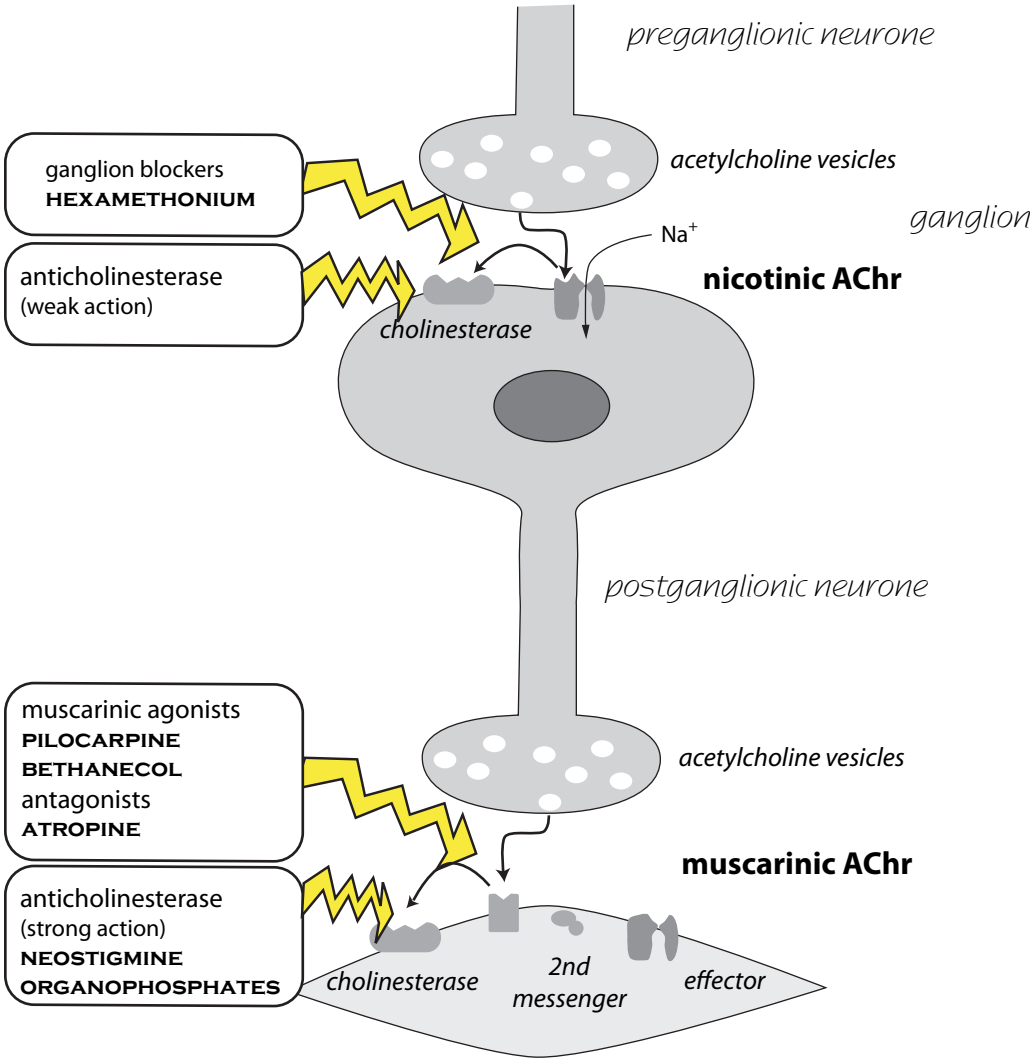
4 Autonomic system

Autonomic effects on the cardiovascular system are covered in more detail in Chapter 6..

Parasympathetic system



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

Only one important group of drugs acting on the autonomic 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 interesting 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 by 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.

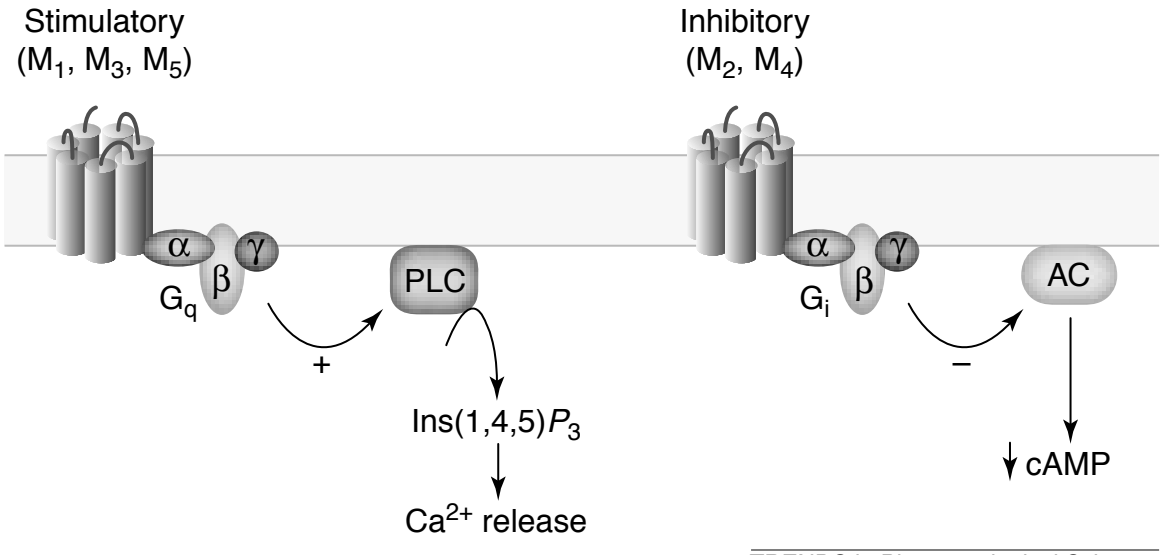
Atropine blocks all muscarinic receptors, but specific drugs are being developed. **Pirenzepine** is a relatively specific antagonist for M1 receptors and is used in the gut to reduce acid secretion.

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



Signal transduction on activation of muscarinic receptors

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 sub-mandibular - 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.

Antagonist affinity estimates at muscarinic M_1, M_2, M_3, M_4 and M_5 human recombinant receptors

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.

