6 Cardiovascular system

The cardiovascular system is one integrated system - changing one aspect with drugs alters everything else. The system is normally controlled within very fine limits by a variety of mechanisms - a knowledge of cardiovascular physiology is essential to understand cardiovascular pharmacology and use cardiovascular drugs safely.

Possible areas of CVS failure

		Problem	*Drugs used*
heart	conducting system	arrhythmias	anti-arrhythmics
	myocardium	reduced contractility	positive inotropes, vasodilators, diuretics
	blood supply	ischaemia	vasodilators, diuretics
	valves	regurgitation	vasodilators
	neural control	rate	chronotropes
blood vessels	hypertension	vasodilators	
blood	volume	hypovolaemia	colloids (crystalloids)
	red blood cells	haemorrhage	whole blood
	proteins	various problems	colloids, clotting factors
	ions	various problems	crystalloids

Heart failure

Heart disease is common in all species but is usually only treated in dogs, cats and horses. The pattern of disease seen does not reflect the incidence in animals; most cases of cardiac arrest (and probably acute heart failure) which occur outside the clinic will die. Acute heart failure ± cardiac arrest commonly follow poor anaesthesia - it can be embarassing to take in a healthy animal and give it back to the owner in a black plastic bag.

Types of heart failure

cardiac arrest

acute heart failure

chronic heart failure (usually presents as congestive heart failure)

The treatment of these is different, although chronic heart failure can (and finally does) progess to acute heart failure then cardiac arrest.

Cardiac arrest

You must know how to carry out cardiopulmonary resuscitation since if an animal goes into cardiac arrest you do not have time to consult your notes!

Drugs are not usually needed until the recovery phase - when a knowledge of pharmacology really is required!

Prevention of cardiac arrest is much better than cure!! Prevent hypoxia and acidosis. Print out the page overleaf and stick it up on the wall where you can refer to it in an emergency.

Priorities in cardiac arrest

Airway - usually intubation

Breathing - intermittent positive pressure ventilation, preferably with oxygen

Circulation - external cardiac massage (fluids)

and only then

Drugs are used as necessary (usually given iv (occasionally down the endotracheal tube) since blood flow to the tissues will be reduced). Drugs are not usually effective for starting a heart that is stopped (although they may be used as adjuncts): in nearly every case the most effective treatment is restoration of the flow of oxygenated blood to the myocardium by external cardiac massage. Drugs are most useful for supporting the heart after resuscitation when the animal is effectively in acute heart failure.

positive inotropes
    adrenaline, dobutamine
antiarrhythmics
    lignocaine
fluids

Cardiopulmonary resuscitation

If the animal has stopped breathing (do not count gasps) and there is no peripheral pulse, check apex beat.
If there is no apex beat, start CPR; if there is an apex beat ventilate with 100% oxygen.

Airway

Visually check / insert endotracheal tube, or,
Emergency tracheotomy (14SWG catheter through cricothyroid membrane), or,
Extend neck and pull tongue forward.
Stop giving anaesthetic drugs, flush circuit with oxygen and set high oxygen flow.

Breathing

Squeeze bag 3 times checking for chest expansion - if chest expands, check pulse again: if no chest expansion, check airway again, or,
Ventilate mouth to nose.
Ventilate every 5 seconds; allow chest to deflate between breaths.

Circulation

Lay animal on right side.
Extenal cardiac massage at 2 beats / second.
Continue ventilation.
Stop and check for pulse every 2 minutes.
Internal cardiac massage is only justified if chest is open or if there are major chest wounds.

Drugs

No drugs necessary in the first 5 minutes, then:
adrenaline 20µg/kg iv, or 100µg/kg intratracheally. Repeat every five minutes with a double dose if no response.
atropine 20µg/kg iv, or 40µg/kg intratracheally once.

After 10 mins CPR:
sodium bicarbonate 1mEq (=mmol)/kg slowly iv into running infusion, preferably 0.9% NaCl. Do not give intratracheally!
Repeat 0.5mEq/kg iv every 10 minutes of CPR.

In hyperkalaemia or hypocalcaemia only:
calcium (boro)gluconate 1mg/kg iv - do not give with bicarbonate.

Stop CPR after 20 minutes if no response.

After heart restarts

Continue ventilation with 100% oxygen and consider:

positive inotropes
adrenaline 5 - 10µg/kg/min iv - titrate to effect on blood pressure, /
dobutamine 2.5 - 10µg/kg/min iv - titrate to effect, /
dopamine 1 - 10µg/kg/min iv - titrate to effect

fluids
sodium bicarbonate in normal saline, Hartmann's, colloids - beware overdose!

antiarrhythmics
only give if absolutely necessary

tachydysrhythmias
lignocaine (without adrenaline) 1mg/kg slowly iv; repeat every 10 mins if necessary up to 3 times, then 20µg/kg/min if necessary
verapamil 20µg/kg iv over 10 mins, repeat if necessary.
bradydysrhythmias
isoprenaline 20 - 200µg/kg/min iv, or,
dobutamine 2.5 - 10µg/kg/min iv to effect

Concurrent activity

Shout for help.
Note time.

When an assistant arrives, they take over ventilation.

Establish iv access - big catheter in a big vein - cut down if necessary.

Start fluids at a slow rate to keep vein open.

Attach ECG

Flush drugs in with 5 - 50mL saline

Check potassium first.

monitor ECG

monitor blood gases and central venous pressure

monitor ECG

bicarbonate, crystalloids, colloids

Acute heart failure

causes
anaesthetic overdose
pericarditis
metabolic illness

Cases which occur outside the clinic will probably die.

Drugs used include positive inotropes (usually β1 agonists), iv fluids, antiarrhythmics and vasodilators (usually nitrates). They are given intravenously to effect and the animal is monitored very closely in intensive care.

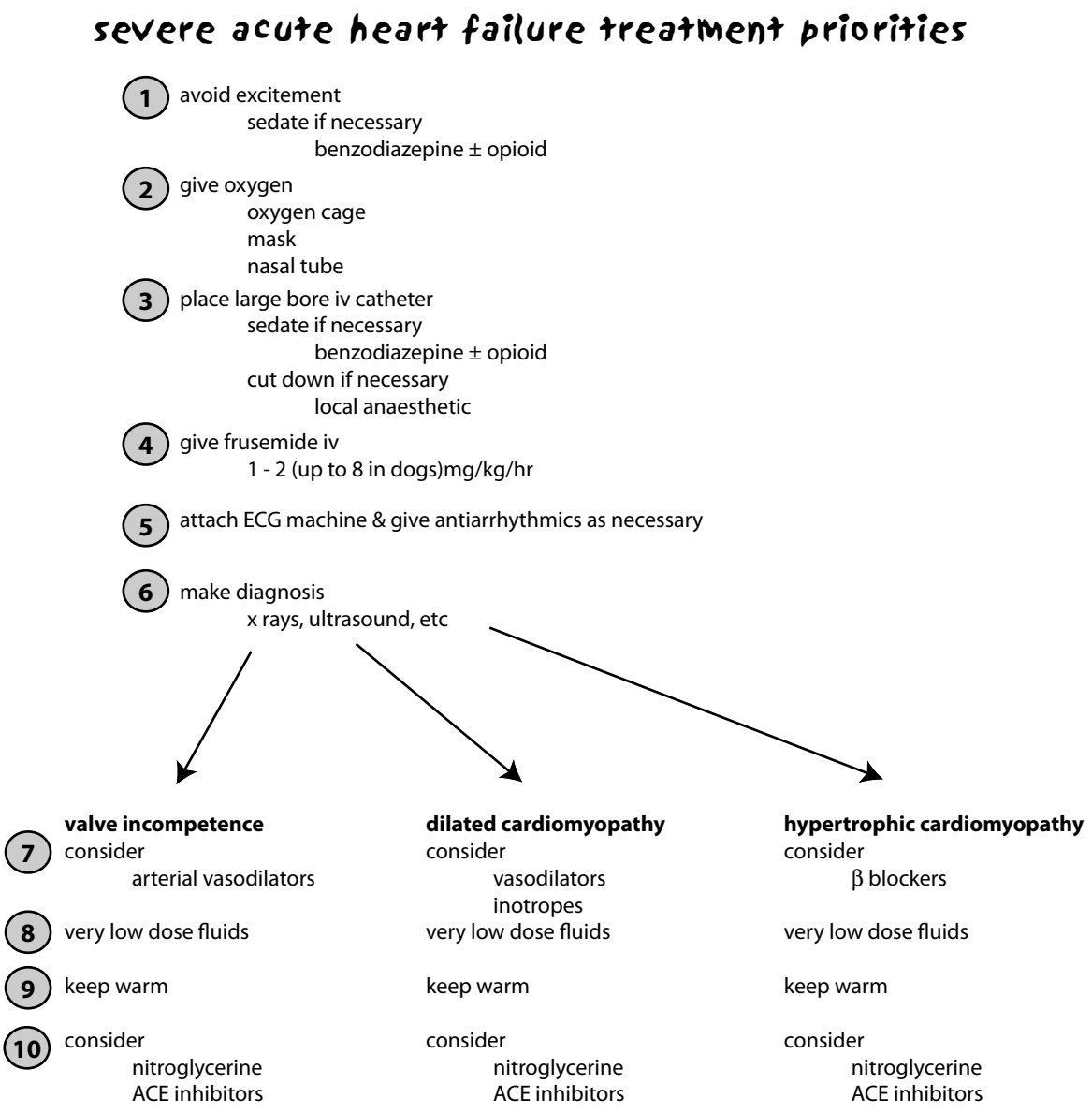
Congestive heart failure

This is commonly seen in practice in dogs and cats which are usually treated as outpatients. It is a syndrome of low cardiac output which can arise from a number of causes. Endocardiosis, usually resulting in leaky valves, occurs in 30% of dogs over 10. As a very broad genralisation, dogs get dilated cardiomyopathy and cats get myocardial hypertrophy. Accurate diagnosis is essential, as some drugs used for one type will make the other type worse.

Heart failure is sometimes classified into backward and forward failure, which is of some use when deciding on drugs:

backward failure - increased right atrial pressure from lack of forward flow through the heart causes blood to dam back to capilliaries. This pressure causes leakage which is seen as oedema.

forward failure - not enough blood flows to the



Priorities for severe acute heart failure. Less severe failure will need less aggressive treatment.

tissues so oxygen demand outstrips supply. This is seen as excercise intolerance.

Backward and forward failure can be further classified into left and right sided failure.

left backward - pulmonary oedema and cough

left forward - poor tissue blood flow - kidneys - drug excretion

right backward - ascites, hepatic congestion (reduced drug metabolism), peripheral oedema

right forward - poor blood flow to lungs - left side filling reduced - left out put reduced

Treatment of congestive heart failure

Dogs commonly develop valvular incompetence or dilated cardiomyopathy, while cats usually get hypertrophic cardiomyopathy. However, as a general rule, the treatment given depends on the severity of the disease rather than the cause. Animals with severe congestive heart failure are usually hospitalised and treated for acute heart failure until stable. Excitement can cause congestive heart failure to become acute!

Treatment

(rest)
(low salt diet)
diuretics
vasodilators (ACE inhibitors)
positive inotropes
antiarrhythmics if necessary

Treatment is required when the normal homoeostatic mechanisms fail to keep arterial blood pressure within the normal range, or when the cardiac output is inadequate for normal tissue perfusion, or when treatment will help decrease the progression of disease.

Therapy has four principal goals
improve tissue circulation
maintain tissue oxygenation
adjust fluid compartments and venous flow to maintain blood flow but prevent congestion
normalise cardiac rhythm

Heart failure

- priorities for cardiopulmonary resuscitation Airway, Breathing and Circulation
- sympathomimetics are often used for acute heart failure in intensive care situations. They must be given by intravenous infusion and effects must be monitored.
- congestive heart failure is treated with diuretics, vasodilators, inotropes and possibly antiarrhythmics

Treatment of congestive heart failure in people has changed in the last 10 years; veterinary treatment may eventually catch up. As well as diuretics and ACE inhibitors, most people with CHF will receive β blockers (± phosphodiesterase inhibitors in the short term). A number of other treatments are coming along:

endothelin antagonists such as bosentan are particularly useful in CHF with pulmonary hypertension

endothelin converting enzyme inhibitors such as phosphoramidon

vasopeptidase inhibitors such as omapatrilat - inhibit ACE and stimulate ANP which causes vasodilatation and natriuresis

recombinant brain natriuretic peptide

You may have to (re)learn your cardiovascular pharmacology in a few years' time!

Positive inotropes

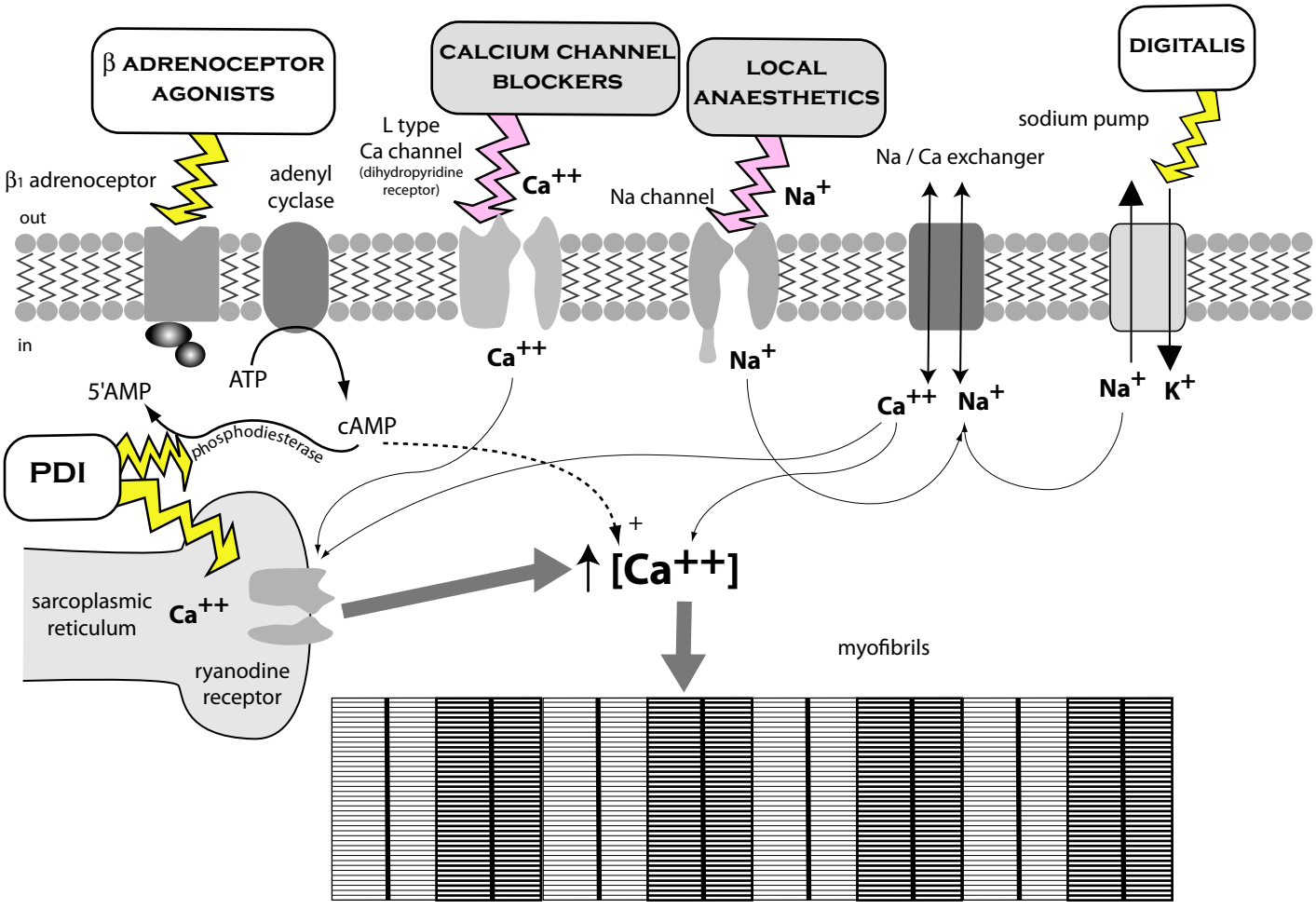
Positive inotropes are drugs which act primarily by increasing myocardial contractility, i.e. they increase the force of myocardial contraction. They require the existence of a cardiac reserve, i.e. a completely decompensated heart will not respond to these drugs. Diseased cells may or may not respond to the influence of the inotropes, depending on:

method by which the drug increases contractility
potency of the drug
type of deficit resulting in a loss of contractility
severity of the defect present in the cell
number of cells involved

The successful use of these drugs results in improvement to either the quality (ie. alleviate clinical signs at rest) or quantity (ie. increase survival time) of life.

There are three main groups of drugs: cardiac glycosides, phosphodiesterase inhibitors and sympathomimetics. As a general rule, cardiac glycosides and phosphodiesterase inhibitors are used for chronic heart failure, sympathomimetics for acute heart failure.

The mechanisms of action vary from class to class. Most drugs are thought to work by increasing the concentration of free calcium ions in the sarcoplasm, usually by triggering release of the calcium stores in the sarcoplasmic reticulum through ryanodine receptors.



Mechanism of action of positive inotropes (white boxes) and negative inotropes (grey boxes). PDI = phosphodiesterase inhibitors.

Sympathomimetics

Definition

sympathomimetic - a drug which mimics the effects of the sympathetic system. Modern drugs used for heart disease are all β_1 agonists.

These may be used for short term inotropic support of a failing myocardium. They have a very short half life and therefore are only really useful as either an iv bolus or as constant rate infusions; ie in intensive care. They are therefore normally used only in acute heart failure. Traditionally, dobutamine has been used in dogs and horses, and dopamine in people, but there is no good reason for this. Adrenaline is cheap, and is the best drug to treat anaphyllaxis in the field. This means that it should always be available and you must memorise the dose rate. Sympathomimetics are primarily used as inotropes, usually for their β_1 agonist effects, but β_1 receptor activation also increases automaticity of myocardial cells so ventricular ectopic beats are a common sign of overdose. These may progress to ventricular tachycardia or even ventricular fibrillation, so ECG monitoring is necessary. Since the object of therapy is to increase arterial blood pressure, this is usually monitored directly.

Tolerance to β_1 receptor activation can occur after as little as 8 hours so long term use is usually limited to 3 days maximum.

effect on	rate	force	SVR	ABP
adrenaline	++	+++	+++	+++
noradrenaline	-	0/+	+++	+++
dopamine	0	+++	0/-	++
isoprenaline	+++	+++	-	-
dobutamine	+	+++	+	+++
dopexamine	0/+	+++	0	+++

nb: different effects occur at different doses (SVR = systemic vascular resistance; ie, vasoconstriction: ABP = arterial blood pressure)

Drugs

Adrenaline (epinephrine USAN) is an agonist at β_1 and α_1 receptors in the heart (positive inotrope and chronotrope) and all adrenergic receptors peripherally (predominantly arteriolar constriction and a subsequent increase in afterload).

Adrenaline usually comes as a 1:1000 solution in brown ampoules (it is light and oxygen sensitive), but it should be diluted to at least 1:10,000 before use. It can be mixed with most iv fluids for infusion, although anything containing calcium is best avoided.

Indications

•cardiac arrest:
to increase the efficacy of electrical defibrillation (asystole and severe bradyarrhythmias) use atropine first

•inotropic infusion in intensive care (must monitor ECG)

•anaphylaxis / analphylactoid reactions (often to drugs) - im or sc bolus injections usually used in the field

Side effects

tachyarrhythmias leading to ventricular ectopic beats and ultimately ventricular fibrillation in overdose - monitor ECG and feel pulse for irregularities. nb tachyarrhythmias are more likely in the presence of halothane.

Noradrenaline (norepinephrine USAN) is mainly an α agonist (vasoconstriction) but has some useful β_1 effects at higher doses. It is indicated for haemostasis of mucosae and has been used for systemic vasoconstriction. It is contraindicated in heart failure (increases afterload).

Isoprenaline (isoproterenol USAN) is a synthetic β_1 and β_2 receptor agonist which increases heart rate more than other catecholamines. It decreases peripheral vascular resistance by its β_2 effects. This may cause a decrease in blood pressure. It has no real place in the treatment of heart failure as it has a positive chronotropic effect ie. increase heart rate, and a potential to cause malignant ventricular dysrhythmias. It is occasionally used to increase heart rate in third degree heart block (but a pacemaker is better).

