5 CNS

CENTRAL NEUROTRANSMISSION

Definitions

neurotransmitter = a substance released from one neurone and acting rapidly, briefly and at short range on a receptor in the membrane of another neurone. It may cause excitation or inhibition of the postsynaptic neurone.

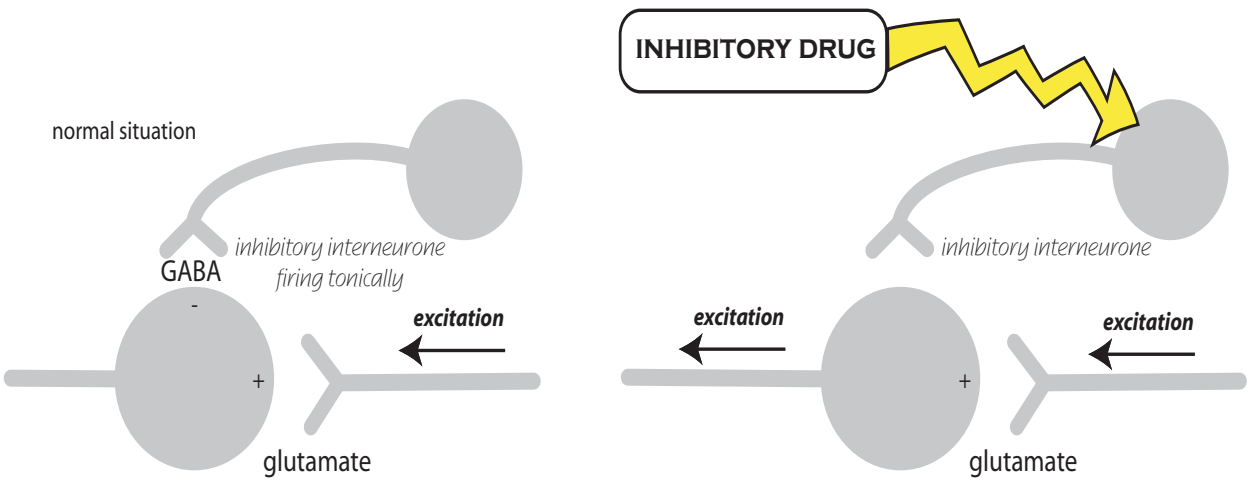
neuromodulator (= neuroregulator) there is no good definition, but they usually act slowly, often at a different site from where they were released. They usually increase or reduce neuronal excitability without causing cells to fire; they may also regulate gene transcription. Most neuromodulators are peptides. As they are well conserved in slimy things they are regarded as being phylogenetically old (but the function of many of them appears to have changed in mammals).

INTRODUCTION

The CNS is the most complex organ system in the body: the physiology of the normal CNS is not well understood, and most drugs given for their CNS effects are used empirically. Many more drugs have side effects either directly on the CNS or mediated by it. The action of most drugs at the receptor level is known, but this is not always useful in predicting their effects on the whole animal. These notes concentrate on the major transmitter systems where the information is least confusing.

The effects produced by a neurotransmitter can be very variable for a number of reasons:

- the CNS is not hard wired - connections are continually changing under the influence of growth factors. There are usually several back-up wiring systems - the importance of these can change with time and disease. Receptors are being continuously recycled - thus their numbers change.
- most neurotransmitters have multiple receptor subtypes at which they can work - so the effects depend on the receptors present on the target cell
- the same receptor subtypes sometimes have different signal transduction mechanisms coupled to different effectors
- their effects can be changed by neuromodulators



Disinhibition - a mechanism for inhibitory drugs to produce an excitatory effect.

The good news is that all neurones are thought to obey Dale's law and release the same transmitter at all their terminals (but don't forget co-transmittors).

Calcium is required for neurotransmitter release, so drugs which interfere with calcium movement can alter neurotransmitter function.

Every neurone has a wide range of inputs (usually both excitatory and inhibitory); what it does will depend on the sum of all these inputs.

Disinhibition

A relatively common cause of confusion is that drugs which are known to be inhibitory can produce excitatory effects in animals under some conditions, eg, anaesthetics. This is usually due to disinhibition.

Time course

milliseconds	fast transmitters
tens of ms	NMDA receptors
seconds - minutes	neuromodulators
minutes - days	receptor up/down regulation
days - weeks	neurone reconnections

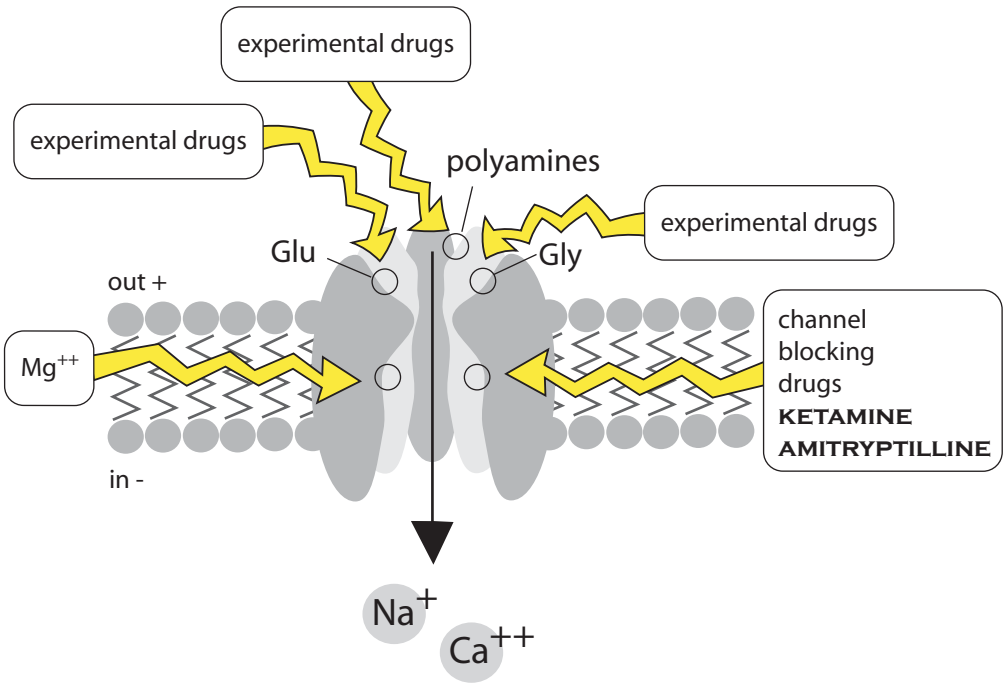
Excitatory aminoacids

Glutamate (and aspartate) will excite virtually all central neurones. It acts at a variety of receptors, usually named after the experimental drug used to characterise them. Fast depolarisation of postsynaptic neurones is caused by activation of the ionotropic (Na^+) AMPA receptor. (The kainate receptor is very similar and is thought to do the same thing, although its distribution in the brain is different.) The NMDA receptor is also a ligand gated ion channel (Na^+ and Ca^{++}) and is an important target of drug action (see below). Metabotropic glutamate receptors (mGluR) (nine subtypes at the last count) are G protein coupled receptors. They are divided into three groups: group I (mGluR 1 & 5) act postsynaptically via IP3, group II (mGluR 2 & 3) act postsynaptically via adenyl cyclase, group III (mGluR 4, 6, 7 & 8) act presynaptically via adenyl cyclase. No useful drugs act specifically at metabotropic glutamate receptors at present but this is likely to change.

Glutamate is released from vesicles in a process that requires calcium. Zn^{++}, and probably other things, are also released from the vesicles.

NMDA receptors

These are a means of amplifying excitatory signals. They are thought to be responsible for long term potentiation which is the physiological basis of memory. Possibly more important from a veterinary practice point of view, they cause



NMDA receptors are ionotropic receptors related to $GABA_A$ receptors. Glutamate is the agonist, but glycine is also required for channel opening. Channel opening can be modulated by polyamines, and the channel can be blocked by magnesium and a number of drugs.

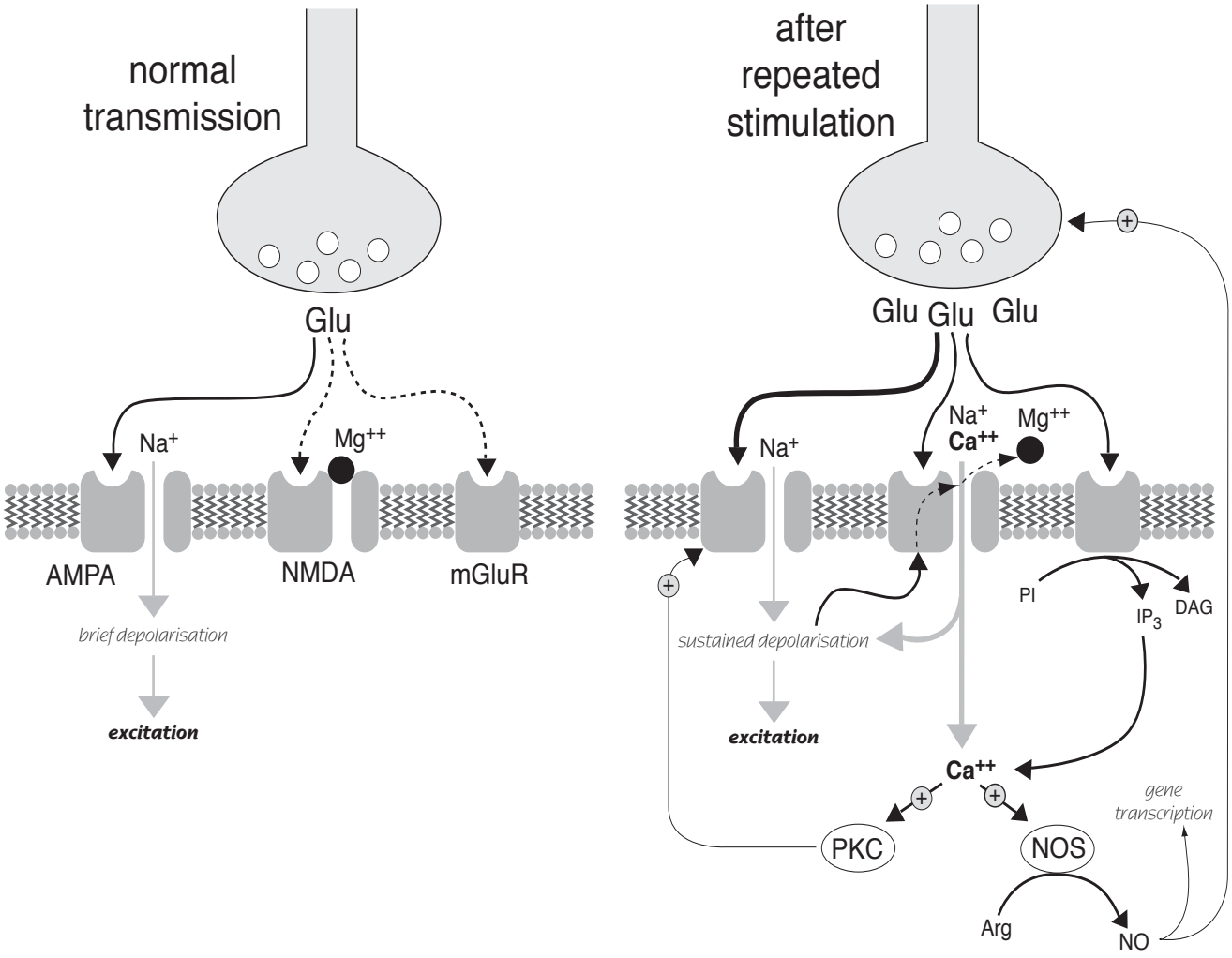
wind up in the spinal cord (and probably the brain stem) which shows up as hypersensitivity to pain (see analgesia notes). They are probably also involved in the propagation of seizures in epilepsy.

They are composed of five proteins, usually one NR1 subunit and four NR2. There are several types of NR2 subunits; NMDA receptors containing NR2B subunits are thought to be important in pain and are being targetted for drug development. Having a variety of subunits to choose from when forming NMDA receptors means that many subtyes of receptors are possible, but the clinical relevance of this is not clear yet.

In most forms of neuronal injury, particularly strokes in people, the mechanism of damage is cells leaking glutamate (from energy metabolism) which then acts at NMDA receptors and lets lots of calcium into the cell. This can kill the cell (excitotoxicty). A drug which could prevent this without side effects would be a huge earner, so there is a lot of effort going into research in this area.

Many useful drugs exert their effects indirectly through NMDA receptors, ketamine directly blocks the channel. It would be undesirable in most circumstances to completely block (loss of memory) or open the channel (excitotoxicity), so most new drugs coming along are partial agonists.

NMDA receptors require glycine to bind to a specific site before the channel can open. *In vivo*, there is always enough glycine around to allow channel opening, but many potentially useful NMDA antagonist drugs bind to this glycine site. (nb, this is not the same as glycine gated Cl^- channels, see below.)



NMDA receptor activation after repeated stimulation. Glu = glutamate, PKC = protein kinase C, NOS = nitric oxide synthase, NO = nitric oxide.

Inhibitory aminoacids

GABA

GABA (γ aminobutyric acid) is widely used throughout the CNS - virtually every neurone will be inhibited by it. It is mainly contained in short inhibitory interneurones. $GABA_A$ receptors are a major site of drug action, particularly for sedatives, anticonvulsants and general anaesthetics. $GABA_A$ receptors are also present on peripheral neurones but what they do there is not obvious. The $GABA_A$ receptor is a ligand gated ion channel which opens when two molecules of GABA bind to it which causes chloride ions to flow into the cell, causing hyperpolarisation and thus inhibiting firing. Blockade of the chloride channel by experimental drugs and toxins causes convulsions.

As well as binding GABA, $GABA_A$ receptors also bind benzodiazepines (sedatives) and, less strongly, barbiturates (injectable anaesthetics). Both classes of drugs potentiate the effects of GABA by various means and cause postsynaptic inhibition. $GABA_A$ receptors are probably also the site of action of most anaesthetic agents. Some drugs also bind to the benzodiazepine receptor to stop the channel opening (inverse agonists - do not confuse with benzodiazepine antagonists which only block the effects of benzodiazepines and have no effect on their own). Endogenous inverse agonists are thought to exist but their function is unknown - exogenous ones make animals anxious which is not usually desirable.

The $GABA_A$ receptor is composed of five subunits, but 19 different subunits have been cloned and there are probably 500 subtypes of natural $GABA_A$ receptors. Drugs specific for these subtypes are likely to emerge. The commonest contains 2 α subunits, 2 x β and 1 x γ. Different subtypes may explain the different patterns of effects seen with "$GABA_A$ receptor" drugs.

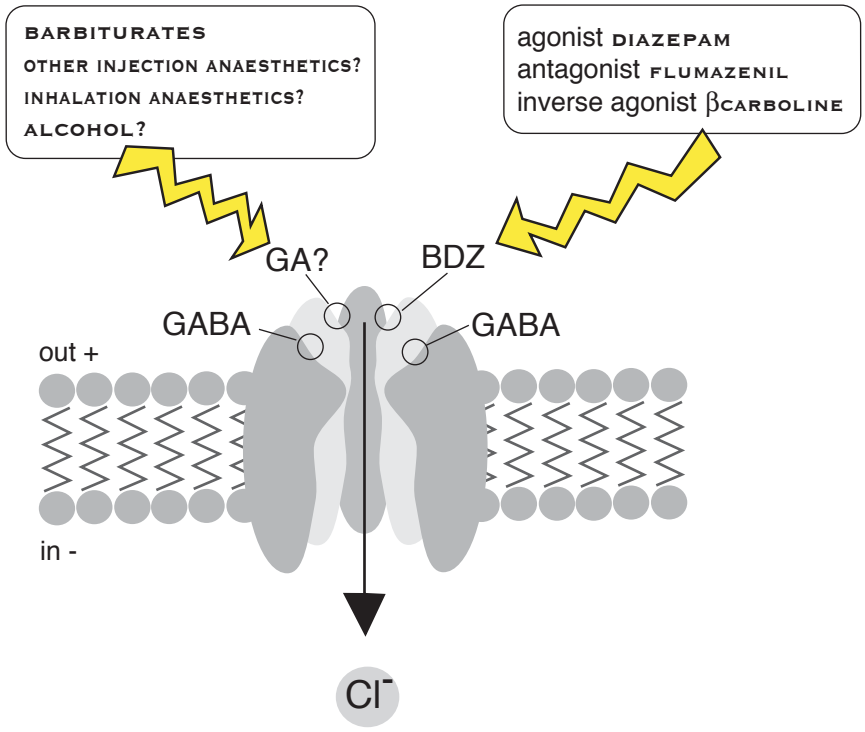
$GABA_B$ receptors have a presynaptic inhibitory action and may be important in the spinal cord but not much is known about their function. They are G protein coupled receptors. There are probably lots of different subtypes.

$GABA_C$ receptors are chloride channels similar to $GABA_A$ receptors but slower acting. They occur in the retina but are probably more important in the cortex. They are much more sensitive to GABA, but do not bind any of the anaesthetic or sedative drugs. So far, their function seems to be the regulation of sleep.

Glycine

Glycine is also an important inhibitory transmitter, particularly in the spinal cord. It binds to a chloride channel receptor very similar to the $GABA_A$ receptor (ie, different from the glycine receptor associated with the NMDA receptor). This is clinically important as strychnine is a competitive antagonist at the glycine inhibitory receptor - in strychnine poisoning, an animal will start to twitch. Tetanus toxin blocks the release of glycine (and GABA) resulting in continuous muscle contraction.

Both the GABA and glycine gated chloride channels are



The $GABA_A$ receptor. GA = general anaesthetic binding site, BDZ = benzodiazepine binding site.

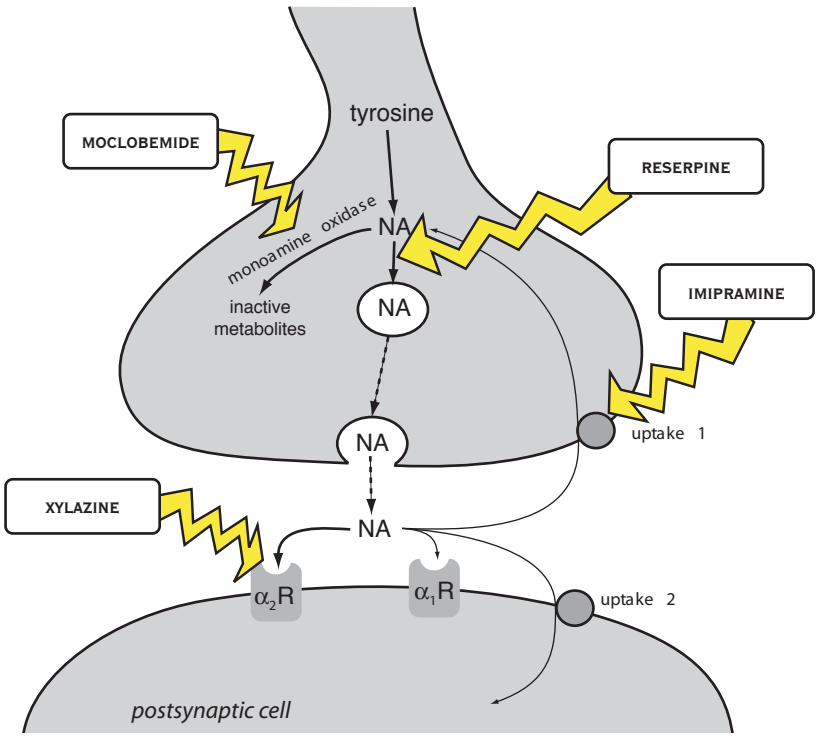
similar to the glutamate gated chloride channels found in invertebrates and which are the target for avermectin parasiticides. In overdose, these commonly used drugs can open GABA and glycine gated chloride channels to cause CNS inhibitory effects in mammals. Avermectins do not usually get into mammalian brains because the P glycoprotein pump in the blood brain barier keeps them out. Some individual animals (particularly collies) are missing the gene for the P glycoprotein and will go into a prolonged coma if given avermectins.

Monoamines

Noradrenaline is an important (mainly inhibitory) neurotransmitter, usually acting at postsynaptic β or α_2 receptors (do not confuse with presynaptic α_2 receptors in the periphery). Activation of α_2 receptors always causes inhibition of the neurone they are on - if the neurone is presynaptic, as in the periphery, the effects can be excitatory. α_2 receptors are important in alertness, sleep, blood pressure control and pain transmission; α_2 agonists are widely used in veterinary medicine for their CNS effects (see under analgesics and sedatives). The endogenous ligand for many α_2 receptors in the CNS may be **agmatine** rather than noradrenaline, agmatine also binds to imidazoline and NMDA receptors.

5HT (serotonin) is widely used as a neurotransmitter but because it acts at a large number of receptor subtypes (at least five different types in the brain - which may be either inhibitory or excitatory, pre or postsynaptic) its physiological role is not clear. 5HT neurones are concentrated in the pons and medulla with diffuse connections up and down. It is thought to be important for sleep, some sensory pathways, feeding behaviour, vomiting, mood, etc, etc. Not many veterinary drugs interact with it directly, although the side effects of some are mediated by 5HT.

In man, depression appears to be associated with a functional lack of noradrenaline or 5HT or both. Depression is not recognised in animals, but antidepressant drugs certainly alter animal behaviour and are often given empirically for this reason. Noradrenaline and 5HT have their action terminated by reuptake into the presynaptic neurone; most antidepressant drugs block this reuptake, eg the tricyclic antidepressants. Monoamine oxidase inhibitors were used in the past for the same purpose but have major side effects. Modern, reversible inhibitors such as moclobemide may be better. Some reuptake inhibitors are more specific for noradrenaline (imipramine) or 5HT (fluoxetine) (or dopamine (selegiline)) but most will block the reuptake of all to some extent. Since these transmitters are also important in the



Noradrenergic transmission in the CNS.

peripheral nervous system, antidepressants have many side effects attributable to excess noradrenaline ± 5HT (some of the older drugs have antimuscarinic effects as well).

Dopamine is a neurotransmitter as well as a precursor for noradrenaline. It is involved in three important pathways; nigrostriatal pathway - important in motor control; the mesolimbic pathway to the nucleus accumbens - the "reward pathway" and the tuberoinfundibular pathway between the hypothalamus and the pituitary. Problems with the nigrostriatal pathway lead to Parkinson's disease in people: this is not recognised in animals but can be induced by dopamine antagonists (many classes of sedatives)! The reward pathway is very important in drug addiction in people, but is probably involved in learning and possibly food intake in animals too. The tuberoinfundibular pathway is important to maintain pituitary secretion (dopamine inhibits pituitary hormone release) - drugs to manipulate this are starting to be used in veterinary practice. Many hormones involved in reproduction are under the control of pituitary derived releasing hormones.

Dopamine also stimulates the chemoreceptor trigger zone to cause vomiting and dopamine agonists are used as emetics.

Dopamine also acts at a large number of receptor subtypes but most known functions are through the D2 subtype family.

Adrenaline is not thought to be very important as a neurotransmitter in the brain.

Other fast transmitters

Acetylcholine acting at nicotinic receptors is involved in some inhibitory circuits on motor neurones. Muscarinic receptors play a role in learning and memory. Since animals do not smoke and do not seem to get Alzheimer's disease, acetylcholine receptors are mainly important in poisoning in veterinary practice - many plants contain cholinergic drugs.

Histamine acting at H1, H2 and H3 receptors can be either excitatory or inhibitory but its physiological role is unclear. It may be involved in sleep. Several histamine antagonists are used in veterinary medicine for their central effects (mainly phenothiazine sedatives), but they all affect other receptor systems as well as histamine.

Purines, **ATP** (co-released with noradrenaline), **AMP** and **adenosine**, have only recently been recognised as neurotransmitters in the brain (as well as doing other things connected to metabolism). Adenosine acts at purinergic A receptors of which there are several subtypes, ATP acts at purinergic P receptors. P_{2x} receptors are important ionotropic receptors (again there are several subtypes), P_{2y} receptors are metabotropic. Expect more new functions for these receptors to be discovered soon. The stimulant effect of caffeine and similar drugs is probably due to an action at purinergic receptors.

Neuromodulators

Peptides tend to be involved in amplifying or damping down signals rather than transmitting signals. Many are involved in inflammation and are released from the peripheral ends of neurones as well as the central ends. They tend to diffuse away from the cells that produce them to affect all the surrounding cells, so they can have a wide range of effects. Peptides such as **substance P** enhance pain signals leading to hypersensitivity (more later). Encephalins such as β **endorphin** or **endomorphin** usually have the opposite effect, although others such as **nociceptin**, and possibly **dynorphin** also enhance pain signals. Morphine (and codeine in invertebrates) are possibly also endogenous neurotransmitters, as well as analgesic drugs. **Neuropeptide Y** is the most abundant neuromodulator in the mammalian brain. It is involved in pain and appetite, among other things. A variety of **cytokines** and **growth factors** also act as neuromodulators, as do a number of peptides first isolated from the gut such as **cholecystokinin** and **vasoactive intestinal peptide.** The list is getting longer all the time. Numerous drugs interact with one or more of these, usually to produce CNS side effects. There are also a number of anomalies - for instance, capsaicin, the hot substance in chillies, acts at specific receptors in the spinal cord and the periphery to increase the release of substance P, but no endogenous ligands for these receptors have yet been found. This area is likely to get even more complicated in the future, and there is plenty of scope for drugs which interact with neuromodulators.

Nitric oxide and **carbon monoxide** are also implicated in neuromodulation. Nitric oxide usually increases excitability, the effects of carbon monoxide are thought to be similar. These gases are produced as needed and rapidly diffuse away. They can be altered by manipulating the enzymes that make them, but appear to be so widely used in the body that increasing or reducing their production causes a vast range of effects.

Arachidonic acid may act as a neuromodulator in its own right, although it is difficult to distinguish its effects from those of its metabolites, the prostaglandins and leukotrienes.

$PGF_{2\alpha}$ may be an important neuromodulator in the brain. A variety of commonly used drugs affect arachidonic acid, including corticosteroids and aspirin type drugs.

Various endocannabinoids, of which **anandamide** is best known, act as neuromodulators in the brain to produce a wide variety of effects, from sleep to analgesia to appetite stimulation to cough suppression.