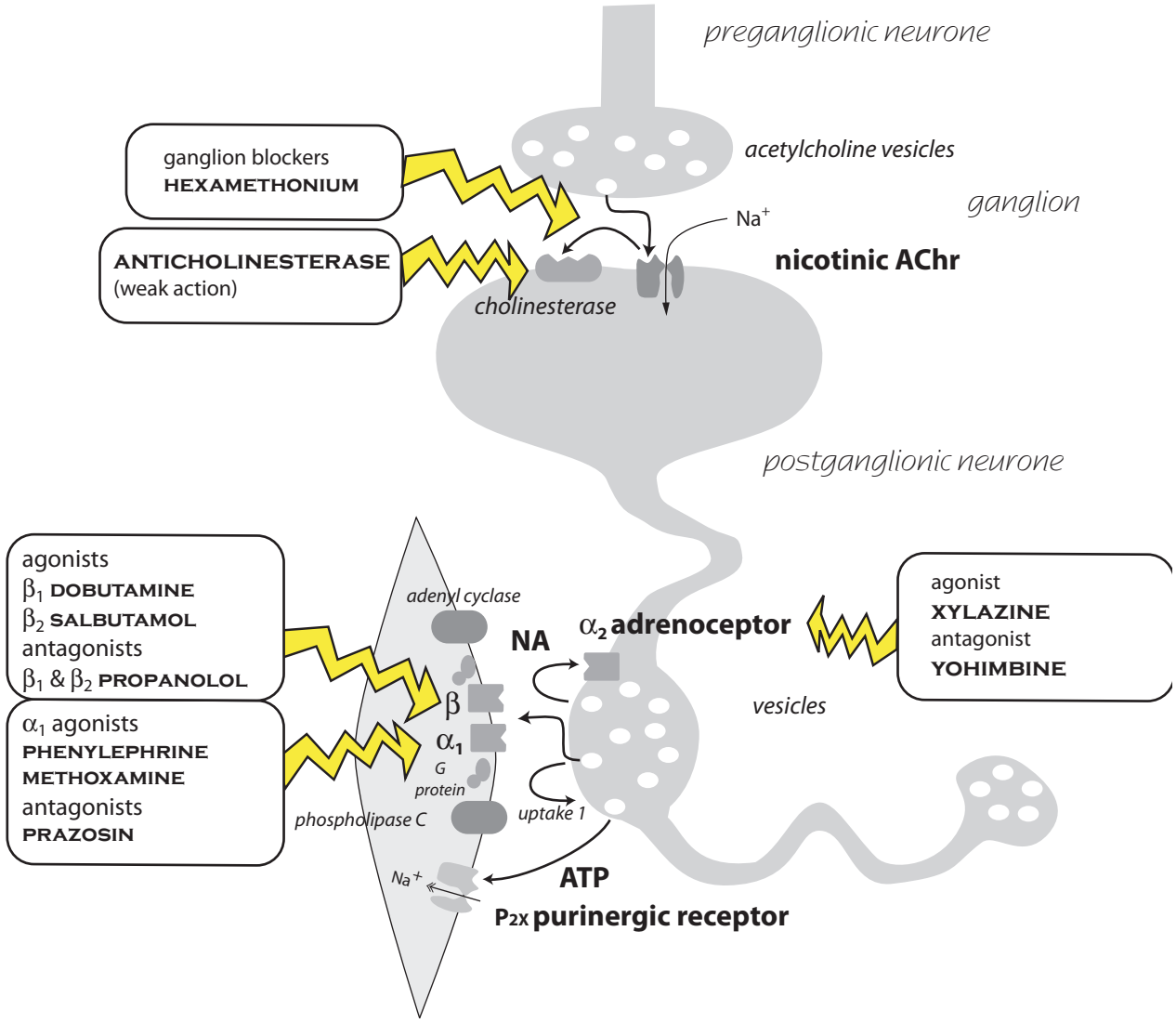
commonly used drugs

atropine

Parasympathetic nervous 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

Sympathetic system



Site of action of drugs on the sympathetic nervous system.

Physiology

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

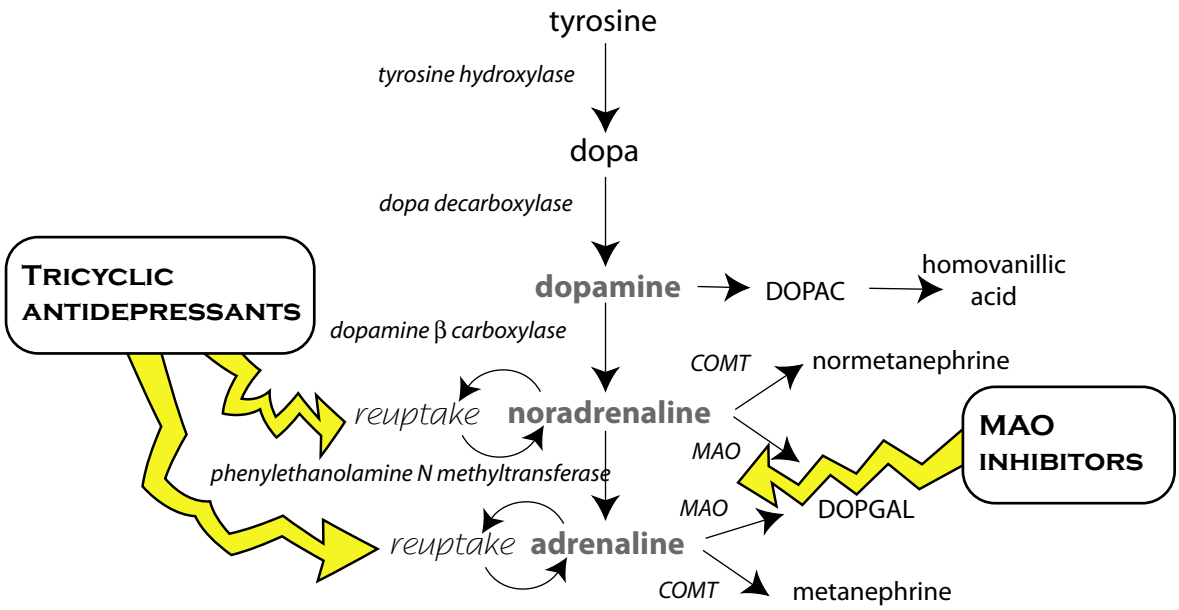
When a post ganglionic sympathetic neurone fires, noradrenaline is released. It acts at α_1 or β_1 receptors (excitatory) on the postsynaptic membrane or on α_2 receptors (inhibitory) on the presynaptic membrane. (Note that CNS α_2 receptors are different - most of them are postsynaptic). Adrenaline will act as an agonist at all these receptors and also β_2 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, α_{2A}, α_{2B}, α_{2C}, α_{2D})which also have different distributions. More specific drugs for these subtypes are being developed.

Peripheral α_2 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



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

receptor	transmitter	useful effects	agonist	antagonist
α_1	adrenaline noradrenaline	vasoconstriction mydriasis	phenylephrine	prazosin
α_2	adrenaline noradrenaline	(vasodilatation) sedation & analgesia	xylazine detomidine	yohimbine atipamezole
α_1	adrenaline (noradrenaline)	+ve inotropy tachycardia	dobutamine dopamine	atenolol metoprolol
α_2	adrenaline	bronchodilatation vasodilatation (musc) uterine relaxation	salbutamol clenbuterol	propranolol (nonselective)
(α_3	adrenaline noradrenaline	lipolysis)		

tissue (although some will not cross the blood brain barrier) so the range of side effects is wide. For instance, α_2 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).

Sympathetic nervous 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 cotransmission is important for the fast component of sympathetic stimulation

NANC transmission

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 applications 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 recptor 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.

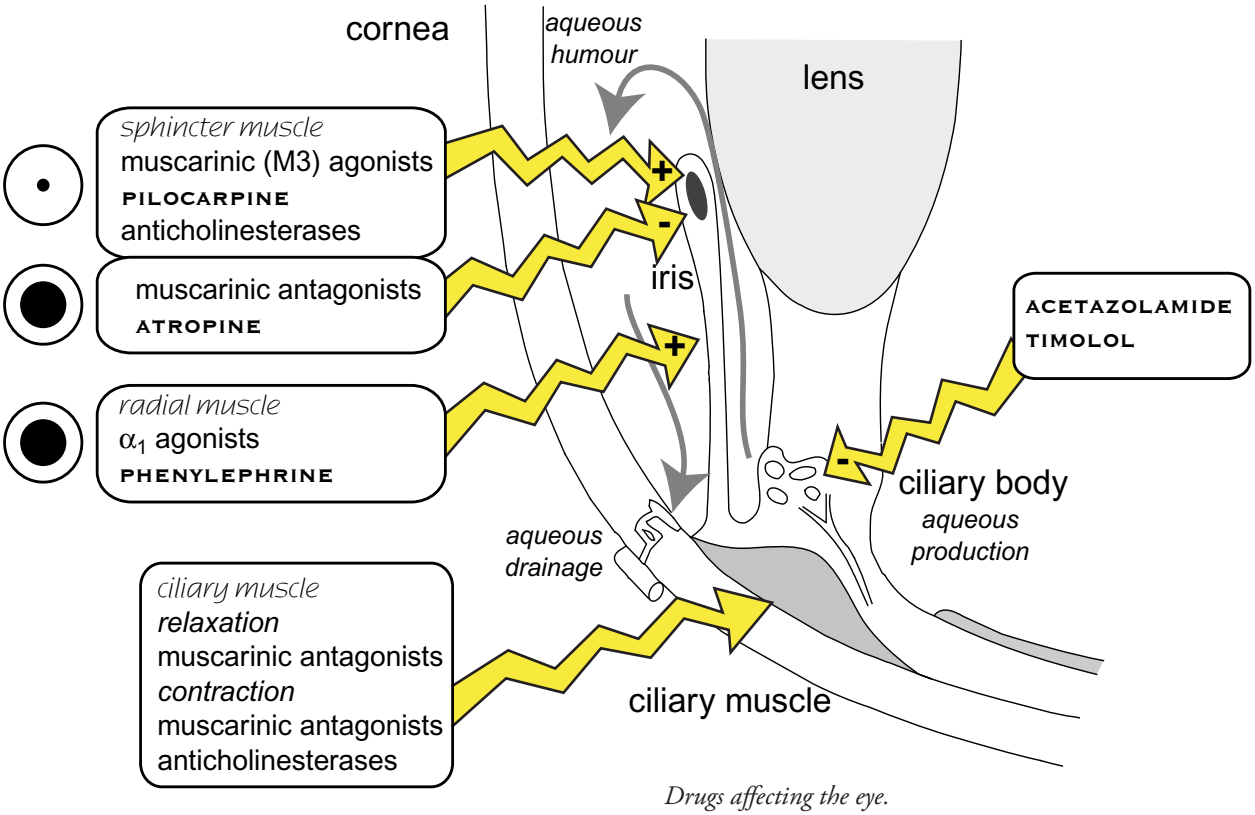
Histamine receptors.