Dopamine is an endogenous precursor of noradrenaline but also has direct effects. At a low dose (2µg/kg/min) it is a dopamine receptor agonist and causes renal, mesenteric, (coronary, cerebral) arteriolar vasodilatation. At a medium dose (2 - 5µg/kg/min) it acts at β_1 receptors to produce positive inotropy. At a slightly higher dose (5 - 10µg/kg/min) it acts at β_1 receptors to cause positive chronotropy and increased automaticity as well. At high doses (>10µg/kg/min) it affects α_1 receptors, either directly or by causing the release of noradrenaline, and causes vasoconstriction.

Since it must be given by infusion, dopamine is usually only used in intensive care, as a positive inotrope in acute heart failure or in shock when renal and mesenteric flow is decreased from vasoconstriction.

Side effects are dose dependent and include tachycardia, supraventricular and / or ventricular arrhythmias, vomiting, hypotension, and vasoconstriction. Since it is used by infusion and it has a very short half life treatment of toxicity is by slowing or stopping it

Contraindications - ventricular fibrillation & uncorrected arrhythmias

It is always given by infusion, starting at a low dose (1 µg/kg/min). Effects are monitored (ECG, ABP) and rate increased until the desired effect has been reached or toxicity (tachycardia, ventricular ectopic beats) occurs. Accurate control of infusion rate requires an infusion pump.

Dobutamine is a synthetic catecholamine with predominant β1 agonist effects which increase contractility and is relatively non-arrhythmic. It favours cardiac output redistribution to coronary and skeletal muscle beds. Renal and mesenteric flows also increase due to a total increase in cardiac output. It enhances AV conduction resulting in mild positive chronotropic effect

It is used to increase contractility in patients in acute heart failure (horses under anaesthesia), and for short term stabilisation of chronic heart failure until longer acting drugs can take effect.

Side effects are similar to dopamine.

Dopexamine is similar to dopamine but longer acting. Not available in NZ at present.

Do not use!

Since most inotropes act to increase intracellular calcium, it seems logical to use calcium salts (gluconate or chloride) as inotropes. They can be effective and used to be used for this purpose, especially after cardiac arrest, but they are much better at causing contraction of smooth muscle than cardiac muscle. This means that they produce intense vasoconstriction - in the coronary and cerebral vessels this will potentiate or even cause ischaemia. Calcium has been shown to reduce survival in acute heart failure and should not be used as an inotrope. Indeed, modern practice is to use calcium channel blockers to cause coronary and cerebral vasodilatation in cardiac intensive care, despite the small reducution in cardiac output they cause.

Dose of adrenaline

Dilute to 1:10,000 (100µg/mL)

- 20 µg/kg im or
- 5 - 20 µg/kg iv or
- 20µg/kg intratracheal, or as a **last resort only**
- 2 µg/kg intracardiac (avoid if possible)

This may have to be given in an emergency - memorise the dose!

Sympathomimetic inotropes

- used for acute heart failure in anaesthesia / intensive care
- give as iv infusion to effect
- monitor ECG for tachyarrhythmias
- in anaphylaxis use adrenaline sc

commonly used drugs

adrenaline
dopamine
dobutamine

Phosphodiesterase inhibitors

This group of drugs includes such familiar substances as caffeine (coffee), theophylline (tea) and theobromine (chocolate). Most of the drugs used in veterinary practice are esters of theophylline, such as **aminophylline** or **etamiphylline**. Newer PDIs specific for cardiac phosphodiesterase have been produced for human use, these include **amrinone**, **milrinone** and **enoximone**. "Viagra" (**sildenafil**) started out as one of these until its interesting side effects were noted. **Oxpentifylline** (pentoxyfylline USAN) is a theophylline type drug which is rather more specific for PDE 4 and has a number of different effects such as TNFα antagonism. It could be useful in CHF but is not usually used.

Mechanism of Action

(See inotropes diagram) Phosphodiesterase normally inactivates cAMP. Inhibition of cAMP degradation leads to increases in intracellular cAMP concentration, and consequent increases in activity of cAMP-dependent protein kinase. This activates many intracellular enzymes by phosphorylation. Calcium dependent enzymes are also activated, leading to stimulation of contractility due to increased effects of intracellular calcium. Their effects are additive with digoxin.

These drugs increase the rate and force of myocardial contraction. They also cause some bronchial and systemic arterial dilatation and increase the alertness of the animal, all of which is useful in dogs with CHF. There are at least 11 different types of phosphodiesterase (and numerous subtypes), so the range of effects is large.

The cardiac specific phosphodiesterase inhibitors (PDI3s) were initially widely touted as an alternative to digitalis in man but are going out of fashion as although they alleviate congestive heart failure, they reduce survival time in man. They seem to improve the quality of life but increase the chances of sudden death, probably from arrhythmias. This is probably acceptable in animals.

PDI4s are currently undergoing investigation as anti-inflammatory drugs. Sildenafil is a PDI5.

Methylxanthines

Methylxanthines (usually theophylline esters such as aminophylline or etamiphylline) are also adenosine A2 receptor antagonists. Adenosine is secreted by most cells in response to high energy usage compared to oxygen availability, and acts as an autacoid to decrease the oxygen demand and to increase oxygen availability through alterations to blood flow.

Effects

Methylxanthines act as weak positive inotropes, but more importantly they relax smooth muscle in bronchi and pulmonary vasculature. They induce diuresis both by increasing cardiac output and hence renal blood flow, and by increasing renal blood flow directly through blockade of adenosine's vasoconstrictive actions in renal vessels. Methylxanthines may also cause central stimulation which is probably a major part of their clinical effect (a previously lethargic dog becomes active again). The relative importance of these effects is different for each drug.

Side effects

CNS excitation - restlessness to convulsions

tachycardia which can lead on to ventricular tachyarrhythmias and sudden death

tachypnoea

Indications

mild congestive heart failure, for bronchodilator effects in patients with myocardial failure, pulmonary oedema or asthma.

Phosphodiesterase isoenzymes. Theophylline (and papaverine) are non-specific inhibitors.

enzyme	subtypes	tissue	inhibitors
PDE1	A, B, C	CNS, blood vessels	
PDE2	A		
PDE3	A, B	myocardium, blood vessels	milrinone, pimobendan,
PDE4	A, B, C, D	airways, inflammatory cells, CNS, stomach	rolipram, oxpentifylline,
PDE5	A	blood vessels, platelets	sildenafil,
PDE6	A, B, C, D, G, H	retina	sildenafil,
PDE7	A, B	skeletal muscle	
PDE8	A, B		
PDE9	A		
PDE10	A		
PDE11	A		

Care

use with caution in animals with
- severe cardiac disease
- gastric ulcers as it induces gastric acid secretion
- hyperthyroidism
- renal or hepatic disease

antagonises β blocker effects

Dose

Theophyllines have a low therapeutic index so determine dosage correctly. Dose obese animals on their lean body weight. Sustained release products offer the advantage of less frequent dosing, better owner compliance and less fluctuation in blood levels but results may be erratic in animals. im injection is painful; iv injection must be very slow, though because of good bioavailability of oral preparations it is rarely used.

Other drugs

Amrinone was the first specific cardiac phosphodiesterase inhibitor but is no longer available in NZ. An intravenous bolus of amrinone in dogs leads to a 60 -100% increase in cardiac contractile force which lasts 5 - 20 minutes, and a 10 - 30% increase in systemic arterial blood pressure. In humans amrinone improves left ventricular performance and this effect is sustained. Withdrawal of therapy results in cardiac decompensation. It was used for short term management of congestive heart failure refractory to other treatment. Its long term efficacy for congestive heart disease has not been evaluated in animals, in people long term survival is reduced.

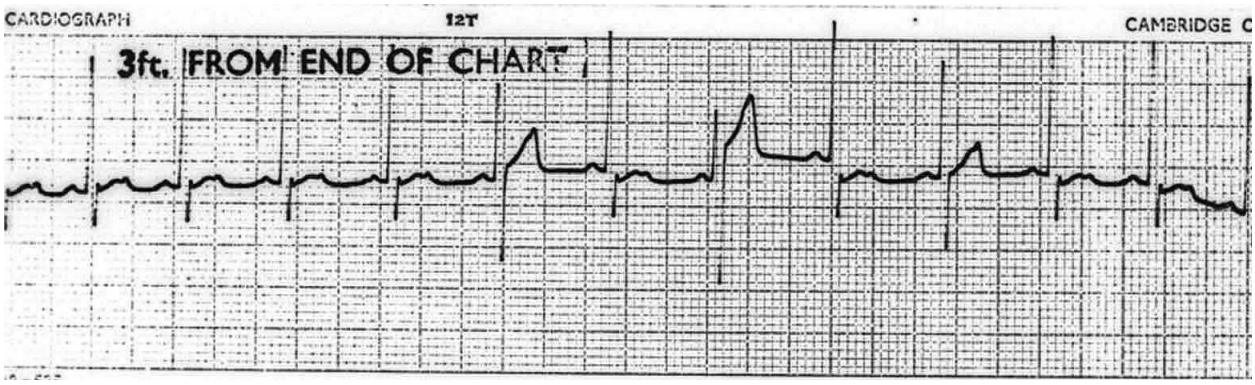
Milrinone is the only cardiac specific PDI available here. It is a methylcarbonitrile derivative of amrinone which is 20 to 30 times more potent than amrinone. Its cardiovascular effects are reported to be similar to those of amrinone but without increases in heart rate. In one trial approxiamately 70% of dogs with myocardial failure responded well to this drug.

Its short half life and duaration of action in dogs mean that it usually has to be given four times daily so is not really practical for outpatients.

Milrinone has a large therapeutic ratio. Ventricular arrhthymias occur in < 5% of dogs with myocardial failure.

Pimobendan is a similar drug which is most commonly used in dogs. In addition to PD inhibition, it is also supposed to "sensitise" the myocardium to calcium. This effect is likely to be useful since it involves no extra oxygen consumption and the myocardial calcium modulation is impaired in CHF. It prolongs life in dogs in dilated cardiomyopathy but not in valvular insufficiency. It is usually used in combination with ACE inhibitors and frusemide. Like the methylxanthines, its major effect may be in the CNS to make the dog feel better.

Oxpentifylline (pentoxyfylline USAN) is not normally used to treat CHF, but may be useful, both as a PDE inhibitor and as a tumour necrosis factor α antagonist (reduces myocardial inflammation).



Beware of these!

commonly used drugs

etamiphylline

Cardiac glycosides

Definitions

A glycoside is a molecule to which sugars are attached. They are commonly produced by plants. The terms "cardiac glycoside" and "digitalis" are used interchangably because these drugs were traditionally obtained from the foxglove *Digitalis purpurea* (digitoxin) or *D. lanata* (digoxin). *D purpurea* is a common weed in NZ and an occasional cause of poisoning (although much rarer than overdose by vets - it tastes disgusting).

Chemistry

They are complex molecules present in a variety of plants, a number of which have been used therapeutically including **digoxin** (the only one available in NZ), digitoxin, oubain (which is probably the endogenous ligand) and lanatoside C. Other cardiac glycosides are usually only encountered as toxins: convallotoxin (from lily of the valley) and squill (from sea holly; previously used as rat poison).

They consist of a steroid nucleus with a lactone ring (responsible for activity) to which are attached three sugars (different with the different drugs) which influence solubility and binding.

Effects

positive inotrope
negative chronotrope

Mechanism of Action

positive inotropic effect: Digitalis glycosides bind to the K+ binding site of the sodium pump. This inhibits Na+ being pumped out of the cell; the extra Na+ is exchanged for Ca++ resulting in an increased intracellular Ca++ concentration which increases contractility (see diagram). Numerous other mechanisms have been proposed but this is currently thought to be the main one.

negative chronotropic effects: Thought to be due to stimulation of central vagal nuclei and potentiation of the effects of acetylcholine in atrial myocardium and in AV conducting tissue. Together this results in an increase of vagal tone. In the atria this increased parasympathetic tone decreases atrial automaticity, depresses atrial conduction and increases the effective and functional refractory periods. At the AV node, increased parasympathetic tone decreases atrioventricular conduction slowing ventricular response to atrial fibrillation and flutter. The most pronounced ECG change therefore, is prolongation of the P-R interval (first degree heart block), although total heart block can occur.

Indications

congestive heart failure caused by dilated cardiomyopathy

supraventricular tachycardias especially **atrial fibrillation** or flutter

There are no large scale studies in dogs but in people, digitalis only benefits a proportion (different in each trial) of patients in sinus rhythm with congestive heart failure.

Pharmacokinetics

Absorption - may be decreased by food. Time to peak plasma concentrations vary depending on the formulation and dose

Distribution - digoxin is approximately 20% bound to serum proteins (species dependent) and the remainder is free in the serum. Digoxin is strongly bound to skeletal muscle but is also distributed widely, with the highest concentration in kidney, heart, intestine, liver and skeletal muscle. Lowest concentrations are found in the plasma and brain. The half life in the dog varies between 14 - 56 hours, in the cat it is between 33 - 58 hours, ie plasma concentrations take several days to stabilise.

Metabolism - approximately 15% is metabolised by the liver. (remember there is decreased hepatic function in both right and left sided heart failure) In some people, metabolism by gut bacteria is important, and antibiotic induced changes in gut bacteria may lead to digoxin toxicity.

Elimination - the remaining 85% is excreted renally by glomerular filtration and tubular secretion so be careful with patients in renal failure and adjust the dose appropriately using therapeutic drug monitoring.

Severe heart disease will affect all aspects of pharmacokinetics - care is required!

Clinical use

Though this is rarely done, in life threatening supraventricular tachyarrhythmias it is possible to rapidly "digitalise" a patient. This process risks inducing serious ventricular arrhythmias, but may be life saving on rare occasions. More usually, digoxin is administered at the maintenance dose rate, allowing the animal to come to steady state over a period of several days. Maintenance therapy doses are usually calculated on the basis of body surface area (see pharmacokinetic notes).

Dosage with cardiac glycosides will vary considerably with the following factors:

•age: as older animals have less skeletal muscle and therefore less binding of drug. Glomerular filtration rate decreases with age and with decreased cardiac output

•obesity: as digoxin is not very lipid soluble, then dosage must be based on lean bodyweight. Conversely, digitoxin is lipid soluble so dosage is unchanged

•electrolyte imbalances: because these drugs compete with K+ for binding to the Na/K ATPase, in hypokalaemia the dose must be reduced and visa versa for hyperkalaemia (monitor serum electrolytes or look at T wave on the ECG). Dosage should also be reduced for hypernatraemia and hypercalcaemia. However, it is better to correct the underlying fluid/electrolyte imbalance first.

•concurrent drug administration

•myocardial failure: If the animal is in myocardial failure or is hypoxaemic they are more sensitive to digitalis.

Monitoring digoxin treatment

Steady state peak and trough concentrations should be maintained between 1.0 - 2.5ng/ml (dog) and 0.9 - 2.0ng/ml (cat).

Mild toxicity is seen at concentrations of 2.5 - 6 ng/ml. Severe toxicity is seen at > 6 ng/ml.

Contraindications

digitalis intoxication
ventricular fibrillation
pericardial disease
(hypertrophic cardiomyopathy)

Care

animals with renal failure or lung disease

Safety and Toxicity

Digitalis has a very low therapeutic ratio. Sudden calcium influx can cause arrhthymias due to electrical instability in myocardial cells, so work up to a steady state on a maintenance schedule and do not use loading doses.

Mild toxicity - anorexia, nausea, vomiting, and diarrhoea. Appropriate treatment is to withdraw digoxin for 24 hours, then give maintenance at 50 % of the initial dose for 12 hours. Use therapeutic drug monitoring to check.

Digoxin can be directly irritant to the gastric mucosa, causing vomiting. This is worse with the tablet formulations, and can be difficult to clinically differentiate from toxicity due to high plasma concentrations. Try using elixir formulations if tablets are causing irritation.

Serious toxicity - increased excitability - ventricular ectopic beats, especially bigeminy, ventricular tachycardia. Give lignocaine or similar drug.

Treatment of acute toxicity

Atropine will help to block the increased vagal tone. Anti-arrhthymic drugs may be used: phenytoin or lignocaine are the drugs of choice. Procainamide or propanolol may also be useful. Digoxin antibodies which mop up the drug are available but difficult to obtain and extremely expensive.

Drug interactions

Do not use quinidine or verapamil as they may increase serum digitalis concentrations. Frusemide decreases renal blood flow and blood volume, requiring a reduced dosage of glycosides due to slower elimination. Frusemide also causes an increased loss of K^+, as do other diuretics (especially thiazides), and thus potentiate digitalis. Drugs that induce or inhibit hepatic microsomal enzymes may also affect dose levels.

Digitoxin is not available in NZ. It is similar to digoxin but as it is primarily metabolised in the liver, could be useful in patients with renal insufficiency (instead of digoxin). It is 70 - 90% protein bound (cf. digoxin which is only 20% protein bound) and has a much shorter half life of between 8-12 hours in the dog. This means that it is possible to achieve therapeutic concentrations on a maintenance schedule in 24-36 hours and if toxicity occurs reduce it in 8-12 hours. This more rapid clearance is one of the reasons some cardiologists prefer this drug to digoxin. The half life in the cat is >100 hours and so do NOT use in this species. (It also has a long half life in man.)

commonly used drugs

digoxin

Cardiac glycosides

- digitalis binds competitively to potassium binding site of sodium pump
- lowered potassium will increase digoxin's effect
- digoxin is a positive inotrope and negative chronotrope
- negative chronotropy can progress to heart block
- side effects - vomiting and anorexia, ventricular tachyarrhythmias
- indications - congestive heart failure, atrial fibrillation with tachycardia

Vasodilators

These have recently become the treatment of choice for treating congestive heart failure in people and dogs, since they have been shown fairly conclusively to prolong life.

Late congestive heart failure leads to vasoconstriction by a variety of mechanisms including increased sympathetic tone, renin - angiotensin system activation and increased ADH concentrations. Arterial vasodilatation reduces afterload, myocardial work, oxygen consumption, pressure across the mitral valve and thus increases cardiac output. Venous vasodilatation reduces preload and oedema.

Vasodilator indications

congestive heart failure
mitral regurgitation
control of ABP during anaesthesia
navicular disease (isoxuprine)
(essential hypertension - not recognised in domestic animals)

Vasodilator side effects

hypotension
reflex tachycardia
plus effects specific to individual drugs

Drugs

A very large number of drugs can cause vasodilatation; it is usually regarded as an undesirable side effect. The main group of vasodilators used for chronic heart failure is the angiotensin converting enzyme inhibitors. These are given orally for long term treatment. Nitrates and calcium channel blockers are less commonly used for both acute and chronic heart failure. They can be given by a variety of routes. Great care is needed if they are given iv in acute situations. A range of other drugs are used rarely, usually in a desparate attempt to find something that works!

Angiotensin converting enzyme inhibitors

Some of the few drugs proven to prolong life in dogs. Many ACE inhibitors are available, there is no obvious difference between them apart from duration of action.

Physiology

The renin - angiotensin - aldosterone system is an important mechanism for maintaining blood pressure in the face of various challenges. Renin release from the juxtaglomerular apparatus is stimulated by a fall in blood pressure, reduced renal blood flow, reduced sodium concentration in the distal tubule, increased renal sympathetic activity and a host of other factors poorly understood. β agonists and PGI_2 also stimulate renin production. Atrial natriuretic peptide reduces renin production: angiotensin II does the same, possibly by the same mechanism. Renin then converts angiotensinogen to angiotensin I.

ACE inhibitors block the enzyme which converts angiotensin I to angiotensin II. Most of their effects can be attributed to a reduction in ATII levels. ATII produces most of its effects at the confusingly named AT1 receptors (see diagram).

ACE is also responsible for breaking down bradykinin which can act as a vasodilator by stimulating PLA_2 which results in the production of prostacyclin, and by causing the release of nitric oxide from endothelial cells.

Most ACE is bound to the surface of endothelial cells, but it can occur in other tissues such as cardiac muscle. ACE inhibitors tend to reverse the cardiac hypertrophy seen in heart failure.