Central neurotransmission

- the main excitatory transmitter is glutamate acting at AMPA (fast), NMDA (medium) and mglu (slow) receptors
- the main inhibitory transmitter is GABA acting at GABA A receptors
- neuromodulators act slowly to amplify or reduce transmission, usually by altering membrane polarisation
- noradrenaline acting at α2 receptors is mimiced by some important veterinary drugs

Local anaesthetics

Definitions

anaesthesia = no feeling

local anaesthesia (= local analgesia) = blockade of transmission in peripheral nerves or spinal cord, usually to try to stop pain signals. (Since most nerves are mixed, motor as well as sensory fibres are nearly always blocked.) The term "local analgesia" is better since pain, but not all feeling, is blocked.

regional anaesthesia / analgesia = block of a major nerve supplying an area of the body using a local anaesthetic drug.

spinal anaesthesia / analgesia = blockade of sensation from large areas of the body by putting a local anaesthetic around the spinal cord.

general anaesthesia = a combination of unconsciousness, analgesia and muscle relaxation produced by a completely different set of drugs (more later)

Some local anaesthetics are used as anti-arrhythmics or anti-convulsants (see cardiovascular notes).

Chemistry

Many drugs have some local anaesthetic effect but the useful drugs all have an aromatic (lipophilic) end joined to a basic amine (hydrophilic) end by either an ester or, more commonly, an amide group. These different links are important in metabolism as this is where the molecule is split to inactivate it.

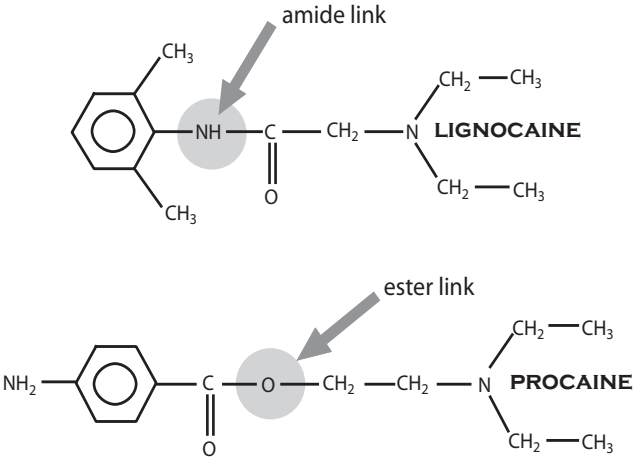
Mechanism of action

Blockade of voltage gated sodium channels in nerve axons. The sodium channels can exist in three states: closed (normal), open (only for milliseconds) and inactivated (after opening). The local anaesthetic binds to the channels in the open or inactivated states. More channels will be in these states if the nerve is actively firing, so local anaesthetics work better in active neurones (use dependance).

A variety of subtypes of sodium channels have been discovered. Some drugs are marginally selective for some subtypes. In future, drugs which just block the selected type of nerve may be clinically available. Current local anaesthetics are not selective and will block voltage gated calcium channels too - these may be important in C fibres.

Types of sodium channels

tissue	sodium channels
CNS	Na_V 1.1, 1.2, 1.3
dorsal root ganglia	Na_V 1.8, 1.9
peripheral neurones	Na_V 1.7
neurones & CNS glia	Na_V 1.6
skeletal muscle	Na_V 1.4
heart	Na_V 1.5



Pharmacokinetics

Absorption

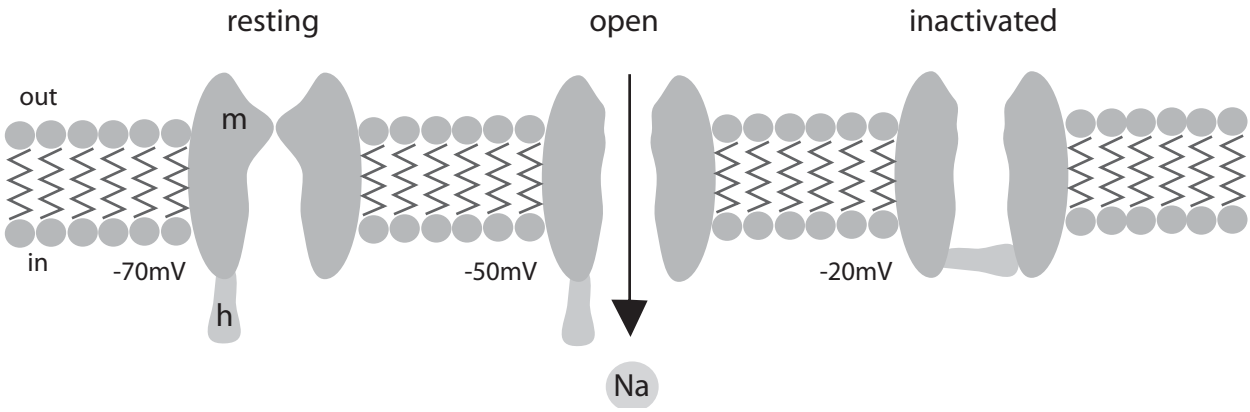
Local anaesthetics are unusual in that they are normally applied directly to the site of action. However, most of them still have to get into nerve cells to work. pKa is important for penetration into neurones, most local anaesthetics have a pKa of 8 - 9. Most local anaesthetics cross the neurone cell membrane (in the unionised form) and get to their binding site from the inside. Some unionised drug may go directly from the outside through the cell membrane to the binding site.

Distribution

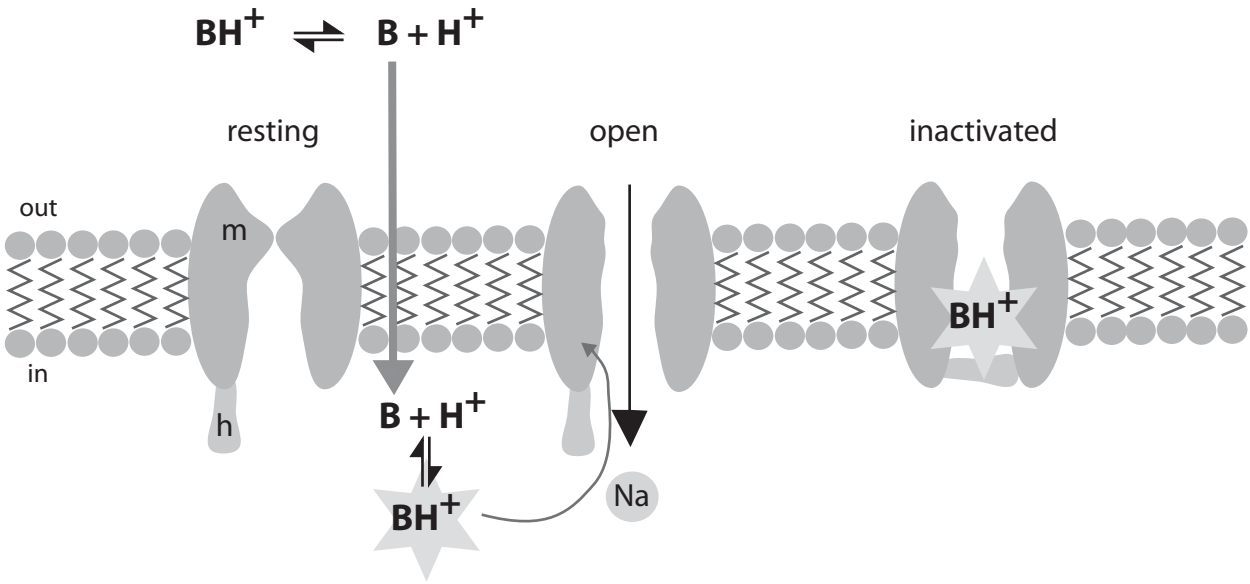
The action of local anaesthetics is terminated by re-distribution. They are rapidly distributed away from the site of action unless vasoconstrictors are given at the same time (**adrenaline**, **felypressin**). These are contra - indicated where the blood supply to an organ may be compromised by vasoconstriction, eg a cow's teat or a dog's toe. Adrenaline is much less stable than most local anaesthetics and has a short shelf life.

Metabolism

Esters are rapidly broken down by plasma cholinesterase, amides are broken down more slowly in liver. Lignocaine (an amide) is amost completely metabolised in one pass through the liver - it cannot be given orally.



Sodium channel gating in neurones. The sodium channel is normally in the resing state, when an impulse comes along it opens for a few milliseconds, then goes into the inactivated state for (usually) several seconds.



Local anaesthetic access to the binding site in the channel pore.

Use dependence

Since local anaesthetics get into the sodium channel more easily when it is open and bind to the channel more tightly in the inactivated state, if the channels are cycling through the three states (ie action potentials are passing along the nerve) the local anaesthetics will work better. Thus rapidly firing nerve fibres will be preferentially blocked. Nerve fibres carrying pain signals tend to be firing more rapidly than others, but use dependence is mainly important in the anti-arrhythmic and anticonvulsant effects of local anaesthetics. In these situations it is sometimes possible to block rapidly firing cells while having no effect on cells firing more slowly.

Differential block

The onset of blockade follows a regular pattern: small myelinated fibres (Aδ) are blocked first, followed by small unmyelinated fibres (C) and then large myelinated fibres (Aα). This means that pain and sympathetic transmission is blocked before motor transmission. This is obviously desirable but is difficult to achieve reliably in clinical situations.

However, at a steady state, a 2 - 4 times higher concentration is required to block C fibres compared to Aα fibres. The discrepancy may be because C fibres have different subtypes of Na_V channels and also possess Ca_V channels.

Toxicity

Usually occurs after accidental iv injection, but some types of block require large doses - it is particularly easy to overdose sheep. The toxic dose of lignocaine in most species is about 7mg/kg.

- •sedation
- •convulsions
- •cardiotoxicity
  - automaticity depressed
  - myocardial toxicity (especially bupivacaine)

Indications

operative analgesia (usually need sedation except in ruminants)
postoperative analgesia
diagnosing lameness (usually horses)
(arrhythmias - not with adrenaline!)
(convulsions)

Administration

•*topical* (eg., eye, larynx) (skin - Eutectic Mixture of Local Anaesthetics, EMLA) - blocks local nerve endings. Remember that most drugs are weak bases so they are dissolved in

acid - ie, they sting when put into eyes!!!

•*local infiltration* (eg., L block for caesarian section) - blocks nerve endings in area to be desensitised. Use a fine needle!

•*nerve block* (eg., paravertebral for caesarian section) - blocks transmission in a specific nerve (and thus the area it supplies). Needs some knowledge of anatomy!

•*epidural* and

•*intra-thecal* - block the area supplied by the nerves arising from the affected part of the spinal cord. Needs more kowledge of anatomy or spinal cord can be damaged. Also blocks motor nerves.

•*Bier's block* (Intra Venous Regional Anaesthesia, IVRA) (eg., for foot operations) - injection into a vein below a tourniquet - blockade of most of the tissues below the tourniquet. nb. analgesia stops when the tourniquet is removed

•*intra-articular* - mainly the synovial membrane. Be extemely careful not to introduce bacteria into joints.

Since iv administration causes side effects, care should be taken that the drug is not injected into a vein; ie aspirate before injecting.

Drugs

By far the most commonly used drug is **lignocaine** (lidocaine USAN). It is chemically stable (can be autoclaved), spreads through tissues, used as 1 or 2% solution parenterally, 4% topically. It has a rapid onset - 5 min, medium duration of action - 30 - 40 minutes (1 hour with adrenaline). Depending on the type of block being used, it is possible to give toxic amounts (maxiumum dose 7mg/kg). It is cheap.

Prilocaine is very similar to lignocaine but less toxic - used for Bier's blocks (IVRA). **Mepivacaine** again is very similar to lignocaine but less irritant - used in horses for diagnostic nerve block (some horses produce a local inflammatory reaction to lignocaine). **Bupivacaine** is more potent, has a slower onset - 20 minutes but longer action - up to 8 hours. This is useful for post op analgesia. Adrenaline is not usually used with this drug. One of its stereoisomers is potentially cardiotoxic - maximum dose 2mg/kg. **Ropivacaine** is similar to bupivacaine but is much less toxic (and even more expensive).

Amethocaine (tetracaine USAN) is the only ester used clinically. It is usually given topically in the eye. **Proxymethacaine** is similar. **Cinchocaine** is sometimes used for spinal blocks but is pretty toxic (it has been used in combination with phenobarbitone for euthanasia). **Benzocaine** is an insoluble local anaesthetic sometimes found in powders applied topically to stop animals itching.

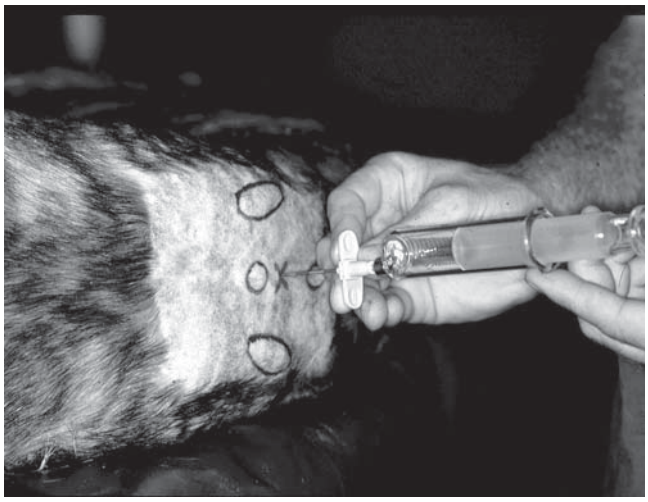
Procaine is obselete - slow onset, poor penetration of mucous membranes, toxic - **do not use.** The similar chloroprocaine may be better but is not available in NZ.

Articaine has taken over in human dental anaesthesia overseas and has just reached NZ. It has a fast onset and long duration, and at least three different routes of metabolism, none of which produce anything nasty (see politics, below). It may become useful in food animals.

Experimental drugs

Tetrodotoxin (TTX) from puffer fish, blue ringed octopus, etc (produced by symbiotic *Vibrio* spp) and saxitoxin (STX) from toxic algae are large organic molecules which bind very specifically to (some) sodium channels from the outside and are used to study sodium channels in the laboratory. They are widely used *in vitro* to block action potentials and are **very toxic**. They are not used therapeutically, but experimental use shows that they can produce up to 20 hours block in people. They may rarely be seen as poisoning cases (usually saxitoxin - there are probably no blue ringed octopus in NZ).

A variety of obscure spider and scorpion toxins also affect sodium channel gating in such a way as to mimic block clinically - hopefully you will not come across these except in scientific papers.



Checking that the needle is in the right place using the "loss of resistance" technique before giving a lumbar epidural injection of lignocaine in a greyhound. X marks the spot!

Sodium channel openers

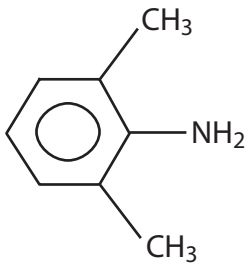
Veratridine is used experimentally; a variety of insecticides such as DDT and pyrethrums have similar effects. Although not used for their effects in mammals, these are occasionally seen as poisoning cases eg, sea anenome poisoning.

Politics

One of the metabolites of most local anaesthetics is 2,6 xylidine, which is a common industrial contaminant and thought to be carcinogenic. This has led to lignocaine being banned in Europe for use in food animals, although it is still the most widely used local anaesthetic in people.

commonly used drugs

lignocaine



2,6, xylidine, a potential metabolite of most amine local anaesthetics except prilocaine. It is probably carcinogenic.

Local anaesthetics

- stop action potentials by blocking sodium channels
- are weak bases which get into cells in the unionised form, become ionised and bind to the channels in the open or inactivated state.
- show use dependence - rate of onset and depth of block are dependent on action potential frequency
- can block pain fibres before motor fibres
- are mainly used for analgesia - particularly in ruminants
- block most excitable tissues if you give too much

Pain and analgesia

Definitions

Pain: no completely satisfactory definition exists; that proposed by the International Association for the Study of Pain (for people) is the most widely accepted: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." ie, pain consists of both a sensory component and an affective component. Some people also include a cognitive component, but I consider this a response to pain. (Other people deny that animals are capable of thinking.)

Analgesia = a lack of pain.

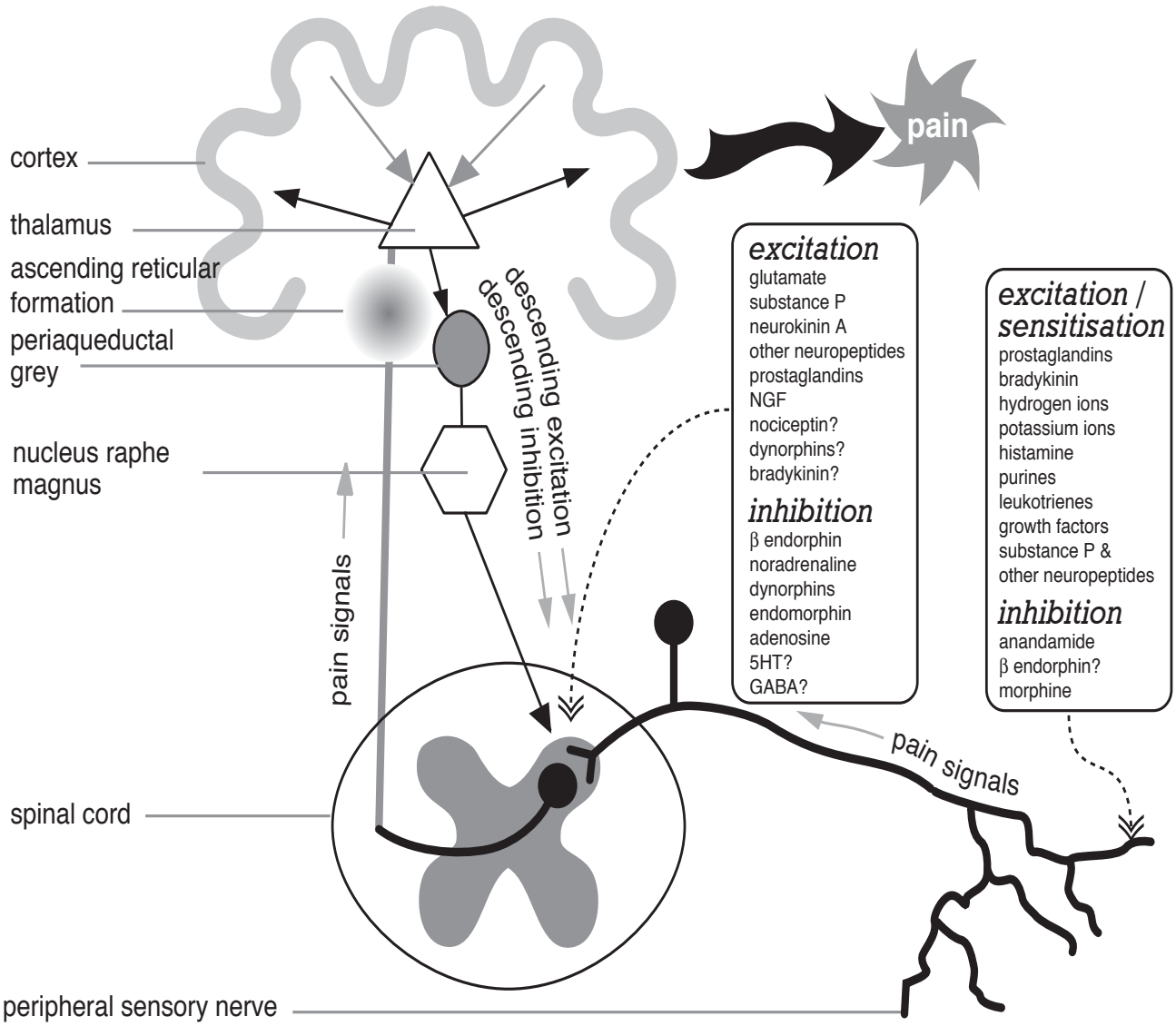
Nociception = the sensory component of pain. Since it is not possible to definitively prove that animals can feel pain, this term is sometimes misused (particularly by American physiologists) to mean pain in animals. A nociceptor is a nerve fibre used for pain signals.

Hyperalgesia and **allodynia** These are conditions which occur after pain perception has been altered by central or peripheral sensitisation. Hyperalgesia occurs when a stimulus which would have been painful before is now more painful; allodynia is when a previously innocuous stimulus (such as light touch) becomes painful. Sometimes these conditions persist after the injury has healed (hyperpathia).

Algogenic = something which produces pain.

Placebo = Latin "I will please" = inactive drug given to people who believe that it will do some good.

Nocebo = Latin "I will hurt" = inactive drug given to people who believe that it will cause problems. Animals which have been inappropriately treated in the past tend to



behave as though any future treatment will hurt, too.

Assessment of pain

In animals, it is only ever possible to measure the **response** to pain, usually by assessing behaviour. Beware - lots of drugs will alter behaviour without affecting pain. Some people have attempted to assess pain objectively in animals by measuring autonomic function (heart rate, blood cortisol concentrations, etc.) but this only measures stress. Pain will cause stress, but so will many other things. **If there is any doubt that an animal is in pain, it should be given analgesic drugs**. A response to the drugs indicates that it probably was in pain (but remember the effects on behaviour): a lack of response may mean the the animal was not in pain or that the analgesia was insufficient.

It is unethical for a vet not to treat pain in an animal under his care.

You **must** be able to recognise pain and know how to treat it in any species you are likely to come across.

Pain pathways

Blocking the afferent pathway or stimulating the inhibitory pathway can provide analgesia. These pathways are not hard wired, ie, the importance of each part can change in the short term and neuronal connections can change in the long term. This is sometimes (confusingly) called plasticity.

Afferent excitatory pathways

injury stimulates Aδ and C fibres - polymodal nociceptors

- •Aδ - sharp localised pain, mechanical stimuli
- •C - burning pain, heat or cold
- ➛ dorsal root
- ➛ substantia gelatinosa of spinal cord
- ➛ spinothalamic / spinoreticular tracts
- ➛ thalamus
- ➛ (cortex) affective rather than sensory?

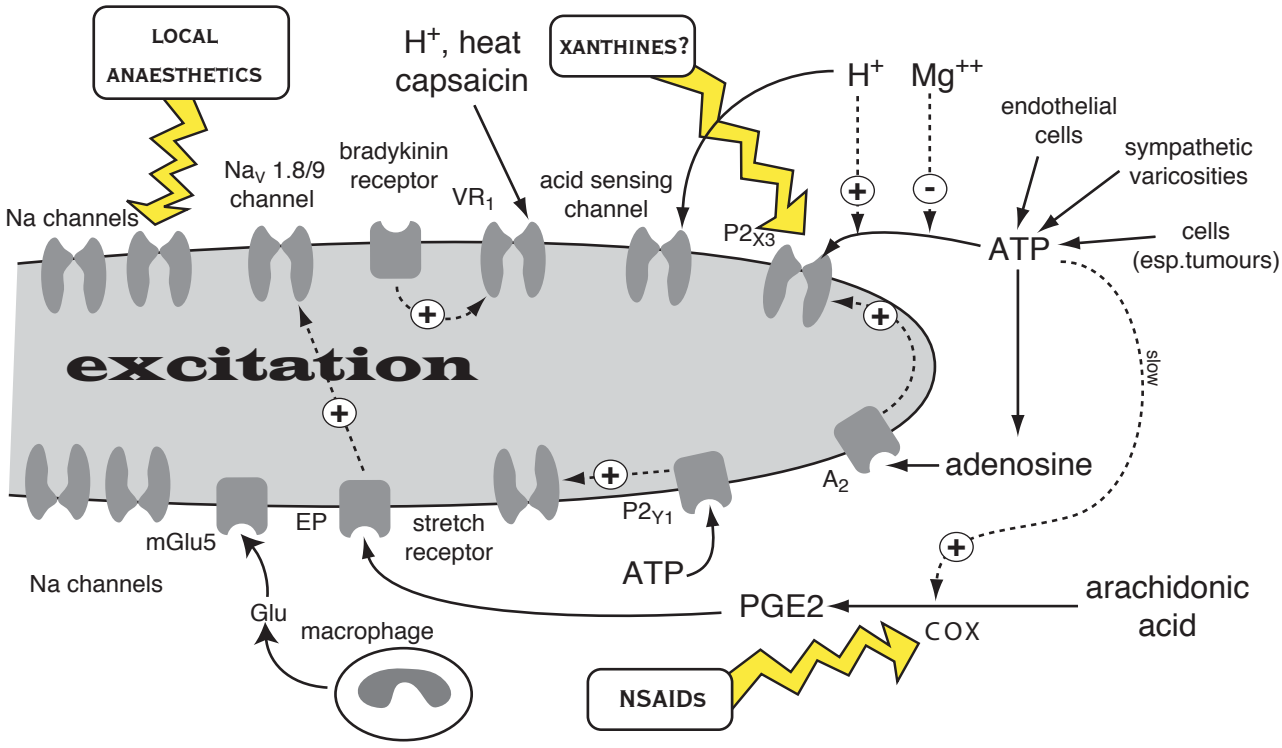
Descending inhibitory pathways

cortex?

- ➛ thalamus
- ➛ brainstem
- ➛ dorsal horn of cord

Recommended reading

Julius & Basbaum, 2001, Molecular mechanisms of nociception, *Nature*, **413**, 203 - 210 A good review of the pathophysiology of pain which is up to date but still readable.



A greatly simplified diagram of a peripheral nerve ending and some of the mechanisms which may cause excitation. Most of the ion channels conduct Na^+ or Ca^{++} or both. EP receptor activation causes sensitisation rather than excitation.

Gate theory

Nociceptive signals may be enhanced or inhibited (gated) in the dorsal horn of spinal cord (and also in the thalamus, although the higher up the pathway one goes, the less is known). Placebo is an important effect in people (much more important than the pharmacodynamic effect for some drugs such as codeine); this must be mediated by the cortex. Placebo effects probably occur in animals, but nocebo may be more important. Animals tend to recognise vets who have done nasty things to them and seem to expect more of the same. This is likely to affect the action of analgesic drugs adversely. Many analgesics mimic or inhibit the action of the endogenous transmitters involved in gating at the spinal level.