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

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

The eye



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.

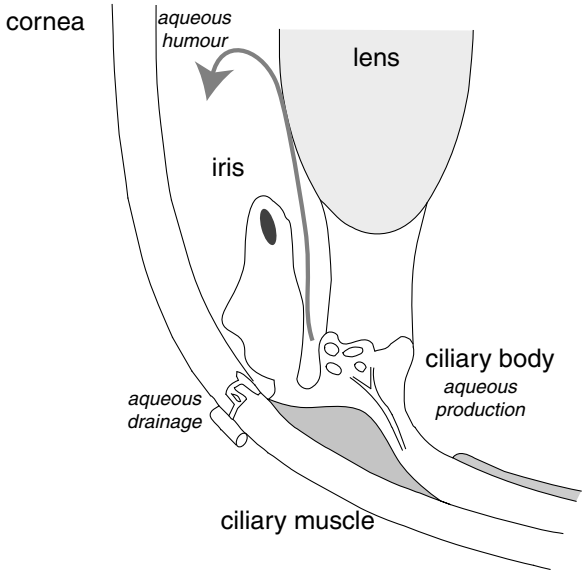
Local Anaesthetics

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.

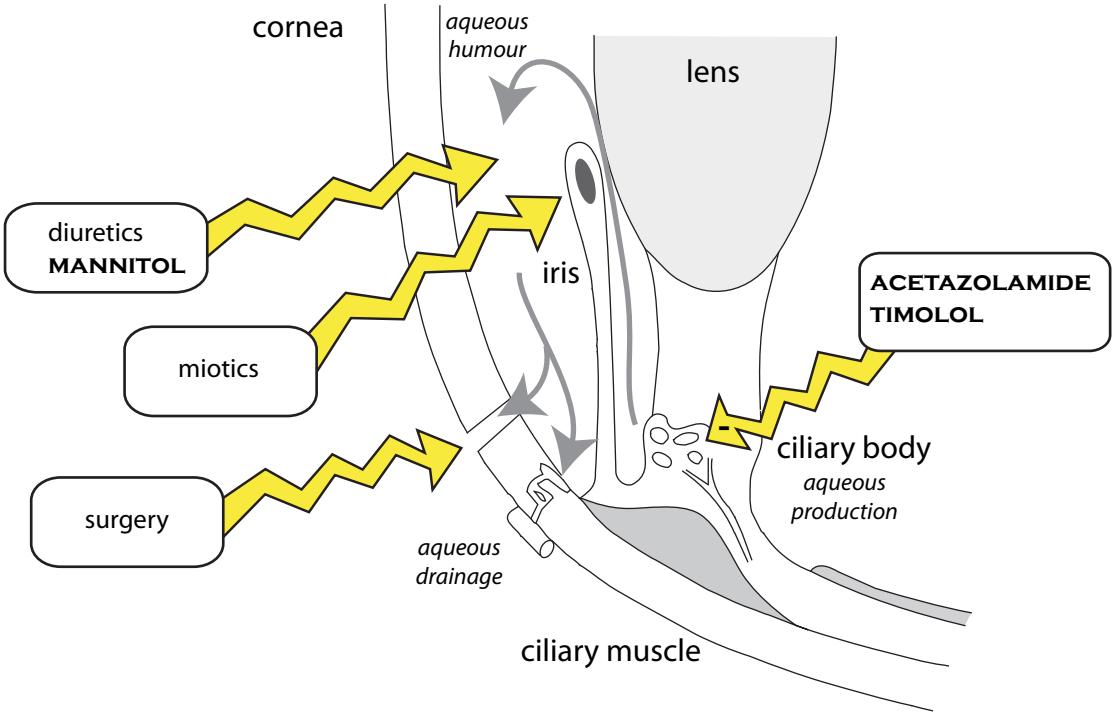
Antibiotics

(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



Left: glaucoma in dogs develops when aqueous outflow is blocked.
Below: 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.



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.

Diuretics

For emergency reduction of intraocular pressure, osmotic diuretics such as **mannitol** (iv) or **glycerine** (po) are usually used. Carbonic anhydrase inhibitors such as **acetazolamide** also have a direct effect on the ciliary body to reduce aqueous formation (see notes on diuretics). **Dorzolamide** is a more modern drug used in people.

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.

Miotics are contraindicated in anterior uveitis / anterior lens luxation.

β blockers

In man, **timolol** is commonly used to reduce aqueous formation. Although it is a β blocker, it may produce its effects on the eye by a different mechanism.

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.

Other drugs

The α_2 agonist **brimonidine** and the prostaglandin analogue **latanoprost** (commonest) are also used in people.

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.

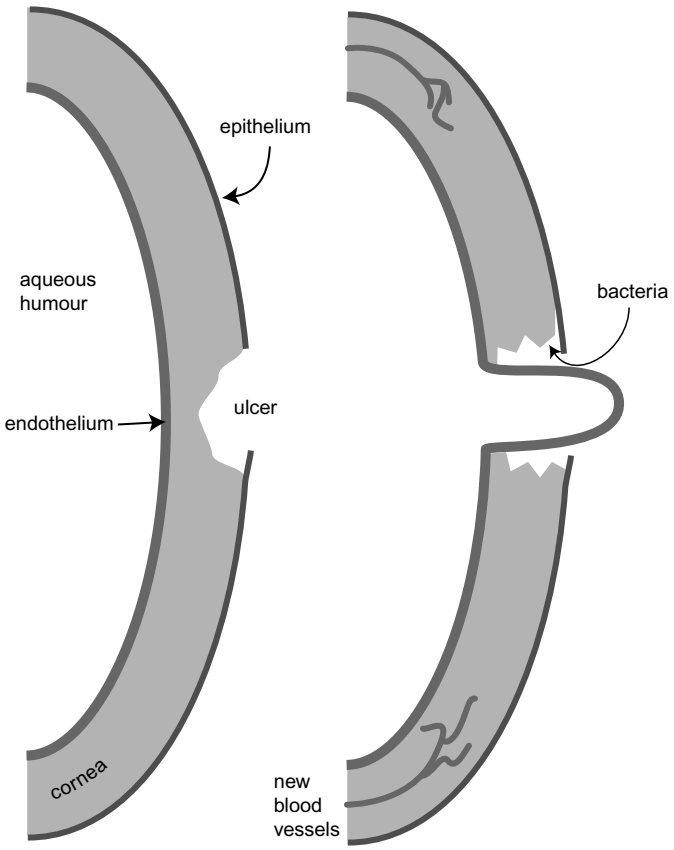
Cyclosporin eye drops are the usual immunosuppressive treatment. Tear production usually returns in 1 - 8 weeks after immunosupression with cyclosporin.

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.



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.

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 miotics (pilocarpine)
- great care is required with steroids

commonly used drugs

corneal examination
fluoroscein

local anaesthesia
proxymetacaine

mydriasis
atropine

miosis
pilocarpine

antibiotics
cloxacillin (large animals)
gentamicin (small animals, horses)

anti-inflammatories
hydrocortisone

The bladder

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
- α_1 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 used for incontinence and urinary 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.

