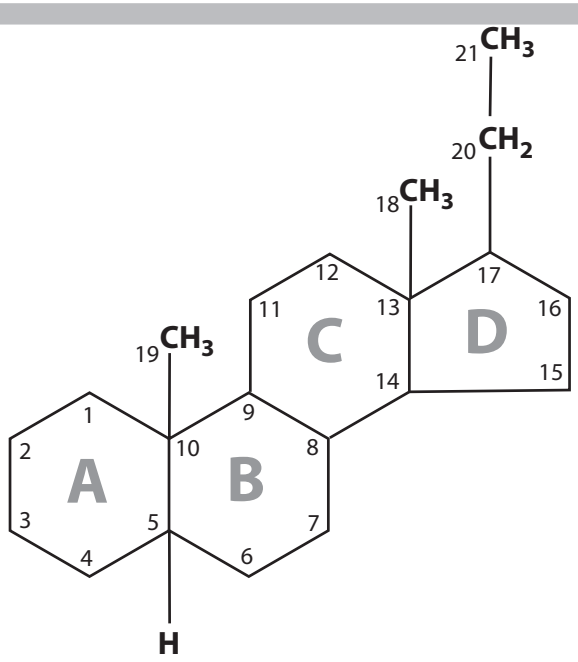
7 Inflammation & Hormones

Inflammation is probably the commonest condition that vets are asked to treat. Although inflammation is usually only a sign of injury or infection, the pain and loss of function associated with inflammation mean that the inflammation must be treated (as well as the primary problem). There is a huge (and growing) variety of chemical mediators of inflammation. Although most of the drugs used today are aimed more or less specifically at prostaglandins, there are thousands of other targets and drugs acting at these are starting to emerge. There are interesting times ahead for students of pharmacology!

Corticosteroids



Pregnane, the basic structure of the corticosteroids.

Steroids are the main group of drugs used to suppress inflammation and the immune system in veterinary practice.

The word steroid refers to the 19-21 carbon pregnane nucleus common to these substances. Many veterinary drugs are steroids, for instance, the sex hormones, anabolic steroids, some anaesthetics and some muscle relaxants. Digoxin also contains a steroid group.

Corticosteroids are produced by the adrenal cortex and come as two classes; *glucocorticosteroids* (= glucocorticoids) - produced in the zonae reticularis and fasiculata; and *mineralocorticosteroids* - produced in the zona glomerulosa

Endogenous glucocorticosteroids are produced by the adrenal cortex in a series of enzymatic steps. The glucocorticosteroids we use therapeutically are mostly structurally modified synthetic analogues of these endogenous glucocorticosteroids. Most of the endogenous glucocorticosteroids and many of the synthetic analogues still retain at least some of both types of effects.

There is a wide variety of preparations available but often the clinical effects are more related to the formulation than the particular drug used. **Hydrocortisone** (= cortisol) is the only endogenous glucocorticoid used therapeutically; **prednisolone** and its prodrug **prednisone** are widely used in dogs, as are the longer acting **betamethasone** and **dexamethasone**. Very potent newer drugs such as **flumethasone** are rarely used. Other drugs, such as **triamcinolone** are sometimes used. If a mineralocorticoid effect is required, **fludrocortisone** is most commonly used.