Effects

In normal healthy animals and people, ACE inhibitors have no effect after a single dose and cause only a small drop in blood pressure after several days' treatment. It seems likely that there has to be increased renin release (and thus more ATI available for conversion to ATII) before ACE inhibitors have much effect. Most dogs with congestive heart failure will have increased sympathetic tone, and may also have reduced arterial blood pressure leading to increased renin release. Some dogs may be on low salt diets in an attempt to cause sodium depletion.

The end result in dogs with CHF is that there is a decrease in venous and diastolic intra-cardiac pressure with a concurrent decrease in afterload and so a resultant increase in cardiac output. They relax both capacitance and resistance vessels, but preferentially affect the kidney heart and brain. They are often used with diuretics such as frusemide (although frusemide probably has some vasodilator action of its own), but the interactions can cause kidney failure (see below). ACE inhibitors have their own mild diuretic and natriuretic effect.

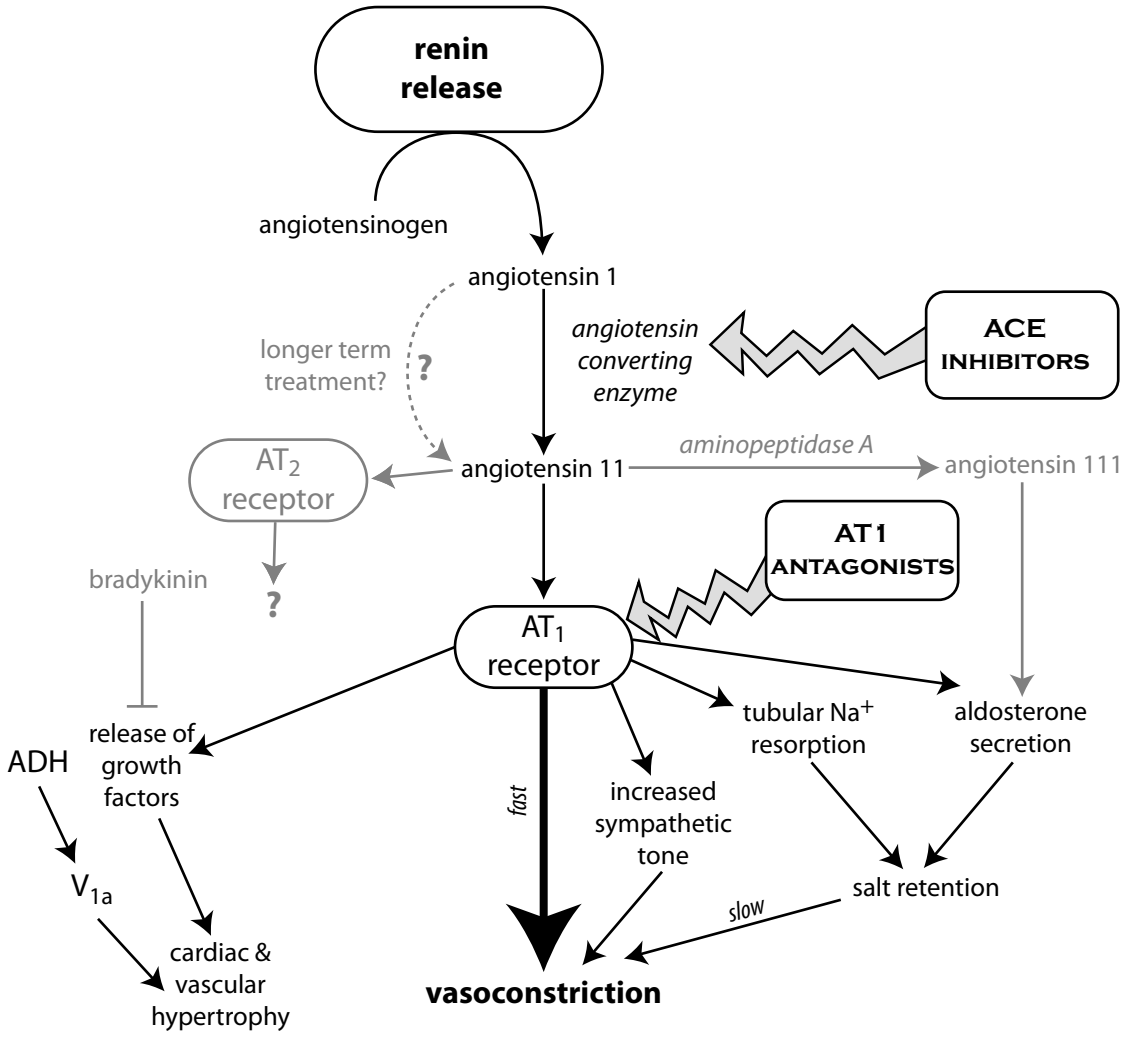
The vasodilatation produced by increased bradykinin may also be important in heart failure.

Indications

vasodilator in the treatment of congestive heart failure, especially valvular disease

Side effects

hypotension in overdose
anorexia, vomiting and diarrhoea
at high doses glomerular lesions and renal failure (monitor BUN and serum creatinine) may be induced



The renin - angiotensin - aldosterone system. The pathways in grey are of unknown importance.

since they also inhibit aldosterone they may cause a hyperkalaemia therefore monitor electrolytes especially if using potassium sparing diuretics as well

In people, ACE inhibitors often cause coughing - thought to be caused by increased bradykinin in the airways.

Precautions

care in renal insufficiency patients

Inside the kidney, there are lots of AT1 receptors on the vasa recta. ATII can alter glomerular filtration rate by constricting the afferent arteriole, by contracting the mesangial cells or by constricting the efferent arteriole. In normal animals, the end result of ATII on GFR is not much change, but in hypotension the effects on the efferent arterioles are thought to predominate. (This is inferred from two experiments using small numbers of dogs which were also sodium depleted, either by dietary restriction or frusemide administration and dietary restriction. They were also anaesthetised, heparinised and subject to very invasive surgery and extracorporeal circulation.) An alternative theory is that the afferent arterioles constrict in direct response to being stretched by increased blood pressure, resulting in constant glomerular flow rates and GFR.

Acute renal failure has been reported after ACE inhibitors in man, but usually in cases of renal artery stenosis, which lowers the pressure in the afferent arteriole. Only two cases have been reported in dogs, both of which also had frusemide (one had digoxin (at toxic levels) as well). It seems likely that the frusemide was at least as much to blame as the ACE inhibitor in these cases. Both had low plasma sodium concentrations (132 & 137mM) which were probably caused by the frusemide. Since ATII helps maintain blood pressure in low sodium states, they were probably hypotensive as well (not measured). Since GFR will depend on the pressure in the afferent arteriole, in the absence of a downstream constriction, that will depend on arterial blood pressure. Thus reduced GFR will result in a reduced amount of urea filtered. However, there is some evidence that in sodium depletion active uptake of urea occurrs to try to maintain the hyperosmolarity in the medulla (normally 66% due to sodium, 33% urea). The dehydration caused by overdosing with frusemide will also cause uraemia (nb. dogs are usually given 4 - 20 times the human maintenance dose of frusemide). If the uraemia causes nausea and vomiting and stops the animal drinking, then a vicious circle will have been set up.

caution in hyponatraemia, pre-existing haematological abnormalities or a collagen vascular disease ie. systemic lupus erythematosus

breeding / pregnant dogs (uterine relaxation)

teratogenic in women

Captopril has a short half life in the dog (3 hours), so must be given two or three times daily. **Enalapril** is basically the same as captopril except that it is a prodrug, which is metabolised by plasma esterases to the active metabolite enalaprilat. This active drug has a longer therapeutic duration

than captopril, enabling once daily dosing in dogs. It has been proven in clinical trials to increase the life span of dogs with congestive heart failure (in combination with the diuretic frusemide). **Benazepril** is similar to the other ACE inhibitors, suitable for once daily dosing. The human drug **quinapril** is sometimes used in dogs because it is cheap.

There are dozens of other ACE inhibitors in human use, which probably also work in animals.

AT1 receptor antagonists such as **losartan** and **candesartan** are starting to be used in people. They may be slightly more effective (AT11 can be formed by other routes than ACE) and have fewer side effects. They are used mainly in patients who do not tolerate ACE inhibitors, and there is no experience in domestic animals.

Nitrates

Converted to nitric oxide (Endothelial Derived Relaxing Factor) in endothelium which diffuses into smooth muscle cells and causes relaxation by increasing cGMP activity. They mainly produce venous dilatation but also arterial at slightly higher doses.

Sodium **nitroprusside** has a very short half life and is only used in anaesthesia / intensive care in critically ill patients having a hypertensive crisis, acute heart failure secondary to mitral regurgitation, severe refractory cardiac heart failure or for cardiovascular surgery. **Do not use unless ABP is being monitored continuously** - it is very easy to overdose.

Pharmacokinetics

Almost instant response from an iv infusion though will return to pretreatment levels in 1-10 minutes once infusion stops.

Metabolised in blood and tissues to cyanide which is converted in the liver to thiocyanate and eliminated in the urine, faeces and exhaled.

Half life is 2-7 mins though this may increase if there is renal impairment or hyponatraemia.

Solutions are unstable and must be protected from light (wrap drip bag & giving set in aluminium foil).

Side effects and Toxicity

hypotension in overdose - give dobutamine
(cyanide toxicity at very high dose rates)

Nitroglycerine (glyceryl trinitrate) can be used like sodium nitroprusside as an iv infusion in intensive care or applied as ointment or patch for more chronic use.The injection is used for acute control of arterial and venous dilatation; the ointment for venous dilatation in cardiogenic pulmonary oedema.

The ointment is designed to be slowly but continuously absorbed with onset of action within 1 hour, duration of action of 2 - 12 hours. Metabolism is rapid - duration of action of iv injection 7 - 10 mins. The ointment is designed to cross human skin - make sure you use gloves and give the animal's owner some.

Overdose will cause hypotension and decreased cardiac output. It should not be used in shock.

Isosorbide dinitrate is very similar, but in tablets.

Other vasodilators

Dihydropyridine calcium channel blockers such as **nifedipine** and **nicardipine** are widely used in people, but not often in animals. These have less cardiac affect than verapamil and diltiazem.

Hydralazine's mechanism of action is unknown but it is a potent direct acting arteriolar vasodilator. This effect is not the same in all vascular beds: - there is more of a decrease in cerebral, coronary, renal and splanchnic vascular beds then in muscle or skin. The increase in renal blood flow causes an increased GFR and helps increase total cation excretion.

It is used in left sided myocardial failure and mitral regurgitation.

Prazosin is now obsolescent. It is an α_1 adrenoreceptor antagonist which dilates both arterioles and veins. It produces less reflex tachycardia and less activation of the renin-angiotensin system (ie. Na retention) than with hydralazine.

It is usually only used for adjunctive therapy of congestive heart failure particularly secondary to mitral or aortic valve insufficiency when hydralazine is not effective or not tolerated, treatment of systemic hypertension or pulmonary hypertension in the dog, or in dogs that do not respond well to other agents.

Side effects and Toxicity

hypotension
may get syncope (orthostatic hypotension)
CNS signs, GIT signs
tolerance develops
Care is required in chronic renal failure

Doxazosin is a modern α_1 antagonist used in man.

Isoxuprine can be used for navicular disease in horses. Its mechanism of action is unknown, but it has some β_2 agonist effect. It is contraindicated in pregnancy, and in mares up to 2 weeks post partum. Its main side effect is tachycardia.

Other drugs not likely to be used for vasodilator effect

potassium channel openers
diazoxide
β_2 *adrenergic agonists*
salbutamol
α_2 *adrenergic agonists*
clonidine (used in man)
xylazine, etc
β_1 *adrenergic antagonists*
labetolol
indirect sympathetic blockers
many drugs
ganglion blockers
hexamethonium
This list is not exhaustive!!

Vasodilators

- reduce afterload and can prolong life in CHF
- nitrates are converted to nitric oxide
- angiotensin converting enzyme inhibitors block production of angiotensin 2 and are probably the best drugs to use in CHF
- hydralazine is sometimes used if nothing else works

commonly used drugs

angiotensin converting enzyme inhibitors
benazepril
captopril
enalapril
nitrates
glyceryl trinitrate

Antiarrhythmics

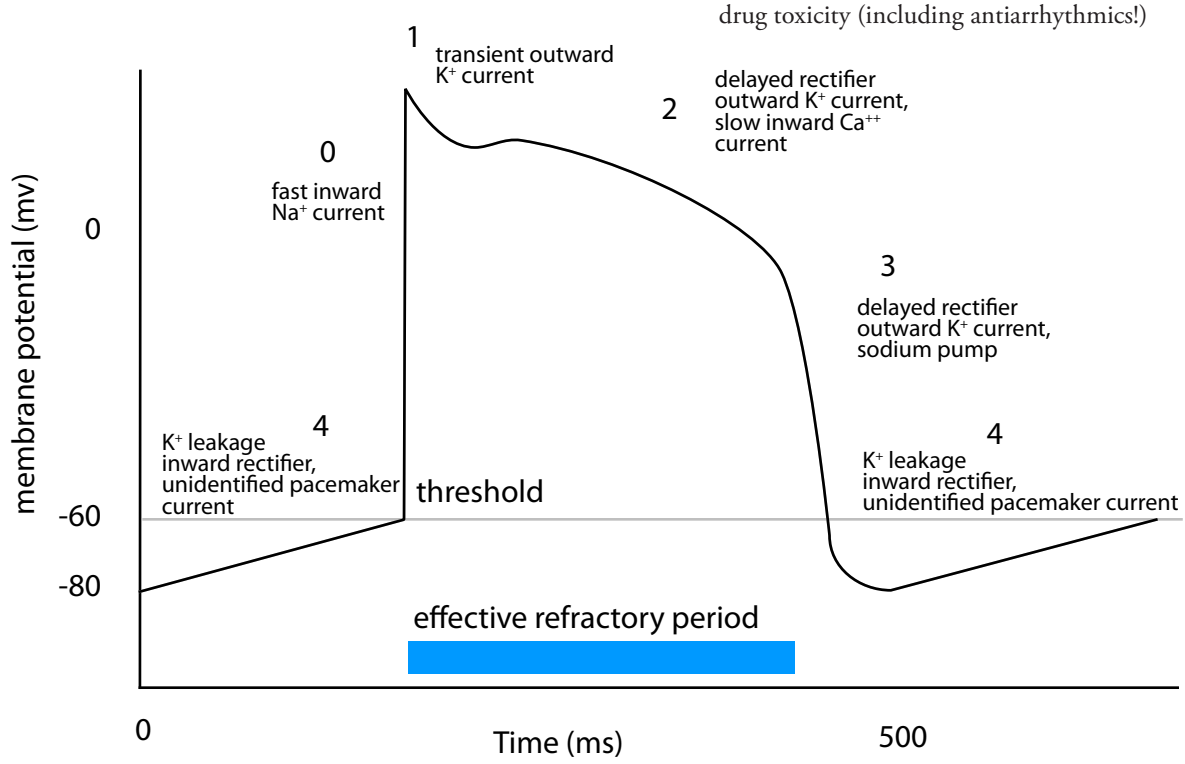
Definitions

arrhythmias (= dysrhythmias) - abnormal cardiac rhythm. They may be abnormalities of impulse formation, conduction, rate or regularity and arise from delayed after-depolarisation or re-entry.

Arrhythmias may not affect the heart's efficiency as a pump and require no treatment, eg sinus arrhythmia which is normal in fit animals. Other arrhythmias eg ventricular fibrillation are immediately life threatening. Most arrhythmias fall between these extremes. (nb, all antiarrhythmic drugs decrease cardiac output to some extent, and may also cause arrhythmias, so you have to be sure that the presenting arrhythmia is worse for the animal than the treatment.)

Causes

other heart disease
hereditary
autonomic system
metabolic disease
    hypoxia
    acidosis
    electrolyte imbalance (particularly K^+)
drug toxicity (including antiarrhythmics!)



Cardiac action potential in conducting tissue. Numbers refer to the phases of the action potential. The resting membrane potential depends on the extracellular K+ concentration, as K+ rises it approaches the firing threshold.

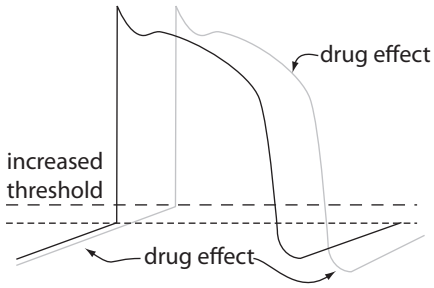
Vaughan Williams classification of antiarrhythmic drugs

I sodium channel blockers (reduce excitability of conducting tissue)
- **Ia eg quinidine**
- **Ib eg lignocaine**
- **Ic eg flecainide**

II β blockers (reduce automaticity) eg propranolol
III potassium channel blockers (prolong action potential) eg amiodarone
IV calcium channel blockers (block nodes & damaged muscle) eg verapamil

nb. many drugs have several effects and do not fit neatly into one class.

Class 1



Sodium channel blockers

Can be subclassified on receptor kinetics - class 1b interact with sodium channels and dissociate again in less than 1 sec, class 1a 1 - 10 secs, class 1c > 10 secs.

Effects

Increased firing threshold, increased effective refractory period. The action potential may be either slightly prolonged or slightly shortened. Action potentials triggered by after depolarisations are inhibited.

Effects on animals will vary according to the heart rate, the tissue and its health (in general, these drugs have a greater effect on diseased tissue). This means that class 1 drugs can have a wide range of effects.

Class 1a antiarrhythmics

Quinidine is mainly used in horses because it is cheap enough to give horse size doses. It is used in supraventricular arrhythmias especially atrial fibrillation.

Quinidine has a short half life in dogs and cats so is not much use for maintenance. It is poorly tolerated by dogs.

Side effects and toxicity

•anorexia, vomiting, diarrhoea

•QRS duration and Q-T intervals are increased - if there is a 50% increase in the QRS then remove drug promptly ie. need to monitor with ECG

•ventricular arrhythmias - increase in Purkinje fibre automaticity

•sudden death from ventricular fibrillation possible

All these are potentiated by hypokalaemia.

Contraindications

myasthenia gravis, complete A-V block, intraventricular conduction defects, symptoms of digitalis toxicity

Care is required in acid-base disorders, hypokalaemia, hypoxia, and renal or liver insufficiency

Interactions

increases digitalis plasma levels - displaces digoxin from skeletal muscle binding and reduces digoxin plasma clearance

increased chance of arrhythmias with diuretics which induce hypokalaemia, ie frusemide and thiazides.

Procainamide is effective against ventricular tachyarrhythmias and was used primarily for these but may be effective against supraventricular arrhythmias in high doses. No longer available in NZ.

Class 1b antiarrhythmics

Lignocaine (lidocaine USAN) is used in life threatening ventricular arrhythmias, particularly v. tachycardia and v. premature complexes. Do not use lignocaine with adrenaline - this is only for local anaesthetic use.

Pharmacokinetics

Absorption - onset of action after iv injection is within 2 minutes and duration of 10-20 minutes

Distribution - rapidly redistributed into highly perfused organs - heart failure may decrease the volume of distribution (Vd is about 4.5 l/kg in the dog)

Metabolism - short half life - 90 - 100 minutes - rapidly metabolised by the liver to active metabolites. This may be prolonged by liver disease or poor hepatic perfusion ie. cardiac disease. If given po, lignocaine is 100% metabolised on the first pass through the liver.

Elimination - less then 10% of a parenteral dose is excreted unchanged in the urine

Side effects and Toxicity

CNS effects - drowsiness, emesis, nystagmus, muscle twitching and seizures - can be very severe in the cat

methaemoglobinuria especially in cats

Treat by withdrawing drug; may need to use diazepam or barbiturates for seizure control as well.

Contraindications

severe SA, AV, or intraventricular heart block

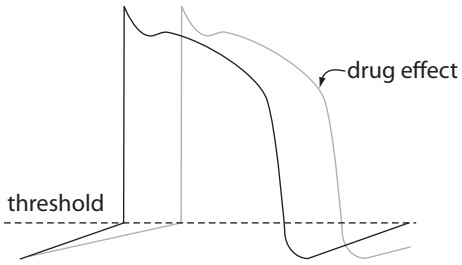
caution in patients with liver disease, congestive heart failure, shock, hypovolaemia, respiratory depression or hypoxia

Tocainide and **mexilitine** are similar to lignocaine but longer acting and are designed to avoid first pass metabolism so can be given by mouth. They are used sometimes for oral treatment of ventricular tachyarrhythmias. **Phenytoin** is again similar to lignocaine but longer acting with more side effects. Not often used.