Transmission	transmitter	receptor	analgesic
normal	glutamate	AMPA	(local anaesthetic) (Ca channel blockers) (experimental AMPA antagonists)
enhanced	glutamate	NMDA	ketamine antidepressants (experimental glycine antagonists)
	substance P	NK1	(capsazepine)
	neurokinin A	NK2	(experimental drugs)
	nociceptin	ORL1	nociceptin antagonists (4 aminoquinolines)
reduced	encephalins	μ & κ opioid	opioids (acupuncture?)
	noradrenaline	α_2	α_2 agonists
	5HT	$5HT_3$?	antidepressants?
	GABA	$GABA_A$	anaesthetics (TENS - Aβ fibre stim)

Response to injury

When injury occurs a cascade of effects follows.

1) direct stimulation of nociceptors - message passed on to brain, reflex withrawal of part stimulated

2) descending inhibition - often before the stimulus is perceived as pain

3) release of chemical mediators - bradykinin, prostaglandins, leukotrienes, 5 - hydroxytryptamine, substance P, thromboxanes, platelet activating factor, noradrenaline, free radicals, histamine, etc, etc

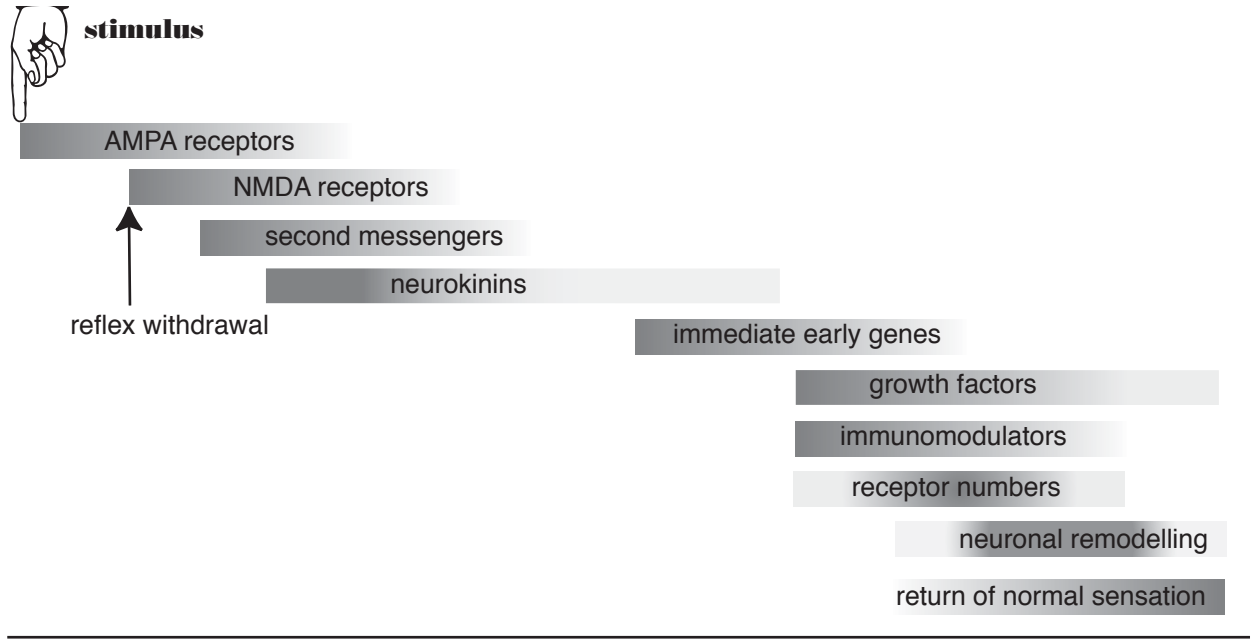
4) sensitisation of nerve endings - by the combination of chemical mediators (bradykinin + prostaglandins may be most important)

5) central sensitisation - NMDA receptors, tachykinins, (metabotropic glutamate receptors??) ± excitotoxicity with loss of inhibitory neurones?

6) recovery of normal sensitisation - may fail causing chronic pain

All this means that **pain will vary over time** and thus the drug requirements to relieve pain will vary over time. There is pretty good evidence in most species that drugs work better (more effective and longer lasting) if given before sensitisation occurs.

This process may apply to other problems apart from pain. There is good evidence that inflammatory bowel disease involves similar processes.



Time course of processes involved in pain.

Analgesia

Types of pain

The effects of analgesic drugs depend on the pain that they are used to treat. There are lots of different ways of classifying pain; probably the most commonly used in people is to divide pain into nociceptive (ie, in response to a noxious stimulus) and neurogenic (where nerve damage produces abnormal signals which mimic pain signals and there is not any obvious damage to tissues). Different types of drugs are used to treat the two types of pain in man but most types of pain in animals are assumed to be nociceptive. This may change as we learn more about pain.

Pain can also be classified as somatic, visceral or central. Central pain is assumed to be neurogenic; there is some evidence that visceral pain (eg, colic) is produced by a different mix of neurotransmitters than in the periphery.

Assessing the intensity of pain, and thus the effectiveness of analgesics, can be tricky. A variety of pain scales have been advocated, which assign numbers (subjectively) to the severity of the pain. Beware statements such as "drug X is twice as good as drug Y since it halves the pain scale".

Management of pain

Successful management of pain requires more than just analgesic drugs. Other things to be considered include:

emotional aspects - nursing, food, warmth
treat the condition!
physiotherapy??
TENS? / acupuncture?
If pain cannot be successfully treated, euthanasia must be considered. If an animal's owner refuses analgesia on the grounds of expense. this is the only option.

Groups of drugs

Many drugs have analgesic effects but few are clinically useful. No drug works in every case. The commonly used groups of drugs are:

opioids
NSAIDs
local anaesthetics
α_2 agonists

There are many other drugs used in people which are less useful in animals (but may be used as adjuvants to one or more of the above drugs):

psychotropics (mainly used for neurogenic pain in man) - tricyclic antidepressants (TCAs), anticonvulsants
odds and sods - capsaicin etc

Sites of action

peripheral nerve endings	local anaesthetics, NSAIDs (opioids?)
peripheral nerve	local (opioids? GABA agonists?)
spinal cord dorsal horn	local, opioids α_2 agonists (NSAIDs??)
brain stem	opioids, α_2 agonists, TCAs, carbamazepine
ventral tegmental area	opioids
cortex	opioids, α_2 agonists,

TCAs, carbamazepine

It is usually a good idea to use combinations of drugs which work at different sites (balanced analgesia), but more of that later.

Pre op analgesia

Drugs are more effective if given before central sensitisation occurs; ie, before the pain starts (sometimes incorrectly called pre-emptive analgesia). After central sensitisation has occurred higher doses are required. Ketamine may be able to reverse central sensitisation, presumably by blocking NMDA receptors. This means that for surgical pain, animals should be given an analgesic in their premed.

Clinical use

mild pain - NSAIDs

inflammatory pain - NSAIDs

severe pain - opioids

surgical pain - opioids + local + NSAIDs, depending on op

Analgesia in food animals can cause problems; giving drugs nearly always involves withholding times for meat or milk (as well as cost), but as a vet you will have a responsibility to try to relieve pain. Persuading farmers that animals in pain are not productive may help.

Further reading

Pain Management in Animals. eds. Flecknell and Waterman, W.B.Saunders, 2000

Pain and analgesia

- pain signals are carried from the periphery to the brain by a number of routes
- pain signals are subject to modulation at several stages, particularly in the spinal cord (gating) which may increase or decrease the signal
- most analgesic drugs interfere with endogenous pain modulation systems
- pain changes over time so drug treatment of pain must change over time
- analgesic drugs are more effective if given before the pain starts
- good nursing is a useful adjunct to analgesic drugs

OPIOIDS

Definitions

Opioids (note spelling) = agonists at opioid receptors (usually taken to be anything which can be displaced by naloxone).

Opiates = naturally occurring drugs extracted from opium (from the poppy *Papaver somniferum*) ie morphine, codeine and their crude extracts.

These are the main drugs used to produce potent analgesia.

Opioid receptors

See table below. Subtypes of all these receptors have been described but their role is not yet clear. σ receptors are not always recognised as opioid receptors.

Most clinically useful drugs are μ agonists:

morphine (& papaveretum - a crude extract of morphine) and its derivatives heroin (diamorphine) & M6G

pethidine and its derivatives fentanyl, alfentanil, sufentanil, lofentanil, carfentanil

methadone & dipipanone

Most of these notes refer to μ agonists, particularly morphine.

Useful effects

analgesia
euphoria

Mechanism of action

Opioids reduce firing in cells carrying pain signals (mainly in the spinal cord, but also in the brain stem): they

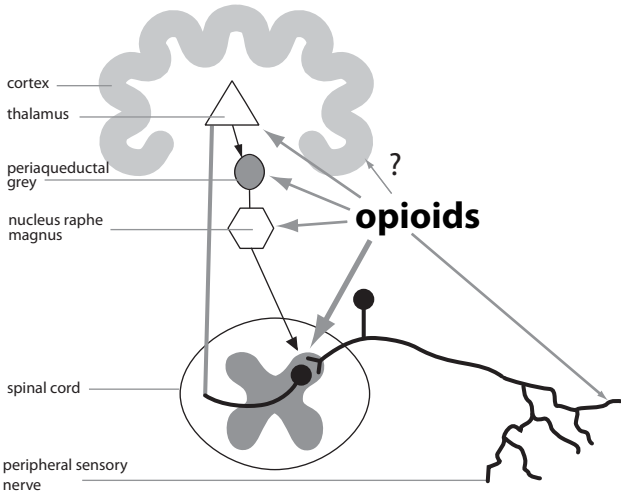
hyperpolarise neurones by opening K^+ channels (GIRK2 (Gprotein coupled inward rectifying potassium channels)). There are sex differences in these channels.

Opioids also reduce transmitter release by closing N type Ca^{++} channels and may directly reduce neurotransmitter release at nerve endings.

μ opioids cause mood effects by stimulating the ventral tegmental area which projects to the reward pathways in the nucleus accumbens via a dopaminergic pathway using D_2 receptors.

There is increasing evidence that morphine has analgesic and anti-inflammatory effects in the periphery. There is also

receptor	endogenous ligand	main effects	agonists	partial agonists	antagonists
μ (MOP)	β endorphin endomorphins	analgesia, respiratory depression, euphoria	morphine, pethidine, fentanyl etc	buprenorphine (etorphine)	naloxone (diprenorphine) (CTOP)
δ (DOP)	enkephalins	analgesia, hormonal effects	(DPDPE)	(etorphine)	naloxone high dose (diprenorphine) (naltrindole)
κ (KOP)	dynorphins	analgesia, dysphoria, diuresis	(U69593, CI977)	(etorphine)	naloxone very high dose (diprenorphine) (nor-binaltorphine)
ORL_1 (NOP)	nociceptin	increases pain	(Ro646198)		(J113397)
σ		psychotic effects, analgesia?	(phencyclidine) ketamine???		



Sites of action of opioids. Morphine is probably so effective because there is synergy between the different actions.

some evidence that morphine injected intra-articularly in horses causes formation of large glycopeptides such as hyaluronic acid. (see anti-inflammatory notes). Opioid peptides may also have a role in control of reproductive hormones and inflammatory cells; they are expressed on macrophages in inflammation. Watch this spot! (or read *Br. J. Anaes.,* 2005, **95**, 42.)

A variety of worms and other animals which are unlikely to feel pain possess opioid receptors, but what they do is anyone's guess. Opioid receptors as a means of producing analgesia is probably a fairly recent evolutionary development.

Side effects

Although the range of possible side effects is large, animals in pain show remarkably few of them, even after high doses. Healthy dogs usually vomit after morphine.

•vomiting - stimulate dopaminergic pathways in the chemoreceptor trigger zone

•sedation (usually only at high doses in normal animals)- non specific inhibition in the ascending reticular formation??

•euphoria - opioid receptors on dopaminergic neurones in the ventral tegmental area project to the nucleus accumbens - the "reward pathway"

•gut effects - slowed peristalsis and sphincter spasm leading to constipation - mainly mediated through the myenteric plexi but also central and direct effects on the smooth muscle cells

•muscle rigidity - mechanism unknown - worse with fentanyl

•respiratory depression - reduce sensitivity of respiratory drive to PCO_2 , made worse by anaesthetic drugs

•urinary retention - increased sphincter tone

•cough suppression - probably mediated by a different receptor system

•increased intra-cranial pressure - mechanism unknown

•addiction - caused by a combination of the euphoric effects of the drug and the unpleasant effects of withdrawal

•histamine release - sometimes occurs after iv morphine administration in the dog - use another route

•bradycardia can occur after large doses - depression of vasomotor centre - give atropine

•miosis - stimulate oculomotor nucleus to increase parasympathetic tone - this effect is often opposed by the effects of excitement

•excitement - mainly cats and horses at high doses - reaction to euphoria??

•segmental pruritus can occur after it morphine. There is a definite link between itch and pain - both may be carried by C fibres - bur exactly hoe morphine produces this is not clear.

•chewing behaviour - sheep and rats

Pharmacokinetics

Absorption

Usually given im or iv. Oral absorption is variable - morphine is about 20% bioavailable. Since the major action is in the spinal cord, opioids are sometimes given intrathecally or epidurally to get direct to the site of action (and stay there). Morphine is best by these routes, but transfer to the brain in the CSF can lead to prolonged respiratory depression.

Fentanyl is available in patches which are stuck on the skin and slowly absorbed.

Distribution

There are large differences in fat solubility; morphine is relatively hydrophilic, fentanyl derivatives are relatively lipophilic.

Metabolism

Morphine is conjugated with glucuronide to produce morphine 3 glucuronide (M3G) and M6G (potent analgesic) Remember cats do not possess glucuronyl transferase! One dose is enough in this species.

Elimination

Large differences between drugs and species. Remember cats! Most opioids also undergo some enterohepatic recirculation.

Indications

analgesia
anaesthetic premedication
(anti-diarrhoeals)
(anti-tussives (stop coughing))

as with all analgesics, opioids are more effective if given before pain starts

Contra-indications

severe head injury? - opioids raise intracranial pressure

upper respiratory tract injury? - block cough reflex thus may cause inhalation of blood clots, teeth, etc.

unconsciousness - unable to feel pain???

Chest injury is sometimes cited as a contraindication for opioids on the theoretical grounds that they inhibit respiration, however, rib injuries are extremely painful and

opioids often result in better respiration in animals with chest injuries.

Drugs

Morphine is the oldest drug and probably still the best. It is certainly the cheapest. An im dose will last about 4 hours in the dog and horse, and up to 24 hours in the cat, but the duration of action will depend on the pain. Morphine produces less obvious analgesia in ruminants, but works in pigs (short acting - about 1 hour after normal doses). It is not licensed for use in food animals. Intrathecal morphine lasts up to 24 hours, but sometimes produces itching of the areas supplied by the cord segments affected. Use sc or im rather than iv in dogs (histamine release). If you really must give it iv, use low doses given **very slowly**.

Methadone is very similar to morphine but more expensive. It is traditionally used in horses because of a myth that it causes less excitement then morphine. It is very long acting in some people, but not in animals. It may cause less vomiting in dogs.

Pethidine (meperidine USAN) works well in people but is very short acting in most animals (30 - 40 mins in the dog): high doses need to be given often. It is metabolised relatively easily by the cat. One metabolite, norpethidine, can cause excitation in people, usually only when it accumulates in renal disease or when pethidine is given regularly. This could be a problem in animals with renal disease. Pethidine is abused by people because it penetrates the CNS rapidly.

Fentanyl, **alfentanil** and similar drugs are very potent, short acting drugs given iv during anaesthesia to cover painful bits of ops or as infusions. Fentanyl is also available as transdermal patches. **Carfentanil** is similar but longer acting, it is usually used for chemical immobilisation of large animals (including deer). **Remifentanil** is a new short acting drug used in people but there is no experience with it in animals yet.

This group of drugs was originally developed for chemical warfare, so there may be others out there which could be useful transdermally.

There are a number of other opioids peculiar to America, oxymorphone is widely used there as a substitute for morphine, and hydrocodone as a substitute for codeine.

Heroin (diamorphine) is not used in animals, and only very rarely in people in NZ. It is a drug of abuse. It is much more lipid soluble than morphine and gets into the CNS faster (so works better at producing euphoria), but once there it is thought to be metabolised to morphine and exert its analgesic effects as morphine.

Residues

Only pethidine is registered in food animals, but does not work very well. It is probably best to use α_2 agonists in ruminants. Opioids work well in pigs but are usually shorter acting than other species.

Other considerations

Most μ agonists are controlled drugs because of the potential for abuse (in people). This means that they have to be locked away and their use recorded (see notes on the law); it also means that drug addicts will attempt to break into clinics to steal them.

The euphoric effects in a drug addict depend on a high concentration getting into the brain quickly. This means that lipid soluble drugs such as heroin, or to a lesser extent pethidine, are favoured over relatively water soluble drugs such as morphine. However, any drug addict desperate enough to break into a vet clinic is unlikely to be choosy.

Mixed agonists

Sometimes called partial agonists. These drugs were developed 20 - 30 years ago in the hope of producing analgesics which did not produce respiratory depression or addiction potential. They are falling out of fashion because they are no less respiratory depressant than morphine at equianalgesic doses and many of them produce dysphoria rather than euphoria. Most are κ receptor agonists and have side effects such as diuresis and occasionally motor effects in people (no information on domestic animals). **Buprenorphine** is probably the only one worth using; it takes about 45 minutes to reach peak effect even after iv injection and lasts 6 - 8 hours in most species except the dog (about 4 hours), but the duration of action depends on dose. It has a higher affinity for the μ receptor than naloxone (see below) so its effects can be difficult to reverse. At higher doses, it is also a ORL1 agonist, and analgesia can be reversed. You are unlikely to see this in practice though.

Butorphanol is sold in NZ as an analgesic for dogs and horses (and an antitussive for dogs). It frequently causes excitment in horses and should be given with an α_2 agonist to provide sedation. It has been withdrawn from human use in most countries because it produces dysphoria, this probably explains its effects in horses. Recent work in people indicates that it may produce analgesia in women but pain in men.

Etorphine (M99) is not available in NZ; it is sometimes used overseas in a neuroleptanalgesic mixture ("Immobilon" sold for horses, occasionally used in wild animal immobilisation). **Beware** - self injection is likely to be **fatal**; several vets have died using this drug. The lethal dose for people is 30 - 120μg. It is a class A controlled drug (see law notes).

Tramadol is not usually classified as a mixed agonist, but one of its stereoisomers is a μ agonist (and the main metabolite of this isomer has a higher affinity for the μ receptor); the other isomer is a monoamine reuptake inhibitor. Increased noradrenaline and 5HT have a synergistic effect on analgesia. Tramadol may also act as an NMDA antagonist.

It is sometimes useful for chronic pain in people but is not great for acute pain. It is not as effective as morphine in dogs and causes dysphoria in 30 - 40% of cats. Use morphine instead for acute pain. Oral tramadol may have some place in arthritis in dogs where NSAIDs produce excessive side effects. It is not a controlled drug at the moment so can be handed out to owners.

	μ	δ	κ	σ	ORL_1
butorphanol	-/(+)		(++)	+	
buprenorphine	(++)	-	(-)?	0	-
nalbuphine	-	-	(++)	+?	
pentazocine	-	+	++	+	
etorphine	+++	+++	+++	0	

Opioid mixed agonists. Brackets indicate conflicting evidence of an action at that receptor.

Antagonists

Opioid antagonists are sometimes used to reverse the effects of overdose. They will also reverse analgesia as well as side effects, so it is usually better to just deal with the side effects of the opioid. If you are using potent drugs such as carfentanil in the field where there is a chance of accidentally injecting yourself, you must have some naloxone available (and know where your veins are).

naloxone - human drug - used for accidents and overdoses. This should be on hand if using carfentanil - people are more susceptible to the respiratory depressant effects of opioids than common domestic species. Only lasts about 20 mins.

naloxone human dose

0.8 - 2 mg (2 - 5 ml of 0.4mg/ml solution) iv to effect. Max dose 10mg

naltrexone - similar to naloxone but longer duration of action. Diprenorphine - antagonist, not available in NZ; nalorphine and laevorphanol are partial agonists rather than antagonists and are obselete.

Remember that the partial (mixed) agonists will also act as partial antagonists, and partially reverse the effects of pure agonists.

Antidiarrhoeals

Opioids reduce passage of gut contents by a combined effect on the myenteric plexus and the CNS. Codeine, loperamide, diphenoxylate and morphine & kaolin are used for this (see gut pharmacology notes).

Antitussives

Depression of coughing may not be mediated by opioid receptors but is produced by most opioids with a similar structure to morphine. Codeine (cheap) and butorphanol (expensive) are sometimes used in dogs. (see respiratory notes).

commonly used drugs

analgesia
morphine
pethidine
buprenorphine

antitussive & antidiarrhoeal
codeine

Opioids

- the main group of strong analgesics
- main effects analgesia and euphoria
- interact with anaesthetics and sedatives to increase sedation
- side effects - vomiting and possibly respiratory depression. Not usually seen in animals in pain.
- overdose causes excitement in cats and horses
- morphine is metabolised very slowly in cats
- if in doubt about an animal's pain - give it morphine

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) (sometimes called aspirin like drugs) are a very large group of drugs of diverse chemical structure with the common property of inhibiting cyclo-oxygenase, and thus reducing prostaglandin production. Prostaglandins perform many functions in the body, including mediating inflammation and sensitising peripheral nerve endings.

There are other groups of anti-inflammatory drugs which are also not steroids - I have referred to them as anti-arthritis drugs. All anti-inflammatory drugs are covered in more detail in 95.409.

Effects

- •anti-inflammatory (see anti-inflammatory drug notes)
- •analgesic
  - peripheral
  - central?
- •antipyretic
- •anti-endotoxic??

Mechanism

The way that NSAIDs produce analgesia may be different from the way they produce their anti-inflammatory effects. Both may be due to cyclo-oxygenase (COX) inhibition in various sites (althogh most NSAIDs have other effects which may also contribute to analgesia). nb. cyclo - oxygenase inhibition is usually assessed by measuring the reduction in circulating thromboxane B_2 rather than PGE_2 levels in the relevant tissue, which may well be different.

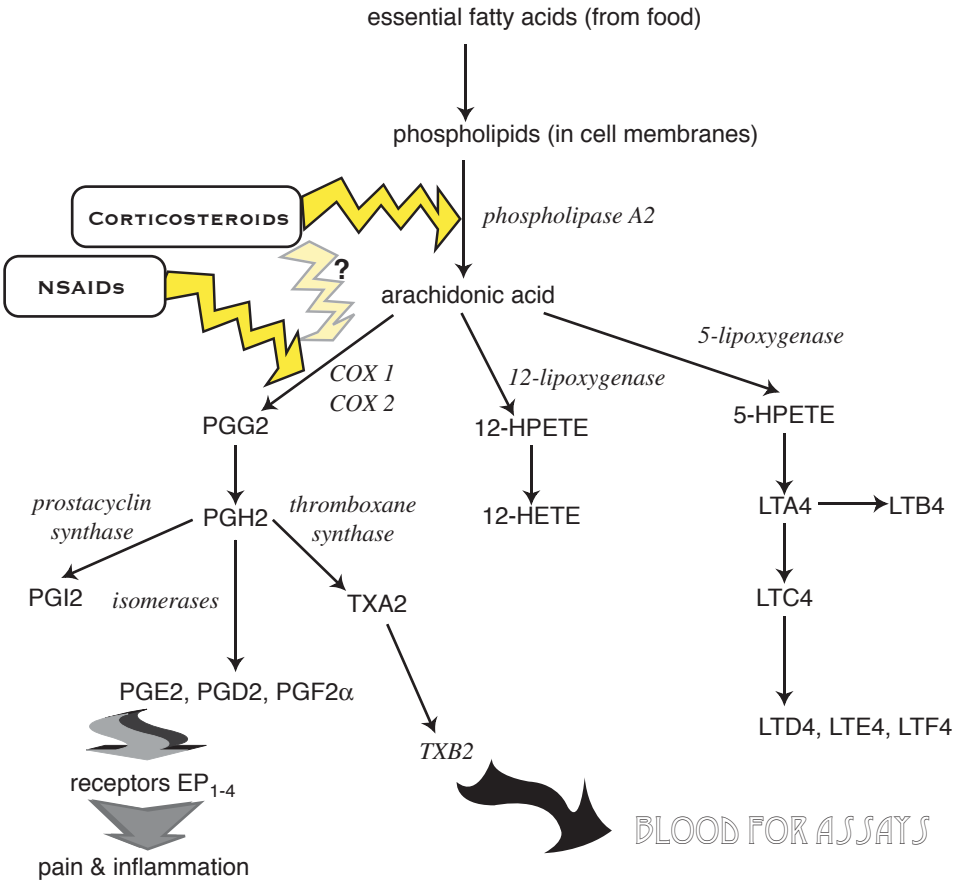
Steroids also reduce prostaglandin production (by acting higher up the cascade) but are not directly analgesic - they are potent anti-inflammatories and by removing inflammation they can reduce pain. NSAIDs are different in that they can produce analgesia in the absence of inflammation.

Cyclo-oxygenase exists in at least two forms:

COX1 - constitutive - responsible for physiological production of PGs

COX2 - inducible - produces PGs during inflammation

A variation on COX1 (COX3) has been reported. It is involved in the action of paracetamol in dogs, but probably not other species. Its significance is unknown at present.



The arachidonic acid cascade. PG = prostaglandin, LT = leukotriene.

All currently used veterinary drugs inhibit both COX1 and COX2 (but to different degrees). Since most side effects are caused by inhibition of COX1, drug development is focussing on finding drugs which only inhibit COX2. **Carprofen, firocoxib** and **deracoxib** are the only veterinary drug which comes close so far (in dogs), **meloxicam** is some way behind. **Celecoxib** and **rofecoxib** are COX2 inhibitors for people, but they may not be specific for COX2 in other species - there are big species differences. .

There has been a recent scare about the cardiovascular effects of coxibs in people. This seems to be only a problem with high dose chronic use, but see *Br. J. Anaes*, 2005, **95**, 281 for al you ever wanted to know on this.

Prostaglandin receptor pharmacology is a developing field. The situation is confused at present; the receptors responsible for some effects (but not the sensitisation of neurones) have been elucidated. However, it is clear that PGD2, E2 and I2 can all sensitise peripheral neurones to the pain producing effects of bradykinin and other mediators.