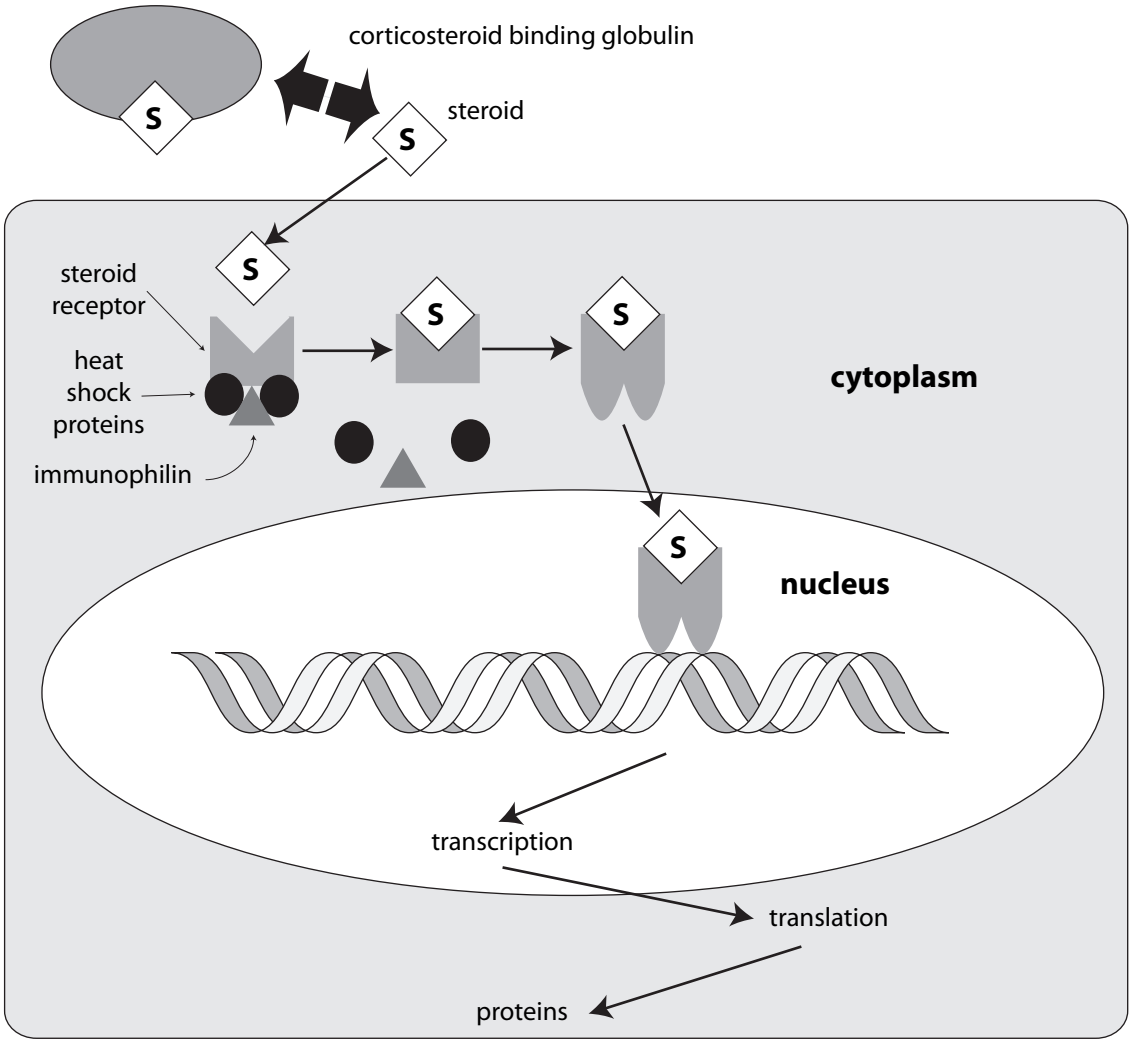
Relative potencies

	Na^+ retention	Anti-inflammatory
Endogenous		
aldosterone	3000	?
corticosterone	15	0.3
cortisol	1	1
Synthetic		
prednisolone	0.8	4
dexamethasone	0	30
betamethasone	0	35
flumethasone	0	700
fludrocortisone	125	10

Molecular basis of action

Glucocorticoids bind to their receptors in the cytoplasm and the receptor - drug complex is then translocated into the nucleus where it interferes with transcriptional regulation to stimulate or inhibit the transcription of mRNA.

Variable responses by different cells to steroid therapy



Cellular mechanism of action of steroids. The steroid receptor complex binds to DNA with its zinc fingers; depending on where it binds, proteins are either produced or production blocked.

may be explained by variable penetration of cells and tissue types, different receptors, variable access to specific DNA sequences in different cells or other variations in intracellular environments.