Class 1c antiarrhythmics

Flecainide is the only one available in NZ. Occasionally used in atrial fibrillation and other supraventricular tachycardias.

Class 2



β adrenergic blockers

Dozens of β adrenergic antagonists (mainly specific β_1 blockers) are available for people but **propranolol** is the only drug widely used in animals (because it is cheap, not because it is a great drug).

Propranolol is a non specific β adrenergic antagonist - ie, it blocks both β_1 and β_2 receptors. Its anti-arrhythmic effects are caused by decreasing catecholamine dependent automatic rhythms and slowing conduction in abnormal ventricular myocardium - also increase the refractory period of AV nodal tissue, so slowing down the ventricular response to atrial fibrillation and flutter and effectively abolishing supraventricular arrhythmias due to A-V node re-entry. By decreasing contractility it also decreases myocardial oxygen consumption

Indications

supraventricular tachyarrhythmias

feline hyperthyroidism to prevent myocardial hypertrophy

(used for congestive heart failure in people)

Pharmacokinetics

Absorption - oral - well absorbed and almost complete - biavailability between 2 - 17% after first pass effect in the liver

Distribution - highly lipid soluble and readily crosses the blood brain barrier

Metabolism - has extensive first pass effect in the liver: half life in dog is 1-2 hours. Effects seen longer than half life because of active metabolites and receptor binding

Elimination - renal with less than 1% unchanged

Side effects and Toxicity

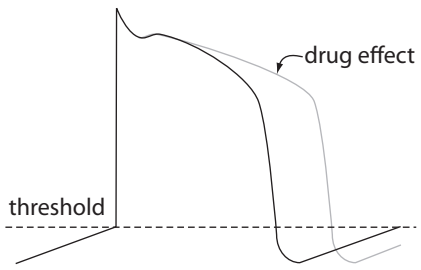
bradycardia, myocardial depression - may make congstive heart failure worse, hypotension, bronchospasm (β_2 block)

can get exacerbation of side effects with acute withdrawal of therapy

Contraindications

- overt heart failure
- greater than first degree heart block
- asthma or chronic lower airway disease due to beta blocking as it may further constrict airways
- caution in diabetics as get decreased sympathetic compensation for hypoglycaemia
- care in patients with renal or hepatic insufficiency
- care when using in combination with digitalis

Class 3



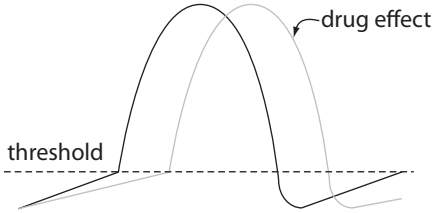
Potassium channel blockers

Rarely used in either man or animals, but most new experimental drugs fall into this class so that situation may change. **Amiodarone** (a thyroxin analogue) is the main drug of this class used in people but has a very long half life and lots of side effects; **bretylium** is sometimes used in dogs with refractory ventricular arrhythmias.

Sotalol is a β blocker which also acts as a class 3 drug and has been used in dogs.

Side effects can include tachyarrhythmias.

Class 4



Calcium channel blockers

Note that some (**verapamil**, **diltiazem**) are more specific (but not completely specific) for the heart and others (dihydropyridines: **nifedipine** etc) are more specific for blood vessels (as vasodilators). They block the inward Ca^{++} current across membranes of myocardial cells and vascular smooth muscle. This inhibits both phase 4 of the action potential and the contractile mechanisms of vascular and smooth muscle. They also slow phase 0 in SA and AV nodes

Verapamil is the drug of choice for severe acute supraventricular tachyarrhythmias and may help with atrial flutter or fibrillation.

Side effects

peripheral vasodilation - hypotension
decreases myocardial contractility
bradycardia

Contraindications

severe congestive heart failure
hypotension
sick sinus syndrome
2nd or 3rd AV block
digitalis intoxication
do not use with propanolol

Diltiazem is similar in most respects to verapamil except that it has more favourable pharmacokinetics, and has been reported to be more effective in feline idiopathic dilated myocardopathy than verapamil. It is usually preferred for long term oral use.

Other antiarrhythmics

Muscarinic antagonists such as **atropine** are used in bradyarrhythmias. **Glycopyrrolate**, which does not cross into the brain, is a bit more specific for the heart and longer acting but expensive. These drugs are often given since they are relatively safe (although tachycardia will lead to myocardial hypoxia).

Digoxin (see inotrope notes) is often used as an antiarrhythmic in man for atrial fibrillation, and to a lesser extent in dogs (do not use in horses for AF - hye usually have a slow ventricular rate and digoxin will make it worse).

Adrenergic β_1 agonists (usually **isoprenaline**) are very occasionally used to treat bradyarrhythmias but reduce the efficiency of contraction (ie, oxygen use increases more than the force of contraction) which is not what is wanted in a hypoxic myocardium. Antimuscarinics are better in the short term, pacing in the long term.

Adenosine is sometimes used for supraventricular tachycardias. It must be given by rapid iv bolus as it is metabolised very quickly. May produce transient asystole!

In hyperkalaemia, **calcium** is sometimes used to control arrhythmias. The hyperkalaemia needs to be corrected as well though - usually by giving insulin & glucose together.

Clinical use

Arrhythmias are usually diagnosed by ECG: resist the temptation to treat the ECG rather than the animal.

1 Identify and remove the cause

hypoxia, electrolyte disturbances, other drugs eg. digitalis or frusemide.

2 Establish the goals of treatment

Can be anything from improving the quality of life to producing a normal ECG. Determine if treatment is necessary ie. assess the risk/benefit.

3 Decide on the best treatment

which may include
drugs
physiological manouveres
cardioversion (DC shock)
pacemaker
combination of drugs and other treatment
no treatment at all (often most appropiate)

Combinations of drugs are sometimes used but should be avoided if possible - many can cause severe drops in cardiac output.

Summary of effects

	Ia	Ib	II	III	IV
SA node automaticity	0/-	0/-	--	+/-	0/+
AV node conduction	-	0	-	-	---
Purkinje fibres					
AP duration	+	-	0	++	-
refractory period	+	++	0	++	-/0
membrane response	---	--	-	0	-/0
automaticity	-	---	-	0	-/0

nb. all will reduce cardiac output to some extent

There is plenty of dispute about when to use which drug: my preferences are:

sinus bradycardia	atropine, glycopyrrolate
atrial flutter / fibrillation	all classes, digoxin
supraventricular tachycardia	Ia, IV, adenosine
junctional tachycardia	all classes except Ib
ventricular ectopic beats	III (II, Ib)
ventricular tachycardia	III (II, Ib)
heart block	pacemaker (isoprenaline)

Antiarrhythmics

• Vaughan Williams classification
I - sodium channel blockers
Ia - atrial fibrillation
Ib - ventricular ectopic beats
II - beta blockers - stress induced tachycardias
III - not used much
IV - calcium channel blockers - atrial tachycardias
• other antiarrhythmics
digitalis - atrial fibrillation
adenosine - supraventricular tachycardias
calcium - ventricular tachycardia due to high potassium

commonly used drugs

Class 1
lignocaine, quinidine
Class 2
propranolol, atenolol
Class 4
verapamil, diltiazem
Others
atropine, adrenaline, digoxin, adenosine, calcium

Diuretics

Diuretics are drugs which cause increased urine production, ie, water and sodium loss. They are used to reduce preload in congestive heart failure and for life threatening situations like pulmonary and cerebral oedema. Most act by increasing sodium ion concentration in the urine and thus drawing water out too. Only **frusemide** (furosemide USAN) is commonly used, the others are occasionally used in specific situations.

Drugs

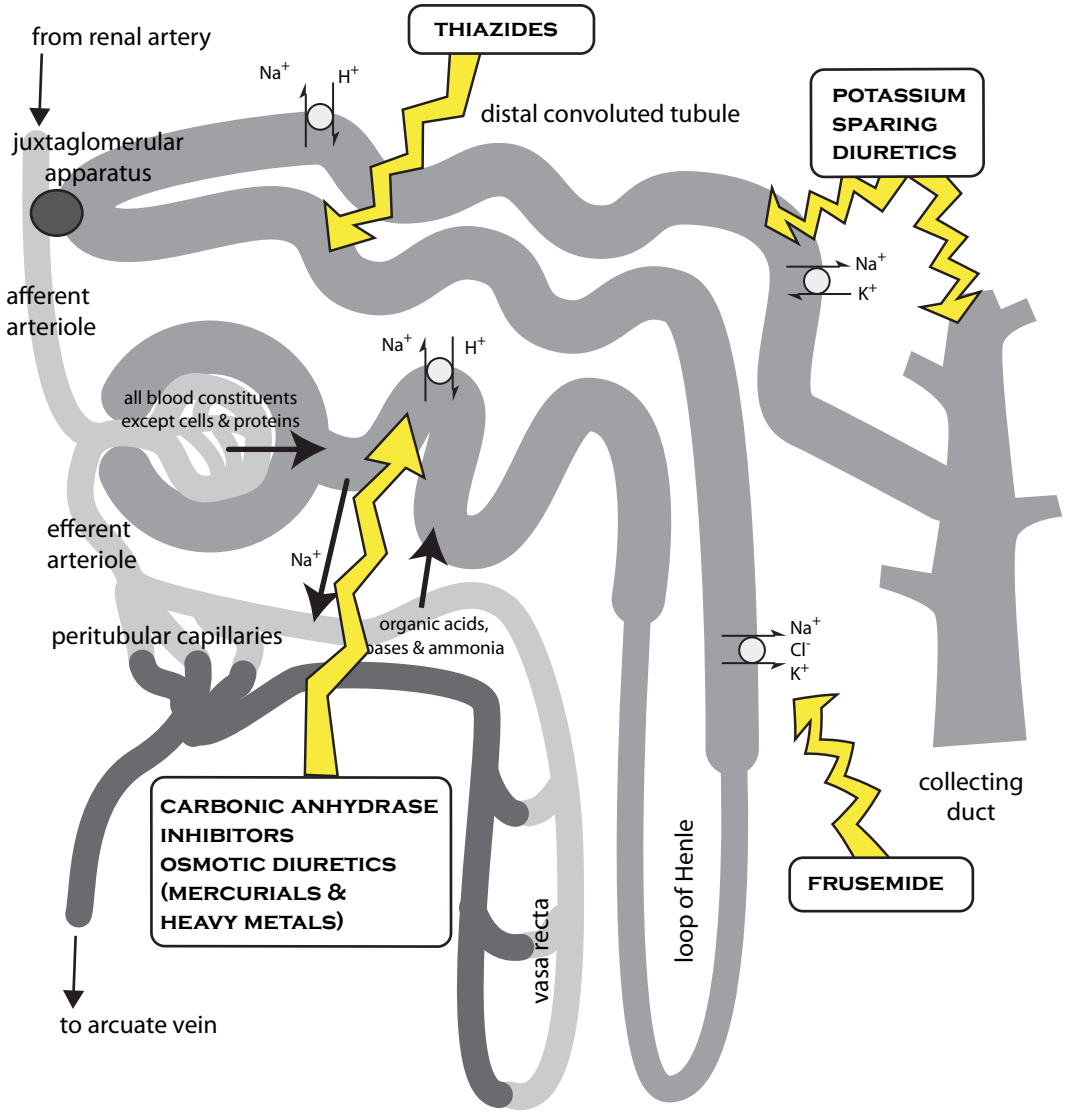
Loop diuretics
- frusemide - most commonly used drug by far

Thiazides
- hydrochlorthiazide

Potassium sparing diuretics
- amiloride
- triamterene
- spironalactone

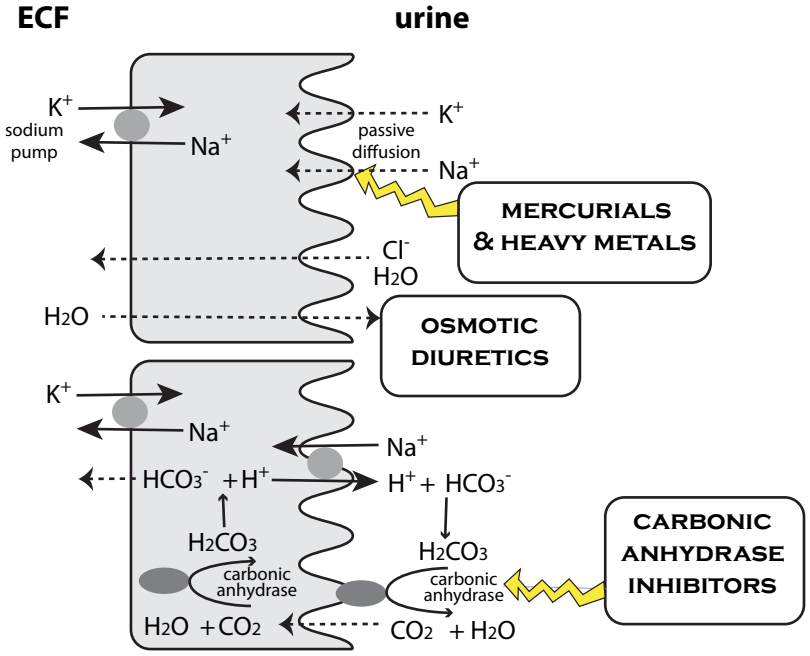
Carbonic anhydrase inhibitors
- acetazolamide

Osmotic diuretics
- mannitol
- glycerine



Sites of action of diuretic drugs.

Drugs acting in the proximal convoluted tubule



Mercurials

Obselete - do not use. You may come across heavy metal poisoning causing renal problems.

Carbonic Anhydrase Inhibitors

Not much used except for glaucoma (see eye notes) because of low efficacy as a diuretic. **Acetazolamide** is the only one in common use, although newer drugs are available.

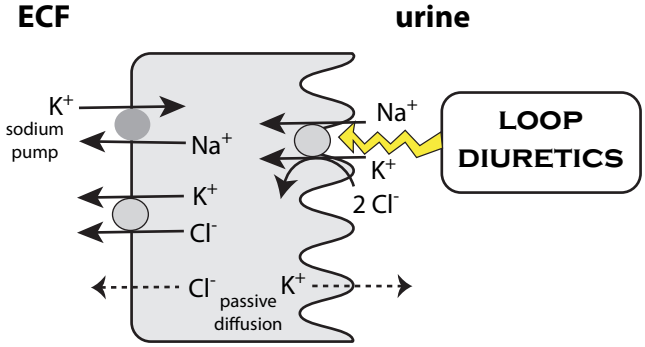
Osmotic Diuretics

These drugs are filtered through the glomerulus, have limited tubular resorption and are pharmacologically inert. **Mannitol** is the only drug commonly used, although occasionally **glycerol** (glycerin) is given by mouth. **Glucose** can be used in anuric or oliguric renal failure to try and establish urine production as it is metabolised if not excreted.

They are freely filtered at the glomerulus and poorly reabsorbed from the tubule causing an increase in osmotic pressure in the tubule and preventing the reabsorption of water. As well as water, there is an increase in sodium, other electrolytes, uric acid and urea secretions due to decreased bulk flow resorption. They may increase renal blood flow and glomerular filtration by causing renal arteriole dilation, decreased vascular resistance and decreased blood viscosity . Because mannitol is not metabolised its use in oliguric renal faliure should be confined to one dose only unless diuresis is achieved.

They are used in cerebral oedema and glaucoma, and are contra-indicated in heart disease - colloids raise venous pressure. Mannitol will cause sloughing if given perivascularly.

Drugs acting in the loop of Henle



Frusemide (furosemide USAN) is the most widely used diuretic in man and animals, almost to the exclusion of everthing else.

It inhibits active chloride transport in the thick ascending limb of the loop of Henle which decreases the total resorption of Na^+ and Cl^- and K^+. This decreases osmolality of the medulla and increases the osmolality of the filtrate presented to the DCT (normally this is hypo-osmalar) to help water resorption, but it is now iso-osmolar and therefore much more water goes through to the distal tubules to the collecting duct. Sodium loss can be dramatic.

Frusemide redistributes blood flow from the juxtamedullary area to the outer cortical regions - it may also act as a venodilator and increase systemic and/or pulmonary venous capacitance.

Indications

It is used as the main diuretic in all species and when there is fluid retention secondary to heart failure:

small animals - congestive cardiomyopathy, pulmonary oedema, cerebral oedema, hypercaluric nephropathy, uraemia, hyperkalaemia and occasionally for hypertension

cattle - post-parturient udder oedema

(*horses* - to help reduce epistaxis by depleting circulating blood volume further, one of the main drugs used illegally in racehorses)

Pharmacokinetics

Absorption - iv onset in 5 minutes, peak effect in 30 minutes, duration 2 hours

oral onset in 1 hour, peaks at 1-2 hours, duration 6 hours

Distribution - highly protein bound - 95 %

Metabolism - half life 15 min - 2 hours, may be increased in renal failure, uraemia, congestive heart failure and neonates. Not very much metabolised

Elimination - small fraction filtered by the glomerulus, rest secreted into the proximal renal tubules by an organic anion pump which is inhibited by probenecid

Side effects

This drug is very potent and is easy to overdose. Overdosage leads to **dehydration** which may be severe. This may also decrease the clearance of concurrently administered drugs and has the potential to cause toxicity eg. digoxin.

Hypokalaemia which may be predisposed to by anorexia (remember digoxin)

Hyponatraemia

Tolerance develops

Caution

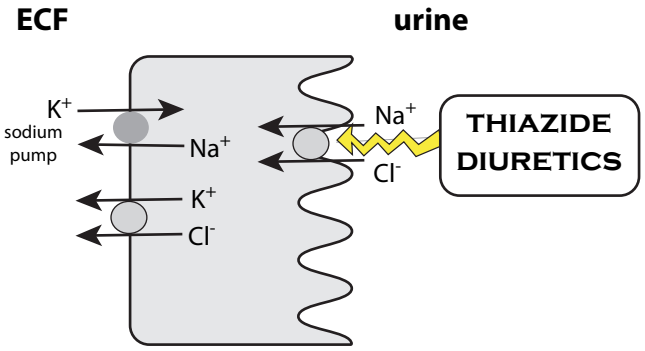
pre-existing electrolyte imbalances or conditions that may lead to these eg. vomiting, diarrhoea

Interactions

aminoglycosides, tetracyclines, cephaloridine to increase proximal convoluted tubule nephrotoxicity. Potentiates the effects of digoxin. Possible interactions with ACE inhibitors (see earlier).

Bumetanide is similar to frusemide but more potent. May be more useful in large animals.

Drugs acting in the early distal tubule



Thiazides

Thiazides were the standard diuretics before frusemide came along, and are still used occasionally, mainly because they are very cheap. Older drugs such as **chlorthiazide** and **hydrochlorthiazide** are most widely used in animals but newer drugs such as **methcyclthiazide** and **cyclothiazide** are used in man.

They inhibit resorption by decreasing membrane permeability to Na^+ and Cl^- which promotes a large increase in urine Na+ and Cl- concentration and mild to moderate increases in urine volume. They also cause secretion of K^+ and increase the excretion of other ions ie. Ca^{++}, Mg^{++}, PO_4 and iodine. Plasma renin and aldosterone levels increase which also increases K^+ excretion. All the thiazides produce a similar level of diuresis. They have anti-hypertensive effects, mechanism is unknown. They can be combined with other diuretics since they work in different parts of the kidney. They are also weak carbonic anhydrase inhibitors but this is not clinically important.

Paradoxically, thiazides reduce the urine output in patients with nephrogenic or pituitary diabetes insipidus, possibly by over compensation of Na^+ resorption in the proximal tubule - this effect is achieved only with a low sodium diet.