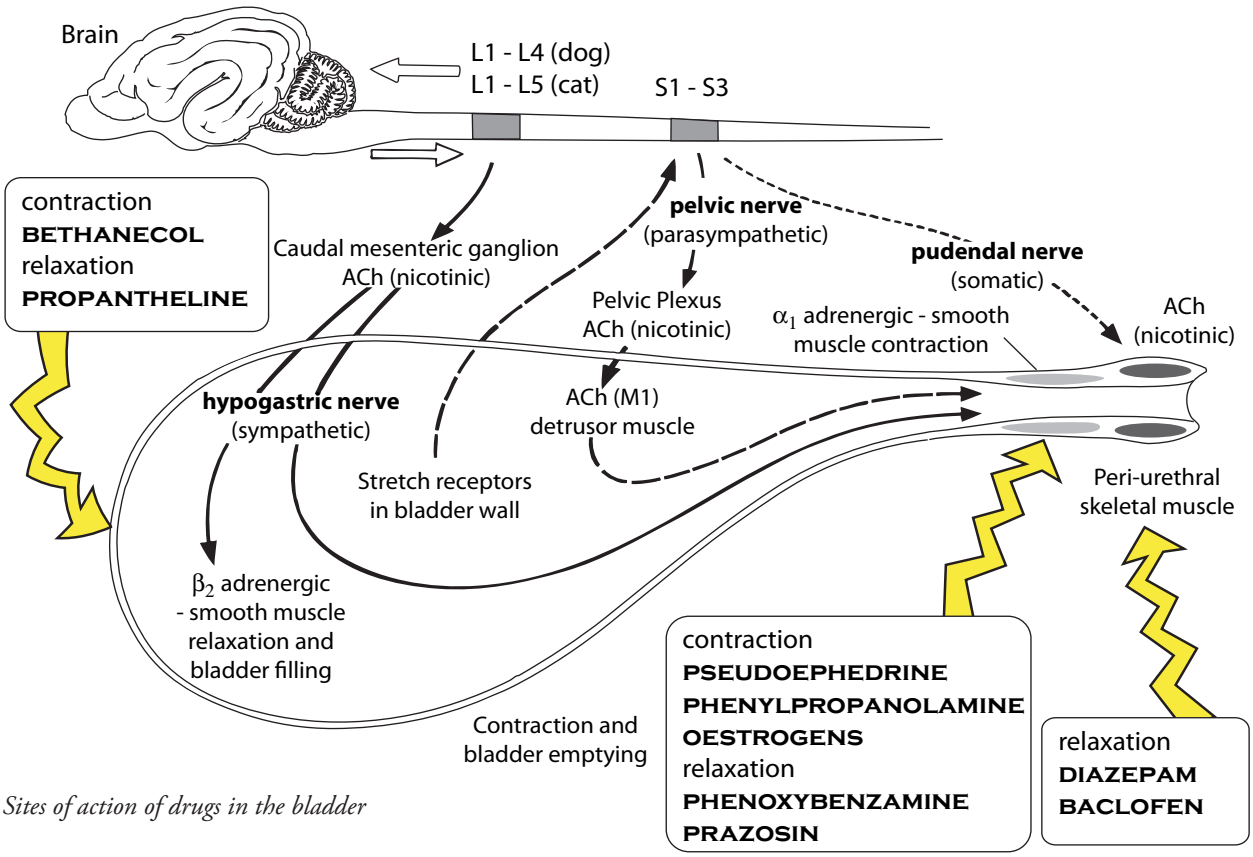
Alpha adrenergic agonists and sex hormones

Urinary incontinence in spayed bitches is a common problem. Oestrogens upregulate α_1 adrenergic receptors in the internal sphincter, a lack of oestrogen reduces the number of α_1 receptors and thus the ability to contract the sphincter. Therefore oestrogens given with α_1 agonists produce the greatest effect. Since oestrogens cause a wide rqange of side effects in dogs and α_1 agonists cause vasoconstriction, low doses of both drugs will reduce the side effects. Oestrogen treatments take several weeks to work but α_1 agonists can work almost immediately. Probably the best treatment strategy is to try α_1 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 α_1 agonists heart disease.

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



Sites of action of drugs in the bladder

and children.

Phenylpropanolamine is the most widely used α_1 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 α_1 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 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

commonly used drugs

cystitis
amoxycillin
ampicillin

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

The uterus

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).

Relaxants

Clenbuterol (β_2 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). 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 β_2 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.**

Sex hormones are covered in more detail in Semeser 2.

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

ANS Toxicities

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 40)
- -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 - Cyanophytes Or Cyanobacteria

Anabaena spp (lakes and rivers both islands)

Microcystis spp (Anacystis spp)

Nodularia spp (Nodularin poisoning of stock in Canterbury)

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)

Lipopolysaccharides (LPS)

Principle toxic effects

Anatoxin-a

• nicotinic depolarising alkaloid neuromuscular blocker

• Potent and fast acting

Anatoxin-a(s)

• 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.

Blue Green Algae

Muscle rigidity, tremors, seizures, paralysis, respiratory paralysis 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.

Organophosphorus and carbamate compounds - anticholinesterase insecticides

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

- 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)
- 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, an-

orexia, 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.

Organophosphorus & carbamate poisoning

- Sources-numerous chemicals in use
- Most do not accumulate in the fat rapidly excreted
- Competitive inhibition of acetylcholinesterase
- Muscarinic, nicotinic and cns effects
- "Aging" of op-enzyme complex
- Potentiation:
- Phenothiazine tranquilizers (30 day wait)
- Blocks acetylcholinesterase
- Levamisol-nicotinic stimulation
- Aminoglycosides-blocks acetylcholinesterase
- SLUDDE – other clinical signs
- Atropine and pralidoxime (pralidoxime is not necessary with carbamate poisoning)

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.

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 Goldα, 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 Mesurolα, 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?

Respiratory system

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 H_20)

•**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 dioxide 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* α_2 agonists and aminophylline

•*morphine* (small doses) decreases respiratory rate, diminishes anxiety, and dilates splanchnic vessels

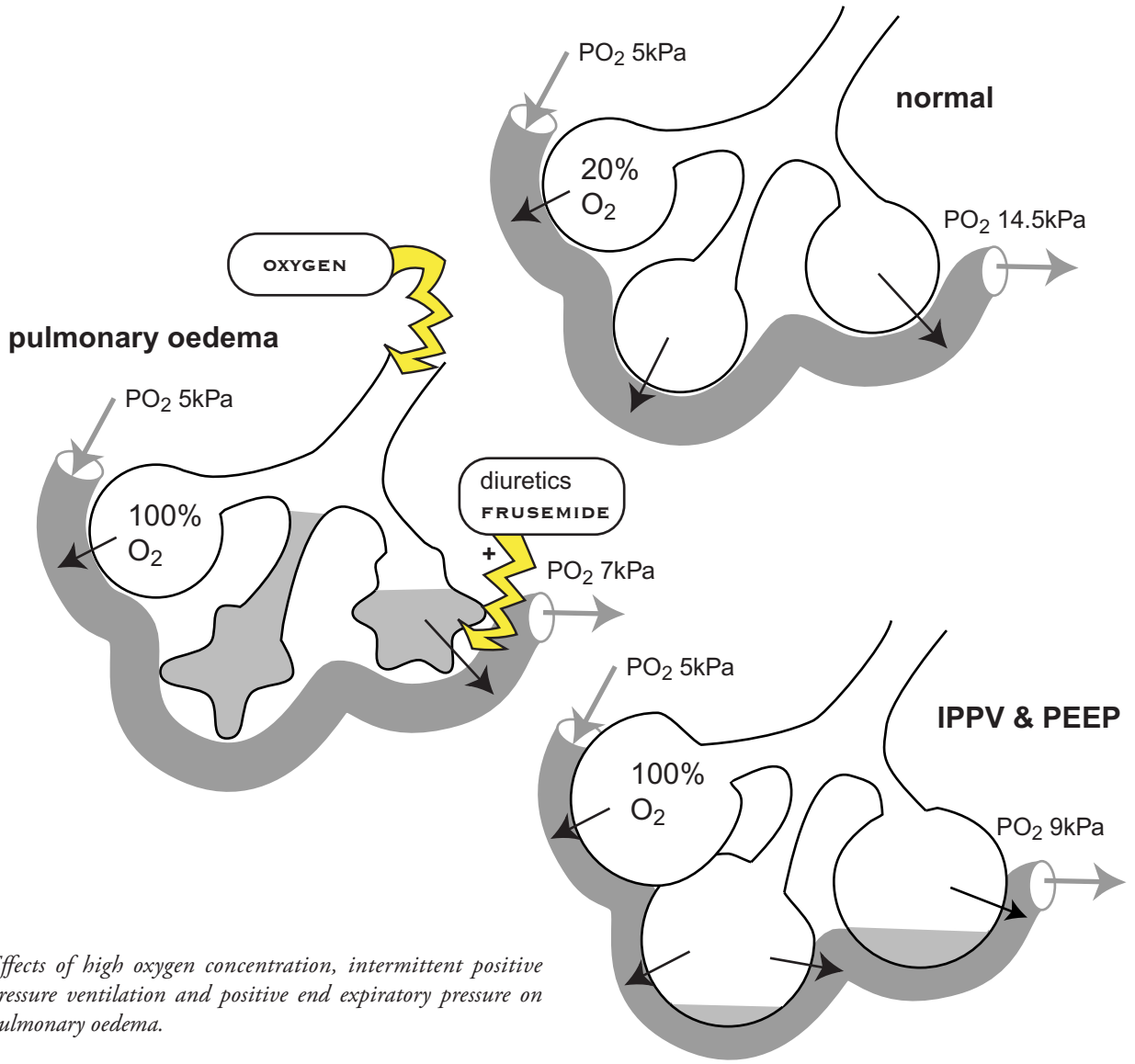
•*plasma expanders* to correct hypo-albuminaemia (gelatin)

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.



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

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.

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 gastropulmonary 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. It is active as a centrally acting muscle relaxant and sedative when administered iv. 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 α_2 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 β_2 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 α 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 α 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 α_1 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

commonly used drugs

oxygen
frusemide
oxytetracycline
codeine
bromhexine

Respiratory system

- 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

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 System Toxicities

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
-CO_2
-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**) Feratoxα 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.