Some (most??) analgesia may be produced in the CNS (probably the brain rather than the spinal cord). There is evidence that prostaglandins interact with several types of glutamate receptors to increase nociception, NSAIDs may block this.

All currently used drugs also have other effects unrelated to cyclo-oxygenase inhibition which could contribute to analgesia. Many scavenge free radicals, which will also reduce inflammation.

Side Effects

when used as analgesics

gastric ulceration - limits use of most drugs to about 5 days at normal doses. Very common but not usually serious.

Normal production of mucus in the stomach depends on PGE_2 (produced by COX1), if mucus production is stopped then the stomach acid will cause ulceration. This can be prevented by giving PG analogues or PGE_1 with the NSAID (see gut pharmacology notes).

kidney damage - only in combination with other factors:

hypotension / hypovolaemia (shock, poor anaesthesia, etc.)
chronic kidney failure
old age
urinary tract obstruction

Kidney failure is rare but often fatal.

When the mean pressure in the renal artery falls below about 65mmHg there is not enough pressure across the glomerulus for filtration to take place. The body responds by producing angiotensin II which constricts the efferent arteriole to keep the pressure in the glomerulus up, but in the long term, this would reduce blood flow through the kidney and cause ischaemic damage. To stop this, PGE_2 causes emergency vasodilatation in the kidney (until blocked by NSAIDs). NSAID induced renal failure can usually be prevented by keeping the blood pressure at normal levels (usually with iv fluids).

The papilliary necrosis associated with NSAIDs is probably caused by interference with COX2, although COX1 may also be involved. COX2 knockout mice die of kidney failure, but of a different sort.

other side effects

increased bleeding time (mainly aspirin)
liver damage (some drugs have specific hepatotoxic effects)
agranulocytosis - very rare

side effects sometimes seen in people

asthma
dermal reactions
uricosuric effect

Analgesic NSAIDs

All NSAIDs have some analgesic effect, but some appear better clinically than others. **Carprofen**, **ketoprofen** **meloxicam** and **flunixin** are the drugs most often used for analgesia rather than an anti-inflammatory effect, but analgesia depends on type of pain and situation of use. Carprofen and flunixin have very different effects on PGE2 production but seem to produce similar analgesia. Coxibs are used in this way in people, but the jury is still out on these in animals.

Older drugs with more analgesic than anti-inflammatory effects include **paracetamol** (acetaminophen USAN) and **dipyrone** (only available here as a mixture with hyoscine).

The distinction between analgesic and anti-inflammatory effects may be less obvious than it would appear from the clinical use of these drugs. Recent evidence indicates that small pain fibres play an important part in the inflammatory response.

Indications

• mild musculo-sketetal damage - strains, osteoarthritis, etc. Inhibition of COX1 can cause increased degradation of articular cartilage by reducing subchondral blood flow and thus speed up the progress of the disease, but the benefits of analgesia usually outweigh this risk. The anti-inflammatory effects of NSAIDs are also useful here.

• mild pain

• equine colic - not all NSAIDs are suitable. Flunixin can be too effective and mask pain (often a sign of gut ischaemia) leading to a false sense of security. Do not use flunixin unless you have reached a definitive diagnosis.

• postoperative pain - not all NSAIDs are suitable; not all ops are suitable for NSAID analgesia. In man, the pain from dental and orthopaedic ops usually responds well to NSAIDs.

• acute inflammation - calf pneumonia, etc (see anti-inflammatory notes)

Pharmacokinetics

(see also anti-inflammatory notes) Half lives are very variable between species. Use with **extreme care** in unlicensed species.

Beware aspirin and paracetamol in cats, phenylbutazone in cattle, naproxen in dogs: unexpectedly long half lives.

Aspirin has an unexpectedly short half life in cattle.

Several NSAIDs have had withholding times established and are registered for use in food animals.

Clinical use

Acute pain - onset of analgesia about 15 mins after im / iv injection. Be careful of shock causing hypotension leading to kidney failure.

Chronic pain - usually osteoarthritis - dosage regime must be arranged to minimise gastric ulceration. Give tablets with food, only give as necessary rather than continuously, use anti-ulcer drugs (see gut pharmacology notes).

Recommended reading

Lees, May and McKellar (1991) Pharmacology and therapeutics of non steroidal anti-inflammatory drugs in the dog and cat: 1 and 2. *Journal of Small Animal Practice*, 32, 183 - 193 & 225 - 235

α_2 AGONISTS

Adrenergic α_2 agonists are widely used, especially in large animals, for chemical restraint. They are also effective analgesics and possibly the most effective class of analgesic drugs in ruminants (see also sedative notes).

Effects

- **analgesia**
- **sedation**
- bradycardia
- rise then fall in arterial blood pressure
- spasm then relaxation of gut
- muscle relaxation
- vomiting (30% of dogs & 40% of cats)
- hypoxaemia (ruminants)
- hypothermia

Drugs

Xylazine has been around since the 1960s for animals, **clonidine** (human drug) is nearly as old. Interest has recently revived in these drugs with **detomidine**, **medetomidine** (one stereoisomer, **dexmedetomidine**, is currently undergoing clinical trials in people) and **romifidine** (an ancient analogue of clonidine which has been brought back from the dead). These drugs have slightly different specificity for $\alpha 2$ subtypes, but there is no clear relationship with their clinical properties. Xylazine has traditionally been used in all species, especially ruminants which are much more sensitive to its effects than other species, medetomidine in dogs and cats, and the others in horses. They are primarily used for their sedative effects but are also useful analgesics.

Mechanism

Adrenergic α_2 receptors are G protein coupled receptors which increase K^+ conduction in same way as opioids (and probably at the same ion channels ($GIRK_2$)) and so hyperpolarise neurones.

Sites of action

analgesia - spinal cord, (locus coeruleus)(some species differences)

sedation - locus coeruleus (ascending reticular formation)

*cardiovascular effects*This can cause confusion. These drugs cause hypertension and bradycardia followed by hypotension. The hypertension is caused by a direct effect on the vascular smooth muscle in resistance arterioles in some vascular beds such as the skin (big arteries are unaffected). The hypotension is caused by an inhibition of the vasomotor centre in the medulla, the thoracic sympathetic outflow and the release of noradrenaline at sympathetic nerve endings. The hypertension usually causes marked vagally mediated reflex bradycardia which is potentiated by reduced release of adrenaline and noradrenaline.

Cardiac output can be reduced by up to 70%.

Most of the clinically used drugs contain an imidazoline ring and so bind to imidazoline receptors. The exact function of these is unknown but I_1 receptors are thought to be involved in blood pressure control - some imidazolines which are not also adrenergic α_2 agonists have been used to lower blood pressure in man. Imidazoline I_2 receptors appearto be on monoamine oxidase B and may also be involved in depression. I_3 receptors are involved with insulin release from the pancreas. α_2 agonists certainly reduce insulin production and thus cause a temporary hyperglycaemia.

respiratory effects

Xylazine appears to cause bronchoconstriction (and possibly pulmonary artery constriction) in ruminants; it may also cause pulmonary oedema. Animals become hypoxic, sometimes severely. It will kill 1.7 deer in 1000. This also occurs with the other drugs, but their use in ruminants is not sufficient for it to show up. It is probably caused by the release of various inflammatory mediators from pulmonary intravascular macrophages.

Respiratory depressant effects are minimal.

Routes of administration

usually im (small animals), iv (large animals)

poorly absorbed sc - blood vessel constriction

spinal administration gives long lasting analgesia without side effects and is clinically useful in ruminants and horses

Medetomidine in particular (at low doses) is useful as part of a balanced analgesia mixture, sometimes given as

an iv infusion.

α_2 antagonists are available (see sedative notes) and are usually used to reverse sedation but **will also reverse analgesia**. This is rarely desirable.

Balanced analgesia

Definition

Balanced analgesia = using several drugs at low doses so that the analgesic effects are additive or synergistic but the side effects are reduced. Combinations usually include an opioid or α_2 agonist and possibly an NSAID plus one or more of the following:

dissociative anaesthetics

Ketamine is the only drug easily available, **tiletamine** mixed with zolazepam (a benzodiazepine sedative) could be used. Their analgesic effects only become obvious at anaesthetic doses but ketamine potentiates other analgesic drugs at very low doses. Ketamine is an NMDA antagonist. It stops / prevents wind up in spinal cord and is also amnesic in man (blocks memory of pain). High doses in combination with α_2 agonists will cause anaesthesia.

dopamine antagonists

Butyrophenones such as **droperidol** (usually used as sedatives) produce deep sedation in combination with opioids. Enhanced analgesic effects have been reported but are dubious.

inhalation anaesthetics

All cause unconsciousness but some cause profound analgesia at low doses. **Nitrous oxide** is the most widely used (50% mixture with oxygen is probably the single safest analgesic - see anaesthetic notes for details). Methoxyflurane (not available in NZ) and **trichloroethylene** are good analgesics at low doses. Their mechanism(s?) are unknown but may involve endogenous opioids.

Drugs used for chronic pain in man

These may sometimes be useful in animals as part of a balanced analgesic technique.

tricyclic antidepressants

These block reuptake of noradrenaline and 5HT which then act on α_2 and $5HT_3$ receptors in dorsal horn of cord. **Amitriptyline** works best in man at doses well below the antidepressant dose. It also blocks NMDA receptors at clinical doses, and this may account for its analgesic action.

sodium channel blockers

These are used for causalgia in people. Lignocaine given intravenously has been used this way in hores, but is metabolised too quickly after systemic administration to be much use. Longer acting sodium channel blockers(see antiarrhythmic drugs) are used in people after testing the effects of iv lignocaine.

topical analgesics

Capsaicin (the hot substance in chillies) depletes C fibres of substance P - causes burning pain first but then blocks pain for days - months

EMLA cream - eutectic mixture of local anaesthetics (lignocaine and prilocaine) - will penetrate skin to cause analgesia. Used in needle shy children, but also useful for repeated blood sampling etc. Useful in laboratory animals. (see also drugs used in the eye)

Clinical use

Combinations of drugs should be chosen for the circumstances of the individual animal. Pain changes with time: different drugs and combinations may work more effectively at different times. Remember **local analgesia** too. In severe pain, particularly neuropathic pain, finer control can be acheived with an iv infusion. Ideally this should be with an infusion pump, but just sticking your drugs into a bag of saline and adjusting the drip rate to suit works very well. **Remember to label the bag!**

The aim of giving combinations of analgesics is to achieve synergy. This is practically impossible to show clinically and very difficult experimentally, partly because there is no widely accepted statistical technique. So far there is only good experimental evidence for synergy between opioids and α_2 agonists (but only by the spinal route) and opioids and NSAIDs. This is a hot research area so things will change in the near future!

Sedatives

Definitions

ataractic (= tranquilliser) - reduces anxiety without causing drowsiness. Usually produce no obvious effect in animals.

hypnotic - produces sleep

narcotic - produces a stupor bordering on general anaesthesia. This state used to be produced in people with opium, hence morphine type drugs are "narcotics" in law.

neuroleptic = ataractic

sedative - produces drowsiness

tranquilliser = ataractic

(do not confuse with analgesic)

In veterinary practice, the distinctions between these classes of drugs is usually not clear - I will refer to them all as **sedatives**.

Indications

- chemical restraint
  - mild sedation
  - heavy sedation
  - neuroleptanalgesia
  - general anaesthesia
- to potentiate anaesthetic drugs
- (travel sickness)

Selection of drugs or technique will depend on

- procedure to be carried out, eg.,
  - examination - very mild sedation only (usually!)
  - radiography - animal must lie still with reasonable muscle relaxation
  - lancing abscess - muscle relaxation less important than analgesia
- species (and sometimes breed and sex)
- animal's temperament

all sedative drugs have a smaller effect if the animal is excited

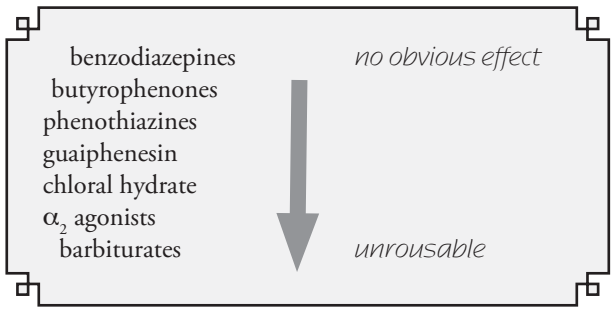
Drugs

There are many drugs used - see below.

Mechanism of action

Most drugs have effects on a wide variety of receptor systems but probably work by reducing input to the ascending reticular formation. Activation of the ascending reticular formation will increase arousal and is thought to be be responsible for consciousness.

Knowledge of the receptors affected by these drugs is important to predict interactions and side effects.



Phenothiazines

Acepromazine is by far the most widely used sedative in all domestic animals. **Chlorpromazine** was the original drug of this class, and although it is still sometimes used in people (for schizophrenia), it is not used in animals any more. It is only mentioned here because the effects of acepromazine have never been properly assessed - it has always been assumed to be very similar to chlorpromazine. **Methotrimeprazine** (levomepromazine INN) is a human drug sometimes used to sedate children - it is supposed to have some analgesic effects. It is usualy used in veterinary practice as an antihistamine, as is **promethazine**.

Effects

- sedation
- anti emetic
- vasodilatation
- lowers temperature
- analgesic / hyperalgesic (depending on the particular drug)
- anti muscarinic
- anti histamine
- extra pyramidal stimulation (Parkinson's disease)

Contra-indications

- stress
- epilepsy / convulsions - D2 antagonism causes dyskinesias

Care with

•shock
•cardiovascular disease - a1 antagonism causes hypotension
•Boxers - collapse - vagal syncope? give with atropine
•stallions - prolapse of the penis

Clinical use

Use the smallest dose which works. Bigger doses prolong the effect rather than increase the depth of sedation. Avoid getting the animal excited before administration. Animals excited after injury would be better sedated by an opioid analgesic.

α_2 AGONISTS

These drugs are especially useful in large animals and have superceded everything else. **Xylazine** has been around for longest and is still widely use in a variety of species. Ruminants are much more sensitive to xylazine than other species - they require much lower doses. Rams and bulls are much more variable in their dose requirements than females and castrated males. Xylazine appears to cause bronchoconstriction in cattle and sheep; it may also cause pulmonary oedema. It will produce a delayed hypersensitivity reaction in many deer; this is fatal in 1.7 animals in 1000. It may be metabolised to 2, 6 xylidine (carcinogenic).

Detomidine was introduced about 15 years ago for use in the horse and is now the standard sedative in this species, although it works in most other species too. A derivative, **medetomidine** is used in small animals (only one isomer, **dexmedetomidine** is active, it is used as an anaesthetic premed in people). Medetomidine is slightly more sedative than the others but it is not possible to produce anaesthesia with it alone in most of the species we deal with (cf. rats and man). **Clonidine** was the original (human) drug; it was first marketed as a nasal decongestant until it was noticed that it reduced blood pressure. It was then marketed as a hypotensive until it was noticed that it also produced sedation and analgesia, when it began to be used in anaesthesia and pain clinics. The moral of this story is that these drugs have lots of side effects! **Romifidine** is a clonidine analogue which was developed at the same time but shelved because of its sedative side effects. It has now been resurrected for horses. It is similar to the others but longer acting.

One attraction of α_2 agonists, particularly in small animals and deer, is that it is possible to reverse the sedation with antagonists. **Atipamezole** (small animals) and **yohimbine** (deer) are used, although there are many more specific experimental drugs such as **idazoxan** (α_2 antagonists were examined as antidepressants for man a few years ago). Remember that **all** the effects of the α_2 agonist will be reversed, **including any analgesia**.

The future?

Orexins, acting on OX_1 receptors on noradrenergic neurones in the locus coeruleus, increase arousal. OX_1 antagonists may potentiate or even replace α_2 agonists.

Benzodiazepines

A large family of drugs which are very widely used in man as sedatives and anxiolytics, they are not good sedatives in domestic animals but potentiate other drugs. When given alone, they sometimes cause paradoxical excitement - probably by making the animal forget it is supposed to be tame! Many also have active metabolites.

The short acting water soluble drug **midazolam** is useful as an intravenous premed, although it will not induce anaesthesia on its own in most animals (as it will in man). The most widely used drug is **diazepam**. It has a medium duration of action in most species (about 20 minutes) although active metabolites may prolong this, especially in combination with other sedatives. **Brotizolam** has recently be licensed as an appetite stimulant for cattle.

Mechanism

Bind to $GABA_A$ receptors and potentiate chloride conductance - hyperpolarise neurones. This can cause generalised reduction in neuronal activity (sedation), or at lower doses can reduce activity in specific pathways, eg, the tonic inhibi-

tory pathway from the ventromedial hypothalamus to the appetite centre in the lateral hypothalamus.

Effects

sedative in ruminants, only sedative in combination with other drugs in other species

anticonvulsant

appetite stimulant - useful in cats and possible cattle

anxiolytic?

These are useful emergency drugs as they do not depress the cardiovascular or respiratory systems at normal doses.

Indications

emergency treatment for convulsions

potentiate anaesthesia

stimulate appetite in cats & cattle

sedation in shocked animals

An antagonist, **flumazenil**, is available but too expensive to use.

As a pharmacological curiosity, benzodiazepine inverse agonists (eg β carboline) also exist. These bind to the receptor but produce the opposite effects to an agonist such as diazepam, ie, excitement and anxiety. They are not used clinically!

There is also a plethora of benzodiazepine like drugs on the human market, usually used as sleeping tablets (eg **zopiclone**). Most of these have not been used in domestic animals but you may sometimes see animals which have eaten their owners' sleeping pills!

Butyrophenones

Azaperone (and **fluanisone** overseas) are used in veterinary practice, **droperidol** and **haloperidol** are human drugs.

They sometimes (often!) cause excitement rather than sedation. Azaperone is traditionally used in pigs to control fighting when mixing groups, and for anaesthetic premed. It has also been used in dogs.

They are useful anti-emetics in dogs at very low doses, and are sometimes used in neuroleptanalgesic mixtures.

In man these are used as antipsychotic drugs (mainly for schizophrenia) - in the past when they were used as anaesthetic premeds, they caused subjective feelings of aggression but prevented the patients doing anything! Dogs and chimps given these drugs can behave aggressively for months afterwards.

They are potent D2 antagonists and often produce twitching, usually ascribed to extrapyramidal stimulation - ie, iatrogenic Parkinson's syndrome.

Use something else if possible.

Obsolete drugs

Chloral hydrate was used in large animals, either iv, oral or per rectum. It is very irritant extravascularly, must be given in large volumes, tastes nasty and is very long acting. It must be converted to trichloroethanol to produce sedation - takes about three mins in horses. Use α_2 agonists instead.

Guaiphenesin is still sometimes used in horses at induction of anaesthesia. It also has to be given in large volumes but does not have all the other disadvantages of chloral. It may be muscle relaxant rather than sedative Use α_2 agonists instead for induction. The only time it may be useful is as a component in "triple drip" anaesthesia.

Phenobarbitone is sometimes useful po in very vicious dogs but is very long acting and easy to overdose. Use only when nothing else works.

Do not use as sedatives

Reserpine - although sold in NZ to "calm" horses, it probably produces the same sort of psychoses as in man. This may make behaviour problems worse.

Magnesium - muscle relaxant rather than sedative. (Low dose magnesium may have a place as part of a balanced analgesic mixture, but it is also very effective at reducing cardiac output.)

Neuroleptanalgesia

Sedatives can be potentiated by adding an analgesic; the neuroleptanalgesia produced is a very deep sedation bordering on anaesthesia. Most neuroleptanalgesics are a mixture of an opioid with a phenothiazine or butyrophenone. Giving unfamiliar combinations of drugs requires that you know your pharmacology if you are not to get a nasty surprise.

When giving drugs which are potent depressives, the condition of the animal must be closely monitored. Neuroleptanalgesia can be as deep as general anaesthesia, but most sedatives have a large range of side effects, particularly on the cardiovascular and respiratory systems. Animals should be checked for heart or respiratory disease before the drugs are given, and the depression produced by the drugs continuously monitored. Most of the drugs mentioned have a long duration of action - the animal must have its airway, breathing and circulation monitored. In most cases a short acting anaesthetic (with intensive monitoring) is preferable to heavy sedation (with the animal left to look after itself when you have finished).

commonly used drugs

acepromazine
xylazine
medetomidine
detomidine
diazepam

Sedatives

- acepromazine produces mild sedation with some cardiovascular depression.
- diazepam is unreliable on its own (except in ruminants) but safe.
- α_2 agonists are best in large animals but cause cardiovascular depression and vomiting in small animals.
- combinations of a sedative with an opioid produce deeper sedation (neuroleptanalgesia).
- deeply sedated animals need to be monitored as for general anaesthesia.

Species recommendations

These are my personal preferences - many other combinations / techniques will work just as well! Producing the correct degree of sedation is an art rather than a science - it depends on the animal and its handlers as well as the drug and the vet. Excitement and pain will reduce the effects of drugs.

Mild sedation

dog acepromazine 20 - 50µg/kg im or sc (higher doses prolong effects without increasing sedation) but be careful in Boxers and large breeds such as Mastiffs - syncope / excessive duration of action.

cat acepromazine 20 - 50µg/kg & morphine 0.5mg/kg im or sc but sedation may not be obvious - competent gentle handling is probably more effective.

horse acepromazine 20µg/kg iv but sedation may not be obvious. Do not use in stallions - priapism may occur.

cattle xylazine 50µg/kg im The effect is variable in bulls.

sheep xylazine 50 - 200µg/kg im very large individual variation in effect - some rams very sensitive.

pigs azaperone 1 - 2mg/kg im - not always effective - quiet handling essential

Heavy sedation

dog medetomidine 30 - 80µg/kg im / sc

cat ketamine 10mg/kg im / sc (no muscle relaxation) or ketamine 5 - 10mg/kg & midazolam 0.2mg/kg im

horse detomidine 10 - 40µg/kg iv

cattle xylazine 100 - 300µg/kg im

sheep xylazine 10 - 20µg/kg im very large individual variation in effect - some rams very sensitive. (medetomidine and benzodiazepines produce reliable heavy sedation but not licensed for food species)

pigs tiletamine & zolazepam plus ketamine and xylazine (mixed together) im: 0.5-1mg/kg of each

Very heavy sedation / neuroleptanalgesia

dog acepromazine 20 - 50µg/kg & buprenorphine 6 - 10µg/kg im (any opioid may be used with acepromazine - papaveretum 0.2mg/kg or morphine 0.1mg/kg are cheapest) very fractious dogs - xylazine 1.3 - 2mg/kg & ketamine 10mg/kg

cat Not strictly neuroleptanalgesic but xylazine 1.1mg/kg & ketamine 22mg/kg produce very heavy sedation / general anaesthesia

horse heavy sedation may be dangerous for the animal and handlers; xylazine 1.1mg/kg iv followed by ketamine 2.2mg/kg iv will produce light general anaesthesia.

cattle, sheep, pigs general anaesthesia usually used

Special situations

Road traffic accidents

animal will be in some degree of shock - analgesics alone usually provide reasonable sedation

dogs buprenorphine 6 - 10µg/kg im
morphine 0.2 - 0.5mg/kg im more potent analgesic (do not mix the two)

cats pethidine 3 - 5mg/kg or morphine 0.5mg/kg

Intensive care

most species benzodiazepines eg
midazolam 50 - 300µg/kg iv or as an infusion
diazepam 0.1 - 0.5mg/kg iv or as an infusion

Colic

horses xylazine 0.5 -1mg/kg iv but will affect gut motility and thus interfere with assessment (but so will other sedatives & analgesics).

General anaesthesia

Definitions

general anaesthesia = a state of unconsciousness with lowered sensitivity to external stimuli.

local anaesthesia (analgesia) = blockade of peripheral nerves.

regional anaesthesia (analgesia) = blockade of peripheral nerves or the spinal cord supplying a larger area (using local anaesthetics).

neuroleptanalgesia = very deep sedation combined with analgesia under which some surgery can be performed.

dissociative anaesthesia = a state in which an animal is conscious but sensory input is dissociated from perception, ie, out of its head.

balanced anaesthesia = a combination of unconsciousness, analgesia and muscle relaxation. This can be achieved by large doses of a single drug or (preferably) small doses of different drugs.

Introduction

A typical anaesthetic may involve:

premed	sedative & analgesic
induction	injection anaesthetic
maintenance	inhalation anaesthetic & oxygen ± muscle relaxant
recovery	analgesic ± antibiotics to cover dirty surgery!

ie. lots of drugs which interact!

General anaesthesia was first induced (in man) 150 years ago using ether, although nitrous oxide as an analgesic had been around for a while before. With ether in man, the patient goes through a (reasonably) predictable series of stages:

1) analgesia
2) excitement
3) surgical anaesthesia
    plane 1)
    plane 2)
    plane 3)
    plane 4)
4) medullary paralysis
5) death

Stages 4 and 5 are to be avoided!

These are really only applicable to ether anaesthesia in man, although inducing anaesthesia with an inhalation agent such as ether or halothane is rarely done because of the excitement phase. Using combinations of drugs, as is routine these days, will tend to alter progress through these stages. When monitoring the effects of anaesthetics, you need to consider **all** the drugs an animal has had.

Mechanism of action

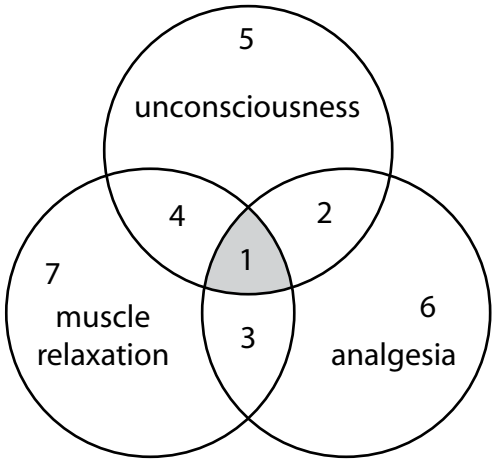
A unitary theory of general anaesthesia has been sought for many years without success. The current consensus is that inhalation anaesthetics bind to the lipophilic residues of various ligand gated receptor proteins, particularly $GABA_A$. They potentiate the effects of GABA with the end result that neuronal activity is decreased, in the same way as with most injection anaesthetics. However, inhalation anaesthetics also have lots of other effects which may be clinically important. An inhibitory effect at neuronal nAChR may be important. Nitrous oxide and xenon preferentially target the NMDA receptor (cf ketamine).