Glucocorticoid effects

Energy metabolism

•antagonistic to insulin
•increase gluconeogenesis
•enhance lipolysis
•protein catabolism (to provide amino acids for gluconeogenesis)

Water and Electrolytes

•decrease calcium absorption (gut)
•increase calcium excretion (kidney)
•polyuria (decreased ADH secretion)
•increase water intake (psychological?)
•increase glomerular filtration rate

Blood and Immune System

•decrease lymphocyte numbers
•decrease eosinophil, monocyte, basophil numbers
•increase neutrophil numbers
•increased release from the bone marrow
•decreased extravascular migration
•lower propensity to marginate on vascular endothelium
•decrease virus induced interferon production
•decrease production of interleukin, prostaglandin, thromboxane, platelet activating factor
•may elevate serum enzymes etc.
serum alkaline phosphatase (common in dogs)
alanine aminotransferase
cholesterol
blood urea nitrogen
•may depress serum thyroxin

Cardiorespiratory system

•chronotropic
•inotropic
•block inflammatory increases in capillary permeability
•permissive to effects of catecholamines
•increase number and affinity of β adrenoreceptors

CNS

•mental dependence
•euphoria
•increased appetite
•depression
•depress chemically mediated pyrexia
•direct inhibition of prostaglandin E2 production in the preoptic hypothalamic vasculature of the thermoregulatory centre

Skin

•calcification of skin
•thinning and weakening of connective tissues

Musculoskeletal system

•inhibition of osteoclast activity
•retardation of growth
•depletion of cartilage matrix
•decreased cartilage compliance
•osteoporosis
•changes to collagen structure

Reproductive system

•normal foetus maturation
•can be teratogenic (cleft palates)
•induce abortion / parturition in some species (alpha substituent group must be present on carbon 16 of the steroid nucleus in order to induce parturition in cattle)
•inhibit spermatogenisis
•inhibit ovulation

Gastrointestinal Tract and Hepatic System

•facilitate absorption of fat
•increase secretion of gastric acid, pepsin, and trypsin
•decreases production and alters the structure of protective mucus
•pancreatitis
•increased fat and glycogen deposits in the liver
•increased serum levels of ALT, GGT and alkaline phosphatase

Anti-inflammatory actions

Glucocorticosteroids exert their anti-inflammatory effects on cells by stimulating or inhibiting the production and effects of:

lipocortin

Lipocortin inhibits phospholipase A2 which mediates release of arachidonic acid from the phospholipids of cell membranes.

LDL receptors

Low density lipoproteins are thought to be a major source of arachidonic acid after the initial release of arachidonic acid from the cell membranes. Glucocorticosteroids inhibit the synthesis and the expression of LDL receptors necessary for transport of LDL into the cell.

COX 2 (inducible cyclo-oxygenase)

Concentrations of COX 2 within inflammatory cells increase dramatically in response to stimuli. The synthesis of COX 2 is directly inhibited by the presence of glucocorticoids. Concentrations of COX 1 are less affected at anti-inflammatory doses.

Cytokines

The production and or effects of some cytokines are inhibited by the presence of therapeutic concentrations of the glucocorticoids:
tumour necrosis factor (TNF)
interleukin 1 (IL 1)
platelet activating factor (PAF)
a variety of 'growth factors'

Lysosomal membrane stabilization

Stabilization of lysosomal membranes has long been reported as the predominant anti inflammatory effect of glucocorticoids. The extent to which this happens, if at all, and its significance is not really known.

The anti-inflammatory actions of glucocorticosteroids at a cellular level are due to
•inhibition of recruitment of leukocytes
•inhibition of elaborating of inflammatory mediators by damaged and recruited cells
•interference in the synthesis and activation of catabolic enzymes
•suppression of the generation of granulation tissue.

