sugars ❑

2. An ED50 is a measure of
   - antagonism ❑
   - effectiveness ❑
   - safety ❑
   - potency ❑
   - affinity ❑

3. Cyclic AMP is
   - a neurotransmitter in the central nervous system ❑
   - inactivated by uptake ❑
   - released by β adrenoceptor agonists ❑
   - an essential fatty acid ❑
   - a CNS stimulant ❑

4. Phospholipase C is an enzyme which
   - is regulated by G proteins ❑
   - converts arachidonic acid to PGG ❑
   - phosphorylates G proteins ❑
   - is a second messenger ❑
   - is a target for steroids ❑

5. Antagonists
   - can be reversible or irreversible ❑
   - have a low affinity for the receptor and a high efficacy ❑
   - produce opposite effects to agonists ❑
   - are larger molecules than agonists ❑
   - are usually non-specific ❑

6. Competitive antagonism exists when
   - the agonist and antagonist bind to the same receptor ❑
   - the antagonism may be overcome by increasing the dose of agonist ❑
   - only the antagonist has appreciable efficacy ❑
   - the antagonist acts through different receptors ❑
   - the antagonist is more potent than the agonist ❑

7. If the EC50 of a drug is 10^{-7} M then
   - the Kd of the drug must be the same ❑
   - maximal response will be at 2×10^{-7} M ❑
   - the drug is a competitive antagonist ❑
   - half the maximal response will be at 10^{-7} M ❑
   - it has a lower therapeutic index than a drug of EC50 10^{-8} M ❑

8. Ionotropic receptors are
- activated by G proteins ❑
- ion channels ❑
- able to use inositol triphosphate as a second messenger ❑
- enzymes ❑
- usually permeable to magnesium ions ❑

9. Partial agonists usually have
- a low efficacy ❑
- the same effect as full agonists but at higher doses ❑
- a maximal effect if there is a large receptor reserve ❑
- an ability to act as inverse agonists ❑
- reduced effects because they desensitise receptors ❑

10. A dog is given an anaesthetic premed containing buprenorphine, an opioid partial agonist, to prevent pain during the operation. It receives fentanyl, a full opioid agonist druing the op, followed by naloxone, an opioid antagonist (to counteract the respiratory depressant side effects of the opioids). How would you control the dog's pain with opioids post op?
- give more buprenorphine iv ❑
- give a bolus of fentanyl iv ❑
- use a different agonist such as morphine ❑
- give a high dose fentanyl infusion iv ❑
- sedate the dog ❑

11. Activated charcoal
- adsorbs acids and alkalies ❑
- results in black stools ❑
- is indicated when bowel sounds are absent ❑
- is used with liquid paraffin ❑
- is an antidote for warfarin ❑

12. Apomorphine
- is usually given orally ❑
- is a good analgesic ❑
- stimulates the emetic centre ❑
- stimulates the chemoreceptor trigger zone ❑
- can be reversed by naloxone ❑