Most injectable drugs bind to $GABA_A$ receptors to facilitate channel opening, and thus hyperpolarise neurones (see neurotransmitter notes). This produces generalised inhibition of neurones, but may also produce excitory effects through disinhibition. Many anaesthetics also have other effects of unknown importance (effects on other receptors and non specific effects). Ketamine is an NMDA receptor channel blocker and is thought to produce its effects by this mechanism.

An endogenous ligand, **oleamide**, has recently been discovered for the general anaesthetic binding site on the GABA receptor. This may mean that specific agonists and antagonists will be available some time in the future.

Overview

1 decide what the animal's requirements are: consider shock, pain, etc.
2 decide what the surgeon's requirements are: muscle relaxation, fast recovery, etc.
3 decide on the best drugs
4 consider availability, cost etc.



Balanced anaesthesia.
1 - surgical anaesthesia
2 - may be useful for some things such as lancing abscesses
3 - difficult to acheive ethically
4 - produced by some drugs, can be useful for x rays
5 - natural sleep
6 - you need to know how to produce this
7 - complete paralysis stops breathing

Injection anaesthesia

Anaesthesia is usually induced by injecting a rapidly acting drug intravenously. The advantages of this are that it is easy, a precise dose can be given, there is a rapid onset of anaesthesia (no excitement stage) and only a syringe and needle are required. The disadvantage is that there is no control over waking - if you give too much you are in trouble.

The ideal iv anaesthetic would be reliable, quick acting, produce no excitment on induction, have no side effects, be rapidly metabolised, produce good muscle relaxation, be analgesic, non-irritant and water soluble but it is non existant!

Pharmacokinetics

The minimum dose is given rapidly iv as a bolus for induction, and then the animal usually wakes up as drug is redistributed away from the brain. However, subanaesthetic plasma levels will still be sedative and potentiate other anaesthetic drugs. Most anaesthetics are very lipid soluble (so that they enter the brain quickly) but this means that they redistribute to fat which then forms a depot and releases the drug back into the circulation.

Selecting the correct dose is most important: the dose required for induction depends on

- •rate of administration
- •route (nearly always iv)
- •concentration
- •stimulation
- •redistribution
- •protein binding
- •ionisation
- •(metabolism)
- •(acute tolerance)

The dose required is reduced by: premedication - especially α_2 agonists, hypovolaemia, old age, debilitation, low plasma proteins, protein bound drugs - eg NSAIDs, anaemia, individual variation.

Drugs

Barbiturates, and particularly **thiopentone** (thiopental USAN: all the barbiturates end in al in American), have always been the drugs most commonly used, although they have recently been overtaken by **propofol** in human anaesthesia.

Thiopentone comes as powder mixed with $NaCO_3$. It is unstable when made up as aqueous solution but keeps for three days in a fridge. It is used as 2.5% solution (pH 11) in most dogs, 1.25% in small dogs / cats, 10% in large animals. Use as dilute a solution as possible.

It produces rapid anaesthesia in one circulation time. It is not analgesic, there is some evidence that it is hyperalgesic. It is a potent respiratory depressant. There is usually transient apnoea after an induction dose - ventilate the animal. It produces transient depression (usually only 2- 3 minutes) of cardiac output and blood pressure. It is only used for induction of anaesthesia (cumulation occurs if used for maintenance (half life about 4.5 hours in dogs) - very slow recovery).

Problems with thiopentone are largely caused by overdosage (see pharmacokinetics above). Muscle relaxation is not always good enough for intubation unless a premed has been given (in people they often use suxamethonium to aid intubation). There are breed variations; greyhounds and similar dogs have a slow recovery. Extravascular injection will cause skin necrosis (high pH, especially more concentrated solutions) - inject lignocaine ± saline around area. Intra-arterial injection will cause pain, necrosis and possibly convulsions, probably because the thiopentone crystallises out and causes arterial spasm.

Thiamylal was used in the USA instead of thiopentone but is no longer available, it was clinically indistuingishable from thio.

Propofol is not a barbiturate but is clinically very similar to thiopentone. It usually comes as a white emulsion (although an aqueous solution is now available as well) in

single use vials under nitrogen which is non irritant (but can cause mild pain in some people, thought to be mediated by P2X and possibly PGE receptors). Its major advantage over thiopentone is that it is metabolised quickly in most species (except some cats) (half life about 40 mins in dogs). Its disadvantages are mild excitatory effects (usually front leg paddling in about 10% of dogs, although opisthotonus can occur) and occasionally rough recovery. It can cause hallucinations in people which often takes the form of sexual disinhibition in women! The usual vehicle contains egg yolk and coconut oil and is an ideal growing medium for bacteria - open ampoules must be thrown away. There have been some suspected deaths from septicaemia in dogs after using old propofol. Wound infections are three times more likely after propofol anaesthesia - possibly because people are tempted to use old propofol.

A newer formulation in detergent is available for veterinary use, but there have also been problems with the vehicle.

New derivatives of propofol which are water soluble and more potent are being developed.

"**Saffan**" ("Althesin") is a mixture of the steroids **alphaxalone** and **alphadolone**. The alphaxalone is thought to produce most of the anaesthesia, with the alphadolone was originally included to help dissolve the alphaxalone. However, recent work indicates that the alphadolone may have significant analgesic effect. It is a good anaesthetic and is rapidly metabolised, even in cats. However, the vehicle (polyethoxylated castor oil - "Cremaphore EL") causes massive histamine release in dogs so it is not used in dogs (although a technique of premeding with massive doses of antihistamines has been described - not recommended). Cats sometimes get oedema of the paws and ears after Saffan; the incidence of this can be reduced by injecting the drug more slowly (use a 25 SWG needle). It is only commonly used in cats although it is a good anaesthetic in most species except the dog. Because of its rapid metabolism it can be used for long term anaesthesia / sedation such as intensive care situations. Recoveries can be excitable if the cat is disturbed. Althesin used to be a popular human anaesthesic but was withdrawn a few years ago after similar problems with the vehicle. Saffan has now been replaced by a preparation of alphaxalone dissolved in cyclodextrin and water ("Alfaxan"). This is also suitable for dogs (in fact, any animal with veins) and is widely used overseas, especially Australia. It is slightly more expensive than the other induction drugs in NZ so is less popular here. Spending 10c extra is often worth it for the fast recovery, though.

Other steroid anaesthetics are under development (although all the candidates so far also cause excitatory effects on recovery). They will be water soluble to avoid the problems with the vehicle.

Ketamine is rather different from the other induction agents. It is a dissociative anaesthetic, which means (in people anyway) that the patient is conscious but not aware of what is being done to them. This may be because it is a good analgesic and completely blocks the memory! It produces no cardiovascular depression at normal doses. It acts rapidly by any route (although it is painful by im or sc injection - pH4). Its main disadvantage is that is produces no muscle relaxation and can actually cause convulsions in dogs and horses. It is used alone in cats and monkeys and combined with other drugs in other species (see below). It is also abused by some drug addicts, and although it is not (yet) a controlled drug in NZ, it should be locked up.

Tiletamine is a similar drug which comes premixed with zolazepam (benzodiazepine sedative) as Zoletil in NZ or Telazol in the USA.

Obsolescent drugs

Methohexitone is barbiturate which is similar but shorter acting than thiopentone. It usually produces excitation on induction and recovery - heavy premed required. It produces much more respiratory depression than thiopentone. Its only real indication was for induction in greyhounds but it has been overtaken by propofol. It is now difficult to obtain.

Pentobarbitone is rarely used for anaesthesia any more. It gives a slower induction and is longer acting than thiopentone. Its main use is for euthanasia, although it can be used for anaesthesia in sheep - faster metabolism than most species. It is sometimes used for long term sedation in dogs (eg, metaldehyde poisoning). Do not use euthanasia mixtures for anaesthesia - they are not sterile.

Metomidate and the human analogue **etomidate** are not available in NZ and are mainly of historical interest, although etomidate is currently undergoing a revival in veterinary anaesthesia in the USA. They produce anaesthesia but no analgesia and are traditionally used in pigs. Etomidate may be of advantage in sick dogs since cardiovascular depression is minimal. Analgesic premed is required for a smooth induction, and sedative premed to stop twitching. Etomidate has been abandoned by human anaesthesia because it causes profound adrenocortical depression.

Obsolete drugs

Laboratory animals are sometimes given these drugs in an attempt to produce long acting anaesthesia with minimal cardiovascular depression. In nearly every case, modern drugs properly administered would be better for the animals and give more reliable results for the experimenter.

α *chloralose* produces 8 -10 hours of stable light anaesthesia in rodents, but no analgesia. It may have a place in some situations.

Urethane is similar, but has more analgesia. It is carcinogenic. Do not use.

Chloral hydrate in overdose will produce a state bordering on general anaesthesia, but with no analgesia. Do not use.

Tribromoethanol has nothing to recommend it. It must be given ip and is very irritant. It quickly decomposes to even more irritant metabolites. It should never be used.

Combinations

neuroleptanalgesics
sedative & hypnotic
α_2 agonist & ketamine
benzodiazepine (midazolam) & ketamine
zolazepam & tiletamine

The sedative overcomes the increased muscle tone produced by the ketamine.

Infusion anaesthesia

With rapidly metabolised drugs like propofol and Saffan, it is possible to maintain anaesthesia by continuously infusing the drug (often with a short acting opioid like alfentanil to supplement analgesia). This has become popular in human anaesthesia but requires an infusion pump which is too expensive for most veterinary practices at present. A much less accurate way (in small animals anyway) is to mix all the ingredients in a drip bag and drip it in. This is sometimes used in horses with a mixture of xylazine, ketamine and guaiphenesin ("**triple drip**"). Human anaesthetists who like playing with lots of kit have tried controlling infusion pumps by computer feed back systems for hands off anaesthesia with reasonable success. The way of the (distant) future?

Euthanasia

Small animals are usually killed by giving an overdose of pentobarbitone iv. Note that these solutions are not sterile as dead animals do not worry about septicaemia. The volume involved in killing large animals this way will not fit easily into a syringe, so other drugs are sometimes added. Various toxic local anaesthetics such as cinchocaine have been used in an attempt to stop the heart; potassium chloride is sometimes used.

Premixed toxic cocktails (T61) have been used which include a muscle relaxant. These should always be given iv as there have been some cases of the muscle relaxant being absorbed before the sedative part of the mix - not a pleasant way to go.

commonly used drugs

thiopentone
propofol
ketamine
alphaxalone

Injection anaesthetics

- usually only given iv to induce general anaesthesia, but can be infused for maintenance
- many factors influence dose required, especially premedication
- overdose usually causes transient apnoea - intubate & ventilate
- all drugs are potentially lethal if used incorrectly
- pentobarbitone is usually used for euthanasia

Inhalation anaesthesia

After anaesthesia has been induced with an injectable drug it is often maintained with an inhalation drug. This also allows the animal to be given supplementary oxygen (30% minimum). Anaesthesia can also be induced with inhalation agents but is usually slow and unpleasant for the animal since these drugs usually produce an excitement phase before surgical anaesthesia. Some of the newer drugs may change this but it is still difficult to get animals to cooperate when you say "take a deep breath...". One exception is young foals and calves, where it may be possible to place a nasopharyngeal tube and induce anaesthesia with gas.

Advantages of inhalation anaesthesia are control of airway, ventilation and uptake and elimination of drug. The disadvantages are that expensive equipment is needed and possible equipment failure is dangerous for the animal (especially the obsolete and unmaintained equipment which seems to end up in veterinary practices).

Pharmacokinetics

Different from most drugs in that the inhalation agents are taken up through the lungs and excreted (mostly) unchanged by the same route. (Some of the older agents may undergo significant metabolism.)

A digression on Dalton

Conventions on dosage of inhalation anaesthetics are slightly confusing. The amount of drug the animal is given is usually expressed as a percentage of inspired gas (sometimes the fraction - $F_{I\,drug}$). Once in the animal it is sometimes expressed as a partial pressure or tension (particularly for gases). This can lead to confusion as there are at least six different units of pressure used in anaesthesia. Remember that at sea level the ambient pressure is approximately 101kPa (the SI unit), 1 atmosphere, 1 bar, 760 mmHg, 15 psi or 1000 cm water! Therefore 4% halothane = 0.04 $F_{I\,hal}$ = 4 kPa

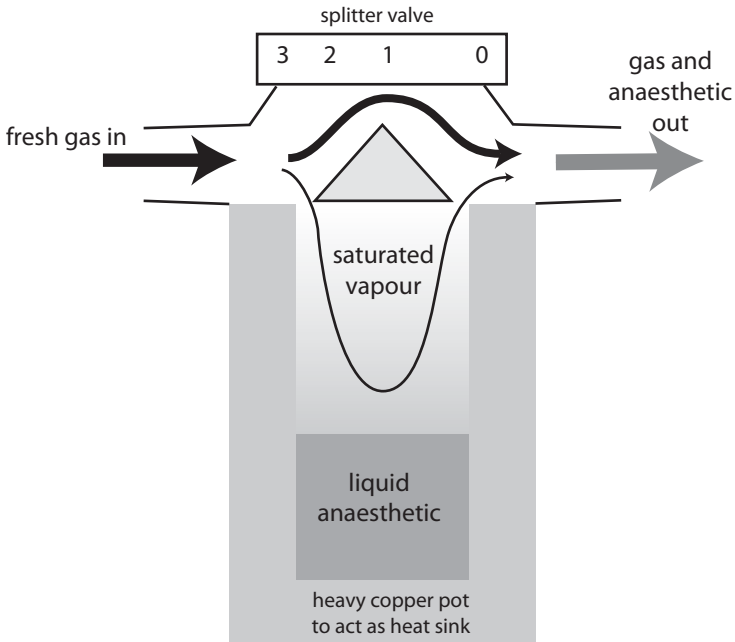
Administration

When inhalation anaesthetics were first used, they were administered by pouring some onto a wad of cotton wool and holding this over the animal's nose. Since the effects of these drugs are critically dose dependant, and overdose results in death, precision vaporisers and complicated anaesthetic circuits were invented to try to control the dose the animal receives. **To deliver the correct dose of drug to the animal you must understand how this equipment works (and how to repair it when it doesn't)!**

Modern precision vaporisers are very accurate but very expensive. In human anaesthesia, there is a trend back towards using simple vaporisers (or even just squirting a bit of inhalation agent in the circuit with a glass syringe) and using sophisticated monitoring equipment to check how much drug the patient is getting. This sort of monitoring equipment is also expensive and is not widely used in veterinary practice (yet - but wait until the first big court case).

Uptake and elimination

If animal is healthy, alveolar concentration is proportional to brain concentration, but lung disease will slow the



A precision vaporiser. Since the saturated vapour pressure of each drug is different, a different calibrated vaporiser must be used for each drug. Deflurane vaporisers are different.

uptake of drug. A number of factors influence uptake and elimination:

physical factors (properties of the drug)

• *saturated vapour pressure* - mainly a factor in vaporiser design unless you use a vaporiser with an anaesthetic for which it was not designed (or a non-precision vaporiser). As vaporisers are very expensive, this is sometimes done but is not recommended as there are big differences between drugs. It is useful to express SVP in kPa - this approximates to the maximal concentration (%) you can get out of the vaporiser.

• *rubber solubility* - mainly a problem with older agents The drug has to pass through lots of rubber / plastic tubing before it gets into the animal.

• *blood brain coefficient* - not clinically significant with current drugs, they all get into the brain very easily.

• *blood gas coefficient* (solubility) This determines speed of induction and recovery. A relatively insoluble anaesthetic will quickly reach equilibrium between inspired and alveolar concentration, a relatively soluble anaesthetic will take a long time. A soluble anaesthetic effectively has a larger volume of distribution, so more drug has to be absorbed to fill this volume and this takes longer. Therefore a relatively insoluble agent will give a fast induction and recovery; eg, desflurane (BG coeff 0.4; ie insoluble) will give a faster induction and recovery than ether (BG coeff 12; ie soluble). NB., if a drug is completely insoluble it will not get to the brain and will not be an anaesthetic. Soluble drugs tend to be more potent - anaesthesia can be produced at lower concentrations. If this did not happen, they would not be useful clinically as it can take a very long time for them to reach high concentrations.

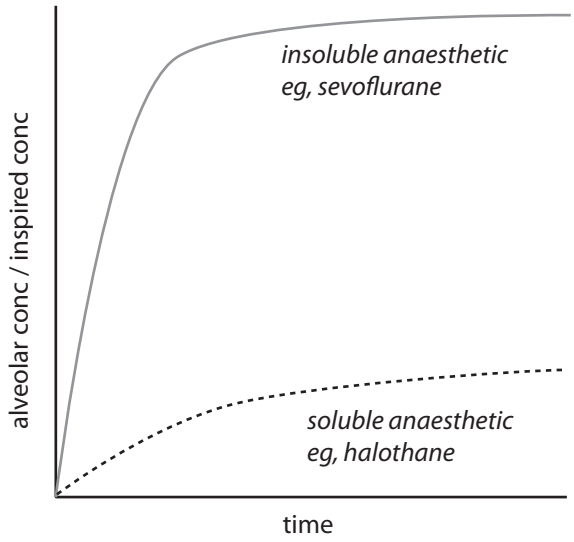
other factors (properties of the animal)

• *ventilation* - in the most extreme case, if an animal is not breathing, it will not take up any drug. It is common to stop an animal breathing with the induction drug. Beware, during intermittent positive pressure ventilation large quantities of drug can be forced into the animal.

• *cardiac output* - again in the most extreme case, if cardiac output is zero, the blood containing the drug will not leave the lungs and systemic uptake will be zero. A low cardiac output will slow the passage from the lungs to the brain.

• *second gas effect* - probably only important with nitrous oxide, and possibly desflurane. If a large proportion of the volume of the gas in the alveolus moves across into the blood, more fresh gas will move into the alveolus to take its place, bringing more halothane (or whatever) with it. This is a way of getting more halothane into the animal faster, ie, faster induction. This will only happen for the first few minutes - it only takes about 10 minutes for nitrous oxide to equilibrate. The opposite occurs on recovery (Fink effect or diffusion hypoxia) where the nitrous oxide diffuses from the blood into the alveolus displacing alveolar gas (including oxygen); this can give rise to hypoxia. 100% oxygen is usually given for several minutes on recovery from an anaesthetic which has used nitrous oxide.

• *lung disease* - thickening of the blood gas barrier in the lungs will slow diffusion. This will mean a slower uptake and elimination of anaesthetic.



Uptake of inhlation anaesthetic agents. Note that the Y axis is a ratio rather than an absolute concentration.

Minimum alveolar concentration (MAC)

This is an important concept. It is the concentration in the alveolus at a steady state which will prevent purposeful movement in response to a supramaximal stimulus in 50% of individuals (ie, it is a type of ED_{50}). It is lowered by sedatives, induction agents, analgesics, nitrous oxide. Usually about 1.3 MAC is required for maintenance but the actual amount required will depend on animal's state of excitment / pain. The MAC is used to compare the potency of inhalation anaesthetics. It also gives you some idea of what to set the vaporiser to at the start of an anaesthetic - **but you will have to change the setting according to how the animal responds!**

Drugs

Nitrous oxide (N_2O, laughing gas) has been around since the 18th century. It was used as a recreational drug until its analgesic properties were discovered. It is a weak anaesthetic although a good analgesic so it must be used with other agents. It produces a rapid induction - it equilibrates in about 10 mins. A number of problems are associated with nitrous oxide:

• diffusion hypoxia - Fink effect - the opposite of the second gas effect

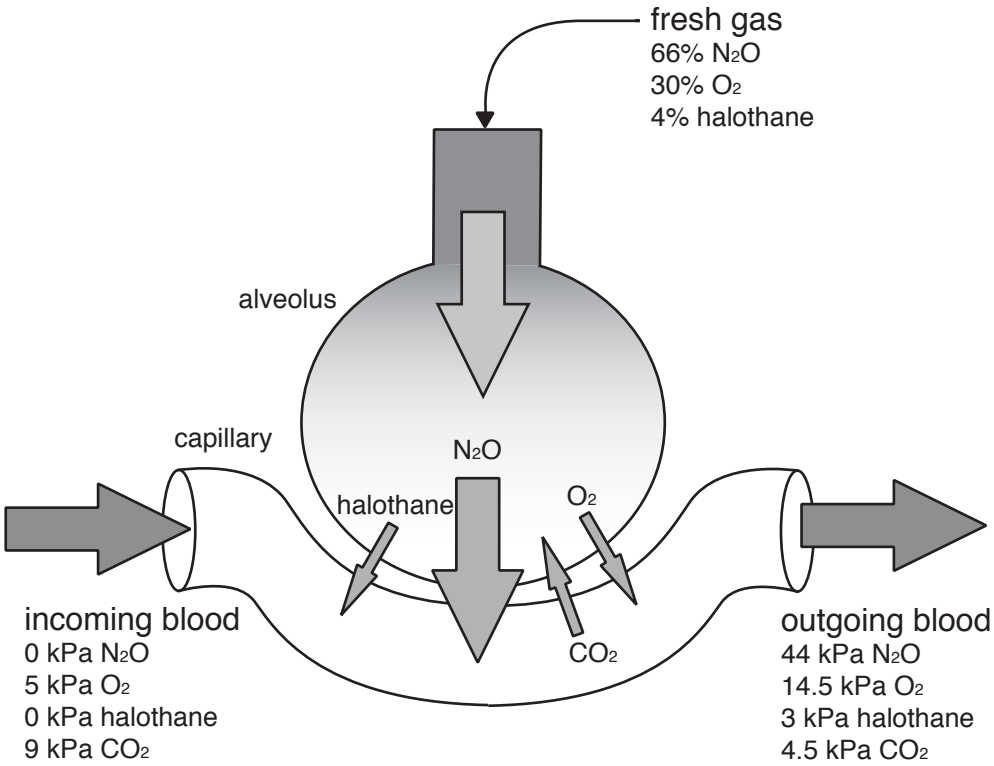
• diffuses into air filled spaces - **beware pneumothorax and colic**

• can build up in circle systems - oxygen analyser must be used or run the system semi closed.

• depresses folate metabolism (long term use > 8 hours)

Since it is a gas, it comes in cylinders and requires pressure regulators, flow regulators etc (more equipment to break down!). However, it is well worth the bother. The main reason to use it is that its analgesic properties mean that much less halothane can be used. This either means smoother anaesthesia or faster recoveries, depending on how it is used.

Halothane is the most important inhalation anaesthetic



Second gas effect - confusing but not clinically important except when using nitrous oxide.

in veterinary anaesthesia by a long way. It is a good general purpose anaesthetic but not a very good analgesic (use with nitrous oxide or injectable analgesic). It is also a poor muscle relaxant. It is best used as the hypnotic part of a balanced anaesthesia technique. Its side effects include:

- •respiratory depression (dose dependent)
- •reduced cardiac output
- •vasodilatation
- •sensitises heart to adrenaline
- •(halothane hepatitis)
- •(malignant hyperthermia in pigs)

When used alone, to provide surgical anaesthesia (ie, high doses), cardiorespiratory depression can be severe. If not enough halothane is used, the combination of halothane and adrenaline can cause tachyarrhythmias, especially in cats.

Halothane hepatitis is a cause of (unnecessary?) worry in human anaesthesia - halothane has been largely replaced by isoflurane (particularly in the USA) and may be withdrawn in the future. Hepatitis after halothane is not a problem in domestic animals but concern about operating theatre staff may cause controls on atmospheric pollution (see scavenging below).

Malignant hyperthermia occurs in some breeds of pig (and people), particularly Pietrain and some families of Landrace pigs. If the pig starts to go hot and rigid, turn off the halothane immediately and ventilate with 100% oxygen. It may also need to be hosed down with cold water. The problem is caused by a mutation of the ryanodine receptor, which controls calcium flux out of the sarcoplasmic reticulum. The definitive treatment is **dantrolene** (ryanodine receptor antagonist), but it is rarely available. Malignant hyperthermia can also occur in other species but is rare. Halothane is sometimes deliberately used in pigs to detect if they are carrying the MH genes (MH is also induced by stress and lowers the value of the meat). About 30% of commercial pigs in NZ have the MH gene. Pigs have been extensively studied as a model for MH in people; but little is known about it in other species.

Isoflurane is similar to halothane but gives a faster induction and recovery. Many dogs object to the smell. It is expensive, but can be useful in sick animals or where a very fast induction and recovery are required. If halothane is taken off the market, isoflurane is the obvious sucessor. It may also cause MH. It produces slightly more analgesia than halothane, and slightly less cardiovascular depression.

Enflurane is a chemical isomer of isoflurane but often produces excitatory effects which make judgement of depth of anaesthesia difficult. It has no obvious advantages and is not often used.

Xenon is occasionally used in people. It blocks NMDA receptors with no effect on GABA receptors and is a very good anaesthetic, but is **very** expensive. Its MAC in dogs combined with the cost mean that it is very unlikely to be used in veterinary anaesthesia.

Old drugs

Older agents include **trichoroethylene** which is almost obselete but worth using in some circumstances. It is a very good analgesic but a poor muscle relaxant and is best used in combination with another agent such as halothane - low dose halothane keeps the animal asleep and trichloroethylene provides the analgesia. It gives a very slow induction and recovery but good analgesia during recovery. **Do not use in a closed system with soda lime** - it reacts to produce phosgene. (Anaesthetic or HPLC grade trichloroethylene should be used for anaesthesia; it is also one of the commonest industrial solvents but solvent grade is full of toxic impurities.)

Diethyl **ether** (= ether) is almost obselete and should be avoided in most circumstances. It is a good anaesthetic but **very inflammable** in air, and **explosive** in oxygen. Its vapour is heavier than air and will roll along the floor and under doors. It gives a slow induction and recovery. The only reason it is still around is that it is the only agent which can be used without supplementary oxygen as it stimulates respiration (but if oxygen is available use it). It is irritant to the airways (peroxide degradation products) - anticholinergic premed required.

Methoxyflurane is not available in NZ and is almost obselete. It gives a very slow induction and recovery, but is a very good analgesic and a good muscle relaxant so is useful for long orthopaedic ops. It is extensively metabolised releasing free fluoride ions which may cause kidney damage (particularly in combination with NSAIDs). Dogs seem to be more resistant to fluoride ions than other species.

Chloroform used to be used in horses because it was cheap. It causes massive liver necrosis in hypoxia and is very good at sensitising the heart to adrenaline. Do not use.