Cynaide treatment.

	sodium nitrite	**sodium thiosulphate**
Cattle	3 gm (10ml of 20% IV)	15 g in 200 ml IV (or 50 ml of 20% IV)
Beasley Notes suggests:	10-20 mg/kg (20% sol)	500mg/kg
Sheep	1 gm (or 10 ml of 10% IV)	2.5 g in 50 ml (dH2O) IV
Dog repeat at 1/2 the initial dose if needed	25 mg/kg IV 1% solution	1.25 g/kg 25% solution

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 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.

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 move-

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.

Characteristics of some respiratory toxicoses

Toxicant	Blood Color	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

ment.

Methylene blue* (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.

*Not a licensed animal remedy.

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

Paraquat Toxicity

- 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)

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 centrilobular 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:

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.

Selenium Toxicity

- 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

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 psg.
1080 psg.

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

Zinc, Aluminium Or Magnesium Phosphide

Zinc phosphide (expected to be licensed pesticide in New Zealand)

Al and Mg already 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

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 exist

Cases

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?

The gut

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^+.

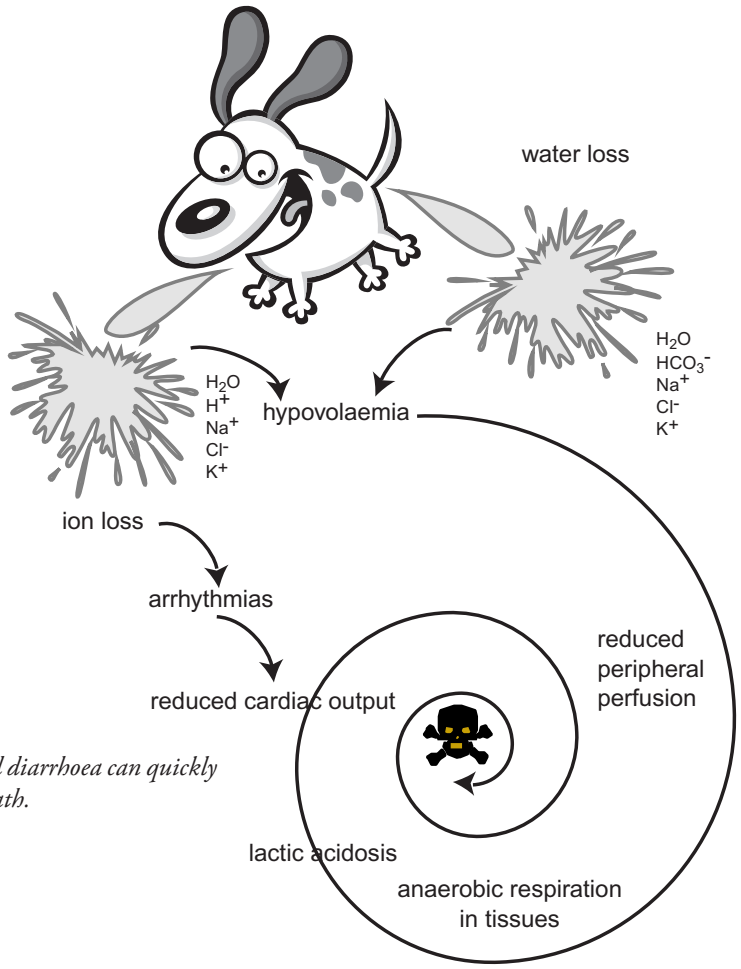
In diarrhoea, lots of K^+ and HCO_3^- are lost as well as water and Na^+.

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.



If untreated, vomiting and diarrhoea can quickly lead to shock and even death.

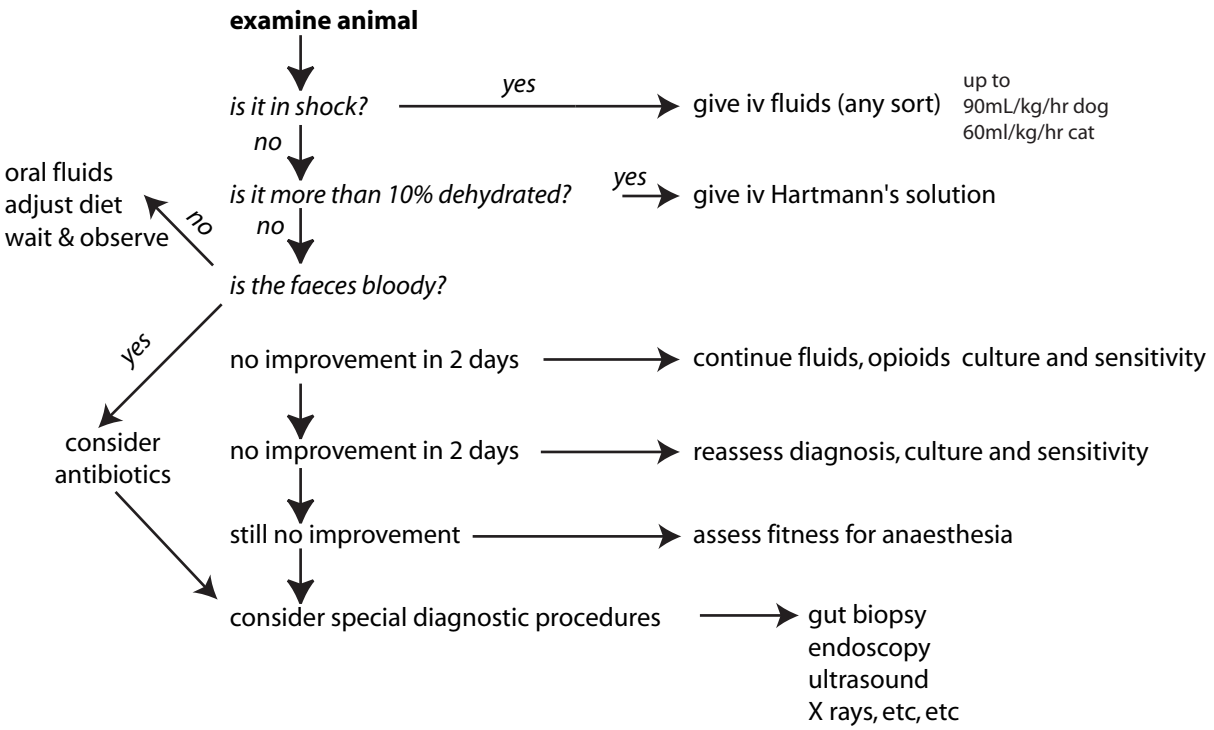
Intravenous fluids

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 obstructions 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.



One approach to the treatment of diarrhoea.