The use of glucocorticosteroids is generally thought to inhibit primary wound healing. Their controlled use, however, can reduce scar formation and reduce the generation of excessive granulation tissue.

Immunosuppressive effects

The different types of leukocytes have differing sensitivities to glucocorticosteroid concentrations and their effects are manifested in different ways. The systemic glucocorticosteroid concentrations required to induce a generalized immunosuppression are much larger than anti-inflammatory concentrations. However, a degree of immunosuppression always follows any systemic glucocorticosteroid therapy. In general one can administer a large single dose of a short to medium acting glucocorticosteroid without any serious adverse affect. However, prolonged systemic therapy can be associated with a number of potentially serious affects. (See immunosuppressant notes below)

Hypothalamic - Pituitary - Adrenal axis

(for diagram see Cushing's disease below)
Endogenous adrenal cortisol production is controlled through the effects of the pituitary produced hormone ACTH. Corticotrophin releasing factor (CRF) and arginine vasopressin (anti-diuretic hormone) (AVP, or ADH), produced in the hypothalamus, are responsible for stimulating the production and release of ACTH from the pituitary. The

secretion of CRF from the hypothalamus generally follows a diurnal pattern in man and some animal species, peaking in the morning and being lowest in the evening. This is not the case for our domestic species. A pulsatile increased secretion of CRF is in response to stimuli which signal increased glucocorticoid need such as exercise, trauma, and cold. High plasma cortisol concentrations act as negative feedback, reducing further synthesis and release of AVP and CRF from the hypothalamus, and ACTH from the pituitary and inhibit further production. The presence of significant concentrations of exogenous glucocorticosteroids will also inhibit the synthesis and release of AVP, CRF, and ACTH and as a consequence markedly suppress endogenous plasma cortisol concentrations.

Extended exposure to significant systemic concentrations of exogenous glucocorticosteroids can result in adrenal cortical atrophy. Persistently elevated concentrations may result in a period when the adrenal cortex is non - responsive, or has a diminished response to either stress induced ACTH release, or even exogenous ACTH administration.

Clinical indications

- •allergy
- •inflammation
- •immunosuppression (see later)
  - autoimmune conditions
  - neoplasia
- •induction of parturition
- •endocrine function tests
- •replacement therapy in Addison's disease
- •trauma - shock therapy (controversial)

Drugs

The glucocorticoid bases in common use are listed in approximately ascending order of potency. This order also corresponds to increasing length of action of the base.

Short acting

hydrocortisone
prednisolone
prednisone

Medium Acting

methylprednisolone
triamcinolone

Long acting

betamethasone
dexamethasone.

Pharmaceutical considerations

The glucocorticoid bases are prepared as salts or esters. The pharmacokinetics of the drug product can be markedly affected by the compounding. Glucocorticoid - base - salt(ester) compounds are prepared in different excipient formulations. The formulation can also markedly affect the pharmacokinetics of the product. Therefore, the potency and duration of effect of a glucocorticosteroid are determined by:

The base

The base compound

The formulation

Examples of base-compounds: hydrocortisone sodium succinate, methylprednisolone sodium succinate, and dexamethasone sodium phosphate.

Most glucocorticosteroid bases can be classed as alcohols which are relatively insoluble in water. The sodium salt of the phosphate or succinate ester is generally used to provide water soluble forms for intravenous or intramuscular injection. Acetate and isonicotinate esters are relatively insoluble. They are usually prepared as aqueous suspensions for subcutaneous or intramuscular injections. Because they are insoluble they are absorbed slowly. These are the depot formulations. Acetonides and diproprionates tend to be the least soluble of this group. Fluorination or esterification with fatty acids or cyclic acetonides increases topical anti-inflammatory activity often without increasing systemic glucocorticoid activity.

Formulations

Tablets, aqueous solutions, aqueous suspensions, alcohol solutions, creams, and ointments are available. Formulation characteristics dictate the possible routes of administration and the absorption characteristics from these sites. Variations in particle size, excipient, pH, and physicochemical characteristics can all affect the absorption of the formulation.