New drugs

The newer agents **desflurane** and **sevoflurane** are not yet fully evaluated in animals (but give a very fast induction and recovery in man). Desflurane is very good in theory but requires special (very expensive) vaporisers, although a solution in propylene glycol may get around this problem. Sevoflurane has been used in more situations in animals and would be my drug of choice if cost was no problem. Some paediatric anaesthetists use them for induction (takes 10 - 60 seconds) and then switch to halothane or isoflurane for maintenance. They may have their use depending on price. Sevoflurane is catching on in human anaesthesia and getting cheaper all the time. These drugs make masking an animal down a practical way of inducing anaesthesia.

commonly used drugs

halothane
isoflurane

Inhalation anaesthetics

- used to maintain anaesthesia after induction with an injectable drug
- relatively insoluble drugs (low blood: gas coefficient) produce a relatively fast recovery
- halothane produces dose dependent respiratory and cardiovascular depression but not much analgesia
- eliminated by respiration - in overdose ventilate with 100% oxygen

NB The clinical effects of all anaesthetic drugs depend on the skill of the anaesthetist!

drug	induct %	maint %	MAC %	mL vap /mL liq	svp (kPa)	blood: gas	$ /100mL liquid	problems
halothane	2 - 5	0.5 - 2	0.9 1.1 (cat)	228	33	2.4	$30	malignant hyperthermia
isoflurane	2 - 3	0.5 - 2.5	1.4 - 1.9	189	32	1.4	$120	
sevoflurane	5 - 7	1 - 3	2.5 - 3.4	143	21	0.65	$240	
enflurane	4 - 5	0.5 - 3	2.2	196	23	1.9	($60)	excitation
methoxyflurane	not easy!!	0.2 - 0.5	0.15	210	3	11	($222)	strong smell
desflurane	4 - 11	2 - 9	7.2 - 10.3	206	89	0.4	$60	heated vaporiser
ether	up to 20	3 - 10	3	232	59	12	$12.50	inflammable / explosive
chloroform	1.5 - 2	0.5 - 1.5	0.8	302	21	8	$9	liver toxicity
trichloro ethylene	max	0.2 - 1.5	0.6	267	8	9	$39.50	+ soda lime = **phosgene**
nitrous oxide	not possible	66	105 (man) 220 (dog 255 (cat)	656	5100	0.47	0.7c (vapour)	diffusion hypoxia
xenon	70	70	60 - 71 (man) 120 (dog & pig)	-	-	0.11	$3 (gas)	cost

(Not all these drugs are easily available in NZ at the moment. Use prices for comparison only!)

Fish anaesthesia

When fish have to be anaesthetised, they are given drugs in their water which are absorbed across the gills and could thus be classified as "inhalation anaesthetics".

Drugs

Tricaine methanesulphonate (tricaine mesylate, MS222) is commonly used and probably best. It comes as a powder which needs to be dissolved in aerated fresh water (not tap water) or sea water as appropriate. **Phenoxyethanol** is an oily liquid which can be useful but may be carcinogenic. It dissolves some plastics. **Benzocaine** (dissolved in ethanol or acetone stock solution) has been used, deep anaesthesia not reliable. A mixture of clove oil and detergent (**Aqui S**) has been developed in NZ to allow handling of salmon. It is sedative rather than anaesthetic and may cause stress (fish generally do not like detergent - it damages their gills). **Ether** can be used at a pinch.

Scavenging waste gases

There has been concern about the effects of occupational exposure to small amounts of anaesthetic drugs in the atmosphere. In NZ, OSH have recently tightened guidelines on the maximum amounts permissible in room air; in Britain and the USA, there are similar guidelines but with different numbers. There is no good evidence that exposure to trace amounts of these drugs harms human health (with the possible exception of nitrous oxide causing abortion in women) but they smell nasty and are better removed. OSH have recently caught on to the fact that vets do not worry about this - so be warned!

A number of things can be done to reduce pollution:

- fill vaporisers in a well ventilated place (out of doors?) without spillage.
- fill vaporisers at the end of a day before you go home rather than in the morning before you start work
- turn vaporisers off when not in use
- use low fresh gas flow rates
- check equipment for leaks
- anaesthetic agents are good for removing stains from clothes but try to resist the temptation to do this!
- scavenge waste gases - but make sure the system does not impose any extra work for the animal
- in the last resort, open the window!

Exposure limits (ppm). In NZ, 3 x 15 minute exposures are allowed per day, as long as they are within the day's limit. NZ exposure limits are legally binding; they are only guidelines overseas.

	NZ 8 hour average	NZ 15 min	UK	USA
halothane	0.5	1.5	10	2
nitrous oxide	25	75	100	25

Anticonvulsants

Definitions

anticonvulsants = antiepileptics = drugs used to treat seizures

status epilepticus = continuous seizures - an emergency situation - give diazepam

Causes of seizures

idiopathic epilepsy (caused by K^+ channel disease???)

distemper

young dogs - active infection

old dogs - ecephalopathy

head injury

encephalitis

CNS tumours

pyrexia / heatstroke

poisoning - metaldehyde

etc, etc

Anticonvulsant drugs can control the signs but cannot treat the cause of the problem.

Epilepsy affects about 0.5% of dogs and cats (same as people). Seizures are classified in people - the situation is confused in dogs and cats but generalised tonic - clonic type (grand mal) type are commonest.

Treatment

Status epilepticus is an emergency - continuous rapid firing of neurones releases lots of glutamate which is neurotoxic in large quantities, particularly to inhibitory interneurones, making seizures worse. **Diazepam** must be given intravenously immediately. If there is no response general anaesthesia is used (thiopentone / pentobarbitone / phenobarbitone). Other drugs such as lorazepam and fosphenytoin are sometimes used in people. Remember **A**irway, **B**reathing and **C**irculation.

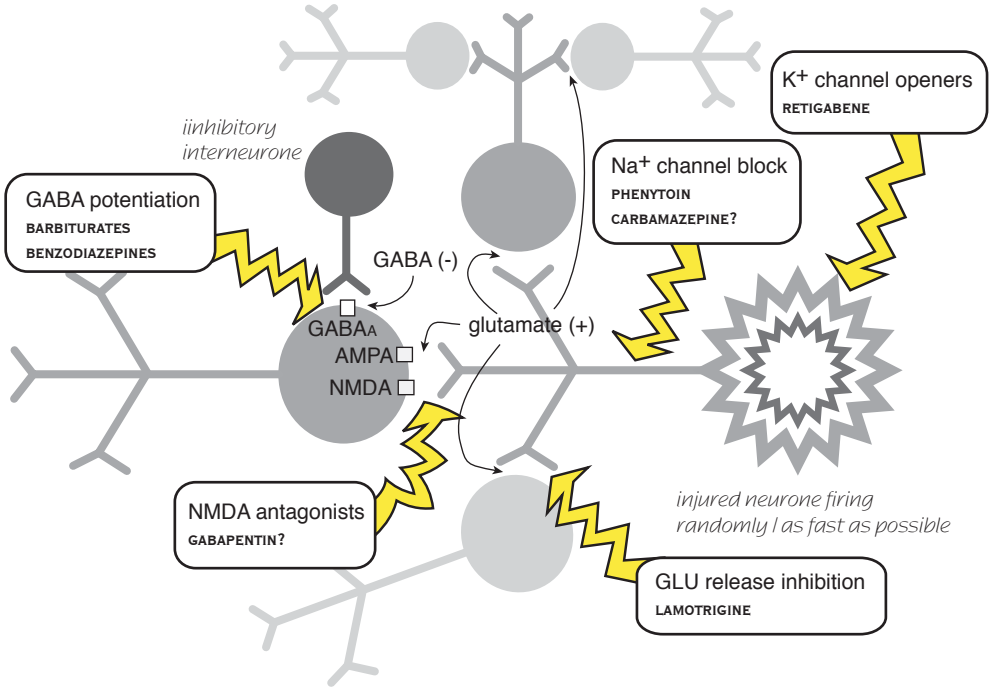
In an emergency, in dogs, cats and foals, give 5 - 10mg doses of diazepam iv to effect. This should stop the seizures for up to 20 minutes and give time for assessment. Diazepam is safe when given iv.

Prevention

Phenobarbitone (phenobarbital USAN) is the most commonly used drug although a variety of others have been tried. These drugs are given long term per os so chronic side effects are important. No drug gives complete control - 33% of dogs have no further fits, 33% improved, 33% not improved after phenobarbitone. Treatment should only be given if fits recur regularly (usually more than one a month).

Drugs

Phenobarbitone is the drug of choice for dogs and probably also cats. It is the cheapest and most effective. It usually



Anticonvulsant drugs' mechanisms of action. Most clinically useful drugs have more than one action.

produces sedation and ataxia for the first few days then tolerance develops to these effects. It takes 2 weeks to equilibrate. This is one of the most potent drugs for inducing P450 enzymes - metabolism of phenobarbitone **and other drugs** is greatly increased. Very rarely, it can cause liver damage.

Felbamate is a relatively new drug which looks promising in dogs but is still expensive. It has a relatively short half life of 5 - 6 hours. Not available here.

Primidone has been used in dogs for many years. It is metabolised to phenobarbitone which is probably responsible for at least 85% of primidone's effect. Cats don't metabolise it as well so it is less effective. Liver damage occurs after high doses - 70% of clinical cases? Use phenobarbitone instead.

Phenytoin and **carbamazepine** are effective in man but their half lives are too short in dogs. Phenytoin is teratogenic and can cause liver damage, although a newer analogue, **fosphenytoin**, may be better. Their main mechanism is sodium channel blockade - use dependent block stops high frequency firing. They induce liver enzymes in about a week - faster metabolism.

Sodium **valproate** has a very short half life in the dog but may work in cats - no enzyme induction. It stops GABA breakdown / reuptake.

The benzodiazepines (**diazepam**) are not much use in dogs as they become tolerant in a few hours - days but may be useful in cats. There are many other benzodiazepine type drugs used in man - most do not work reliably in dogs and cats or are so short acting that they are useless.

Bromide passes through GABA receptors more easily than chloride and hyperpolarises cells in the same way. It is cheap and is unlikely to kill the dog, but has little else to recommend it. It is effective in about the same proportion of cases as phenobarbitone (~ 70%) but sometimes works when phenobarbitone does not (and vice versa). It has not been used for 30 years in people because of unpleasant subjective side effects but is being revived as a treatment for dogs in the USA. It is ethically dubious to make an animal's remaining life a misery with drugs in order to avoid being sued for killing the animal. It should be avoided in cats as it is less effective than in dogs and makes approximately 50% of them cough, which can lead to irreversible lung damage and death.

Gabapentin and **lamotrigine** are newish drugs which work well in people, but are also metabolised too quickly in dogs to be of much use. Gabapentin is sometimes added to combinations for dogs.

Topiramate is sometimes used in people. It is supposed to be synergistic with phenobarbitone but there is no experience of its use in dogs.

Combinations

Combinations of older drugs are a last resort - in people these combinations are no better than an adequate dose of one drug. In veterinary practice, combinations of phenobarbitone and bromide (at low doses) are sometimes used. Combinations of phenobarbitone and more modern drugs may be useful, but there is very little information on this as yet. These are usually used as a last resort before euthanasia. Remember that most anticonvulsant drugs will potentiate anaesthetics, but enzyme induction will shorten their effect. This can provide nasty surprises.

Treatment failure

Seizures occurring while an animal is taking an anticonvulsant drug do not necessarily mean that the drug is not working. The original disease may be getting worse, the dose may be too low, the animal may have developed tolerance or the owner may have forgotten to give the drug. Monitoring plasma levels is a useful way of checking (see formulary for therapeutic plasma levels).

Remember that these drugs only suppress seizures; they do not treat the causative disease, which may be progressing.

Drugs which may trigger epilepsy

Avoid phenothiazines and butyrophenones - they lower seizure threshold and can cause extra pyramidal effects which can easily be confused with seizures. Several anaesthetic drugs can lower seizure thresholds, but this is not usually a problem under anaesthesia. Avoid fluoroquinolone antibiotics, especially in combination with NSAIDs in dogs prone to epilepsy.

The future??

Response to drugs in man is similar to dogs - ie a large proportion of cases are not improved. This has led to the development of lots of new drugs which have not yet been evaluated in domestic animals, particularly NMDA antagonists. The drugs of choice for dogs could change radically in a few years.

Electrical stimulation of the cervical vagus works in many people with epilepsy which is refractory to drugs. This has not been reported in dogs yet! Stimulation of various parts of the brain, either electrical or magnetic, appears to work in some people and some models of epilepsy, as does chopping out bits of the brain (usually parts of the hippocampus).

More interestingly from a pharmacological point of view, a ketogenic diet has been shown to be effective at preventing epilepsy in children. If the mechanism of this was understood, new drugs might follow.

In the longer term, gene therapy to replace defective potassium channels is a possibility in people.

Elimination half lives of some anticonvulsants (hours - except for bromide).

	dog	cat	man
phenobarbitone	42 - 100 (24 - 30)	34 - 43	70 - 100
primidone	2 - 7		6 - 12
phenytoin	2 - 4	24 - 108	15 - 24
carbamazepine	1		24 - 48
valproate	1.5 - 3	8.5	8 - 15
ethosuximide	17		16 - 70
diazepam	2 - 5	2	24 - 72
clonazepam	1 - 5		24 - 36
felbamate	12		23
bromide	25 - 46 days		11 days

Anticonvulsants

- diazepam is used in animals actually having fits
- phenobarbitone is used to prevent seizures
- bromide is added to phenobarbitone as a last resort
- both diazepam and phenobarbitone potentiate the effects of GABA
- both suppress fits without treating the cause

commonly used drugs

phenobarbitone
diazepam

Stimulants

CNS stimulants are occasionally given to animals, but there are practically no indications for them.

Doxapram is sometimes used as a respiratory stimulant, particularly in new born animals. However, its effects are not confined to the respiratory centre, and it will cause general CNS stimulation (and increased energy requirements). Most respiratory problems in new born animals are caused by airway obstruction: giving a drug which increases cerebral oxygen requirement will make the situation worse. The only indication for doxapram is to counteract the effects of a respiratory depressant drug where it is not possible to perform IPPV for some reason. However, if it is not possible to perform IPPV, you should not be giving respiratory depressant drugs!

Amphetamines are widely used drugs of abuse in people, and probably in racing animals, particularly greyhounds. There are no indications for them in animals, and it is unethical, and in most cases illegal, to give them to animals (or even possess them).

Methylphenidate (Ritalin), a cocaine analogue, is given to children in a similar way to behaviour modifying drugs are given to dogs and cats. Its only possible indication in animals is narcolepsy, which is very rare. Modafinil, a stimulant with an unkown mechanism of action is also used in people for narcolepsy. There is no experience of its use in domestic animals. It is sometimes abused in people as a "cognition enhancer".

Methylxantines have a mild stimulant effect, but are usually used for their other effects. If you need to use a CNS stimulant in an animal, use one of these.

Psychopharmacology

The use of drugs to treat behaviour problems in animals (psychopharmacology) is in its infancy. Much of the available data is anecdotal, based on individual clinical cases treated successfully (unsccessful cases are not written up). The drugs used are usually not registered for use in animals. There is a tendency to prescribe drugs used in the treatment of human psychiatric disorders for the treatment of animals but there have been very few trials in which the use of such drugs in cats and dogs was examined. Behavioural treatment should be used in combination with drugs.

Beware side effects: many of the drugs used to alter behaviour act on monoamines, an effective overdose of noradrenaline or 5HT can have severe cardiovascular effects (serotonin syndrome).

Problems in cats

Inappropriate marking

Anxiolytic drugs, antidepressants and progestins have been used. They reduce the anxiety and stress being experienced by the cat. This allows the cat time to become habituated or desensitized to the stressor and the owner time to modify the environment to reduce the stressor. Drugs assist in the treatment of inappropriate marking but may be ineffective if used without environmental modification.

Many drugs are used to reduce anxiety in humans. The definition of anxiety in domestic animals remains unclear but it is widely accepted that inappropriate marking in cats is often due to anxiety. The most commonly used anxiolytic in the cat is **diazepam** (Valium) 1 to 2 mg/cat (0.2 - 0.4mg/kg) twice daily for 4 weeks then once daily for 4 weeks thereafter decreased by half for each week in the third month.

Many cats revert to inappropriate marking when administration of diazapam is stopped. Diazepam improves the problem of inappropriate marking in 55 to 75% of cats treated and is as effective in males as females. Longer acting benzodiazepines, lorazepam, oxazepam or clonazepam may also be useful in the treatment of inappropriate marking (Stogdale, 1992).

Sedation may leave the cat more vulnerable to road traffic accidents and predatory dogs. Increased appetite and weight gain are common. Interestingly, increased affection is regularly seen. Fatal hepatic toxicity has been reported in cats within 11 days of receiving diazepam.

Buspirone is a $5HT_{1A}$ antagonist used as an anxiolytic in people. It may be effective in the treatment of inappropriate marking in cats (0.5 - 1mg/kg po 2 - 3 times daily). Buspirone has little sedative effect and appears to produce little tolerance in humans. It does not cause withdrawal symptoms. If the cat does not respond to treatment then use something else. Buspirone was effective in 55% of cats treated by Hart et al. (1993).

Tricyclic antidepressants are the most commonly used drugs in the treatment of depression in humans. They do not interfere with short term memory and thus are useful in behaviour therapy in animals. **Amitriptyline**, **clomipramine** and **fluoxetine** are commonly used. Treatment should continue for 2 to 3 weeks after the undesirable behaviour has stopped. The medication should then be gradually reduced over an eight week period. Amitriptylline stopped inappropriate marking in 80% of cats (Stogdale, 1992). Sleepiness was seen initially but it wore off during the first two weeks of treatment.

Progestins, such as **megoestrol** in tablet form and **medroxyprogesterone** in injectable form, have antiandrogenic and antianxiety effects. They are commonly used for sexually dimorphic problems which have not responded to neutering. They may work by selective binding to sites in the hypothalamus which reverse the action of testosterone sensitive action centres. They should not be used initially in the treatment of inappropriate marking because of their side effects.

In the treatment of inappropriate marking it is the antianxiety effect of progestins which is utilised. They are reported as being effective in about 30 to 50% of neutered cats however other reports conclude that they are effective in 48% neutered males and 18% spayed queens. If the treatment is successful then results should be seen within the first week after initiation (Halip et al, 1992). It has been suggested that if megoestrol acetate doesn't work then medroxyprogesterone may or vice versa.

Progestins should be used as a last resort since the risk of side effects is high.

Problems in dogs

Aggression

There are several different types of aggression and it is important to diagnose the cause of aggression before initiating treatment. In addition the social milieu in which aggression occurs must be considered before treatment is embarked upon. Behavioural therapy and castration are often effective in reducing or eliminating aggression but on occasion drugs are needed to supplement these forms of therapy. Painful conditions especially those of the ears, shoulders and hips are probably more important in the development of aggression than we usually recognise.

Male aggression, especially intermale aggression, may respond to castration. If castration is not possible or if aggression continues afterwards then progestins (**medroxyprogesterone**) may be effective .

Acepromazine tablets may be effective in the short term control of aggression (0.5 - 2.0 mg/kg every 8 to 36 hours).

The anti androgenic progestagen **delmadinone** (Tardak) may also be effective. It is thought to work by inhibiting pituitary gonadotrophin release and by affecting a behavioural (sex) centre. The effects are reversible. Dose dogs <10 kg - 1.5 - 2.0 mg/kg, 10 to 20kg - 1.0 - 1.5 mg/kg, >20kg - 1 mg/kg bodyweight by sc or im injection.

An effect should be seen within 5 days. If not seen within 8 days repeat treatment. Otherwise repeat treatment at 3 to 4 weeks. Thereafter repeat as required. Do not use in dogs with history of poor libido or poor fertility if such dogs are to be used later for stud purposes. Do not use if other steroids are being given.

The use of diazepam for the treatment of fear aggression in dogs is not recommended as it sometimes acts to cause aggression by, it is speculated, reducing fear.

Obsessive compulsive behaviour

The obsessive-compulsive behaviour in dogs which include tail chasing (Bull Terrier types), flank sucking (Doberman), fly biting (Cavalier King Charles Spaniels) and acral lick granuloma are similar to stereotypic behaviour seen in humans such as hair pulling and hand washing. The pathological background to these activities remain ill defined but it is believed that aberrant serotonin metabolism is involved although some attribute the activity to abnormal endorphin metabolism. It is suggested that the anatomical focus of the disorder is the limbic system and studies have implicated the basal ganglia in the region of the caudate nucleus in humans.

Obsessive compulsive behaviours are characterised by being repetitive behaviours in excess of requirements and often interfering with normal activities.

Differential diagnosis of obsessive compulsive behaviour in dogs include the following;

•boredom - responds to increased activity, environmental enrichment, increased human attention

•attention seeking behaviour - responds to increased attention and desensitization or counter conditioning

•hyperactivity usually responds to increased exercise levels. True hyperactivity is extremely rare and affected dogs only stop their activity when exhausted. These dogs respond to treatment with **methylphenidate** (Ritalin) 5 mg orally every 12 hours (up to 20 to 40 mg daily) or amphetamines (dextroamphetamine) 0.2 to 1.3 mg/kg orally as required (not recommended for ethical reasons). These drugs stimulate non-hyperactive dogs to become hyperactive and hyperactive dogs are calmed. Treatment is usually for life though it may be suspended for a week or two every 6 months to determine if hyperkinesis returns. NB. these are drugs of abuse in people.

•anxiety especially separation anxiety (see below)

•infectious or metabolic disease. Distemper may cause repetitive activities.

•neurological disease. Nerve conduction dysfunction has been implicated in cases of self mutilation. CNS neoplastic conditions may also cause repetitive activities. Epilepsy.

•self mutilation due to dermatological or other medical reasons.

•self mutilation due to aberrant endorphin metabolism may be treated by **naltrexone** (dog) 2.2mg/kg orally every 12 or 24 hours (cat) 25 - 50 mg/ cat every 12 to 24 hours. If naltrexone doesn't block the response then it is probably not due to aberrant endorphin metabolism.

Obsessive compulsive behaviour may be the appropriate diagnosis if the dog or cat does not respond to the therapies discussed above and if it interferes with normal behaviour.

Obsessive compulsive behaviour disorders have been treated with tricyclic antidepressants; **amitriptyline** (1-2 mg/kg twice daily for dogs); **clomipramine** (can cause arrhythmias and should be used only after the dog has had a thorough cardiac examination). Because it is potentially dangerous, treatment should start at about 0.5mg/kg every 12 hours increasing over a 5 week period to 3mg/kg or 200mg per day whichever is less. Should any side effects develop the treatment should be stopped or the dosage reduced. Usually treatment should last for 5 weeks to determine how succesful it is. If clomipramine is successful it will have to be continued for life. **Imipramine** and **fluoxetine** (0.5 - 1mg/kg once daily) have also been used, as has **doxepin** 3-5mg/kg orally every 12 hours increasing to a maximum of 150mg/kg every 12 hours. The minimum dose is given for 10 days and should be doubled if no effect seen.

Separation anxiety

A common problem in young dogs and may be expressed as persistent barking or destruction / digging when the owners are absent. This type of anxiety is usually treated by counter-conditioning and habituation. However counter

conditioning for the treatment of anxiety is usually more successful if combined with medication. Two drugs considered to be particularly useful in the treatment of seperation anxiety in dogs are; **clomipramine** (1 - 2mg/kg twice daily) and **amitriptyline** (1-2 mg/kg twice daily). Both are very useful for dogs which bark or groom excessively when alone. Usually given about 1 hour before everyone leaves the home. Treatment continued for up to 3 months and then tailed off gradually. Fluoxetine (1mg/kg once or twice daily) is also useful.

Phobias

Diazepam given before or during a storm may be useful in reducing the expression of the phobias. However diazepam does change some dogs behaviour for the bad and they may become aggressive and destructive. **Use with caution in nervous dogs!**

Recommended reading

Burghardt WF 1991. Using drugs to control behaviour problems in pets. *Veterinary Medicine*; 1066-1075.

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Stogdale L. 1992. Treatment of feline behavioral problems. *Canadian Veterinary Journal* 33;149.

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Poisons affecting the CNS

Excitation

Toxicants Associated with Seizures

-Strychnine and Brucine
-Carolina Jessamine (Gelsium)
-Tetanus
-Metaldehyde
-Fluoroacetate (1080)
-5-Fluorouracil
-Castrix (Crimidine)
-Acute Fluoride Toxicosis (Toxicant Affecting the Teeth and Skeletal System)
-Japanese Yew (Taxus) in dogs (also Toxicants Affecting the Heart)

Toxicants Associated with Stimulation or Seizures

-Organochlorine Insecticides
-Karaka - Corynocarpus laevigatus
-Diphenyl aliphatics and miscellaneous organochlorine insecticides
-Cyclodiene organochlorine insecticides
-4-Aminopyridine
-Chocolate, Caffeine and other Methylxanthines
-Nitrofurans
-Dutchman's Breeches (Dicentra)
-4-methyl Imidazole
-Water Deprivation/Sodium Ion Toxicosis (salt poisoning)
-Amphetamines
-Cocaine
-Tremorgenic Mycotoxins including penitrem, roquefortine/Nervous Ergotism/
- Paspalum staggers (Claviceps paspali) ergot
-Ryegrass staggers- Lolitrem B
-Dwarf mallow (Malva neglecta)
-Zinc Phosphide/Alumininum Phosphide
-Water Hemlock (Cicuta)
-Fitweed (Corydalis)
-Milkweed (Asclepias)
-Carolina Jessamine (Gelsemium)
-Calycanthus Shrub (Bubby Bush) (Calycanthus)
-Desert Spike (Oligomeris)
-Daffodil, Jonquil (Narcissus)

Chocolate Poisoning

(Methylxanthine-theobromine)

Sources

Baking chocolate, candy bars, chocolate chips etc

Toxicity

Dogs will readily eat a toxic dose (100-250 mg/kg)
Chocolates vary in theobromine content for example:
Baking chocolate 14 mg/gram
Chocolate chips 5 mg/gram
Hershey's dark chocolate 5 mg/gram
Hershey's milk chocolate 2 mg/gram
Cadbury's candies usually contain less theobromine than American chocolates
e.g. A 10 kg dog can be poisoned by 60 gm of dark or baking chocolate or 560 gm of milk chocolate.