Indications

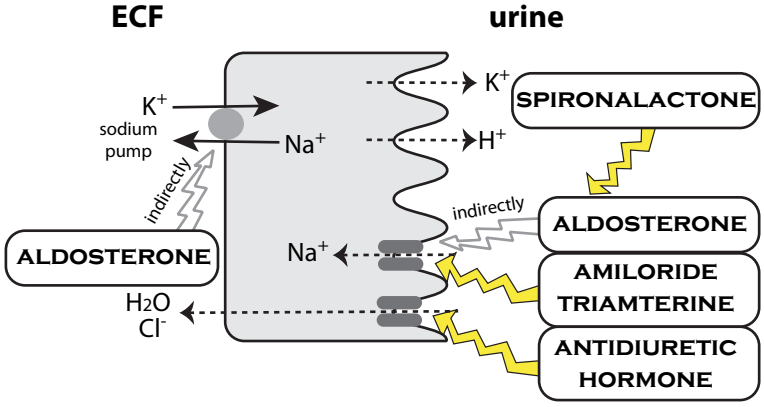
nephrogenic diabetes insipidus
general diuretic for moderate diuresis
systemic hypertension
prevent recurrence of calcium oxalate uroliths in dogs
post-parturient udder oedema in dairy cattle

Contraindications

Renal failure or compromised renal function - they reduce renal blood flow and glomerular filtration rate. In azotemic animals measure BUN and/or serum creatinine levels before treating.

Overuse causes changes in electrolytes and/or fluid balance, particularly hypokalaemia - **remember digoxin**.

Late distal tubule / early collecting duct



Potassium sparing diuretics

Aldosterone is a steroid hormone which binds to a nuclear receptor which stimulates transcription mRNA which codes for the basolateral Na/K-ATPase pump and the luminal Na^+ channels. This leads to an increase in Na/K-ATPase pump activity and therefore an increase in Na+ resorption. K^+ is lost in exchange for resorbed Na^+ to maintain electronutrality.

Spironolactone is structuraly similar to aldosterone and acts as a competitive antagonist of aldosterone. Therefore spironolactone inhibits aldosterone's action on the cells located between the distal renal tubules and the collecting ducts called the "principal cells of cortical collecting ducts" and causes an increased excretion of Na^+, Cl^- and water and a decreased excretion of K^+, NH_4, $P0_4$ It has no effect on carbonic anhydrase or renal transport mechanisms. It has its greatest effect in patients with hyperaldosteronism. It usually elicits only mild diuresis. It is useful in congestive heart failure because of its interactions with the RAAS, but also interacts with oestrogen and testosterone receptors and is going out of fashion in people because of this.

Indications

limited degree of diuresis when used on its own

-used in combination with other classes, especially loop diuretics, in patients where hypokalaemia due to other diuretics is likely to cause serious problems especially if on digitalis or if unable to supplement with dietary potassium

- used in combination with other classes in cases of severe fluid retention eg. refractory ascites, pulmonary oedema secondary to heart failure which is non-responsive

Used for heart failure in people ± ACE inhibitors - too expensive in animals.

Pharmacokinetics

Absorption - gradual onset of action, peak at 48-72 hours, duration for 2-3 days after therapy has stopped

Distribution - 98% bound to plasma protein - CBG - corticosteroid binding globulin and albumin

Metabolism - rapidly metabolised to a number of metabolites one of which (canrenone) is thought to also have diuretic activity

- spironolactone has a short $t_{1/2}$ of 1-2 hours in humans where as canrenone has a $t_{1/2}$ of about 20 hours

Triamterene and **amiloride** directly block sodium channels on apical (luminal) membrane and therefore decrease Na^+ flux which in turn causes a decrease in K^+ transport. This only occurs if Na/K transport is increased ie. using other diuretics or there is a physiological defect. They have no effect on normal animals. They act within 2 hours, peak 6-8 hours, duration 12-16 hours

These drugs can produce hyperkalaemia if they are combined with potassium supplementation or ACE inhibitors.

commonly used drugs

frusemide

Diuretics

- loop diuretics most important in veterinary practice
- main indication is oedema of whatever cause
- very potent - beware overdose
- hypokalaemia potentiates digoxin
- mannitol - beware accidental perivascular injection

Poisons affecting the kidneys

Metals and Inorganics

-cadmium
-zinc
-boric acid
-mercury
-copper (see toxicants causing gut toxicity)
-uranium
-bismuth
-phosphorus (see toxicants affecting the liver)

Organic Compounds

-vitamin K3 (menadione) (in the horse)
-cantharidin (blister beetles)
-sulphonamides
-amphotericin-B
-nephrotoxic antibacterials (except sulphonamides)
-oxytetracycline
-bacitracin
-polymyxin-B
-gentamicin
-neomycin
-carbamate fungicides
-carbon tetrachloride
-phenolics
-diquat (herbicide)
-stillage liquid from ethanol production (in cattle) (not confirmed)
-analgesic nephropathy (nonsteroidal anti-inflammatory drugs)
-ethylene glycol (antifreeze)
-oxalic acid
-vitamin D, especially vitamin D3 (cholecalciferol)

Plants

-vitamin D containing plants
-*Cestrum diurnum*
-*Solanum malacoxylon*
-soluble oxalate containing plants
-beets (*Beta*)
-rhubarb (*Rheum*)
-halogeton (*Halogeton*)
-greasewood (*Sarcobatus*)
-curlydock (*Rumex*)
-lambsquarters (*Chenopodium*)
-*Kochia scovaria*
-other nephrotoxic plants
-pigweed (*Amaranthus retroflexus*)
-oak, acorns (*Quercus* spp.)
-cocklebur (*Xanthium*)
-lily (*Lilium*) and daylily (*Hemerocallis*)
-raisins and grapes

Nephrotoxic Mycotoxins

-ochratoxins
-fumonisins
-citrinin
-hybrid Sudan or Sudan grass (*Sorghum* spp.) (equine cystitis, ataxia syndrome) secondary to paralysis and ascending pyelonephritis)

Cholecalciferol

(Vitamin D3)

Source

Commercial product available for possum control. Plant toxin

Toxicity

reported from as low as 2 mg/kg
Serious toxicity at >10 mg/kg
LD50 is reported as 13 mg/kg by Rumbeiha et al
Cats are more sensitive than dogs and younger animals are more sensitive.

Toxicokinetics

Absorption
well absorbed from jejunum (small intestine)
Bile salts are required
Distribution
Lymph before blood than highest concentrations seen in Plasma, lymph, kidneys and fat.
Binds to alpha 2 globulin (protein)
gets across placenta-will cause supravalvular aortic stenosis in rabbits born to does treated with D3
Metabolism
by liver and kidney see textbook for metabolic cascade, metabolites have LONG half-lives
Excretion
primarily in faeces, some enterohepatic circulation
a small amount (2%) excreted in urine
D3 and metabolites have a long half-life which means treatment may be prolonged for several weeks to control hypercalcaemia.

Physiological Effects

Vitamin D3 or cholecalciferol is a positive regulator responsible for calcium homeostasis in the body. An excess of cholecalciferol results in the following:
Hypercalcaemia
Increased absorption of CA and P from Small Intestinal Tract
Mobilise Ca from bone
Decrease renal excretion
Hypercalcaemia slows the heart rate; conduction dysfunction QT shortened and PR prolonged when Calcium is greater than 3.49 mmol or 14 mg/dl (depending on the value the lab reports)

Calcium deposits throughout body tissues, heart, blood vessels, kidney and lungs

Vasoconstriction results in an increase in vascular resistance which increases renin release, which can lead to severe renal ischemia and tubular necrosis.

Decrease in ADH levels (inhibited by hypercalcaemia)

PU/PD

Dilute urine

Electrolyte disturbance Na and K+ losses

Renal failure and calcium deposits in the renal medulla especially the Loop of Henle and the collecting ducts.

Heart conduction failure

Calcitriol in the GIT

- binds to intracellular receptor in the intestinal cells which stimulates the synthesis of carrier protein

- mobilises calcium from the bone (active transport of Ca in osteocytes)

Calcifediol and Calcitriol

-enhance reabsorption of Ca and Phosphorus from the proximal tubules (kidney)

Clinical Signs

Latent period of about 8-24 hours after ingestion before clinical signs appear.

12-24 hours clinical pathological changes of hypercalcaemia and hyperphosphataemia

Progressive clinical signs resulting from hypercalcaemia:

Initially lethargy, weakness, and anorexia,

then vomiting, polyuria, polydipsia, constipation and dehydration

urine is hyposthenuric

Severe GIT signs may have blood in faeces

Haematemesis is a grave sign

Azotaemia

Cardiac abnormalities like bradycardia, ventricular arrhythmias, PR interval prolonged and QT shortened

Sometimes dyspnoea due to bleeding into the lungs

Neurological: Twitching, seizures-uncommon but reported, depression and stupor

Diagnosis

Clinical signs often develop 12-36 hours after consumption of a toxic dose.

Laboratory diagnosis

A serum calcium level higher than 4.99 mmol/L is characteristic and highly suggestive of cholecalciferol toxicosis.

An elevated serum phosphorus level may precede the hypercalcaemia by as much as 12 hours and could serve as an early nonspecific indicator.

The urine specific gravity is 1.002-1.006.

Increased BUN and creatinine levels are common as the toxicosis continues.

Excessive active 1,25-dihydroxyvitamin D metabolites are present in renal tissue, but the analysis is difficult and few laboratories would be able to perform it.

Post Mortem

Gross lesions include petechial haemorrhages in tissues, pale streaks in kidney tissue, and raised plaques in the intima of large vessels, haemorrhagic gastritis.

Microscopic lesions may include mineralisation of the kidney tubules, coronary arteries, gastric mucosa parietal pleura, pulmonary bronchioles, pancreas and the urinary bladder. The renal tubules may be necrotic or degenerative.

Treatment

Detoxification therapy is essential when the exposure is recent (3-4 hours). The first treatment with activated charcoal should include or be followed by a laxative.

Activated charcoal is essential and should be repeated for several days due to the enterohepatic circulation.

Treat the hypercalcaemia with fluid therapy of normal saline, frusemide for diuresis.

Saline diuresis promotes calcium excretion

Frusemide for diuresis (5 mg/kg IV initially then 3 mg/kg q8h)

If the hypercalcaemia is not responsive consider using pamidronate

Corticosteroid administration of prednisone (2 mg/kg q8-12h) inhibits the release of osteoclast-activating factors, reduces intestinal calcium absorption and promotes hypercalciuria. May not be necessary if using pamidronate.

Pamidronate (Pamisol)1.3-2 mg/kg when serum calcium levels are high (superior to calcitonin)

Salmon calcitonin (4-6 IU/kg subcutaneously q3-6h increase to 10-20 IU/kg if the animal does not respond) may be administered to reduce excessive serum calcium levels

Avoid Sunlight.

Prognosis is generally guarded to poor depending on severity and responsiveness of the hypercalcaemia. In animals presenting with haematemsis the prognosis is grave.

Treatment is continued until for at least two weeks (frusemide and prednisone). Remove treatment for 24 hours

Cholecalciferol Poisoning

- Hypercalcaemia and Hyperphosphataemia
- Enterohepatic circulation (repeat use of activated charcoal)
- Renal Failure but.....
  cardiovascular effects
  gastrointestinal effects
  CNS depression/ ± seizures
- Treatment
  Fluids
  Frusemide
  Prednisone
  ± calcitonin depends on the severity of hypercalcaemia
  Avoid sunlight
  Low Calcium diet
  Phosphate binders (aluminium hydroxide)
- Long treatment period
- note: new research has indicated some value in using pamidronate disodium (Pamisol)

and check calcium levels. If elevated continue frusemide and prednisone and monitor at weekly intervals. If calcium level is normal after 24 hours, monitor at 48 hours and 72 hours.

Ethylene Glycol

Systems Affected:
Respiratory-Acidosis
Urinary
CNS

Sources

Radiator antifreeze
other automotive and heat exchange uses

Susceptible Species

Birds and Mammals - particularly dogs and cats

Toxicity

(Lethal Dose):

95%	EG	Diluted 50:50 EG:water
Feline	1-2.5 ml/kg	15 ml
Canine	4-5 ml/kg	13.2 ml/kg
Poultry	7-8 ml/kg	
Cattle	2-10 ml/kg	

ADME / Pathogenesis

• Unmetabolised EG is rapidly absorbed; same toxicity as ethanol.
• Peak blood levels 1-4 hours post exposure
• Plasma half-life of EG is 2.5-3.5 hours
• EG excreted unchanged in the urine, first 4 hours up to 24 hours.
• Metabolism of EG critical to therapy
Liver:
Disposition of glyoxylic acid:
oxidation to oxalic acid (.25-3.7%)
Oxalic a. + Calcium = calcium oxalate crystals
3 Stages of Toxicity:
1. 30 min to 6 hours CNS/ethanol-like
diuresis-dehydration and polydipsia
2. 12-24 hours -Cardiopulmonary effects
heart and respiratory rate increase
3. 12-72 hours oliguric renal failure
ocular lesions-detached retina, oedema and anterior uveitis
*rate limiting steps (different species favor different metabolic pathways)

Toxicity

Glycoaldehyde is more toxic than ethylene glycol, but it is rapidly metabolised to glycolic acid.

Glycolic acid is believed to cause metabolic acidosis and probably nephrosis., more toxic than EG.

Glycoxylic acid is more toxic than any of the other metabolites, but it has a short half-life that it does not appear to accumulate in concentrations high enough to have toxic effects.

Oxalic acid combines with calcium to form calcium oxalate crystals which may precipitate in the renal tubules and to a lesser extent in the brain vasculature and other tissues. The presence of oxalate crystals does not correlate with the nervous system effects. Surviving animals usually make complete recovery of the CNS.

Diff Diagnosis

head trauma, encephalitis, drug overdose, acute nephritis, acute diabetes mellitus

Clinical Pathology

Mild lymphopenia and neutrophilia (mature)
Haemoconcentration (PCV. Total Protein)
Blood Urea Nitrogen, creatinine, phosphorus, glucose
calcium, blood Ph < 7.3
Hyperkalaemia
Hypochloraemia, low bicarbonate
metabolic acidosis
Anion gap and Serum Osmolality useful
Anion gap > 25 meq/L (normal 10-15)
Osmolality > 10 mOsm/L (normal ± 5-10)
Urine specific gravity- isothenuric or dilute
Birefringent crystals

Diagnosis

history of exposure with clinical signs
blood or urine analysis if early < 24 hrs
anion/osmolality
A plasma EGT spot test is available for quick determination of EG ingestion.

Gross Pathology

dehydration
hyperaemia of GI, swollen kidneys and pulmonary oedema
uraemia and evidence of renal failure

Microscopic Lesions

calcium oxalate or hippurate crystals-kidney, but brain and muscle ± renal tubules dilated ± crystals; Birefringent crystals

Treatment

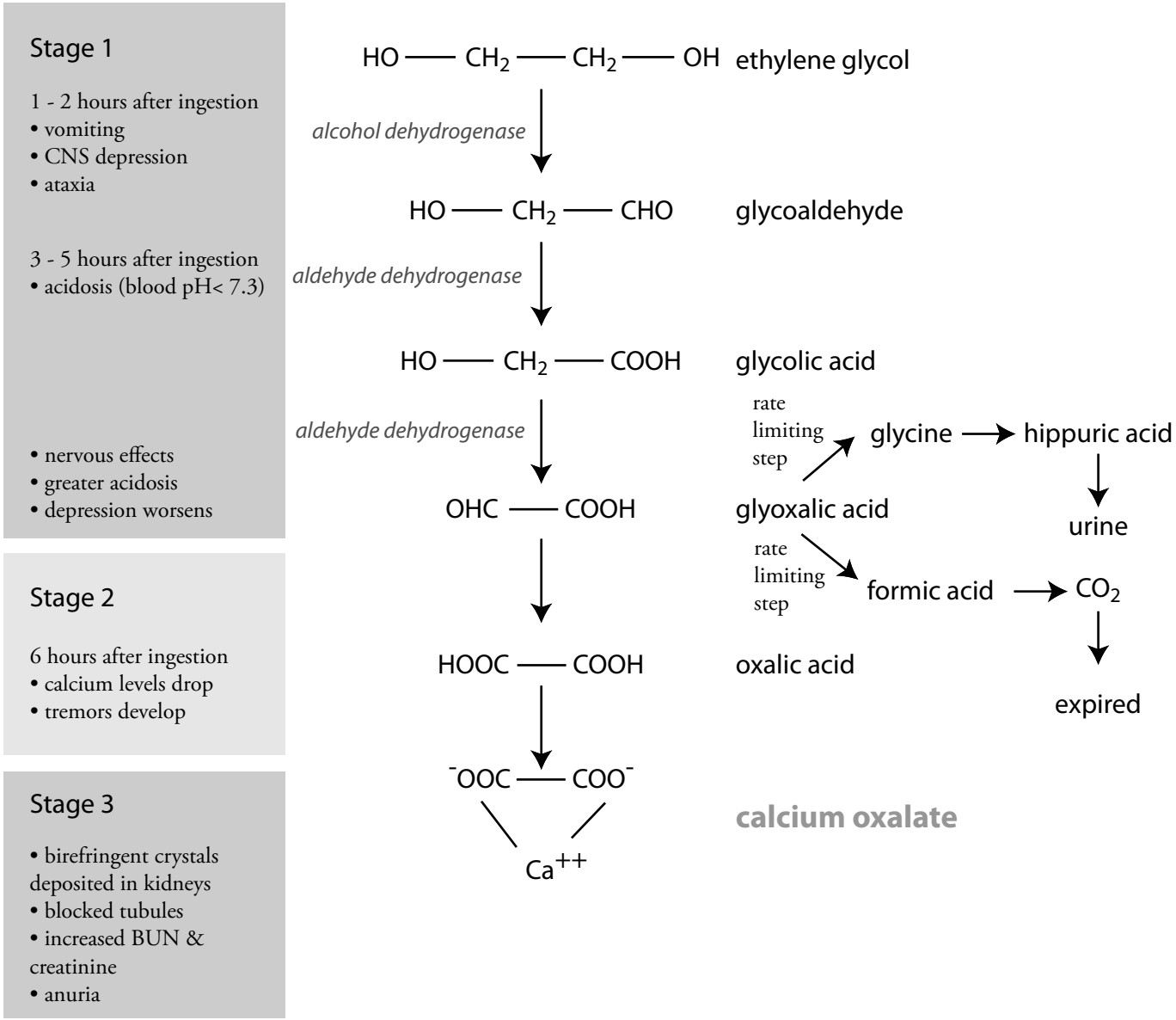
Stage 1: (Early exposure/no clinical signs)
emetics, activated charcoal, gastric lavage
Ethanol (depression) < 18 hours
Bicarbonate
Stage 2 and 3:
Bicarbonate, fluids
Peritoneal dialysis (haemodialysis better)
diuretics?

Ethanol Therapy

Ethanol competes with ethylene glycol for alcohol dehydrogenase

Dogs

20% ethanol in saline IV 5.5 ml/kg
Repeat every 4 hours for 5 times, then every 6 hours for 4 times
+ 5% bicarbonate IV at 8 ml/kg**



Stages of ethylene glycol poisoning.

(**IF metabolic acidosis; if values are available, calculate base deficit and treat with bicarbonate as required).

Evaluate ionised calcium levels and supplement as needed

Cats: Ethanol Therapy

5 ml/kg of 20% ethanol in saline solution IV

every 6 hours for 5 treatments, then every 8 hours for four treatments.

6 ml/kg of 5% bicarbonate (see note under dogs on base deficit and calcium requirements)

(NB this treatment prolongs EG's half life)

Sodium bicarbonate therapy should be based on serial plasma bicarbonate levels when available:

Bicarbonate Deficit (mEq)

0.5 X B.W. (kg) X [24 - Plasma Bicarb (mEq/L)] = mEq of sodium bicarbonate needed

To prevent overdose give only 80% of the calculated dose---**very** slowly preferably in fluids

Alternative Ethylene Glycol Treatment:

fomepizole (4-Methylpyrazole, 4 MP): **for dogs only; in place of ethanol therapy**

More effective and safer treatment than ethanol.

Inhibits alcohol dehydrogenase

Treatment must be started within 8 hours of EG ingestion.

Cases

Case 1

Feracol, a cholecalciferol-based possum bait, is ingested by your client's working dog several hours ago.

What treatment is indicated?

What is the mechanism of toxicity of Campaign®?

What serum biochemistry(ies) is/are altered by Campaign® toxicity?

What clinical signs might you expect to see with this poison?

What treatment is recommended for a dog presenting with clinical signs of poisoning?

What is the prognosis for a dog with clinical signs?

Give a brief explanation of your answer.

Blood

Definitions

Thrombus = blood clot

Thrombosis = excessive clotting in blood vessels

Thrombo-embolism = blood vessel (usually arterial) blockage caused by a bit of clot breaking off and getting jammed in a blood vessel down stream.