Pharmacokinetics

Available pharmacokinetic information doesn't always correlate with observed duration of clinical effect due to the molecular mechanism of action of glucocorticosteroids and because many assays are not sensitive enough to measure pharmacologically significant glucocorticosteroid concentrations e.g. one equine pharmacokinetic report quotes that prednisolone was assayable for 7 days following an intramuscular injection of 200 mg of prednisolone acetate into the gluteal musculature. The same paper reports the endogenous cortisol concentrations were depressed for 21 days following the same injection.

Absorption

formulation effects

oral preparations - available predominantly as free bases

aqueous solutions - most readily and rapidly absorbed

short acting aqueous suspensions - dissolve quickly into body fluids, are relatively rapidly absorbed, produce peak blood concentrations within a few hours after injection and are totally eliminated from the body within 3 days of administration.

organic solutions in polyethylene glycol, e.g. azium solutions = dexamethasone alcohol dissolved in polyethylene glycol. (other organic solvents are also used) - some precipitate at the site of injection and are absorbed at a slightly slower rate and hence produce lower peak plasma concentrations which are maintained for slightly longer

long acting or depot formulations e.g. methylprednisolone acetate - can take from 1 - 4 days to achieve (relatively low) peak plasma concentrations - may take a number of weeks for plasma concentrations to decline to undetectable concentra-

tions - may associated with local tissue damage around the site of injection - major species and individual variations in both the extent and duration of HPA axis suppression - may suppress endogenous plasma cortisol concentrations for only 3 days in the horse but up to 12 weeks in cattle.

Ester/salt effects

hemisuccinate, succinate and phosphate esters are the most water soluble products available. They are used when rapid glucocorticoid effect is desired, when the intravenous route of administration is chosen, and can also be injected intramuscularly and subcutaneously. They are relatively rapidly absorbed and result in high early plasma concentrations.

Alcohol and isonicotinate in propylene glycol have been used intravenously (in the horse) . Their duration of effects are predominantly determined by the glucocorticoid base when administered intravenously. They form depots when injected intramuscularly.

The acetate, diacetate, trimethylacetate, tebutate and phenylpropionate esters are poorly water soluble; their absorption tends to be slow and sustained. When given by the intra-articular or intra-lesional route, high concentrations will be maintained locally for a long time. When given im, these esters form depots resulting in low plasma concentrations for periods of at least 2 to 14 days, depending on the dose, base, formulation and species injected.

Acetonide esters are used topically and are poorly water soluble. They bind to keratin slowing systemic absorption.

Free bases or the salt of an organic acid form (such as betamethasone benzoate) are also used.

Distribution

Widely distributed in the body both intra and extracellularly. Cortisol is approximately 90% protein bound in plasma. About 75% to the steroid binding globulin transcortin and 10 - 15% to serum albumin. Transcortin has a high affinity, particularly for cortisol or prednisolone, but low capacity, whereas albumin has a low affinity but much higher capacity.

Metabolism

Most glucocorticosteroid compounds are rapidly hydrolyzed in plasma or synovial fluid to release their active base. Methylprednisolone sodium succinate is not readily hydrolyzable in plasma and along with prednisone and cortisone requires hepatic metabolism to be converted into their active form, and thus are unsuitable for local or topical administrations.

Biotransformation is complex, but reduction of the double bond between C4 and C5 occurs mainly in the liver. This inactivates the molecule which is conjugated with glucuronic acid and excreted via the kidneys

Elimination

Very variable. Metabolites are excreted in the urine - very little faecal or unchanged urinary excretion. Elimination of depot preparations is absorption rate limited.