Clinical Signs

Signs appear 2-4 hours post ingestion
Restlessness, panting, vomiting, urinary incontinence (diuretic effect), sometimes diarrhoea
Cardiac arrhythmias, premature ventricular contractions, muscular stiffness, hyperreflexia, ataxia, seizures and coma.
Death from 18-24 hours to several days due to cardiac arrhythmias or respiratory failure.

Treatment

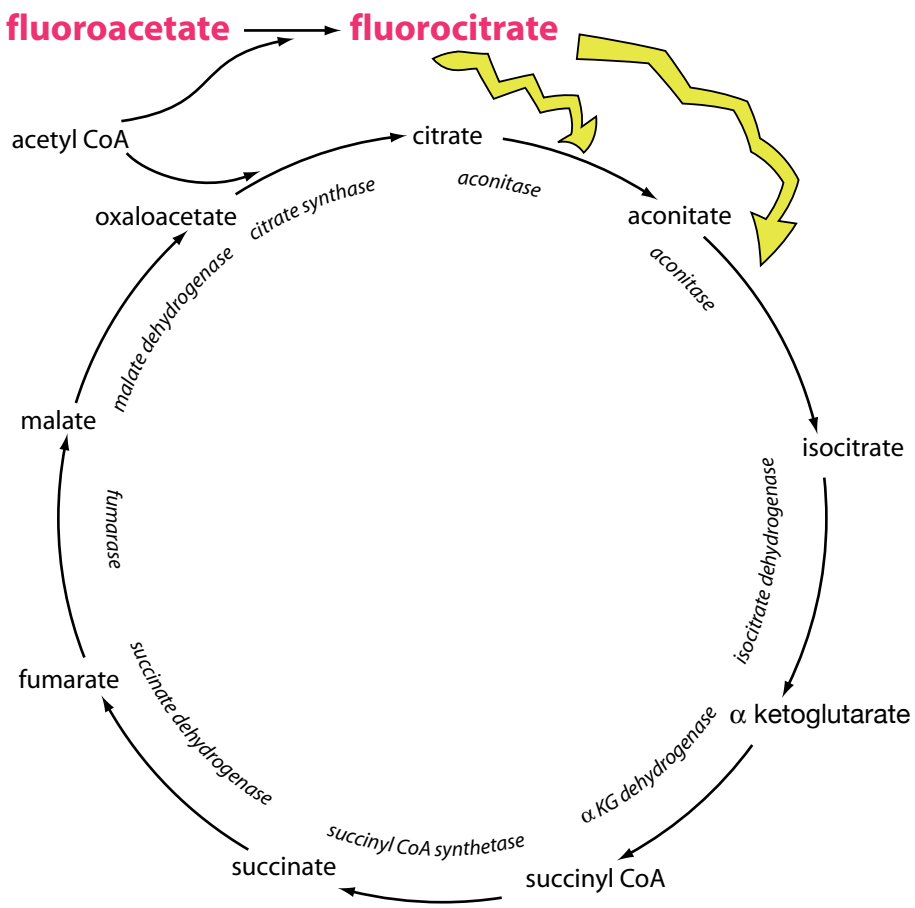
Decontaminate if recent exposure, prevent further absorption of the theobromine with activated charcoal.
Provide symptomatic treatment for the patient, which may include intravenous fluids, control seizures with diazepam. Cardiac function needs to be monitored and premature ventricular contractions in dogs should be treated with lignocaine. Persistent tachyarrhythmias may require beta blockers.

1080

Sodium monofluoroacetate, SMFA, Compound 1080

sources

Used to control rodents and other pests.
Secondary poisoning of cats and dogs occurs from the ingestion of dead or dying poisoned animals.
Fluoroacetamide (Compound 1081) was developed as a less toxic alternative to 1080
Fluoroacetate also occurs naturally in a variety of plants in



Mechanism of action of 1080.

Africa (*Dichapetalum cymosum* and *D. toxicarum*), Australia (*Acacia georginae*, *Gastrolobium* spp and *Oxylobium* spp) and South America (*Palicourea marcgravii*).

Compound 1080 is also an important toxic metabolite associated with the chemotherapeutic anticancer agent 5-fluorouracil and some fluorinated ethanes that may be toxic when inhaled.

Toxicity

Animals have different susceptibilities to 1080 (and 1081) poisoning. The reason for the wide variation in toxicity is not known. Birds are the most resistant to poisoning, then rodents, primates, horses, rabbits, ruminants and carnivores. Because tissue residues are minimal, the ingestion of muscle from a poisoned carcass is unlikely to cause toxicity in carnivores. Compound 1081 is as toxic as 1080 but with a slower onset of action, and animals may display fewer neurological signs. The toxic dose of 1080 for dogs or cats is as little as 0.05 mg/kg. The quantity of 1081 necessary to kill dogs, rabbits and sheep is 2-5 more than the 1080 dose.

Clinical Signs

Clinical signs may appear from thirty (30) minutes to as long as two (2) hours after ingestion depending on the dose. The variable latent period is a result of the delay in conversion of fluoroacetate or fluoroacetamide to fluorocitrate and its accumulation to toxic levels.

Dogs: display central nervous excitation and gastrointestinal hyperactivity.

Neurological signs in dogs include anxiety, frenzied behavior such as running and howling, and hyperesthesia.

Carnivores usually vomit, salivate, urinate and defecate after ingesting 1080.

A hypermotile gastrointestinal tract with tenesmus also occurs.

Hyperthermia has been reported in dogs.

Convulsions begin after a brief period of hyperexcitability.

Tonic and clonic convulsions may occur between periods of frenzied and normal behavior.

Dogs in the agitated state are not responsive to external stimuli.

Coma and death from 2-12 hours after the appearance of clinical signs.

Cats may have both cardiac dysfunction and neurological signs. The poisoned cat may become depressed or excited, vocalize and be hyperesthetic to light and touch. Hypothermia (37 C), cardiac arrhythmias and episodes of bradycardia between convulsions also have been reported in cats.

Ruminants (cattle and sheep):

Cattle show signs of heart failure, gastrointestinal irritation, stagger, sweat, tremble, or die suddenly. Sheep ingesting an oral dose of 1 mg/kg had decreased ruminal movements, restlessness, frequent urination, muscle tremors, polypnoea and an increased heart rate.

Clinical Pathology

hyperglycaemia and metabolic acidosis

twofold increase in serum glucose has been reported.

Dogs- citrate levels are elevated at least two or more times in serum and heart;

Hypocalcaemia - cats ionized calcium rather than total serum calcium decreased

Cardiograms of cats poisoned with 1080 show a prolongation of the QT interval corresponding to a decline in ionized calcium levels.

Confirmatory Tests

A diagnosis of 1080 poisoning is based on clinical signs, access to the poison and the analysis of the compound in bait or vomitus. Residues of 1080 are most likely to be found in vomitus or stomach contents, a minimum of 50 grams of vomitus being required for analysis. Animals that ingest a minimum lethal dose of 1080 are unlikely to have detectable levels in body tissues.

Treatment

Because of the rapid onset of clinical signs (2-3 hours) it is often difficult to treat animals after ingestion of 1080. Also it is believed that symptomatic and supportive care is unrewarding once clinical signs have appeared.

Recent successes in Australia and New Zealand suggest that treating animals with sodium bicarbonate or acetamide may improve survival.

The rationale of using sodium bicarbonate relates to the metabolic acidosis associated with 1080 poisoning and the effects of citrate accumulation on serum calcium.

Other treatments have been suggested which could remove or by-pass the biochemical lesion in the citric acid cycle. The current human therapy consists of giving acetamide by intravenous infusion.

The recommended treatment procedure is to:

1. Induce emesis if the animal is fully conscious. Emetic capsules containing 1g zinc sulphate are available from Pest Control Boards.

2. Gastric lavage and oral administration of activated charcoal will help remove residual poison in the stomach and adsorb 1080.

3. Lightly anesthetize the animal with pentobarbital sodium. (Gas inhalant anaesthetics are useful to maintain an appropriate plane of anaesthesia.)

4. Place an IV catheter and connect the animal to a saline (0.9% NaCl) drip.

5. Over the next 15-30 minutes infuse sodium bicarbonate (8.4%w/v) through the giving port at the dose rate of 300 mg/kg (equivalent to 3.6 ml/kg of 8.4% sodium bicarbonate). Alternatively, half the calculated dose is given as a bolus and the remainder infused slowly. The 8.4% sodium bicarbonate solution is approximately equivalent to 1 milliequivalent (mEq) per ml each of sodium and bicarbonate. Administration of sodium bicarbonate may worsen hypocalcemia and cause hypokalemia.

6. Monitor serum calcium and potassium levels and supplement as required. Alternatively use 0.5 to 1.5 ml/kg of 10% calcium gluconate (or 10% calcium chloride) by slow intravenous infusion or subcutaneous injection may be used to aid in the control of convulsions and for combating hypocalcaemia.

7. Maintain anaesthesia and fluids until the animal appears to be recovering (e.g. without convulsing), usually 12-18 hours. Animals are usually discharged within 48 hours after presentation.

Alternatively if acetamide is available the following treatment was reported to be highly effective in the treatment of dogs in conjunction with proper decontamination.

With the aid of a microwave oven, dissolve 15 grams of acetamide granules in 1 litre of a 5% glucose solution. Administer 10 ml/kg over 15 minutes and reduce to 8 ml/kg/hr until the litre is finished. A second litre is made and administered at 5 ml/kg/hr. Additional acetamide can be administered as needed. The heart rate may greatly increase with acetamide treatment.

Prognosis

The prognosis is poor to grave depending on the amount of 1080 ingested and the severity of clinical signs at presentation.

Gross And Histologic Lesions

Post mortem findings in carnivores exposed to 1080 are non-specific. Rigor mortis is rapid in onset. Hypoxia due to convulsions may cause general cyanosis, congestion of visceral organs, agonal petechial hemorrhages on the myocardium and pulmonary congestion. Other findings may include an empty stomach, enteritis and a flaccid, pale heart in diastole. Histopathological changes of the brain may include oedema and lymphocytic infiltration of perivascular tissue.

Differential Diagnoses

Differential diagnoses associated with convulsions or central nervous systems disorders include strychnine, chlorinated hydrocarbons, lead, hypomagnesemia, hypocalcemia,

1080 Poisoning

- clinical signs
  - vomiting
  - salivation
  - urination
  - defaecation
  - hyperaesthesia
  - dogs-hyperactivity (wild running and barking)
  - cats-vocalization
- metabolic acidosis-sodium bicarbonate treatment
- hypocalcaemia- (ionized calcium) calcium gluconate
- hyperglycaemia-dogs
- serum citrate accumulation
- seizures-barbiturates
- no antidote-supportive therapy
- acetamide therapy
- rapid onset of rigor mortis with extensor rigidity

garbage intoxication, brain injury, cardioglycosides, taxine (Japanese yew) and methylxanthines.

Metaldehyde

Sources

Slug & snail bait

"Shake and bake" more shake than bake though

Other uses less common – fuel for camping stoves

Toxicity

Recognised LD50 for dog is about 200 mg/kg

Mechanism of action

Partly known but not fully understood

MA readily crosses BBB

Decrease in inhibitory NT GABA,

Decrease in NA and 5-HT lowers threshold for convulsions

Increase in monoamine oxidase (MAO) activity (important for metabolism of NA and 5-HT)

Clinical Signs

Onset of clinic signs several minutes to about 3 hours.

Initially grimacing, restlessness, anxiousness

CNS- depression, muscle tremors, hyperaesthesia (abnormal increased sensitivity-skin), incoordination, ataxia (blindness (reversible) reported)

GIT-salivation, vomit, diarrhoea,

Tachycardia, cyanosis, acidosis-hyperpnoea

Opisthotonus and convulsions,

Cats-nystagmus, clonic-tonic convulsions otherwise similar to the dog (clonic=contract/relax; tonic=prolonged contraction)

Hyperthermia. 42-43 C common

Severe acid-base change = Metabolic acidosis

If survive may see liver failure!!!

Diagnosis

Confirm metaldehyde in stomach contents or in serum, urine or liver (check with lab) keep tissues frozen

Postmortem

Congestion, hyperaemia, haemorrhages-liver, kidney, lungs, GI mucosa, endocardium and lymph nodes

Pulmonary oedema

May see failure of blood to clot

Collect stomach contents for analysis (+ blood, serum, liver)

Treatment

First of all **decontaminate**-improves survival rate and shortens treatment time!!!

Diazepam (Valium) methocarbamol (Robaxin), barbiturates

Phenobarbitol may help increase metabolism-clinically significant?

Metaldehyde Poisoning

- Acute CNS AND GIT effects
- Hyperthermia
- Metabolic Acidosis and potential liver failure
- Treatment aims: Decontaminate, Control seizures and correct metabolic acidosis
- Awareness of role of neurotransmitters: GABA, NA and 5-HT depletion

Symptomatic care aware that liver failure and acidosis are features.

Ryegrass Staggers

Ryegrass staggers (RGS) is a nervous disease of sheep as well as cattle, horses and deer. The disease is common in Australia and New Zealand and is reported from several other countries. RGS (sometimes called perennial ryegrass staggers) should not be confused with grass staggers (hypomagnesaemia) or annual ryegrass toxicity, a serious and usually fatal disease of sheep in Australia. Ryegrass staggers occurs in sheep grazing pastures dominant in perennial ryegrass (Lolium perenne). Outbreaks occur mainly in summer and autumn under close grazing conditions.

Aetiology

Lolium endophyte (Neotyphodium lolii) is responsible for the production, in perennial ryegrass, of the neurotoxins responsible for this disease, the most important of which is lolitrem B. The mechanism of neurotoxicity is related to BK ion channels in the brain that regulate neuronal excitability. The channels, which are voltage and calcium regulated, are inhibited by lolitrem B.

Lolium endophyte is found in the leaf, sheath, stem, and seed of ryegrass. The infection causes no disease and transmission is seedborne rather than from plant to plant.

Endophyte is found in greatest prevalence in ryegrass in the summer and autumn, with lowest numbers appearing in the winter.

Lolitrem B is found in highest concentration in the leaf sheath of the outer or oldest leaves. These findings suggest that grazing the lower parts of the plant will produce the greatest numbers of sheep with ryegrass staggers.

The mechanism of neurotoxicity is by blockade of BK potassium channels. A concentration of 5 µg/g of Lolitrem B in the plant will produce tremors within a few days of ingestion.

Clinical Signs

Sheep

• Morbidity rates vary considerably between flocks and seasons. There is also a wide range of susceptibility to the disease.

• at rest show few obvious clinical signs.

• when disturbed and made to walk or run the clinical signs immediately become apparent.

• Sheep develop signs within 7-14 days of being placed on toxic pastures.

• mild clinical signs are a slight trembling of the head

and fasciculation of the skin muscles of the neck, shoulder and flank regions.

• increased severity = head nodding and jerky limb movements.

• Interference with postural reflexes follows; seen as swaying while standing and staggering during movement.

• a stiff-legged stilted gait may develop with short prancing steps, usually resulting in collapse to the ground.

• Sheep roll in lateral recumbency with head extended, arched back and rigid extended limbs held in a spasm of several minutes' duration.

• This is followed by sudden muscular relaxation and apparent recovery.

• The animal then slowly regains its feet and walks away, often still showing tremors but with very little locomotory incoordination.

Cattle

The signs seen in cattle are similar to those seen in sheep.

Horses

The clinical signs in horses are similar to other grazing animals. Horses may develop a persistent unsteadiness. Clinical signs reported include:

normal appetites, with hypermotile intestinal sounds, and mild to severe ataxia;

horses with a sawhorse stance, stumble when forced to walk, often losing their balance, a severely affected horse is barely able to walk, loses its footing when the tail is pulled laterally, and become recumbent when blindfolded.

Following an attack of ryegrass staggers, working horses may be unreliable for riding or driving for some time. Evaluation of the horse's condition should be done before putting a horse back into work.

Alpacas

The predominant clinical signs of ryegrass staggers in young alpacas were head and neck tremors.

Ryegrass Staggers

• fungal neurotoxin lolitrem B causes trembling, tetanic spasms and jerky gait
• horses may have persistent unsteadiness
• no known antidote. symptomatic and supportive care are provided.

Pathology

• no specific haematological or serum biochemical changes

• elevations in serum aspartate transaminase and creatine phosphokinase.

• No macroscopic changes are present in the nervous system.

• In protracted cases histological lesions in the Purkinje cell axons with oesinophilic swellings (torpedoes).

Prevention

• Reseed pastures with ryegrass containing "safe" endophyte

• prevent the development of ryegrass dominance should also lessen the risk of severe outbreaks, the encouragement of clover growth by ensuring adequate spelling between grazings from early summer swards should be practised.

• Control of RGS outbreaks by grazing management alone, or by other precautions such as feeding supplements.

Treatment

There is no known antidote for lolitrem B. Supportive care and feeding are necessary in severe cases.

Poisons with Mixed Effects

-Lead
-Mercury
-Ammonia toxicoses (urea) (also toxicoses causing acidosis)
-Pyrethrins and pyrethroids
-Rotenone
-Tricyclic antidepressants
-Fumonisins-mycotoxin associated with corn/leukoencephalomalacia in horse
-Yellow star thistle (*Centauria*)
-Russian napweed (*Centauria*)
-Locoweeds (*Astragalus* and *Oxytropis*)
-Hexachlorophene
-Bromethalin containing rodenticides
-Vacor (rodenticide-now banned)
-DEET
-Methionine
-Carbon disulfide (fumigant)
-Avocado (*Persea americana*)
-Horse chestnut (*Aesculus*)
-Buckeye (*Aesculus*)
-Morning glory (*Ipomoea*)
-Hallucinogenic and disulfiram type mushrooms
-Ethylene glycol (see under kidney toxicities)
-Hypomagnesemia (grass tetany)
-Boric acid
-Phenothiazine tranquilizers
-LSD
-Mescal bean (*Sophora secundiflora*)
-Cocklebur (*Xanthium*)
-Tall buttercup (*Ranunculus*)
Thiaminase containing plants and other substances
-Bracken fern in horses (*Pteridium*)
-Male fern (*Dryopterus*)
-Horsetails (*Equisetum*)
-Kochia (thiamine responsive polioencephalomalacia

in cattle;

-Thiaminase and thiamine deficiency in cats: raw fish, especially when fed to cats

Lead

Affected animals

Lead poisoning has been reported in most domestic animals and humans. Most cases reported in surveillance in new zealand over the past 10 years (1990-1999) have been in cattle and dogs.

Sources

Lead is found naturally as sulphide, oxide or carbonate ores, and with silver.

Lead-based paint

Soil contamination

Industrial and atmospheric lead

Lead in petrol

Metallic lead – car batteries, lead piping, shotgun pellets, ceramics, solder and asphalt.

Lead in oil

Miscellaneous sources

Absorption, distribution and excretion

Absorption

There are two major routes of absorption, the alimentary tract, in particular and the respiratory tract.

Distribution, pathogenesis and storage

Blood, nervous tissue, bone, placenta, muscle tissue,

Excretion

The main excretion of ingested lead is via active transport into the bile and finally into the faeces. However absorbed lead is excreted through the bile duct, urinary system, milk, sweat and saliva.

Mechanism of action

The exact mechanism of toxicity on a molecular level is not known. The toxic effects of lead generally affect the nervous system, gastrointestinal tract and haematopoietic system.

Clinical signs

Cattle

Both acute and subacute poisoning occurs. The acute form is more likely to be seen in calves.

Acute: this form occurs frequently in calves.

Animals are affected within a few hours to 2 days after ingestion of the poison.

The onset of signs is very sudden, animals may just be found dead.

Death may occur 1-2 hours after a fatal dose and up to 24 hours after onset of the clinical signs.

Initial signs are staggering, bellowing, champing of the jaws, frothing at the mouth and eye rolling.

CNS signs predominate. Convulsions develop and are intermittent becoming tonic and clonic. The pupils become dilated; opisthotonos and muscle tremor especially of the head and neck are common features.

Hyperaesthesia to touch and sound with apparent blindness is seen.

Head pressing, charging objects blindly will occur particularly with older animals.

Cardinal signs are increased.

Death occurs from asphyxiation.

Subacute: this form occurs mainly in adult cattle with the following features.

Course is over 3 to 4 days.

Anorexia, dehydration and dullness.

Incoordination, circling and apparent blindness and salivation.

Muscle tremors and hyperaesthesia.

Abdominal pain, belly kicking, rumen atony and constipation.

Frequently die near water.

Sheep

Lead poisoning of sheep is usually manifest by a subacute syndrome as in cattle.

Chronic - cattle, sheep and goats

Ruminants are resistant to chronic lead poisoning but two syndromes of posterior paresis have been described in young lambs in lead mining areas. Impaired gait, osteoporosis and unthriftiness were features of one syndrome. In the other, gait abnormalities were reported with incomplete flexion of joints and limbs.

Horses

The signs in horses are less marked than cattle; unthriftiness leading to paralysis and sudden death has been reported. Extensive paralysis of long tract nerves is reported leading to paralysis of the vocal cords and severe dyspnoea.

Dogs

A high incidence of lead poisoning in dogs is now recognised. In most epidemiological studies, acute lead poisoning occurred in dogs under one year of age.

gastrointestinal signs:

Intermittent vomiting

Anorexia

Diarrhoea/constipation

Colic.

Nervous signs:

Hyperexcitability

Hysterical barking

Chomping fit

Paraplegia

Loss of coordination

Muscle spasm

Photophobia and blindness

Hyperaesthesia

Behavioural changes.

Cats

Although cats are rarely diagnosed with lead poisoning, this may be due to the lack of clear measures with which to recognise toxicity.

The most frequently reported clinical signs in urban cats:

Anorexia

Vomiting

Depression and lethargy

Poultry and birds

Clinical signs seen have been:

Anorexia

Lethargy and emaciation

Bile stained diarrhoea

Nervous signs including convulsions and imbalance, head rotation (looking backwards) and falling from perches. (Falcons and hawks).

Sudden death (chickens).

Clinical pathology & confirmation of a diagnosis

The confirmed diagnosis of lead poisoning presents some difficulties. There are two categories of laboratory tests used in the detection of increased lead contact. Measurement of tissue lead content and measurement of the metabolic effects caused by lead. Beyond question when bone, kidney or liver is available for analysis, lead poisoning can be positively identified. Unfortunately, when the animal is alive, there is no one quantitative evaluation that can adequately define the body lead burden.

In most instances the diagnosis is achieved by blood lead measurements (bpb) following clinical signs and bpb is currently still accepted as the best single laboratory test for the identification of increased pb absorption following poisoning.

Haematology and basophilic stippling of erythrocytes

The presence of many nucleated erythrocytes, without a severe anaemia is strongly suggestive of lead poisoning. Although studies vary, in general, roughly half the small animals affected by lead poisoning will have nucleated red blood cells (nrbc) (5-40 nrbcs/100 white blood cells) and about 25% will have basophilic stippling.

Blood lead estimation (bpb)

• Contact the diagnostic laboratory before sending samples.

• Usually a 10ml sample in a heparin anti-coagulant and 20ml-30ml of clotted blood is adequate. Elevated bpb levels in the presence of clinical signs confirms a diagnosis of lead poisoning,

• If the blood lead levels are questionable, a urinary lead test before and 24 hours after chelation therapy may be useful. A tenfold increase in urine lead values is seen in lead poisoning.

• Alternatively, a significant decrease in ☒-aminolevulinic acid (☒-ala) concentration in urine after chelation therapy is suggestive of lead poisoning.

Faecal lead levels

• Faecal levels of lead represent unabsorbed or excreted lead derived from bone deposits and are of limited value unless considered in conjunction with bpb

Delta-amino levulinic acid (δ-ala)

• Lead affects the haem synthesis of all the haem producing cells. Delta-amino levulinic acid is one of the precursors of haem which requires the enzyme ala dehydrase to incorporate it into the system. Lead inhibits the activity of this enzyme, so that the concentration of ☒-ala increases in the systemic circulation, until it is removed from the circulation and excreted via the kidney.

• Urinary δ-ala reflects the susceptibility of individual animals to lead intoxication and is related to the presence of clinical signs.

Other urine tests

• Urine analysis from lead intoxicated animals may show hyaline and granular casts, proteinuria and glucosuria.

• Over time urine cannot be concentrated

Radiology

• Radiodense objects in the gastrointestinal

• In chronic lead poisoning "lead lines" may appear in the metaphyses of long bones.

Bone marrow aspirations

• An increased myeloid:erythroid ratio is not considered to be diagnostic of lead poisoning, unless other variables such as blood lead levels are also elevated.

Electroencephalogram changes

• Lead poisoned animals show various degrees of irregular, generalized, slow wave activity with an increased wave amplitude.

Post mortem & pathology samples

Post mortem findings:

• Usually nonspecific.

• Gastrointestinal tract may find paint flakes or other lead-containing substances.

• Glandular stomach and intestines are usually inflamed and often a greenish diarrhoea.

• Kidneys are swollen with oedema, so that the gyrae are flattened and discoloured.

• White bands are sometimes found in the metaphyses in the transversely transected long bones of immature dogs

• If the necropsy is not performed immediately the muscles develop a dirty green or red discolouration.

Microscopically kidneys show damage to the epithelial cells of the proximal convoluted renal tubules,

Loss of nephrons and a focal increase in the interstitial connective tissue, infiltrated with lymphocytes and other mononuclear inflammatory cells.

Acid-fast, intranuclear inclusion bodies ± in kidney and liver cells, more likely in osteoclasts.

The cerebral lesions in chronically intoxicated animals range from status spongiosus, astrocytic swelling, and nerve cell degeneration to severe cavitation and vascular proliferation. There is usually a peripheral neuropathy as well.

Treatment

It is important to remove the animal from the source of intoxication if possible.

Cattle

Acute lead poisoning of cattle is almost always fatal. In cattle, saline purgatives (magnesium sulphate 500-1000g as a drench may be helpful). The soluble lead salts will be precipitated as insoluble lead sulphate and the cathartic action is also valuable. When large flakes of paint have been ingested such treatment is of limited value.

Thiamine (250-1000 mg/day for 5 days) promotes recovery in cattle.

Phenobarbitone (30 mg/kg iv to effect) or chloral hydrate (50-70 mg/kg iv as 5 or 7% solution) are recommended for seizure control.