The usual therapeutic aims in veterinary medicine are to encourage blood clotting at the site of injury and prevent clotting in the circulation. Possible targets:

vascular smooth muscle - vasoconstriction restricts flow to the affected area

platelets - platelet adhesion and aggregation forms a viscous mass (platelet plug)

clotting factors - activation of clotting factors results in polmerisation of fibrin to form a stable clot

Anticoagulant poisoning is commonly seen in dogs which have eaten coumarin rat poisons (eg, warfarin).

Haemostasis

The normal response to haemorrhage is

•blood vessel constriction

•platelet aggregation to form a plug

•followed by activation of the clotting cascade to form a fibrin thrombus

In veterinary practice, bleeding can be reduced using

•Good surgical practice. Far and away the most important way of preventing and stopping bleeding.

•Artificial substrates for clots

calcium alginate
oxidised cellulose
absorbable gelatin
microfibrillar collagen

usually as pads applied to large bleeding areas, eg liver

•Exogenous clotting factors supplied as whole blood or fresh frozen plasma. After extensive haemorrhage and replcement by colloids, the clotting factors may be so diluted that they no longer work. Topical fibrinogen and thrombin sprays and bandages are under trial in the US.

•Topical vasoconstrictors - adrenaline and noradrenaline. Usually applied to mucous membranes or other large areas which are oozing blood.

•Anticoagulants such as heparin are used in disseminated intravascular coagulation (where bleeding is caused by all the clotting factors being used up). Should not be used for haemostasis in other situations

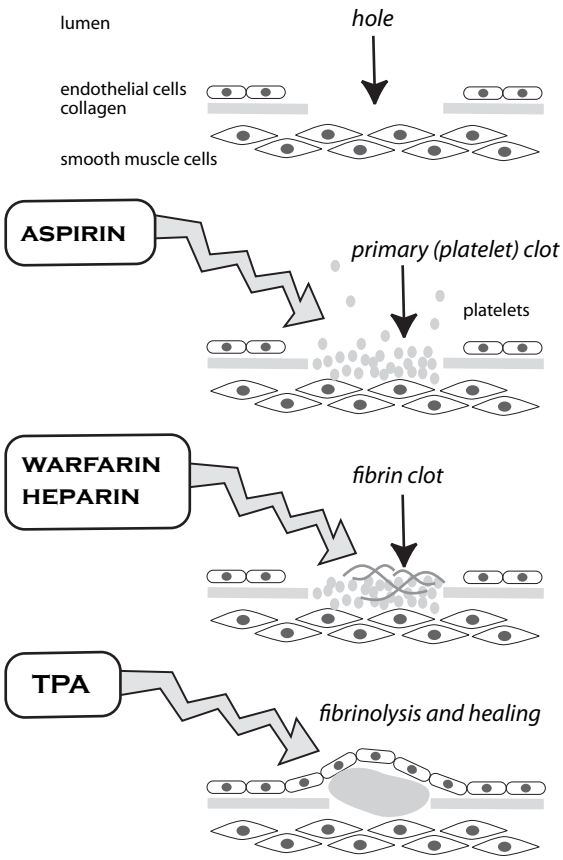
•(Hypotensive anaesthesia) No longer used for haemostasis but it is useful to remember that if an animal stops bleeding under anaesthesia its blood pressure may be dangerously low / zero!

•Parenteral haemostatics are not much use except in special circumstances. They include **tranexamic acid**, which binds plasminogen thereby preventing its cleavage to plasmin - antifibrinolytic. Small intravenous bolus dosing stimulates the chemoreceptor trigger zone and reliably elicits vomiting in dogs and cats without any generalized CNS depression or excitment often associated with other emetics such as xylazine and apomorphine.

Tranexamic acid is indicated in treatment of overdose with fibrinolytic agents, low plasma fibrinogen, haematuria, (uncontrollable haemorrhage) and poisoning (to induce emesis). It is contraindicated in pregnancy and where there is intravascular clotting. Massive overdoses cause few immediate or untoward effects. The possibility of inducing multiple intracirculatory thromboses must be considered.

Drugs used to treat clots

There are many drugs used in people to break clots down and restore blood supply to areas distal to the clot (mainly used in myocardial infarction). These are not usually used in animals because they are very expensive and the damage is very gross / irreversible when the animal is presented for treatment (drugs usually have to be given within 3 hours to be effective). In veterinary practice it is usual to try to prevent further clotting using anticoagulants or antiplatelet drugs. All these drugs can cause massive bleeding - animals have completely bled out after their use. As a broad generalisation, anticoagulants are used to treat venous thrombosis, antiplatelet drugs for arterial thrombosis.



Drugs affecting clots. Aspirin and warfarin prevent clotting, tissue plasminogen activator breaks down clots.

Parenteral anticoagulants

The only common drug is **heparin**. It is a high molecular weight glycosaminoglycan isolated from cattle lungs or pigs' guts. Only five sugar residues are required for action, so low molecular weight heparins are sometimes used. It is rapidly metabolised (2 hours). Clotting times are usually monitored during use.

Mechanism of action

Binds to antithrombin III to activate it. The complex rapidly inactivates circulating thrombin, and to a lesser extent factors XIIa, XIa, IXa and Xa.

Indications

•maintaining iv catheter patency - catheters are flushed with saline containing a small amount of heparin

•prevention of clotting in response to other intravascular hardware (mainly people at the moment)

•venous thrombosis

•disseminated intravascular coagulation

Side effects

bleeding, hypersensitivity reactions (reduced with low molecular weight heparins)

Contraindications

liver disease, haemorrhage (except DIC)

do not give im - haematoma formation. iv is best.

In overdose give **protamine** sulphate, 1mg/100units heparin by **slow** iv injection (causes hypotension if given fast).

Oral anticoagulants

These are nearly all coumarins, of which **warfarin** was the first to be widely used (as a rat poison). Some rats have developed resistance to warfarin, and there are a variety of second generation coumarins such as **brodifacoum** used as rat poisons now. These generally have a much longer duration of action. The most modern drugs in this class (not in NZ yet) have half lives of weeks in dogs.

Warfarin is typical of the coumarin group. It is a stable analogue of vitamin K. Although widely used as an anticoagulant in people, it is mainly seen as a poison in veterinary practice. It competes with vitamin K for the recycling enzymes and inhibits vitamin K dependent clotting factors (prothrombin, VII, IX, X).

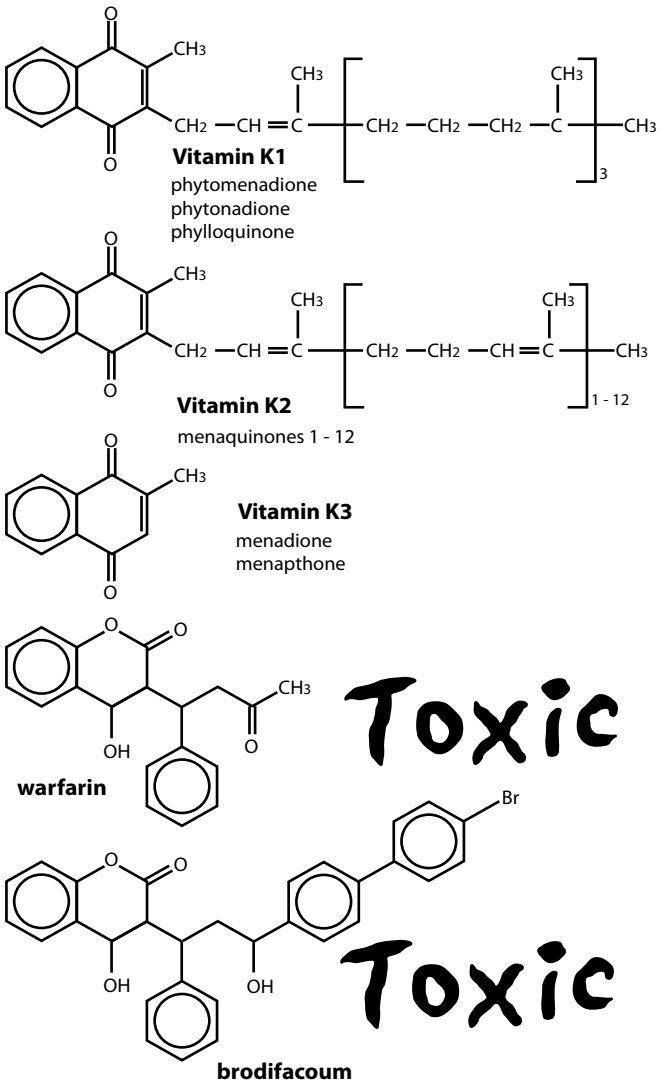
Indications

venous thrombosis

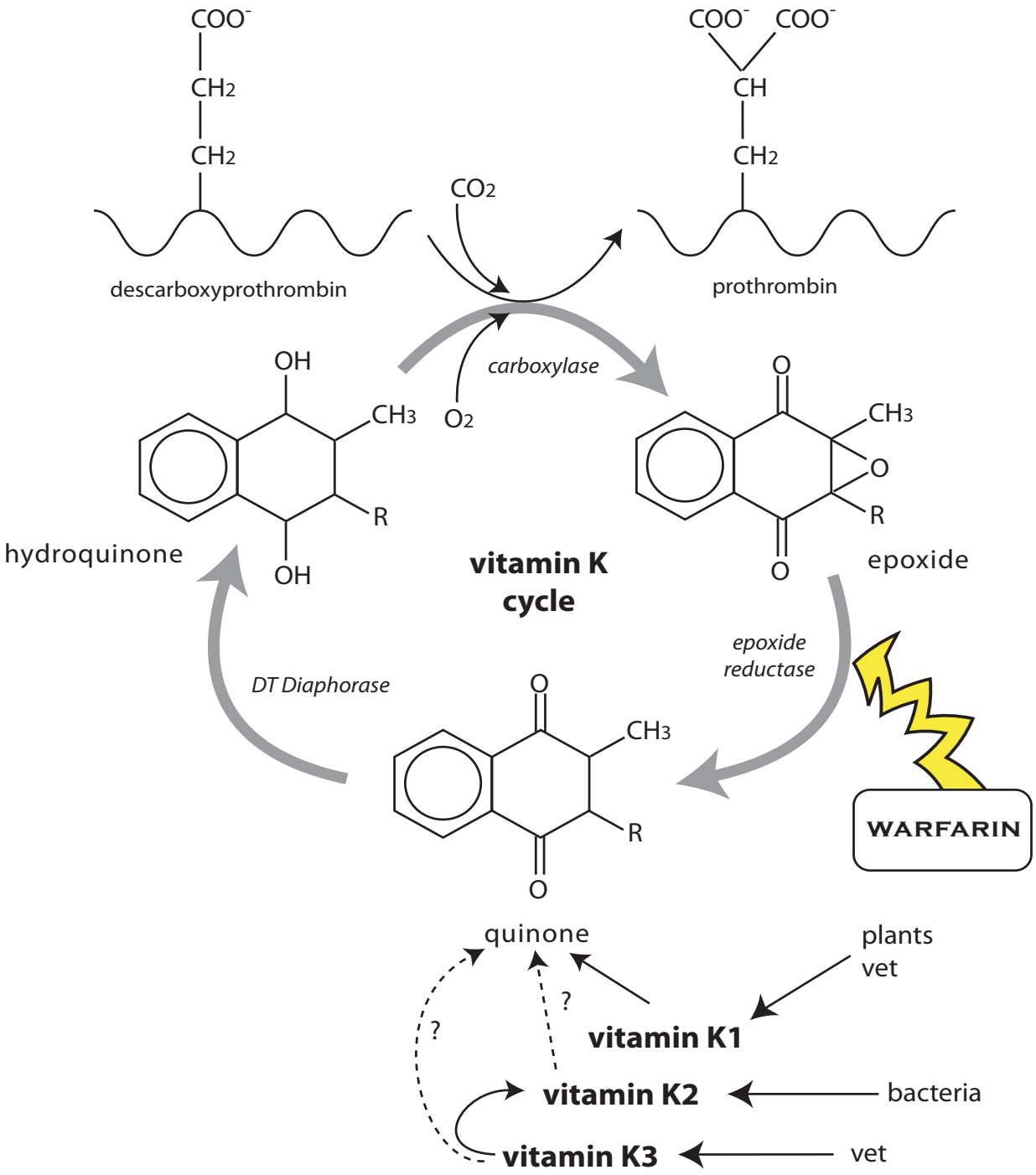
thromboembolism in cats

disseminated intravascular coagulation

navicular disease ?



Vitamin K analogues.



Vitamin K cycles between the hydroquinone and the epoxide in the process of making prothrombin (and factors VII, IX and X). Coumarins block this cycle and prevent the production of prothrombin. Exogenous vitamin K is taken up in the quinone form.

Contraindications

malnutrition, haemorrhage

Pharmacokinetics

highly plasma protein bound - can be displaced by other highly bound drugs eg phenylbutazone.

Since it interferes with the production of clotting factors, existing stocks must be used up before any anticoagulant effect is seen - usually 8 - 10 hours.

Side effects

bleeding

Treatment of warfarin overdose

In severe cases a transfusion of fresh blood ± intensive care may be necessary. **Phytomenadione** (vitamin K1, phytonadione USAN, phylloquinone, etc.) competes with warfarin for the binding site (other forms of vitamin K are much less effective). In mild cases it will start to work in about 30 mins after iv injection but no signs of improvement may be evident for more than 2 hours. It is usual to continue with oral K1 for 10 - 14 days after warfarin overdose; 30 days after brodifacoum. Assessing prothrombin times will show if treatment can be stopped.

Vitamin K comes in many different forms, all of which have many different names. K1 is probably the only one

which works in dogs, avoid K3 (menadione, menaphthone) even though it is cheap (it works in chickens and is added to their feed by the ton).

Further reading

Walker and Royston, 2002, British Journal of Anaesthesia, Thrombin generation and its inhibition: a review of the scientific basis and mechanism of action of anticoagulant therapies. **88**, 848 - 863

All you ever wanted to know about coagulation and more!

Anti platelet drugs

These are used to prevent the formation of thrombi. **Aspirin** is the only drug widely used in veterinary practice, usually for thrombo-embolism in cats. It inhibits cyclo-oxygenase in platelets and blocks production of thromboxane A2 (which causes platelet aggregation). It can cause bleeding. The dose required is usually low enough to avoid other side effects. Since it irreversibly acetylates platelets, it is only given once every 3 - 4 days.

Prostacyclin (PGI_2, epoprostenol) ia a physiological antagonist of thromboxane A_2. Very expensive.

Fibrinolytics

Not often used in veterinary practice - too expensive. The dose is critical - too much and the animal will bleed out.

Alteplase is recombinant human tissue plasminogen activator. It breaks clots down and is much better in people than streptokinase or urokinase. It can cause bleeding so do not use if there has been recent trauma or a major operation, hypertension, bacterial endocarditis or acute pancreatitis. Plasmin is starting to be used in people instead.

Streptokinase is isolated from *Streptococcus haemolyticus* B strain. It is antigenic and may produce hypersensitivity. Binds to plasminogen but not preferentially bound to fibrin and will lyse everything . It is not a PA inhibitor. It is degraded by the reticuloendothelial system. **Urokinase** is isolated from human renal cells Does not need to bind to be active. Not preferential to fibrin, much more expensive than streptokinase, cleared by the liver.

Stanozolol is an anabolic steroid which may have fibrinolytic properties that may be helpful in feline aortic thromboembolism. (clinical studies yet to be done).

Anticoagulants for collecting blood

These drugs are not given to animals directly but used to stop blood clotting during collection for storage (in fridge) and infusion later. They work by chelating calcium. Long term storage is largely for RBCs, clotting factors only last a few hours (plasma must be separated rapidly and frozen to preserve clotting factors).

With **acid citrate dextrose**, RBCs keep 3 weeks (in fridge) - the citrate is metabolised in the TCA cycle, dextrose in RBCs. **Citrate phosphate dextrose** - RBCs keep 4 weeks, **citrate** - RBCs keep 3 days.

Since these drugs chelate calcium, it may be necessary to give extra calcium to ensure normal clotting after infusing large amounts of blood (give 2mmol Ca++ to 4 units blood).

Ethylenediaminetetraacetic acid (always called **EDTA**) damages platelets - it is used for **in vitro** blood samples for haematology **only**. (It is only used parenterally in severe cases of heavy metal poisoning - see toxicology notes).

Poisons Affecting Haemostasis

Vitamin K

-damaged or mouldy sweet clover (*Melilotus*)
-mouldy Lespedeza (*Lespedeza*)
-**coumarin and indandione anticoagulant rodenticides** and pharmaceuticals
-idiopathic, vitamin K-responsive coagulopathy in swine

Liver and 2° coagulopathy

-Aflatoxin
-Many others

Bone marrow damage

-**bracken fern** (*Pterydium*)
-trichloroethylene-extracted soybean oil meal
-benzene (bone marrow effect)

Severe shock / DIC / other coagulopathy

-Garbage Toxicoses
-Pit Vipers

Anticoagulant Toxicity

See Veterinary Clinical Toxicology textbook

First Generation – First product a coumarin (warfarin), in NZ coumatetralyl used

Indanediones-"first" generation – pindone, diphacinone and now difethialone in NZ

Second Generation – brodifacoum (Talon), bromadiolone, flocoumafen (Storm)

Sources

Rodenticides, Pesticides

Mechanism Of Action

Interference with the normal blood clotting factors as a result of impaired synthesis leading to reduced concentrations of clotting factors II (prothrombin), VII, IX AND X, due to competitive inhibition of the enzyme vitamin K

Warfarin

Species	Toxic level Single Dose	Toxic level Repeated Doses
Dogs	5-50 mg/kg	5 mg/kg for 5-15 days
Cats	5-50 mg/kg	1 mg/kg for 5 days

Indanediones

	Single Oral LD50 mg/kg			
Generic	Dog	Cat	Pig	Rabbit
Diphacinone	3	15	150	35
Pindone	2.5			150

Brodifacoum*

Species	LD50 (mg/kg)	Species	LD50 (mg/kg)
Dog	0.25-3.6	Rat	2.8
Cat	0.25-2.5	Duck	2.7-4.6

** Horses have had prolonged clotting times (OSPT and APTT) after ingesting 0.125 mg/kg of brodifacoum.*

epoxide-reductase leading to the prolongation of OSPT,. APTT and ACT. The clotting factor precoursers to II, VII, IX, & X are called PIVKA (proteins induced by vitamin K antagonism) proteins. Vitamin K is required for the addition of dicarboxylic acid groups to the clotting precoursers and for calcium binding to form clots. PIVKA is elevated in vitamin K responsive coagulopathies.

Death due to a generalised bleeding disorder.

ADME

• Absorption rather complete but slow, insoluble in water so small intestine is the likely site of absorption but very little animal data is available.

• Peak plasma levels in 6-12 hours

• Warfarin highly bound to plasma protein

• Liver, spleen and kidney may have high concentrations

In the dog the plasma half-life is 14.5 hours for warfarin, 4.5 days for diphacinone and 6 days for brodifacoum.

Clinical Signs

Signs rarely appear before 24 hours after ingestion usually a lag of 3-5 days

Death without other clinical signs due to cerebral haemorrhage or other internal haemorrhage

Depression

Anorexia

Anaemia (Pale mucous membranes, dyspnoea)

Epistaxis, tarry faeces, other sites of bleeding

Heart rate, pulse - result of anaemia

Bleeding into joints-lameness

Abortion

Icterus if prolonged toxicosis

Diagnosis

History is important

Evidence of haemorrhage

Collect blood from both the patient and a normal animal and submit to the laboratory in citrate blood tubes. (check with lab first as normals not always required)

One stage prothrombin time (OSPT) earliest changes in clotting cascade due to extrinsic pathway (also common) and T½ of Factor VII 6.2 hours or APTT-which measures intrinsic pathway (and common) T½ of Factor IX is 13.9 hours. (Factor X 16.5 hours and Factor II 41 hours) NB Bruere's notes (1990) have a typographical error onT1/2 for clotting factors. These half-lives are for dogs. New edition has corrected values.

(Elevated prothrombin time from 24-48 hours post ingestion);

Chemical Analysis of blood or liver

Treatment

• If recent exposure-within last several hours and no clinical signs use emetics

• If dose calculated is potentially toxic, need to use Vitamin K_1 therapy

If clinical signs are present: Parenterally (SQ or IV-only with fluids, slowly); then orally

• Severe clinical signs-transfusions + Vitamin K parenterally.