Selecting an appropriate drug

Think about:

cost
route of administration
time to onset of effects
duration of effects achieved
duration of effects desired
importance of sodium retaining effects
anti-inflammatory potency
HPA axis effects

Contra-indications

•diabetes mellitus
•pre-existing catabolic disease
•bacterial or fungal infections
•ocular viral infections, corneal ulceration
•growth in young animals
•pregnancy
•surgical (or other) wounds

Drug interactions

•cause microsomal enzyme induction.
•additive with some diuretics or Amphoteracin B in causing depletion of potassium.
•increase digitalis toxicity (K+ depletion)
•insulin antagonism
•decrease metabolism of cyclophosphamide
•erythromycin inhibits the activation of methylprednisolone
•increased risk of gastric ulceration from NSAIDs given concurrently
•may potentiate other drugs inductions of seizures.

Adverse Effects

Therapy of less than 3 - 5 days rarely causes any serious adverse effects unless other risk factors exist, e.g. diabetes mellitus, fulminant bacterial infection.

Some adverse effects occur routinely even with short duration of therapy:
•alteration to haematology - "stress leukogram"
•hepatic enzyme leakage into plasma - elevates ALT and SAP and interferes with diagnostic tests
•depressed total serum thyroxin concentration but the animal remains euthyroid (sick euthyroid syndrome)
•polydypsia, polyuria, polyphagia
•foetal abnormalities especially cleft palate
•abortion (C16 substituted glucocorticosteroids only)
•peptic and gastric ulceration

Some adverse effects occur especially with long term therapy
•increased susceptibility to infections
•myopathy
•behavioral changes
•osteoporosis
•inhibition of growth
•calcinosis cutis
•hyperpigmentation
•thinning of the skin
•collagen diseases

An Addisonian crisis (cardiovascular collapse, respiratory collapse, coma, death) may occur especially with

sudden withdrawal of long term therapy due to HPA axis suppression

Dosing strategies

Serious adverse effects are almost always avoidable. Incorrect or negligent use of these drugs is the most common reason for adverse effects. Adverse effects and toxicity can be largely avoided by use of the correct dose rates and regimens for different indications. In general, an adequate dose should be used by an appropriate route for the required speed of onset, then the dose tapered off to nothing / as low as possible depending on the condition.

•cats and birds are less sensitive and require higher doses than most other species

•if therapy is short duration then tapering of dose rates and regimens is not necessary.

•if therapy lasts for longer than 1 - 2 weeks (prednisolone) or 1 week (dexamethasone) then before therapy is interrupted the dose rate must be gradually tapered to a maintenance dose rate and the dose interval must be lengthened to 48 hours to allow the HPA axis to reawaken.

•only short acting glucocorticoids can be used for alternate day dosing (hydrocortisone (12 hr), cortisone (12 hr), prednis(ol)one (12-36 hr), methylprednisolone (12-36 hr)) - long acting glucocorticoids are not suitable for alternate day dosing (dexamethasone, triamcinolone, betamethasone)

Mineralocorticoid effects

Mineralocorticoids are used solely in the treatment of adrenal cortical insufficiency (Addison's disease) since most glucocorticosteroids used in replacement therapy have insufficient mineralocorticoid activity to sufficiently control electrolyte excretion. Drugs such as desoxycorticosterone pivalate (DOCP) (injectable, specific mineralocorticoid, used in USA) or fludrocortisone (tablets, used everywhere else) are used to produce increased extracellular fluid volume, sodium and fluid retention, potassium and hydrogen ion loss and increased glomerular filtration rate. A shortage of fludrocortisone has prompted research on ways of getting more mineralocorticoid effect from glucocorticoids. For instance, liquorice inhibits the enzyme which inactivates glucocorticoids in the kidney and prevents them having a mineralocorticoid effect and may be useful in dogs.

commonly used drugs

glucocorticoids
short acting
hydrocortisone
medium
prednisolone
long acting
betamethasone, dexamethasone
mineralocorticoids
fludrocortisone

clinical use

- indications - all species: inflammation of whatever cause
- dogs & cats - immunosuppression (at high doses)
- (cattle - induction of calving)
- beware iatrogenic Cushing's syndrome

Cushing's syndrome

Cushing's syndrome results from too much circulating corticosteroid. There are three main causes:

•*iatrogenic* - the commonest cause in veterinary practice!!