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

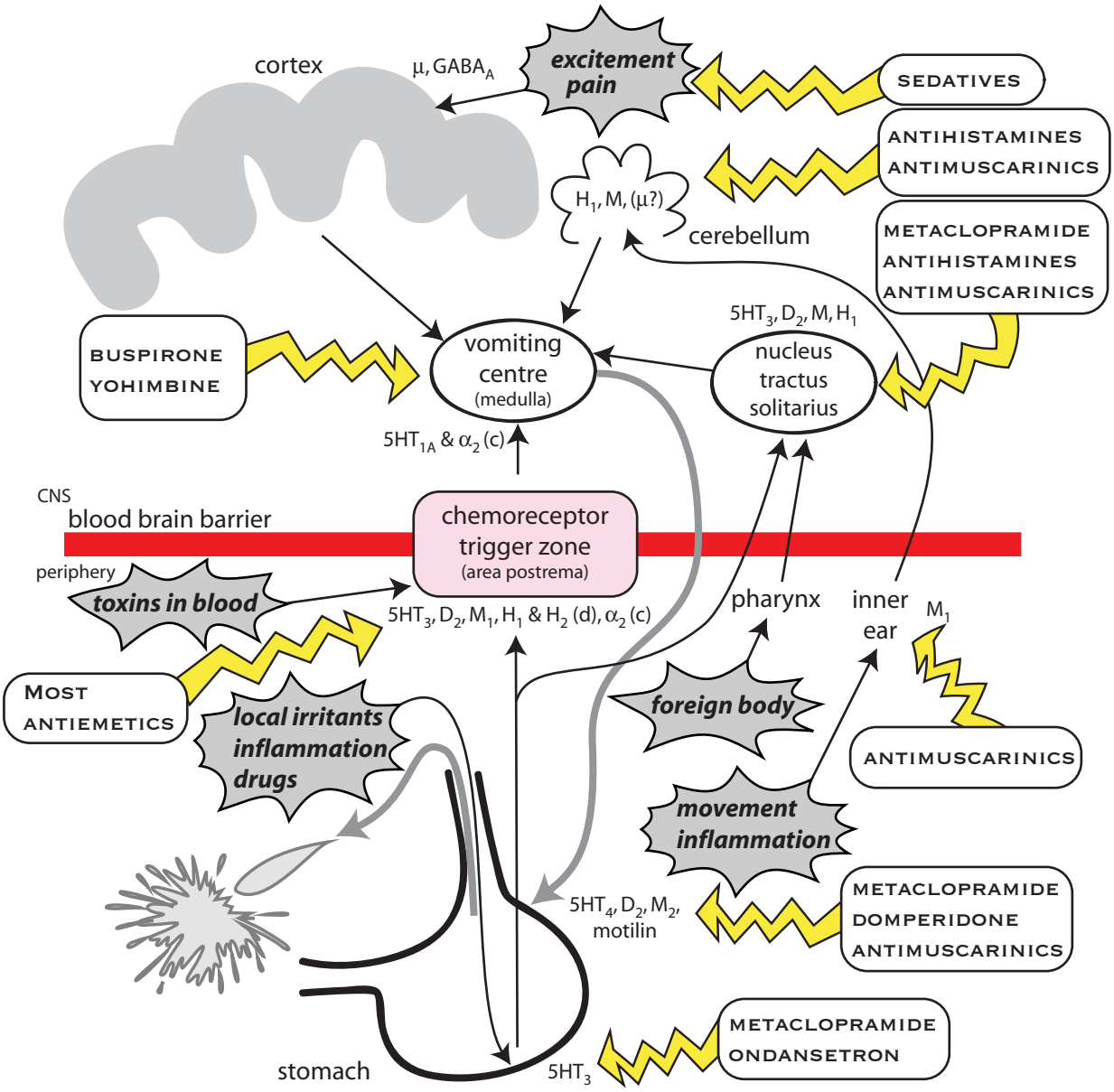
Some of the most generally effective antiemetics are phenothiazines such as **prochlorperazine** which act as dopamine D_2 antagonists in the vomiting centre and the chemoreceptor trigger zone, although they also have weak anticholinergic activity and a variety of other effects. Because of their inhibition 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 α_1 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.

Antihistamines

Antihistamines, such as diphenhydramine, cyclizine and meclozine primarily inhibit vomiting by blocking H_1 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 D_2 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 $5HT_4$ agonist, which adds to its antiemetic effect. In slightly higher doses it is also a $5HT_3$ antagonist, which also potentiates the antiemetic effects. Droperidol is a very potent D_2 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



The physiology of vomiting from a pharmacologist's point of view. There are species differences in the receptors involved; (d) dog only, (c) cat only. 5HT$_{1A}$, 5HT$_3$, 5HT$_4$ - 5 hydroxy tryptamine receptors; α$_2$ - adrenergic receptors; D$_2$ - dopamine receptors; GABA$_A$ - γ aminobutyric acid receptors; H$_1$, H$_2$ - histamine receptors; M$_1$, M$_2$ - muscarinic acetylcholine receptors, μ - opioid receptors.

to these or to prokinetic drugs such as cisapride (a 5HT$_4$ agonist). They may have some sedative effect. Domperidone (D$_2$ 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 D$_2$ antagonists are not seen.

Neurokinin1 antagonists

Maropitant has been recently intoduced. It seems to work well in most causes of vomiting except motion sickness. There is only limited clinical experience so far. Similar drugs are used in people.

Anticholinergic drugs

These are rarely effective as antiemetics 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.

5HT$_3$ 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; 5HT$_3$ 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 D_2 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. α_2 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 $5HT_{1A}$ 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 obtai 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, H_2-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 H_2antagonists and proton pump inhibitors can cause many interactions.

H2-Receptor Antagonists

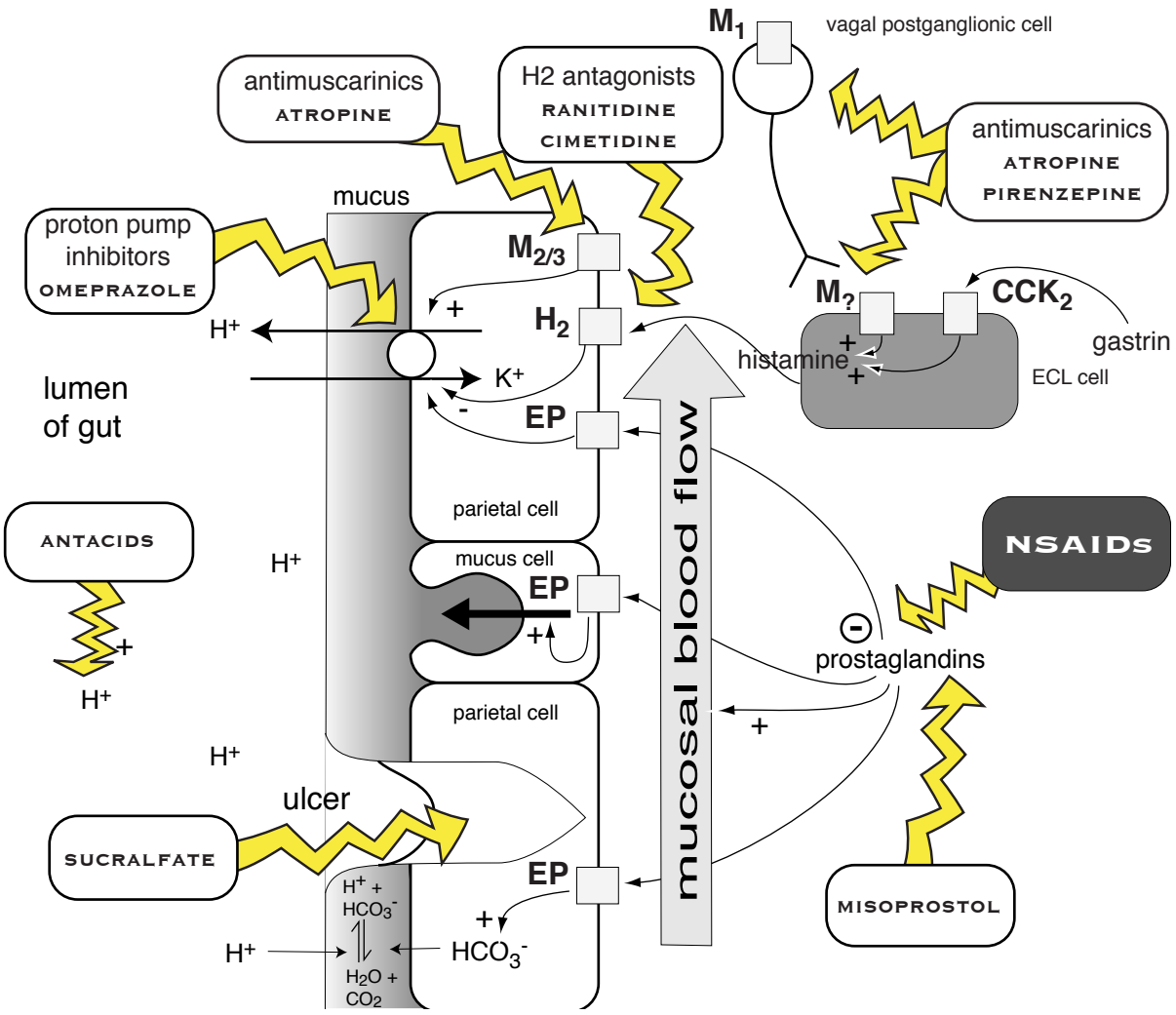
Cimetidine inhibits histamine-stimulated gastric acid secretion in dogs and cats. **Ranitidine** is more potent and longer acting, but both work well clinically. **Famotidine** is a newer H_2-receptor antagonist that has been promoted as being more effective than both cimetidine and ranitidine: studies in dogs have suggested that it is of similar clinical efficacy to ranitidine. H_2-receptor antagonists cause minimal side effects even at high doses. There is evidence that, at least in people, tolerance to H_2 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 H_2 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.



*Sites of action of drugs used to treat gut ulcers. Note that NSAIDs **cause** ulcers.*

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 bicarbonate 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 M_1 receptor antagonist) inhibits gastric acid secretion without the effects on gastric motility mediated by drugs acting on M_2 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 D_2 antagonist, its effects on motility are probably caused by its $5HT_4$ 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 $5HT_4$ 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. $5HT_4$ 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 M_3 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 CB_1 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 antiinflammatory 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.