In poisoning by second-generation anticoagulants prolonged treatment will usually be necessary. This is because the second-generation anticoagulants have a long biological half-life.

a) In animals which are showing advanced clinical signs of intoxication, fresh whole blood transfusion (10-15 ml/kg body weight) is recommended accompanied by parenteral (i.e. subcutaneous) administration of vitamin K_1 (2-5 mg/kg body weight/day). Some clinicians recommend dividing this dose and giving it twice daily. Note: plasma or synthetic products may be substituted for fresh blood as appropriate.

Where transfusion is not undertaken a reduced dose of vitamin K_1 can be administered intravenously. Care must be taken that this procedure does not induce anaphylaxis and to avoid the risk the dose should given in a 5% dextrose solution and diluted to 1 mg/ml.

Parenteral administration of vitamin K_1 should be continued for 1-2 days or until the animal is stable (based on observation and clinical tests such as the one-stage

Animal Condition	treatment				
(signs)	induce vomiting	blood transfusion	parenteral vit K1	oral vit K1	observe
Severe signs		√	√	√	√
Early mild signs			√	√	√
No signs, but suspected bait consumption	√[2]			√	√

1. Observe for several weeks and monitor blood by the OSPT assay
2. Only where bait consumption is known to have occurred recently. Use activated charcoal.

prothrombin time assay (OSPT). Thereafter, oral doses of vitamin K_1 are recommended for a period of up to four weeks. The dose can be gradually reduced over this period. The animal must be closely observed for any recurring clinical signs during treatment and for a month after treatment. The animal should be taken off the vitamin K_1 for at least 48 hours to measure the OSPT. If the OSPT is normal, a second test in 36-48 hour may be necessary. If OSPT is normal at that time then vitamin K_1 may be discontinued but advise the clients to keep a close eye on the animal. If the OSPT is prolonged than the vitamin K_1 should be reinstituted immediately and continued until the OSPT remains normal. After oral dosing the improvement in clotting times may be delayed for 6-12 hours.

b) In animals showing early signs of intoxication and where anticoagulant poisoning is highly suspected (e.g. Flocoumafen, (Storm)) but in which the condition does not warrant blood transfusion, parenteral administration of vitamin K_1 (2-5 mg/kg bodyweight/day) is recommended initially. This treatment should be followed by the oral administration of vitamin K_1 for a further four weeks, with the dose gradually decreasing over this period. Vitamin K_1 absorption is enhanced by feeding with fatty foods. Blood samples should be taken where practicable, to monitor coagulation during treatment. Frequent observation should be continued for at least a further month.

c) If it is suspected that an animal has consumed anticoagulant rat bait, the induction of vomiting is only recommended when very recent ingestion is suspected. Close observation for a week is recommended and vitamin K_1 can be given orally as a prophylactic measure. Where there is strong evidence that rat bait has been ingested, close observation and the monitoring of blood coagulation, as outlined earlier, is recommended. Orally administered vitamin K_1 is recommended for a period of four weeks.

Summary of treatment of anticoagulant toxicosis in domestic animals.

Cases

Case 1

"Bouncer", a 15 kg dog is presented to your clinic at 7.30 am. The owner observed the dog eating rat bait left in the garage after its morning walk at around 6.30 am.

a. What treatment would be indicated at this time?

b. What do you need to know to establish your plan of action?

c. If the dog ate approximately 200 gm of Talon, which is .05 gm/kg, did Bouncer get a toxic dose?

Case 2

A 30 kg labrador is presented with epistasis from the nose and rectum. You examine the dog and note tachypnoea, tachycardia, pale mucous membranes and abdominal distention. A PCV and clotting time is ordered STAT. The owner tells you that a rodenticide was left in the garage a week ago. This morning the client noticed that the boxes (2) are empty, but it is unknown if the dog or mice have eaten it. The product name is Talon[R].

The PCV is 15 and the clotting time is prolonged. What is your treatment plan for this dog?

What advice do you give the client about the duration of treatment and reevaluation?

Anticoagulant Poisoning

- Haemorrhage
- Competitive inhibition of Vitamin K epoxide reductase
- OSPT increased first
- Warfarin/1st generation shorter T½
- Brodifacoum long T½ (dog 6 days) requires long treatment of 30+ days
- Pindone leaves muscle and other tissue residues
- Vitamin K_1 therapy
- Menadione (K_3) can be toxic
- Wait at least 48 hours after vitamin K_1 is withdrawn to check OSPT.)

Anaemia

Definitions

anaemia - a condition where numbers of circulating red blood cells or haemoglobin are low. Usually assessed by measuring packed cell volume.

haematopoiesis - the process of making blood cells.

polycythaemia - too many red cells

Anaemia can be caused by a number of factors which come down to decreased RBC production caused by nutritional deficiencies or bone marrow abnormalities (non regenerative anaemias); and increased RBC removal caused by haemolysis or chronic bleeding (regenerative anaemias). In severe cases blood transfusion may be necessary but the definitive treatment depends on the cause of the condition. Autoimmune haemolytic anaemia is relatively common in small animals and is treated with immunosuppressive drugs.

Iron compounds

Iron deficiency anaemia is mainly a disease of piglets kept under intensive conditions. They require about 7mg iron / day which would normally be obtained from eating soil; sow's milk does not contain this amount. If untreated, piglets will develop clinical signs at 3 - 6 weeks old, they are usually given a depot injection of iron in the first week (by the farmer). This is becoming less important as piglets are weaned younger (sometimes 3 weeks old). Rarely, the sow is given iron (must be ferrous salt) most of which passes through her; the piglets obtain the iron by eating the sow's faeces.

Too much circulating iron in the piglet encourages bacteria to grow (iron is necessary for most bacteria and is often a limiting factor in their growth) causing problems like polyarthritis.

Iron dextran is the main form of injectable iron for the treatment of iron deficiency in piglets at 3 days old. It stains meat (and everything else!) yellow so should be injected behind the ear rather than the gluteals.

Gleptoferron is not available in NZ, it is used in same way as iron dextran in piglets.

Various "tonics" for horses are marketed containing ferric (ammonium) citrate; iron must be in the ferrous form (usually ferrous gluconate) to be absorbed orally.

Copper is also necessary for iron utilisation. Ruminants can be deficient in copper and are usually given oral supplements of a variety of trace elements.

B vitamins

Vitamin B12 acts sequentially in the pathway (with vit C & folic acid) which leads to the synthesis of nuclear proteins in cell division. In deficiency, erythropoiesis is arrested and megaloblasts (large nucleated RBC's which contain more haemoglobin and do not function normally) are released. Deficiency is caused by malabsorption in gut disease so it must be given parenterally.

Cobalt is required for synthesis of vitamin B12 by ruminal micro-organisms. Low cobalt in pasture leads to bush sickness on volcanic soils. Treatment is a slow release cobalt bullet or pasture top dressing.

Folic acid deficiency occurs in steatorrhoea and chronic diarrhoea. Requirements are increased in pregnancy.

Anabolic steroids

Stimulate erythropoiesis. (See also growth promoter notes). They may be used to treat anaemia of some chronic diseases, especially chronic renal failure where their main effect may be to reduce the uraemia which depresses erythropoiesis. Binds to cytoplasmic protein receptor and enhances protein synthesis and diminishes urinary nitrogen excretion.

Unlicensed use is illegal in food animals.

Anti-catabolic effects

•inreases nitrogen retention and utilisation
•stimulates appetite and haematopoiesis
•increased retention of calcium, phosphorus and potassium
•Improves blood flow and perfusion,
•reduced blood pressure in microcirculation.
but nutrition must be adequate

General Indications

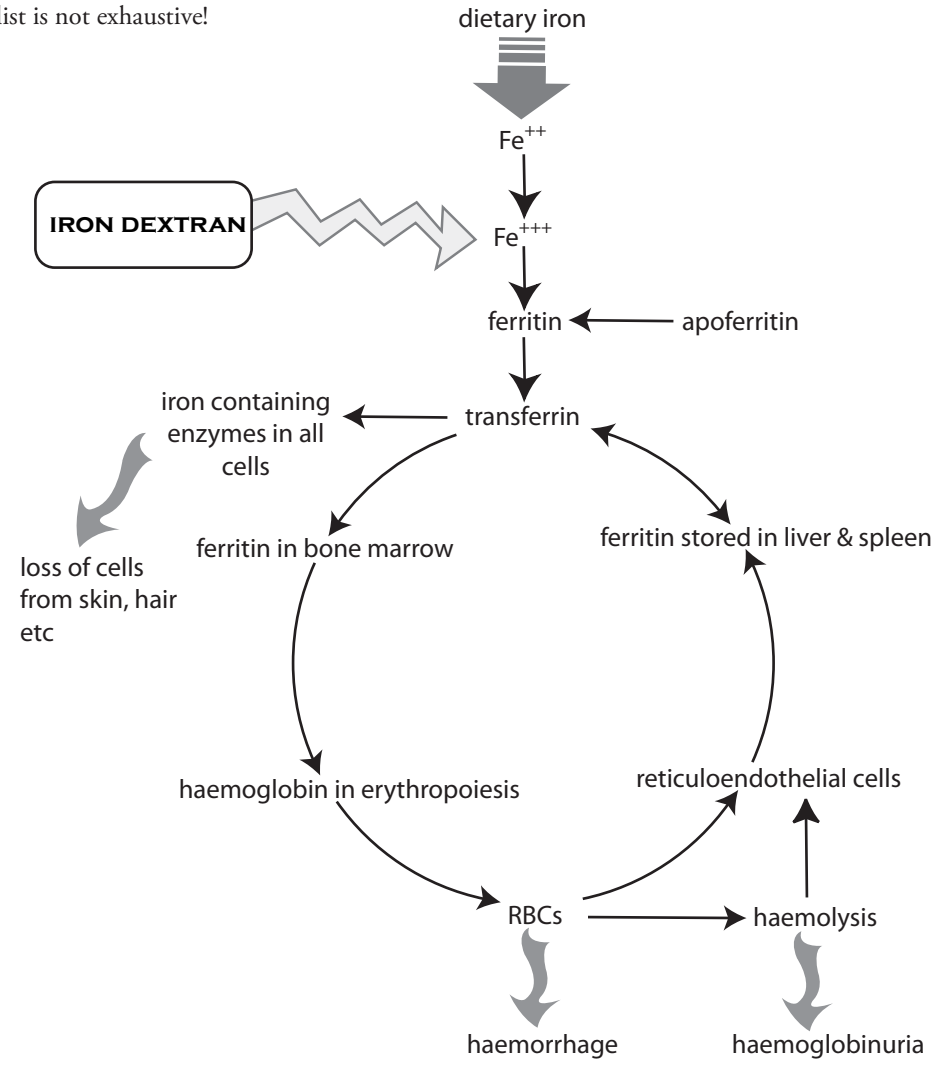
•stimulate erythropoiesis in anemia due to renal failure and other causes.
•aid in convalescence
•appetite stimulant
•promotion of healing in bones, tendons and surgical wounds.
•antagonise catabolic effects of glucocorticoids
•enhance conditioning of performance horses
•growth promoters

General Precautions

•potential to cause excessive retention of water and Na, Ca, K, Cl, and phosphate.
•may suppress clotting factors II, V, VII and X - •potentiates anticoagulants - may increase prothrombin time
•requires dose adjustment if insulin is used (decreased insulin requirement)
•reproductive problems (decreased fertility)
•virilisation at high doses (most are testosterone

CAUSE	SPECIES	TREATMENT
acute anaemia of unknown cause	all	whole blood (fresh)
nutritional deficiencies		
iron	piglets	iron preparations
vitamin B12	dog & cat	parenteral B12
cobalt (required for B12 synthesis)	ruminants	oral cobalt
folic acid	dog & cat	oral folates
bone marrow abnormalities		
chronic renal failure (reduced erythropoetin production)	dog & cat	anabolic steroids erythropoetin
aplastic anaemia		
iatrogenic		
oestrogens	dog & ferret	withdraw drug
anticancer drugs	dog & cat	reduce dose?
toxins	all	
infections	all	
excessive RBC destruction		
autoimmune haemolytic anaemia	dog & cat	immunosuppressives
drug reactions	all	withdraw drug
infections		
parasites, eg Haemobartonella	all	treat infection
viruses	all	symptomatic

This list is not exhaustive!



derivatives)

•renal or hepatic dysfunction affect pharmacokinetics, which is important to withdrawal times

•potential hepatotoxicity in overdose

•potential for human abuse

Interactions

Potentiate anticoagulants

Laboratory or non-significant findings:

decreased protein-bound iodine

decreased T4 and thyroxine-binding globulin

creatinine and creatine secretion may be decreased

blood glucose may be decreased (therefore may decrease insulin needs)

affect liver function tests (BSP retention, ALT, AST, bilirubin and alkaline phosphatase)

Monitoring

Response to all drugs used to treat anaemia is usually monitored by assessing the PCV. For all anabolic steroids, some monitoring is necessary - clinical or chemical assessment, monitor for androgenic changes, fluid electrolyte imbalance, liver disease, red cell response, weight changes and appetite.

There is anecdotal evidence that **nandrolone** is clinically superior to other anabolics for erythropoiesis. Nandrolone is believed to directly stimulate red cell precoursers in the bone marrow and enhance erthropoietin synthesis in renal failure. Also promotes body tissue building and reverses catabolism and has some androgenic effects.

Ethylestrenol is an orally active anabolic steroid with high anabolic: androgenic ratio (19:1) sometimes used for erythropoisesis. Effects will take at least a week to appear. **Stanozolol** has an anabolic: androgenic ratio 4:1. It may enhance fibrinolysis and so be useful in feline thromboembolism.

Other erythropoietics

Erythropoietin (EPO) is the main regulator of red cell production. It is an endocrine hormone synthesised in the kidney-peritubular cells of the proximal convoluted tubules (a small amount is synthesized in the liver in some species). Synthesis increases with decrease in PO_2, inhibited by increase in PO_2 (responds to anemia via decreased PO_2). It acts on a bone marrow receptor-erythroid progenitor cells but the exact mechanism of action is unknown. It also increases synthesis of haemoglobin. Concentrations are usually reduced in chronic renal failure.

The commercial product is recombinant human EPO: It is prohibitively expensive at the moment. It is a 30,000 MW glycoprotein with human albumin as a carrier: allergic reactions can occur, may manifest as a lack of response to treatment.. Animals must have proper nutritional support. Iron and other essential nutrients must be adequate for EPO to work.

Animals should respond in 2-6 weeks. The use of anabolic steroids may enhance the effect on haematopoiesis.

Erythropoietin is widely abused by human athletes; there ia also potential for this use in horses and greyhounds. In horses it works well for a few weeks then it provokes antibody production which eventually induces anaemia.

Lithium (carbonate) has been reported to stimulate erythropoiesis and has been suggested to aid in the recovery of dogs with oestrogen-induced bone marrow hypoplasia. Blood concentrations must be monitored because of its potential (probable) toxicity.

Polycythaemia

Absolute polycythaemia can occur due to:

Disease

Myeloproliferative

Polycythaemia vera

elevated EPO in response to:

pulmonary disease

high altitude

cardiovascular disease

testosterone

decreased PO_2

renal neoplasia

hyperadrenocorticism

treatment

try to eliminate cause

Relative polycythaemia is usually caused by dehydration: treatment is iv fluids.

commonly used drugs

platelet inhibitors

aspirin

anticoagulants

heparin

acid citrate dextrose

coagulants

vitamin K1

Fluids & Electrolytes

Although salty water is not considered a drug by all, it is the single most useful way of treating sick animals.

The main function of the blood is to transport oxygen and nutrients to the tissues and take waste products away. To do this there must be adequate volume for the heart to pump, adequate lung function to get oxygen into the blood and adequate tissue blood flow to get oxygen to the cells.

Composition of blood

plasma
- water
- proteins
  - albumin
  - globulin
  - clotting factors
- electrolytes
- glucose
- waste products

cells
- red blood cells
- white blood cells

platelets

Problems can arise from deficiences or (rarely) excesses of any of these components.

Fluid loss

The distribution of body water (very rough figures):

• total body water	65% body weight (adults)
	80% body weight (neonates)
• intracellular fluid	45% bw
• extracellular fluid	20% bw
• blood volume	9% bw
• plasma volume	5% bw

In very fat animals these figures will be lower.

Common routes of fluid loss:

haemorrhage (not necessarily external)
vomiting
diarrhoea
not drinking
anaesthesia (breathing dry gas)
laparotomy / thoracotomy (evaporation)
burns

The body will adjust the fluid compartments to try to maintain blood volume to preserve blood flow to the vital tissues. Eventually this breaks down and shock results.

Shock

Shock is a state of generalised failure of perfusion of tissues. This is the end stage of most diseases although it is sometimes classified by the causative factor eg endotoxic shock, cardiogenic shock. Initially the body copes by directing most of the cardiac output to the vital organs and drawing water into the cirulation from the interstitial and intracellular fluid compartments but the condition may progress to the point where the compensatory mechanisms are inappropriate and result in positive feedback.

Every body system is affected by shock. Reduced blood flow to the tissues means that anaerobic respiration takes place and lactic acid builds up. The arterioles of non - essential tissues are vasoconstricted by sympathetic outflow and adrenaline but the acidic conditions will eventually cause vasodilatation releasing hydrogen ions into the circulation and reducing cardiac output and thus arterial blood pressure.

The first priority in most types of shock is to treat the hypovolaemia with fluids (almost any fluid will do to start with). The acidosis can then be corrected with bicarbonate and the cause of the shock treated. Treatment of cardiogenic shock is different - see diagram.

A huge number of drugs have been advocated for use in shock but there is no convincing evidence that any of them have any useful effect. Corticosteroids in high doses are usually given in the hope that they will do something despite the fact that they have only been shown to improve the outcome if given before shock develops.

Parenteral vs oral fluids

Regulation of water and electrolytes (and thus blood volume) is a function of the kidney. If there is not enough blood flow to the kidney, this regulation breaks down. However, if the kidneys are working and the animal is not vomiting, oral administration is best - the kidneys are better at working out the animal's requirements than most veterinary surgeons. The commonest situation where oral fluids are used is diarrhoea.

In most other circumstances, intravenous administration (via a large bore indwelling catheter) is best. If the animal's blood volume is low, a vein may be hard to find. The answer is to do a sterile cut down onto the vein (see next page); this is quicker and better for the animal than prolonged poking about in the region of the vein followed by administration of fluids by an inappropriate route.

If all else fails, fluids can be given intraperitoneally. Since the peritoneal cavity is only a potential space under normal circumstances, the chances of hitting an organ with the needle are high.

Subcutaneous administration is not a good way to give fluids because if the animal has a low blood volume / acidosis the blood vessels supplying the skin will be constricted. This is done to divert blood to vital organs but also means that the fluid will not be absorbed. Some fluids (dextrose 5%) will cause vasoconstriction directly and actually draw fluid

out of the circulation into the subcutaneous depot.

Intraosseous administration has been advocated in puppies and kittens. Injections by this route are extremely painful in man, when a neonatal animal is so sick as to be unable to fight back it is hardly sporting to subject it to excruciating pain as well. Infection is another problem when using this route - the consequences are likely to be disastrous.

General indications for fluids

for oxygen carriage
- whole blood
- packed cells

for volume expansion
- colloids
  - plasma
  - gelatins
  - starches
  - hypertonic saline
  - (dextrans)

(but almost any fluid will do in an emergency)

for water and electrolyte replacement
- crystalloids
  - NaCl 0.9%
  - NaCl 0.18% & dextrose 4%
  - dextrose 5%
  - Ringer's solution
  - Hartmann's solution
- concentrated electrolyte solutions
  - KCl (must be diluted)
  - $NaHCO_3$- 8.4% (must be diluted)
  - Ca (boro)gluconate
  - Mg hypophosphite (often with Ca)
  - $MgSO_4$

for parenteral nutrition
- lipid emulsions
- amino acid solutions
- propylene glycol (ruminants only)
- Na propionate (ruminants only)
- glycerol (ruminants only)

Dose calculations

Start by assessing:

•existing deficit - careful history, clinical examination, laboratory tests

•continuing losses - measured directly

•maintenance requirements - 40ml/kg/day

After fluid replacement starts the animals should be **assessed regularly** and the dose adjusted according to clinical progress. Remember that not all animals have read the book - some will need more than others!