•*excessive production of ACTH* from the pituitary (usually a tumour)

•*adrenal tumours* or hyperplasia

Treatment of iatrogenic Cushing's involves tapering off the dose of steroids (see notes above); the other two have traditionally been treated with **mitotane** in dogs (surgery in man), although several other drugs are starting to be used, particularly selegiline. Cushing's in horses is usually caused by excessive ACTH production and is treated with dopamine agonists such as **pergolide**.

Drugs

The most commonly used drug in dogs has been mitotane, but it is an unpleasant drug and safer alternatives are coming into use. Selegiline has been licensed in the USA in the dog and there are a variety of human drugs coming onto the market.

It was discovered in the 1940s that the insecticide DDD (similar to DDT) destroyed the adrenal glands in dogs. The o,p' isomer (mitotane, = o,p' DDD) was found to be responsible. It has a direct cytotoxic effect on the zonae fasiculata and reticularis of the adrenal cortex and probably acts by killing mitochondria. Mitotane also inhibits steroid synthesis.

Mitotane's absorption is poor and variable in dogs. It is best when tablets are crushed up in oily food but this exposes the owner to the drug. Very fat soluble - taken up with fat.

Side effects are a major problem: overdose will cause Addison's disease (low corticosteroids). Some dogs will develop Addison's even at low doses. This often kills dogs. Steroid supplementation may be necessary. Anorexia, vomiting, lethargy and ataxia may also occur.

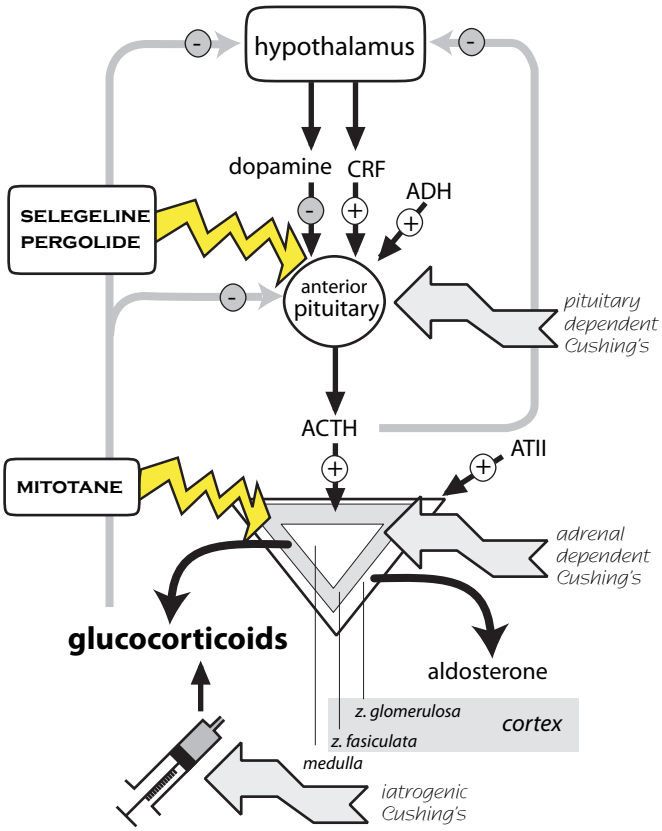
Other drugs sometimes used in Cushing's syndrome

drugs which act on the HPA axis, such as **selegeline** (= l deprenyl) (monoamine oxidase B inhibitor - stops dopamine breakdown (also stops 5HT breakdown - interacts with pethidine to kill dogs)), **bromocriptine** (dopamine agonist) and **cyproheptadine** (dirty 5HT antagonist). In horses, **pergolide** at low doses is the drug of choice.

drugs which reduce steroid synthesis, such as **metyrapone**, **aminoglutethimide**, **trilostane** (shown to work in dogs but not available in NZ yet), **etomidate**, **suramin** are not often used in animals.

drugs which block steroid receptors, the only current example is **mifepristone**. Beware, this will cause abortion in pregnant animals (and women).