Lead is immunosuppressive which may necessitate treatment for bacterial infections.

Dogs and cats

Emetics, enemas and cathartics will help eliminate lead and lead objects. Magnesium sulphate is again a good choice of cathartic, but use care to avoid dehydration and electrolyte imbalances.

In less acute cases, administer egg white to complex with the lead, followed by an emetic and then a cathartic to remove the complex as some of its compounds are soluble in excess albumin. Tannic acid or strong tea (small animals 200-500mg in 30-60mls water) followed by an emetic or purgative to ensure prompt removal of the tannates may also be given.

N.B. It is important to ensure that all lead is removed from the alimentary tract before starting chelation therapy, as these agents increase the absorption of lead.

Chelating agents are used to remove lead from soft tissues by forming non-toxic complexes, which can then be rapidly excreted in urine or bile. The main chelating agents are calcium edta, calcium disodium edta, d-penicillamine and dimercaptosuccinic acid (dmsa). Dimercaprol also known as bal (british antilewisite) will chelate lead but it is potentially nephrotoxic and is painful, particularly if the drug is not injected deep into the muscle.

Calcium EDTA

To prevent the development of a caedta toxicosis the dosage regimens are limited to five days.

Dose rate recommended - 25 mg/kg sc every 6 hours for 2-5 days. The daily dose in small animals should not exceed 2g per day and do not treat for more than 5 consecutive days.

May also be used in large animals (cattle) at 55mg/kg given twice daily, subcutaneously or by slow intravenous injection.

D-penicillamine (small animals)

Dimethylcysteine the d-isomer of penicillamine, is an orally administered chelator.

Dimercaptosuccinic acid

Dimercaptosuccinic acid (dmsa), an orally administered chelator, has been shown to be safe and effective in reducing blood lead concentration in dogs. The drug is not currently available in new zealand.

Supportive therapy

The gastrointestinal signs of lead intoxication usually subside with chelation therapy and do not require further treatment. Cerebral oedema is the primary cause of the neurological signs, and these can be treated with 20% mannitol or dexamethasone. Diazepam or pentobarbital may be required to control convulsions. Thiamine therapy in lead poisoned calves has caused a dramatic reduction in clinical signs and reduced the concentration of lead in tissue. Fluids may be required for dehydration. If there is an improvement within 24-48 hours, then the prognosis is favourable.

Long term effects

Behavioural changes, visual motor impairment, recurrent seizures and lack of concentration may be permanent in both dogs and children, due to the permanent damage of small capillaries in the brain and death of some of the neurones. Chronic nephritis has also been reported in man.

Lead Poisoning

- Numerous sources of lead – old paint, batteries, used oil etc
- Lead is bound to rbcs, stored in bones, excreted in the urine
- Gastrointestinal upset and neurological signs
- Diagnosis: when bone, kidney or liver is available for analysis, lead poisoning can be positively identified. Blood levels (☒) and basophilic stippled erythrocytes in blood smears supports the diagnosis of lead poisoning
- Decontamination and chelation therapy generally successful
- Other symptomatic treatment as required: eg. seizure control

Pyrethrins and pyrethroids

Sources

Pyrethrins and pyrethroids are used extensively for insecticide control particularly in small animals (dog and cat) but all species can be accidentally poisoned. They are natural insecticides produced from extracts of pyrethrin flowers of the genus chrysanthemum. The pyrethroids are synthetic insecticides that resemble pyrethrins in structure and action. They include-

Type 1 pyrethroids which do not contain an alpha-cyano moiety e.g. permethrin.

Type 2 pyrethroids which contain an alpha-cyano moiety.

Environmental sources include pyrethrum flowers and pyrethrin insecticides

Pyrethroids are synthetic pyrethrins used as insecticides

Pyrethrins and pyrethroids are used topically or in collars for flea control in small animals.

Sprays for fly control and household insect control

Toxicokinetics

Pyrethrins are lipophilic and readily absorbed orally, dermally or by inhalation. Because of their rapid metabolism, the pyrethrins and pyrethroids are poorly distributed throughout the body, if at all.

Mode of action

The pyrethrins act on sodium channels in the axonal membrane, decreasing and slowing inward sodium conductance and suppressing potassium outflow. These insecticides are often termed as open channel blockers. They may also inhibit adenosine triphosphatases (atpases), which may affect cation conduction at axonal membranes. The net result is decreased action potential amplitude and the generation of repetitive nerve impulses.

In addition, type 2 pyrethroids interfere with binding of GABA and glutamic acid at receptor sites. This antiinhibitory action could lead to hyperexcitability of nervous tissue and contribute to the clinical signs.

Toxicity

Type 2 pyrethroids (ie. Those with the alpha-cyano moiety) are generally more toxic than type 1 pyrethroids. Acute oral toxicity of common pyrethrins ranges generally from 1000-2000 mg/kg body weight.Drugs, chemicals and nutritional changes that alter the effectiveness of the mfo system can change toxicity of the pyrethrins and pyrethroids.Mfo inhibitors (e.G. Piperonyl butoxide, n-octyl-bicycloheptene dicarboximide (mgk-264) suppress the hydrolysis of pyrethrins and pyrethroids, increasing their toxicity. Commercial pyrethrin insecticides contain synergists.

Only products labeled for use on cats should be applied as cats are sensitive to these compounds.

Clinical signs

Clinical signs mainly involve the nervous system and may vary slightly depending on the type of pyrethroid. In experimental animals (eg. rats) type 1 pyrethroids cause an increased response to stimulation, muscle tremors, excitement and paralysis, while type 2 pyrethroids induce salivation, weakness and a distinctive "writhing" or burrowing syndrome. In dogs, cats and large animals, the clinical signs are usually similar for both types of pyrethroids.

Treatment

Symptomatic and supportive treatment. Administer diazepam if seizuring. If not effective consider other anticonvulsive treatment. If methocarbamol, a muscle relaxant, is available it is efficacious in controlling muscle tremors in many poisoned cats.

Poisons causing CNS depression

- alpha-chloralose
-white snakeroot (*Eupatorium*)
-rayless goldenrod, jimmyweed (*Isocoma wrightii*, formerly called *Haplopappus*)
-opiates and opioids
-marijuana
-ivermectin especially in collies and related breeds
-amitraz
-piperazine (same mechanism as ivermectin)
-benzodiazepines
-phenothiazine in small animals
-tranquilizers
-barbiturates
-benzyl alcohol or benzoic acid in cats and neonates
-citrus oil extracts
-sleepy grass (*Stipa*)
-ethylene glycol
-ethanol (usually cage birds; reported in ethanol silage fed cattle)
-methylene chloride and numerous other hydrocarbon solvents

Alpha-Chloralose

Source

Alpha-chloralose is used as a general anaesthetic for laboratory animals, as a rodenticide and has been used to immobilise depredating birds. In New Zealand it has been used on coastal airports where seagulls are in danger of causing air strike to planes landing and taking off. Alpha-chloralose is sold in wheat, barley or pea bait and as a paste for the control of sparrows and other birds. The compound is the active ingredient of Pestoff or Alpha-chloralose Bait or Paste and is a schedule III poison. As a rodenticide, alpha-chloralose should be used outside, as much of its effect is lost in warm buildings.

Species Affected

All species are potentially at risk but significantly more cases occur in cats, dogs and birds. Dogs and cats can be poisoned secondarily by eating birds or rodents killed by alpha-chloralose.

Pathogenesis and Toxicity

Alpha-chloralose acts upon the central nervous system, and has both stimulant and depressive properties. Alpha-chloralose selectively depresses neurons of the ascending reticular formation, suppressing the normal arousal response. At the same time small doses increase motor activity producing myoclonic movements, that progress to deep anaesthesia as the dosage increases. Alpha-chloralose also reduces the body temperature so that its toxicity is particularly effective in small animals like mice which have a greater surface area/volume ratio.

Within the body, alpha-chloralose is biotransformed to chloral, which is converted to trichlorethanol, then conjugated with glucuronic acid in the liver and excreted in the urine as urochloralic acid. This is rapidly excreted and is not a cumulative poison. The LD50 ranges from 42 mg/kg for a duck, 100 mg/kg for a cat and up to 600 mg/kg for a dog.

Clinical Signs

Initially there is a mild ataxia with poor coordination of movements. Hyperexcitability and aggressiveness are exhibited early in the toxicosis. Cats in particular will hiss, spit and claw the air with their front paws. Tonic convulsions develop and there are records of cats in a posture with the front legs extended as though attempting to cling to a moving object. In dogs salivation is seen and convulsions are of a more clonic nature.

Affected animals lose sensitivity to pain and yet have increased reaction to touch, sound and other stimuli. The pupils are widely dilated.

Severe poisonings rapidly progress to weakness, shallow respirations, tonic convulsions and death from respiratory failure. However death is rare in domestic animals from accidental ingestion and with good nursing a favourable prognosis can usually be given.

Birds that ingest treated seed or paste with alpha-chloralose may show clinical signs that include excitement followed by depression leading to deep anaesthesia and death.

There are few reports of significant clinico-pathological changes or post mortem features in domestic animals. Lesions reported in seagulls include severe oedema of the lungs and some degree of amyloidosis of the spleen.

Laboratory Specimens

Stomach contents, liver and urine samples may be sent for analysis. Forty-five percent of alpha-chloralose is excreted in the urine within 24 hours of ingestion, and early samples may be useful if obtainable.

Treatment

Animals need to be restrained in well padded cages to prevent self injury. Warmth may need to be provided. Try to maintain body heat but avoid excessively high temperatures; 25-28°C is the ideal range.

Birds should be placed in a warm dark place, allowed to recover fully and then released.

Unless the animal is showing CNS signs, evacuation of the gastrointestinal tract by use of emetics, gastric lavage and laxatives should follow. Seizures may be controlled by diazepam (Valium) and it may be necessary to administer oxygen by artificial ventilation.

Osmotic diuresis should be instituted. Some clinicians recommend analeptic drugs if the animal is in deep coma e.g. bemegride or methylamphetamine. In other circumstances they should be avoided.

Ivermectin/avermectins

Source

used as internal and external parasiticide

unlike the other products mentioned, this is applied by injection, pour on or oral liquid/tablets/paste to kill external and internal parasites

many uses are "extra-label"

avermectin products associated with toxicities e.g. abamectin

usually a history of administration of the drug, use of horse paste wormer on dog or

use of cattle injectable on small animals or treatment of livestock

Mechanism Of Action

-Ivermectin acts as a GABA agonist.

-GABA binding to GABA A receptors opens chloride channels in the CNS of mammals. This action leads to a depression of neurons.

Ivermectin Poisoning

- Some breeds of dog particularly collie and collie crosses are most susceptible to poisoning.
- GABA binding to GABA A receptors opens chloride channels in the CNS leading to depression of neurons (coma and sometimes death in the most severe case).
- Supportive treatment required for several weeks depending on amount ingested

-the reason why ivermectin is generally less toxic to mammals is that most GABA receptors are within the CNS and hence "safely" protected from the blood by the blood brain barrier (insects and nematodes have no barrier)

-Some (not all!) Collies are more susceptible to ivermectin toxicity due to a mutant gene MDR1. The MDR1 mutation causes a defect of p-glycoprotein, a large transmembrane protein in the blood brain barrier, which allows macrocyclic lactones such as ivermectin and abamectin to enter the brain. Because these act as γ-aminobutyric acid (GABA) agonists, they increase the effects of inhibitory nerve pathways in the central nervous system, leading to depression and stupor.

Clinical Signs

clinical signs relate to inhibition of upper CNS

ataxia (starting hind limb), incoordination, depression progressing to coma

mydriasis or miosis, apparent blindness, absence of menace reflex

hypersalivation, emesis

other signs reported:

vocalization (dog and cat)

dementia (cat)

pyrexia (dog)

no response to sound (dog)

bradycardia (dog)

Diagnosis

necropsy: take samples from brain to analyze for ivermectin concentrations; also plasma, liver and fat

Treatment

One of the major principles in treating ivermectin is to **treat long enough**

Dogs have had a successful recovery after being comatose for up to 7 weeks from ivermectin ingestion

drug is recirculated by enterohepatic circulation

serial doses of activated charcoal and 1-2 doses of saline or osmotic cathartic will enhance elimination

no specific antidote (at least none that don't have severe side effects of their own)

supportive and good nursing care is critical

Marijuana

(*Cannabis sativa*)

Marijuana is the dried leaves and flowers of the hemp plant, *Cannabis sativa*, hashish is the resin extracted from the

plant. The toxic ingredient is tetrahydrocannabinol (THC), which ranges from 1-6% of the leaves and flowers. THC is highly lipophilic.

Pets may eat marijuana cigarettes, butts or other products containing cannabis. Cattle have been known to consume the tops of plants and suffer moderate neurological signs and gastroenteritis with diarrhoea. Horses and mules have died as a result of grazing *Cannabis sativa*.

Toxicokinetics

THC is readily absorbed from the gut and the smoke is absorbed via the lungs. Enterohepatic recirculation helps to maintain drug levels and produces a variety of hepatic metabolites.

Prolonged drug residues are not likely and most metabolites are excreted in approximately 24 hours.

The mechanism of THC is not clear. Action may be related to changes in levels of biogenic amines in the CNS. The lethal dose for dogs is 3 g/kg, but death from marijuana is unlikely.

Clinical signs and diagnosis

The diagnosis of marijuana toxicity may be problematic because histories may be false.

The main clinical signs include marked CNS signs sometimes alternating between depression and excitement. Ataxia and incoordination have been reported. Dogs may experience hallucinations shown by barking and excitement.

There may be pinpoint pupils, vomiting, dry mucous membranes, tachypnoea and hyperthermia or hypothermia if large amounts of cannabis are ingested.

In a reported poisoning of horses and mules the predominant clinical signs were marked dyspnoea, muscle tremors and froth from the mouth.

A diagnosis may be confirmed by the detection of THC in plasma or urine.

Treatment

Detoxification using emetics, activated charcoal and cathartics is recommended. Because THC possesses antiemetic properties, emetics may not be useful.

Supportive therapy should be used but CNS drugs should not be given unless they are necessary to save the animal's life. Diazepam may be used to control excessive excitement or agitation.

Cases

Case 1

A client calls for your advice after his dog was seen eating a possum carcass. The history suggests that the possum was likely poisoned as a result of a recent 1080 drop.

What advice would you give your client concerning treatment of 1080 toxicity?

What is the mechanism of toxicity of 1080?

What are the signs of 1080 toxicity in the dog?

What treatment is recommended if signs occur?

Case 2

A cat is presented with clinical signs of muscle trembling and spasms. The owners used a topical flea product on the cat. On closer questioning, the owners tell you that the product was labelled for dogs and contains permethrin.

Is permethrin toxic to cats?

How would you handle this case?

Poisons causing paralysis

(May eventually include respiratory paralysis)

-any nicotinic agent including cholinesterase inhibitors at high doses

-curare

-suxamethonium

-blackwidow spider (*Latrodectus* spp.)

-larkspur (*Delphinium*)

-botulism

-tick paralysis (*Dermacentor* or *Amblyoma*)

-arsanilic acid

-organophosphorus compounds (OPIDN) (not all are insecticides)

-triortho-cresyl phosphate (TOCP)

-EPN (insecticide)

-leptophos (insecticide-not on market)

-haloxone (anthelmintic)

-lathyrism-rough pea, vetchlings (*Lathyrus*)

-hybrid sudan (*Sorghum*)

-guajillo (*Acacia berlandieri*)

-locoweed (*Astragalus*) (miserotoxin = a 3-nitro compounds:

-citreoviridin (mycotoxin)

-patulin (mycotoxin)

-mephenesin

-tetrodotoxin

-puffer fish (tetraodon and fugu)

-poison dart frogs-central and south America

-Californian and European newt (*Taricha*) (a salamander)

-unk (*Bombia*) (a salamander)

-saxitoxin and neosaxitoxin

in paralytic shellfish poisoning-from cockles, mussels, clams. (Especially the Alaskan butter clam, *Saxidomas giganticus*) and especially oysters

-all from the dinoflagellate (*Conyaulaux* spp.). Also contain the similar acting neosaxitoxin.

-karaka - *Corynocarpus laevigatus*

-dwarf mallow (*Malva neglecta*)

-in red tide. same dinoflagellate in fishes

-in blue-green algae (*Aphanizomenon*)-May contain both saxitoxin and the similar acting neosaxitoxin

-ciguatera (icthyosarcotoxin)

-red snapper
-other fish
-sulphonamides (peripheral neuritis)
-selenium (subchronic selenosis in swine
-cycad palms

Toxicants Primarily Causing Respiratory Paralysis

-H_2S (paralysis via CNS)
-aminoglycoside antibiotics plus any anaesthetics, muscle relaxant

Toxicants Causing Primary Muscle Dysfunction and /or Paralysis

-2,4-D and other phenoxy herbicides
-Lasalocid (Bovatec) in dogs and other ionophores (monensin etc)

Chlorinated Phenoxy Compounds

e.g. 2,4 dichlorphenoxy acetic acid (2,4D) 2,4,5, tri chlorphenoxy acetic acid (2,4,5 T)
4 chloro 2 methylphenoxyacetic acid (MCPA)

Use

Selective herbicides (broad leaf killers)
commonly used
low order of toxicity (dog is more susceptible)

ADME

Rapidly absorbed in acid pH (stomach contents), protonation (add hydrogen ion).
No significant metabolism, excreted as unchanged acid in the urine.
2,4,5-T may undergo enterohepatic circulation.

Mechanism Of Action

Uncouple oxidative phosphorylation esp. chlor-phenols

Clinical Signs

Increased respiration, decreased ATP, increased Temp, more toxic when environmental temperatures are high.
Weakness, fatigue, collapse, sweating
Convulsions, death (sometimes sudden death)
Rumen stasis commonly observed.
Rigor Mortis develops quickly and is pronounced.
2,4-D has a direct effect on muscle membranes causing increased irritability and rigidity followed by paralysis.
but, primary sign of toxicity is usually
gastrointestinal haemorrhage, anorexia, bloat, intestinal carcinoma (esp. sheep), rumen atony, diarrhoea.
Other clinical signs may be oral mucosal ulceration, temporary infertility in bulls etc.

Treatment

Remove from further access, usually sprayed pastures.
Activated charcoal and saline cathartic
Alkalinise urine to increase elimination.

Pathology

Usually no gross pathology, in some cases may see GI ulceration or the following signs rarely:
Congestion of kidney, hyperaemia of lymph nodes, congested friable liver MAY be seen on PM.
Clinical pathology changes include an increase of CPK, SGOT/AST, LDH and AP.

Ionophore Toxicity

monesin, salinomycin, lasalocid, narasin

Uses

Growth promotants and coccidiostats

Sources

contaminanted feed, accidental feeding of treated calf pellets to horses, ingestion of bullets by dogs

Mechanism Of Action

Ionophores interact with the carrier mechanism that regulates potassium transport across mitochondrial membranes, inhibiting ATP hydrolysis and diminishing cellular energy production. Electron micrographs have confirmed that monesin causes severe mitochondrial damage.
Ionophores may alter calcium transport by changing the sodium component of the sodium-calcium exchange diffusion carrier in the cell membrane, leading to the accumulation of calcium in the cell and mitochondria and possibly causing cell death.

Clinical Signs

Horses
initial signs
- anorexia
- uneasiness, profuse intermittent sweating
- polyuria then oliguria

intermediate
- progressive ataxia (12-36 hours)
- colic, stiffness
- posterior paresis
- recumbency then standing

advanced
- tachycardia
- hypotension
- hyperventilation and dyspnoea - death

Cattle
- Anorexia, 24-36 hours post ingestion

depression, weakness, ataxia
dyspnoea
diarrhoea; apparent recovery then myocardial failure

Dogs
(females tend to be sensitive than male dogs) [cats are similar to dogs]
Progressive, bilaterally symmetrical, ascending muscle weakness, which progresses from the hind to forelimbs followed by quadriplegia, hyporeflexia and hypotonia. If the respiratory muscles are affected than dyspnoea and apnoea in a severe case. The mental status and cranial nerve function tend to remain normal. Pain perception is maintained and

Ionophore Poisoning

- Disrupts the intra- to extramitochondria ion gradients.
- Neuromuscular paralytic syndrome beginning caudally and moving cranially
- Increases in: creatine kinase, lactate dehydrogenase, aspartate transaminase, urine protein and
± myoglobinuria
- Supportive care; prognosis depends on initial severity of clinical signs
- Pale skeletal and cardiac muscle with necrosis (may be mild or not detectable)
- Differential diagnosis: botulism, myasthenia gravis, polyradiculoneuritis, amitraz, ivermectin

the dog will still be able to wag its tail.

Laboratory Diagnosis

serum alkaline phosphatase (AP) increased
bilirubin increased after 24 hours
serum calcium decreased for 12-18 hours
BUN increased
Serum creatinine elevated at 24-36 hours, but may return to normal
Creatine kinase increased many fold
Haematocrit elevated
Lactate dehydrogenase (LDH) increased for 36 hours
Serum Potassium decreased after 24 hours
Aspartate transaminase AST increased
Feed analysis (Tissue residues are extremely unlikely)

Gross Lesions

Generally:
Mild haemopericardium, epicardial haemorrhages and a pale myocardium,
Cardiac lesions may be mild or not detectable.
Cattle: hydrothorax, ascites and pulmonary oedema, multifocal areas of myocyte necrosis in the heart.
Cattle dying within 3 days of overdose may have a marked degranulation of pancreatic acinar cells.
Mild rumenitis

Treatment

Decontaminate and supportive therapy
There is no antidote or specific treatment.

Paralytic Shellfish Poisoning

(Red tide-*Gymnodinium catenatum*)

Source

Saxitoxin found in sea water, aerosolised toxin or ingestion of contaminated shellfish. Currently found on the west coast of the North Island but has the potential to spread to the Marlborough Sounds and other parts of the South Island coasts.

Toxicity

Mice oral LD50 of 263 µg/kg

Clinical Signs

Humans develop signs including burning sensation to the lips, tongue, face progressing to the rest of the body within 30 minutes. Paralysis and death may result. Cats and dogs develop ataxia, recumbency and convulsions. Death within 2-24 hours depending on the dose.

Treatment

Symptomatic care, no antidotes available. Animals that survive after 24 hours may have some persistent weakness for weeks after exposure.

Cases

Case 1

Tasha, a pony of unknown age, was presented for evaluation of a chronic condition of weight loss, depression and reluctance to move. The owners had purchased oral vitamin B12 and Biostart (a broth containing Lactobacillus and digestive enzymes thought to promote a healthy gut flora) to feed Tasha. Tasha's condition continued to decline and the vet was called out to see the pony.

On examination of the pony and further history, the pony had been losing weight over about a six week period. They also mentioned they had been giving the pony a "treat" of calf pellets over the last two months. The pony (height 14 hands, 200 kg) was in poor body condition, depressed, anorexic and had not defaecated for at least two days. She was reluctant to move and seemed to prefer to stand in shady areas. Abnormal clinical findings included slightly icteric mucous membranes, a low body temperature of 37˚C, hard, dark faeces in the rectum and reduced gut sounds. Her heart rate was measured as 42 beats/min and respiration was 10 breaths per minute.

On further examination of the calf pellets, it was found that they contained monensin. Calculations of the concentration in the feed and the amount fed suggested that the pony was ingesting about 2 mg/kg of monensin daily for about two months.

Blood was taken for a CBC and biochemistry. Results of the haematology revealed a regenerative anaemia, increased numbers of band and segmented neutrophils, high numbers of monocytes and an increase in fibrinogen. Liver and muscle enzymes were within normal. Albumin levels were decreased. No other abnormalities were noted.

What other species are susceptible to monensin toxicity?

What is monensin's mechanism of toxicity in animals?

What are the clinical signs of monensin poisoning in the horse?

Is this monensin poisoning in the pony?

Practice exam questions

Multiple choice questions

1. Local anaesthetics produce clinically useful effects when given
   - onto the skin ❑
   - around a nerve ❑
   - by mouth ❑
   - per rectum ❑
   - intramuscularly ❑

2. General anaesthesia
   - is an inability to respond to surgery ❑
   - may be induced with xenon ❑
   - is similar to the effect produced by LSD ❑
   - always involves excitation ❑
   - includes cardiovascular depression ❑

3. General anaesthetic agents
   - potentiate GABA B receptors ❑
   - are only effective in mammals ❑
   - open sodium channels at normal doses ❑
   - raise intracellular calcium levels ❑
   - potentiate GABA A receptors ❑

4. Codeine
   - often causes diarrhoea ❑
   - is used to treat vomiting caused by morphine ❑
   - is equipotent to morphine as an analgesic ❑
   - depresses the cough reflex ❑
   - is an alkaloid produced by ergot ❑

5. Analgesia
   - means a lack of feeling ❑
   - means a blockade of the nociceptive pathways in the spinal cord ❑
   - may be produced by $\alpha 2$ agonists in the sheep ❑
   - is the same as anaesthesia ❑
   - may be produced by intrathecal injection of substance P ❑

6. Which drug would be the first choice for treating status epilepticus in a dog?
   - acepromazine ❑
   - lignocaine ❑
   - diazepam ❑
   - phenobarbitone ❑
   - suxamethonium ❑

7. Thiopentone sodium
   - 5% solution has a pH of about 4 ❑
   - is one of the best drugs for maintenance of anaesthesia ❑
   - does not cause cardiovascular depression ❑
   - does not cross the placenta ❑
   - has an elimination half life of about 4.5h in the dog ❑

8. Detomidine
- is a phenothiazine sedative ❑
- produces anaesthesia in horses ❑
- may have its effects reversed by flumazenil ❑
- produces analgesia in horses ❑
- usually causes tachycardia in horses ❑

9. Local anaesthetic use dependence means that
- animals become tolerant to the effects ❑
- drugs must get into the sodium channel from inside the neurone ❑
- C fibres are preferentially blocked ❑
- rapidly firing neurones are preferentially blocked ❑
- bupivacaine is a useful antiarrhythmic ❑

10. You need to sedate a dog which has been in a road traffic accident for X rays. The dog has a fractured femur, a suspected fractured pelvis and is going into shock. The best course of action is to

wait and see what happens ❑
- treat the shock, immobilise the fractures and forget about the X rays ❑
- give it acepromazine, X ray it quickly, then decide what to do ❑
- give it a big dose of morphine, treat the shock and X ray it ❑
- euthanise the dog ❑