Rate of administration

This depends entirely on the seriousness of the condition. A maxiumum rate of 90ml/kg/h iv is sometimes quoted but the limiting factor is usually the resistance (ie, size) of the intravenous catheter / needle. If you want the fluid to go in quickly use a big, short catheter, or better still, lots of them! This can be a problem in horses, as iv catheters only come in human sizes. Some specialized large cathers are available but are expensive.

If the volume of oral fluid administered is greater than the volume of the animal's stomach then the fluid will rapidly come back up and you will find yourself treating inhalation pneumonia.

Oral rehydration fluids

These should be used in preference to iv fluids where possible. They usually come as a dry powder which is made up with tap water into an isotonic/ slightly hypotonic solution just before administration. Constituents vary but usually include:

- Na^+ to draw water with it
- K^+, Cl- to replace losses
- glucose and glycine to activate organic molecule cotransport systems and increase Na+ uptake
- bicarbonate precursors to correct acidosis
  - acetate (1mmol = 1mmol HCO_3^-)
  - citrate (1mmol = 3mmol HCO_3^-)
  - propionate (1mmol = 1mmol HCO_3^-)

They may also contain starches to be metabolised for energy (adding extra glucose would increase osmolarity of solution and reduce water uptake) and flavourings. Palatability is a problem in small animals.

Only sugar and salt are strictly necessary, the other components are just to improve efficiency. The WHO has published a recipe for third world children: 3.5g salt, 2.5g sodium bicarbonate, 1.5g potassium chloride and 20g glucose made up to one litre with water. This could be used in animals if necessary, although the bicarbonate will change stomach pH enough to cause problems with milk clotting if both are given together.

Indications

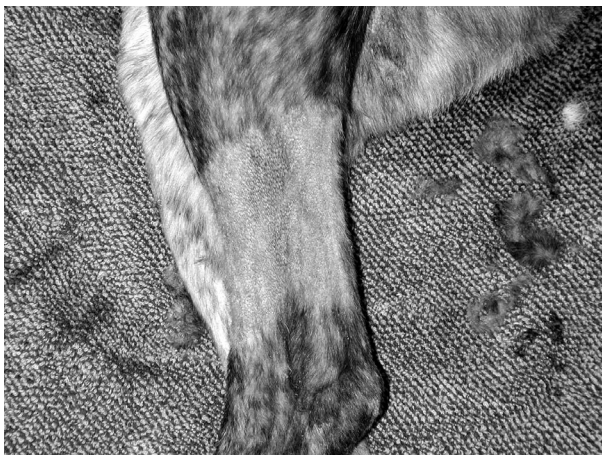
mild diarrhoea - especially neonatal animals - cheap enough to use in farm animals

water deprivation

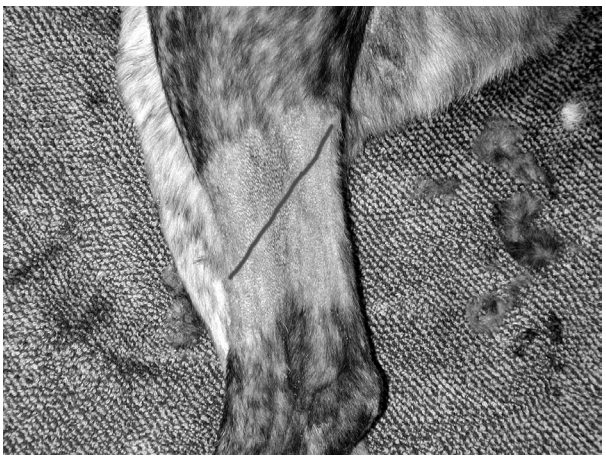
Contraindications

vomiting, severe electrolyte imbalances or shock

They are usually given *ad lib* in place of drinking water (the animal must be well enough to drink), but if giving by stomach tube, give little and often. The dose depends on the size of the animal's stomach - too much will cause regurgitation ± inhalation pneumonia).

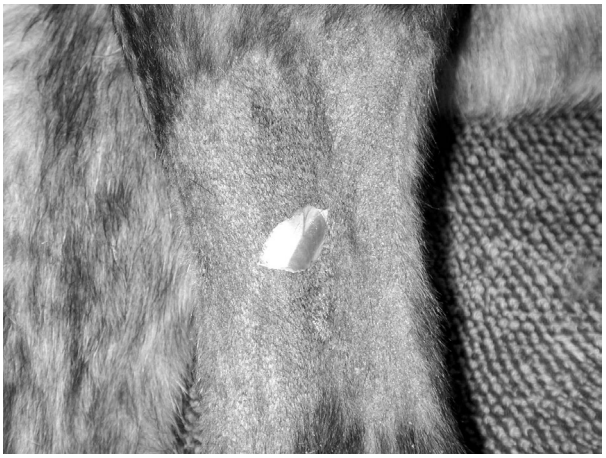


1. Lateral aspect of the back leg aseptically prepared.



2. Position of the lateral saphenous vein.

3. 1cm incision just to one side of vein.



4. Blunt dissect on to vein.

5. Isolate vein.

6. Insert tip of catheter for 3 mm.

7. Slide catheter off stylette, and remove stylette.

8. Suture **securely** *in place!*

condition	loss	fluid used
haemorrhage	all blood components	mild: colloids (crystalloids) severe: (fresh) whole blood
dehydration (not drinking enough)	water	NaCl 0.18% & dextrose 4%, dextrose 5% (KCl 10-20mmol/l added after 2d)
vomiting	water, $H^+Na^+K^+Cl^-$	NaCl 0.9%, Hartmann's (KCl 10-20mmol/l added)
diarrhoea	water, $HCO_3^-Na^+K^+Cl^-$	mild: oral fluids severe: Hartmann's - extra KCl & $NaHCO_3$ needed (unless Addison's or acute renal failure)
severe V & D	water, $H^+HCO_3^-Na^+K^+Cl^-$	colloid & Hartmann's
peritonitis	plasma & ECF	colloid & Hartmann's
gut obstruction	water, $HCO_3^-Na^+Cl^-$	colloid & Hartmann's & $NaHCO_3$
urethral obstruction / ruptured bladder	retention of H^+ & K^+	NaCl 0.9% & dextrose 5% (& soluble insulin?)

Intravenous fluids

Giving fluids iv is the quickest way to get them to where they are required. Some knowledge of physiology is required to get the dose right - overdosing can be fatal. Too much fluid in the circulation will increase preload on the heart. This is not good for animals with heart disease; in normal animals, signs of congestive heart failure will start to show. Pulmonary and peripheral oedema are most obvious. Pulmonary oedema is often fatal.

Electrolytes such as potassium and bicarbonate are needed inside cells but are given iv - it takes time for them to diffuse into cells. If the solutions are given too quickly, it is possible to have an excess in the blood at the same time as a deficit in the tissues. Since the heart is one of the organs with the best blood supply, this can lead to arrhythmias.

The circumstances in each animal will be different. The only safe way of using fluids is to monitor the effects of treatment closely. Central venous pressure measurement is very useful - at the very least you should look at the large veins to see if they are distended. CVP can be measured with an improvised water manometer (bits of giving set and a 3 way tap) connected to a central vein.

Blood

Whole blood is the fluid of choice for major blood loss but it is expensive and time consuming to collect and store. Blood is usually taken into flexible bags containing acid citrate dextrose (ACD) or citrate dextrose phosphate (CDP) (see anticoagulant notes). ACD will preserve red cells in blood stored at 4˚C for 3 weeks, CDP for 4 weeks. Clotting factors and platelets will be degraded in hours.

Indications

used where RBCs are required

acute bleeding - PCV below 20%

chronic problems - PCV below 15% (dog), 10% (cat)

Packed cells (what is left after plasma has been removed) are used where only RBCs are required and suspended in saline before use.

Fresh blood (collected using ACD or CPD but not stored) is used where RBCs and / or clotting factors and / or platelets are required. Beware of transfusion reactions (see anaesthesia notes). There is also the potential for spread of infections, parasites and tumours.

There are no satisfactory substitutes for blood yet but since there is a potentially enormous (human) military market a lot of time and money is being expended looking for a fluid which can carry oxygen, be infused without worries about reactions and has a long shelf life. The nearest so far are perfluorocarbon mixtures which do all these things but are not broken down or excreted by the body. One product is on sale in Japan but worries about long term effects mean that it has not been licensed anywhere else. Cross linked haemoglobin solutions (Oxyglobin) have recently been developed overseas and work in dogs but are not available in NZ yet.

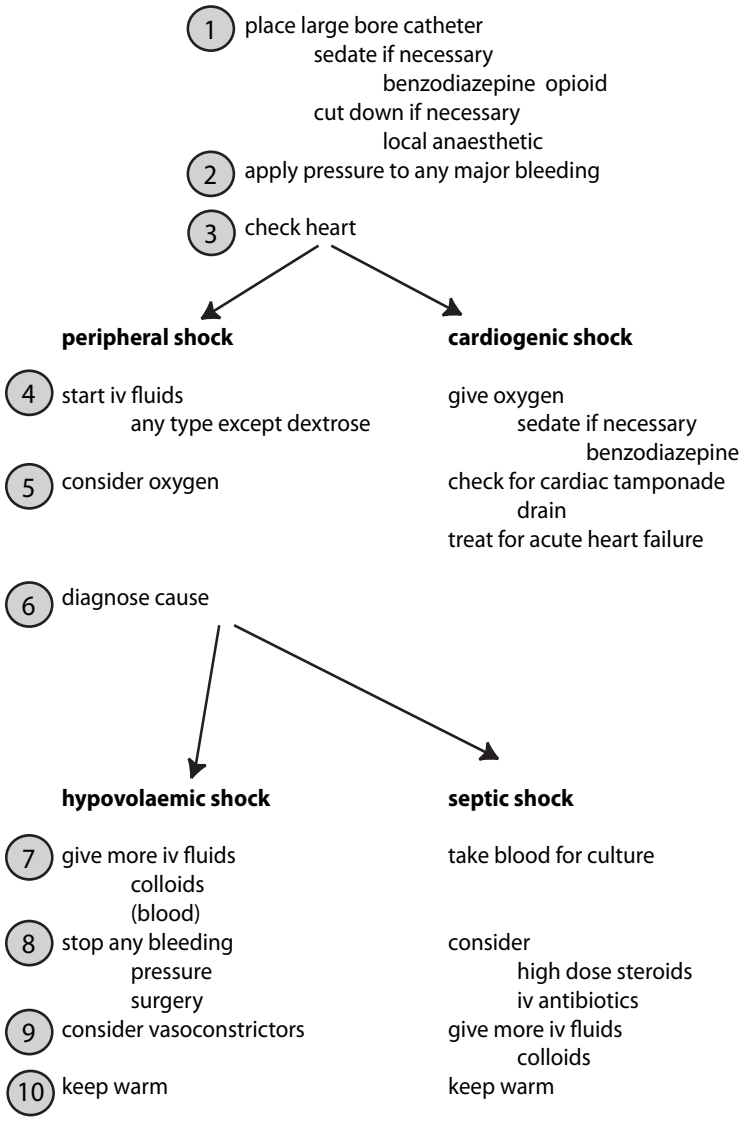
Colloids

These stay in the blood vessels where they maintain blood volume.

Fresh frozen plasma, if collected, separated and frozen immediately, is a useful source of clotting factors as well as a plasma expander. Lasts about 12 months at -80˚C or 3 months at -20. Collecting, separating and storing takes time and equipment. There is the possibility of spreading diseases by tranfusing plasma. Human plasma is sterilised to kill HIV, but this is never done in veterinary practice. Mild allergic reactions are common.

Gelatin solutions (Haemaccel, Gelofusin) are the

shock treatment



most widely used plasma expanders overseas. Useful duration of effect 2 - 3 hours. They are ridiculously expensive in NZ. They are made form cross linked bovine gelatin from BSE free countries.

Hydroxyethyl starch solutions are stable, have a long plasma half life (about 8 hours), a long shelf life - ideal but very expensive.

Anaphylaxis to all of these have been seen in man.

Dextrans are obsolete as plasma expanders. They interfere with blood clotting and are now only used (rarely) for this purpose. Lower molecular weight dextrans (40kDa) can cause kidney failure. Avoid.

Crystalloids

These move rapidly out of the blood vessels into the ECF, but can still be useful to expand the blood volume in emergency.

Sodium chloride 0.9% solution (**normal saline**) is distributed throughout the ECF. Its lack of bicarbonate or a precursor tends to lower pH, but in acidosis, increased blood volume may improve kidney blood flow and thus kidney regulation of pH leading to a reduced acidosis. Long term use will require extra potassium.

Sodium chloride 0.18% and dextrose 4% (**dextrose saline**) solution is useful for sodium and water maintenance.

Dextrose 5% solution is used as a means of supplying water. The dextrose is quickly metabolised; it is not enough to provide significant energy to the animal. Distributed throughout the body water. Do not give sc - electrolytes diffuse into the pool of dextrose solution drawing water with them and making the situation worse.

Ringer's solution is similar to normal saline but with some potassium. Also tends to lower pH.

Hartmann's solution (sodium lactate infusion, very similar tolactated Ringer's) is used for ECF replacement as it contains lactate as a bicarbonate precursor. It will tend to raise the pH. Although Ringer was British and Hartmann American, "Hartmann's solution" is used in the UK (and NZ) and "lactated Ringer's solution" in the USA.

Sodium chloride 7% solution (**hypertonic saline**) (3% or 5% are sometimes used) is used as a plasma volume expander. It draws water out of the ECF into the circulation which increases cardiac output and tissue perfusion in hypovolaemia. It may also have a direct stimulant effect on the heart. Effects only last 20 - 30 mins so normal crystalloids and

/ or colloids must be given as well. The small volume of injection makes hypertonic saline (4ml/kg iv followed by normal fluids) useful as a first aid measure in large animals.

It is used for first line treatment of hypovolaemia - more dilute solutions / water to drink must be given afterwards; and in head and lung injuries (draws oedema fluid into the circulation). It should not be used in severe dehydration.

Electrolyte additives

Potassium chloride solution comes in several strengths which **must be diluted** before use. They are usually mixed into a bag of crystalloid. Note that injecting potassium into a bag is not the same thing as mixing it with the bag's contents - a bolus of potassium will rapidly stop the heart. Longer term fluid therapy (>12 hours) usually requires potassium supplementation. **Make sure that you label the bag** in an obvious way.

Hyperkalaemia can be treated by correcting acidosis, giving insulin in 5% dextrose to promote uptake of potassium by cells and by giving calcium borogluconate to oppose the cardiac effects of potassium.

Sodium **bicarbonate** 8.4% solution is used because it contains 1mmol/mL which makes the sums easier. If you come across other concentrations you will have to do some more maths. For instance, a 5% solution contains 50g/L. The molecular weight of sodium bicarbonate is 84, so a 5% solution contains 50/84 = 0.6mol/L (mmol/mL).

Bicarbonate must be mixed with other solutions before use. Normal saline is the fluid usually used - bicarbonate is incompatible with anything containing calcium (many other solutions and most drugs) (calcium carbonate is insoluble and precipitates out). Bicarbonate is distributed throughout the body water but administration is calculated to replace the circulating deficit, since correcting the acidosis will lower plasma potassium levels. A blood gas sample is taken and the amount of bicarbonate required is obtained by multiplying the base excess (a negative number in acidosis!) by the blood volume (roughly 10% of body weight).

For example; if a 500kg horse has a base excess of -10mmol/L in a blood (usually arterial) sample, it needs 10mmol/L of bicarbonate to restore acid base balance in the blood. Since its blood volume is about 50L, the amount of bicarbonate required is 50 x 10 = 500mmol or 500mL of 8.4% solution.

Once this amount of bicarbonate has been infused (over 60mins), the base excess is checked again because some will have been redistributed.

Beware of overdose - this will cause a paradoxical acidosis in the CNS. Give too little bicarbonate and reassess teh animal rather than giving too much.

Calcium (boro) gluconate solutions (the boron is added only to improve solubility) are used in cows and ewes for milk fever (40% solution) and in bitches for eclampsia (10% solution). The amount of calcium given to cows does not correct the deficiency; the aim is merely to tilt the balance in favour of homoeostasis. Administration of calcium salts sc causes intense vasoconstriction and sometimes necrosis of the overlying skin so give them iv.

Magnesium sulphate / chloride solutions are used in cows for grass staggers. iv administration causes muscle paralysis and can stop the heart - it should be given sc.

Compound calcium / magnesium / phosphorous mixtures are often given iv to cows where it is not clear which mineral or combination of minerals is deficient. Given iv in grass staggers followed by magnesium solution sc.

Compound trace elements

Usually given as an oral supplement to ruminants. **Remember that animals only need a trace** - any more will probably be toxic. Selenium is very easy to overdose - beware of Se injections in animals which have been dosed orally or been on pasture with Se supplemented fertiliser.

Parenteral nutrition

Avoid if at all possible! Consider enteral feeding by nasogastric or pharyngostomy tube before embarking on parenteral feeding. A dedicated catheter into a central vein is required; maintenance of this catheter and prevention of phlebitis and infection is tricky.

Lipid emulsions and **amino acids** are expensive, are ideal bacterial growth media and can be irritant. Care is required with iv **glucose** since it causes an osmotic diuresis.

Drugs for ketosis in ruminants

Ketosis occurs when there is a sudden increase in demand for energy, e.g. at the start of lactation in dairy cows or towards the end of pregnancy with twins in beef cows and ewes. The liver becomes depleted of glycogen and undergoes fatty change which leads to anorexia which exacerbates the problem. **Glucocorticoids** are sometimes used to promote gluconeogenesis but can cause premature parturition. Prevention by sorting out the diet is better than cure.

Propylene glycol, sodium **propionate** and **glycerol** are all rapidly metabolised to glucose in cows and ewes. Dose varies with the preparation / severity of the condition. These drugs are given orally as glucose precursors to break the vicious cycle - **not** to provide all the energy requirements of the animal.

commonly used drugs

Hartmann's solution
normal saline

Fluids

- in emergency any iv fluid is useful to expand plasma volume
- colloids stay in blood vessels, crystalloids redistribute to other compartments
- use oral fluids rather than iv where possible
- avoid parenteral nutrition - use pharyngostomy tube
- prevent metabolic disease in ruminants rather than wait and then try to cure it

Practice exam questions

Multiple choice questions

1. Congestive heart failure in the dog may be treated with
   - atropine ❑
   - frusemide ❑
   - sodium nitroprusside ❑
   - mannitol ❑
   - bradykinin ❑

2. Ventricular ectopic beats may be usefully treated with
   - lignocaine ❑
   - atropine ❑
   - nicardipine ❑
   - isoprenaline ❑
   - digoxin ❑

3. Useful effects of digoxin include
   - negative inotropy ❑
   - atrio-ventricular node blockade ❑
   - bronchodilatation ❑
   - euphoria ❑
   - increased potassium secretion ❑

4. Side-effects of dopamine infusion can include
   - splanchnic vasoconstriction ❑
   - ventricular ectopic beats ❑
   - heart block ❑
   - convulsions ❑
   - Parkinson's syndrome ❑

5. Quinidine
   - is a Vaughan Williams class 1 drug ❑
   - is an isomer of chloroquine ❑
   - is useful in the treatment of ventricular tachycardia ❑
   - prolongs phase 4 of the cardiac action potential ❑
   - is rapidly metabolised to lignocaine in the plasma ❑

6. Diuretics which are clinically useful in the dog include
   - mannitol ❑
   - glycerol ❑
   - bethanecol ❑
   - mersalyl ❑
   - propantheline ❑

7. Hydrochlorothiazide may
   - inhibit carbonic anhydrase at clinical dose rates ❑
   - cause diabetes mellitus ❑
   - produce sedation ❑

cause potassium loss ❑
quickly give rise to tolerance ❑

8.Piglet anaemia may be prevented using
oral vitamin B 12 ❑
oral ferrous sulphate ❑
intramuscular desferrioxamine ❑
intravenous ferric sulphate ❑
intramuscular gleptoferron ❑

9. The best treatment for severe acute haemorrhage is
gelatin solution ❑
0.9% saline solution ❑
5% dextrose solution ❑
blood with acid citrate dextrose ❑
heparin ❑

10. 7.5% saline
has a positive inotropic action ❑
blocks sodium channels ❑
is a good treatment for dehydration ❑
is useful in cardiogenic shock ❑
may cause hypokalaemia ❑