Antibioticsare **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 administration, 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.

commonly used drugs

saline solutions
cimetidine, ranitidine
metaclopramide
sulphasalazine

Pancreatic disease is covered under inflammation and hormones.

The gut

• treatment of 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, prostaglandins or sucralfate - not antacids or NSAIDs
• drugs which increase motility - metaclopramide, cisapride, erythromycin
• drugs which reduce motility - codeine
• colitis - sulphasalazine

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 moleculer 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. 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, LD_{50} 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). LD_{50} 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 troachar 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 replacer 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.

commonly used drugs

ethoxylated alcohols
monensin

Bloat

- prevention is better than cure
- in emergency relieve ruminal tympany - try stomach tube first
- treatment - polyethoxylated alcohols, check rest of herd
- prevention - good husbandry or monensin

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

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.

Arsenic Poisoning

- 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)
  Skin: dermal necrosis
- PM-red mucosa that peels away
- Diagnosis- liver and kidney
- Treatment-chelation BAL, supportive therapy/ fluids

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 LD_{50} 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.

• Plant sprays about 3% $CuSO_4$ as a fungicide

• Drinking water added $CuSO_4$ as a supplement (remedy used in US for strangles in horses, reduce spread).

• Compounded feed pellets/rations (accident in formulation)

• Injectable Cu

Cu glycinate

CuCaEdetate both slower release therefore safer

Cu oxyquinoline or dicuprene (Cujec). This product is very close to its toxic dose and is therefore not recommended for cattle.

• Pasture topdressing-not used much now-a-days.

• Copper poisoning in calves fed milk substitute is frequent cause.

Pathogenesis

Stored in liver-mitochondria (cytochrome), microsomes (ER), cytoplasm and bone marrow as metallothionein.

Stored in RBC's-erythrocuprin, superoxide dismutase

Transported in blood bound to ceruloplasmin and albumin

Poorly absorbed

Excreted in the bile

Interacts with molybdenum which can be used in treatment of Cu toxicity and vice versa.

Acute Toxicity

Single acute oral toxic dose is 25-50 mg/kg

Clinical signs

similar to other heavy metal poisoning:
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

Copper Toxicity

• 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
• Metallic sheen to kidneys
• Diagnosis- kidney (liver unless haemolytic crisis)
• Treatment-Chelation for affected animals (penicillamine)
• Herd prevention: Ammonium molybdate

shown to be effective. (difficult to obtain)

• Fluid Therapy to decrease haemoglobinuric nephrosis

• Orally treat rest of flock:

100 mg NH_3molybdate and 1 gm (anhydrous)Na_2SO_4 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 $CaSO_4$) is effective.

White wool in black sheep is a sign of Cu deficiency. (Sulphate in the diet affects the Cu antagonism, it is thought that sulphate displaces Mo).

White Phosphorus

Sources

Phosphorus is commonly used as a rodenticide and possum control. Livestock and pets eat baits intended for rats, rabbits or possums or eat poisoned animals. Cases have been on the decline due to decreased use of phosphorus baits.

Red phosphorus (non toxic) vs white (yellow) **highly** toxic

White Phosphorus - Garlic like odor, fluorescent

Due to instability in air the bait is mixed with oil or grease.

ADME

Absorbed from skin, GI and respiratory tracts.

Pathogenesis

Mechanism of action unknown

Clinical Signs

• Acutely within hours of ingestion:
gastrointestinal, abdominal and circulatory signs

• Interim or latent phase with apparent recovery
(48 hours to several days)

• Recurrence of clinical signs:
Vomiting, hematemesis, icterus and hepatic failure
CNS dysfunction

Severe abdominal pain, tendency to bleeding with hypoprothrombinemia

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.

Phosphorus Toxicity

- 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 (icterus)
- 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)

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

Sources

Therapy and prohylaxis for Facial Eczema (zinc oxide)
Footrot baths (zinc sulphate)
Galvanized iron piping, fencing, metal trays
Anticorrosive paints.
Zinc batteries

ADME

Absorption is in competition with other divalent cations, e.g. Cu^{++}, Fe^{++}, Cd^{++}, Ca^{++}, Pb^{++}. Interferes with iron and copper uptake.

Ruminants: rumen, abomasum, small intestines

Monogastrics: small intestines

60% loosely protein bound, 30% tightly bound.

excreted by bile (liver) and pancreas

zinc salt solutions close the oesophageal groove goes straight to the abomasum.

Mechanism

Chronic zinc toxicosis interferes with absorption and utilization of iron and copper.

Zinc salt solution precipitate proteins therefore get gastroenteritis (zinc oxide)

Absorbed Zn is widely distributed, therefore:

tissue damage is widespread, interferes with sulphur and nitrogen, protein precipitation, and enzyme inhibition.

Clinical Signs

Similar to other metal poisonings:

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 PO4

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)

Zinc Toxicity

- 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.

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

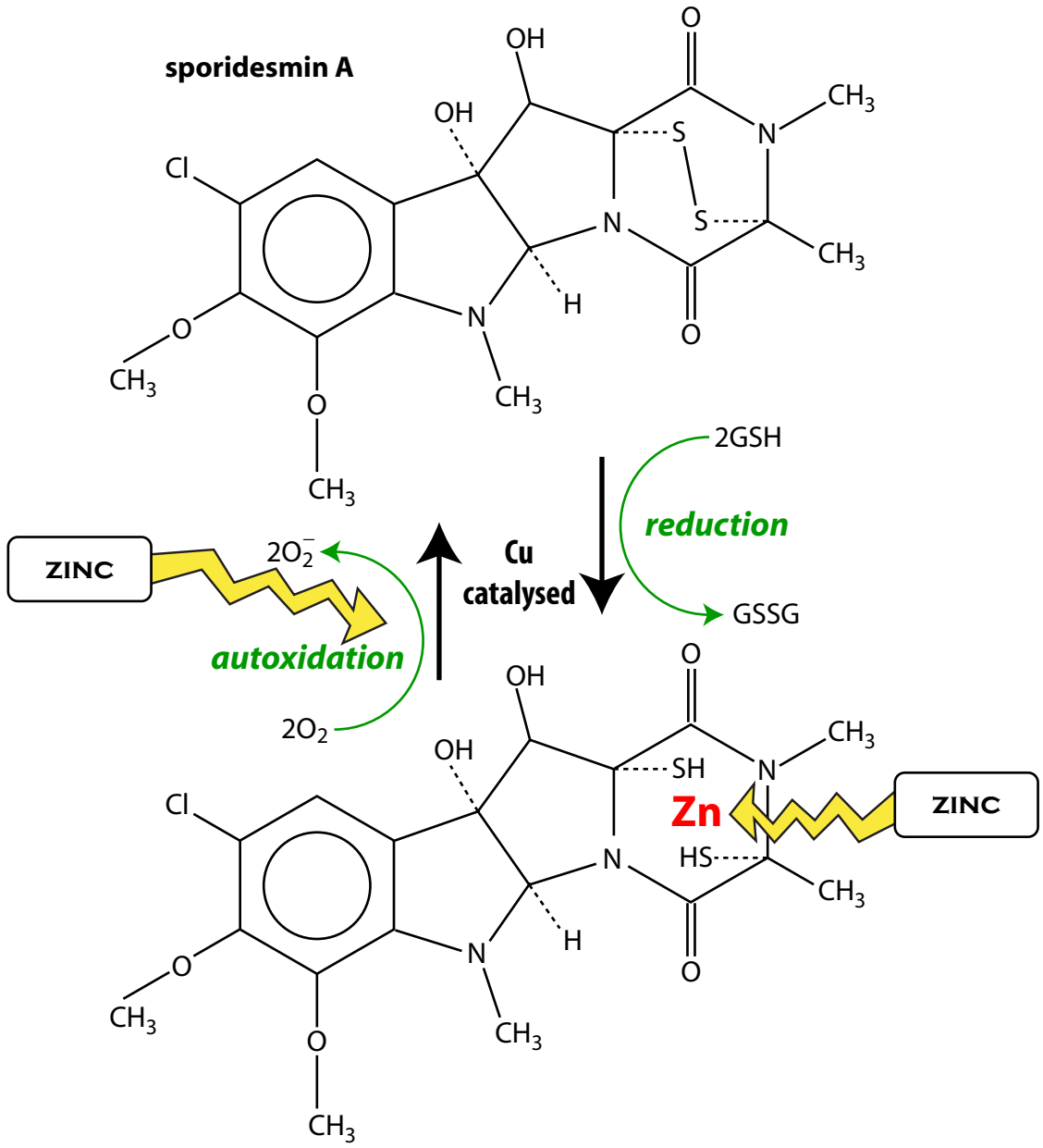
(Sporidesmin toxicity)

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

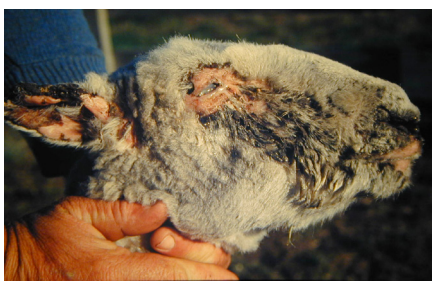
The disease is a hepatogenous photosensitization caused by the hepatotoxin sporidesmin which is produced by the saprophytic fungus *Leptosphaerulina chartarum* (formerly *Pithomyces chartarum*) Under the warm moist conditions of autumn, *L. chartarum* proliferates on pasture litter producing the toxin 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 phylloerythrin leads to photosensitivity on exposed nonpigmented skin. The concentration of the major liver enzyme, gamma



The reduction and autoxidation of sporidesmin, a mycotoxin produced by Leptosphaerulina chartarum, generates an "active oxygen". The reaction involves the disulphide bridge of the mycotoxin, which is readily reduced by interaction with thiols, including glutathione (GSH), a predominant cellular thiol. The di-thiol (see figure) 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 administration 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.



glutamyltransferase is used in the diagnosis of the disease and in the selection of F.E. resistant animals.

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 and 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).

Ragwort (Pyrrolizidine Alkaloids) Poisoning

- Long lag time between ingestion and clinical signs appear
- Liver injury due to pyrrole metabolites damaging hepatocytes
- High doses necrosis of the liver
- Low chronic doses-giant hepatocytes
- Acute toxic dose-severe liver damage, haemorrhage and death
- Dry plant remains toxic
- Known to be carcinogenic (PAs can be transferred in milk)

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 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.

a. What is the likely cause of this scenario?

b. What would you do for the affected calves?

c. What would you expect to find on post mortem?

d. 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

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 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 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.

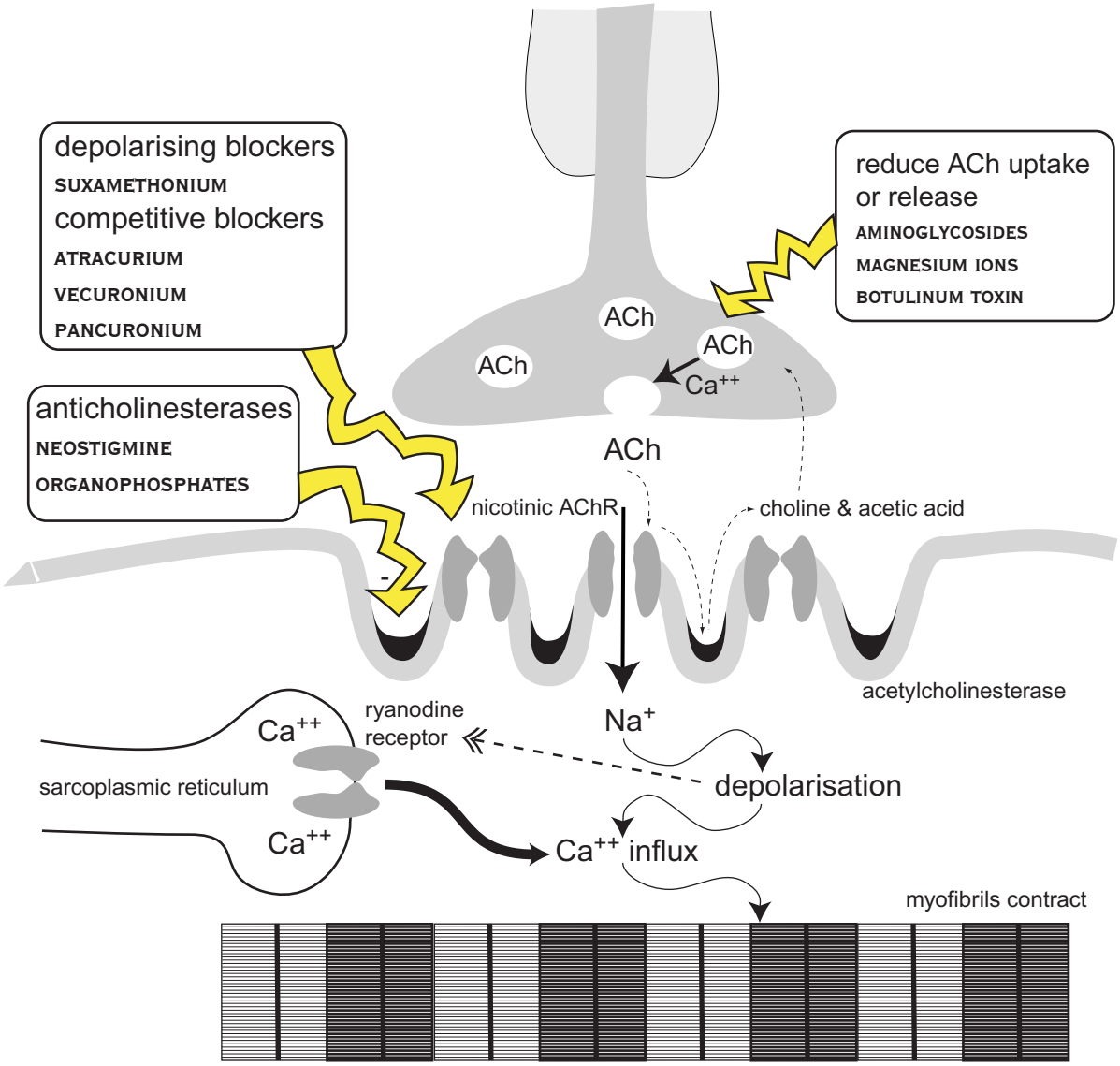
some breeds of rabbits are very sensitive to its effects

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.



Sites of action of drugs used to alter muscle contraction.

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 and never available when needed.

commonly used drugs

none

Neuromuscular 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

Practice exam questions

Multiple choice questions

1. Noradrenaline acting on α_1 receptors may produce
   - tachycardia ❑
   - vasoconstriction ❑
   - bronchoconstriction ❑
   - lachrymation ❑
   - relaxation of the uterus ❑

2. Mydriasis may be produced by
   - prazosin ❑
   - morphine ❑
   - pilocarpine ❑
   - isoprenaline ❑
   - phenylephrine ❑

3. Atropine
   - is a competitive antagonist at nicotinic receptors ❑
   - increases salivary secretion ❑
   - lasts for 5 minutes when applied to the eye ❑
   - is useful in the treatment of organophosphate poisoning ❑
   - can prevent motion sickness in dogs ❑

4. The effects of α_2 adrenoceptor agonists usually include
   - excitement ❑
   - vasodilatation ❑
   - hypoglycaemia ❑
   - diarrhoea ❑
   - tachycardia ❑

5. Suxamethonium
   - is a competitive antagonist at the NMJ ❑
   - blocks transmission in ganglia ❑
   - is an agonist at muscle nicotinic receptors ❑
   - is hydrolysed by acetylcholinesterase ❑
   - is composed of seven subunits ❑

6. The skeletal muscle nicotinic acetylcholine receptor
   - is activated by a change in membrane potential ❑
   - is selectively permeable to sodium ions ❑
   - changes conformation when bound by two molecules of acetylcholine ❑
   - ion channel opens when atracurium is bound ❑
   - is identical to the ganglionic ACh receptor ❑

7. Vomiting in the dog can be controlled using
   - apomorphine ❑
   - xylazine ❑
   - diazepam ❑
   - kaolin and morphine ❑
   - metoclopramide ❑

8. The best treatment for mild diarrhoea in calves is

- a mixture of sulphonamides and aminoglycoside antibiotics ❑
- codeine per rectum ❑
- a 3rd generation cephalosporin antibiotic ❑
- metaclopramide ❑
- oral fluids ❑

9. Chronic obstructive pulmonary disease in horses may be prevented using

- acetyl choline analogues ❑
- histamine ❑
- adrenaline ❑
- sodium cromoglycate ❑
- penicillin ❑

10. You have been treating an 8yr old mongrel with NSAIDs for severe hip arthritis for 3 wks. The dog initially improved but is now anorexic, depressed and unwilling to move. Endoscopy reveals gastric ulceration. The best course of action is

- continue NSAIDs as it is more important to treat pain than the ulcers ❑
- stop the NSAIDs ❑
- continue NSAIDs but add misoprostol ❑
- prescribe morphine tablets instead of the NSAIDs ❑
- continue NSAIDs but feed the dog a balnd diet ❑