Dexamethasone is sometimes given to diagnose Cushing's syndrome (dexamethasone suppression test). It should suppress the production of ACTH and steroid in a normal dog but interpretation of abnormal results can be tricky. Care is required in horses.



The hypothalamic - pituitary - adrenal axis.

NSAIDs

Definitions

NSAIDs = non-steroidal anti-inflammatory drugs. Usually only includes drugs thought to have a similar mechanism of action to aspirin, although there are many other drugs which are anti-inflammatory but are not steroids.

NSAID effects

anti-inflammatory
analgesic (see analgesic notes)
anti-pyretic

Some NSAIDs also have anti-thrombotic and anti-endotoxic effects.

The proportion of each effect is probably different for each drug, but this is difficult to prove. There are major species differences.

Molecular basis of action

The primary mechanism of action is inhibition of cyclo oxygenase (COX) and thus diminished generation of thromboxane, prostacyclin, and the prostaglandins, particularly PGE2. Since these compounds have a huge variety of functions, reducing their production causes a huge number of effects.

Other mechanisms include
•free radical scavenging
•upsetting oxidative phosphorylation
•disrupting G protein signaling
•inhibition of neutrophil activation
•inhibition of neutrophil adhesion
•inhibition of leukocyte recruitment
•inhibition of proteoglycan synthesis
•inhibition of phospholipase A2
•prostaglandin receptor antagonism

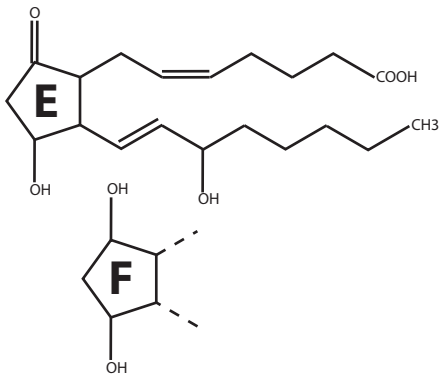
There are major differences in the efficacy of NSAIDs against the cyclo oxygenase enzymes of various species and tissues. This may be due to variable affinities for COX1 & COX2 (this also varies between species).

Selectivity for COX2 in the dog (although these figures are contentious):

carprofen	129
fenamates	15
meloxicam	3
phenylbutazone	2.6
flunixin	0.6
ketoprofen	0.2
aspirin	<0.3

Etodolac may be selective for COX2 in horses.

Differences in efficacy may also be caused by difference in predominant end product normally generated by the isomerases of different cells e.g. platelets & thromboxane or neutrophils & PGE_2 and PGI_2; variable penetration to the site



Prostaglandin names: prostaglandin E2 (top) and F (bottom). The the letter refers to the substituents on the ring: the 2 refers to the number of double bonds.

of action or different microenvironments which affect drug enzyme affinity. This can be of clinical importance: COX 2 inhibitors increase the risk of thromboembolism by blocking PGI_2 but not TXA_2.

Some drugs also block the lipoxygenase pathway.

Acetyl salicylate (aspirin) irreversibly inactivates the cyclo oxygenase of platelets (COX 1) by acetylating it. Most other NSAIDs in most cell types bind reversibly and competitively to cyclo-oxygenase.

Anti-inflammatory actions

Inflammation is part of the body's defensive response to injury. However, there can be therapeutic and management advantages in partially controlling this response and its associated clinical signs. NSAIDs are thought mainly to affect acute inflammatory processes through inhibiting the generation of the eicosanoids (thromboxane, prostacyclin, and the prostaglandins). They are not thought to dramatically affect the progression of chronic inflammatory processes which are mediated by other mechanisms (many different cytokines are involved). However, chronic inflammation is often associated with intermittent episodes of acute inflammation and some degree of relief from the clinical signs associated with these episodes can be gained with the use of NSAIDs.

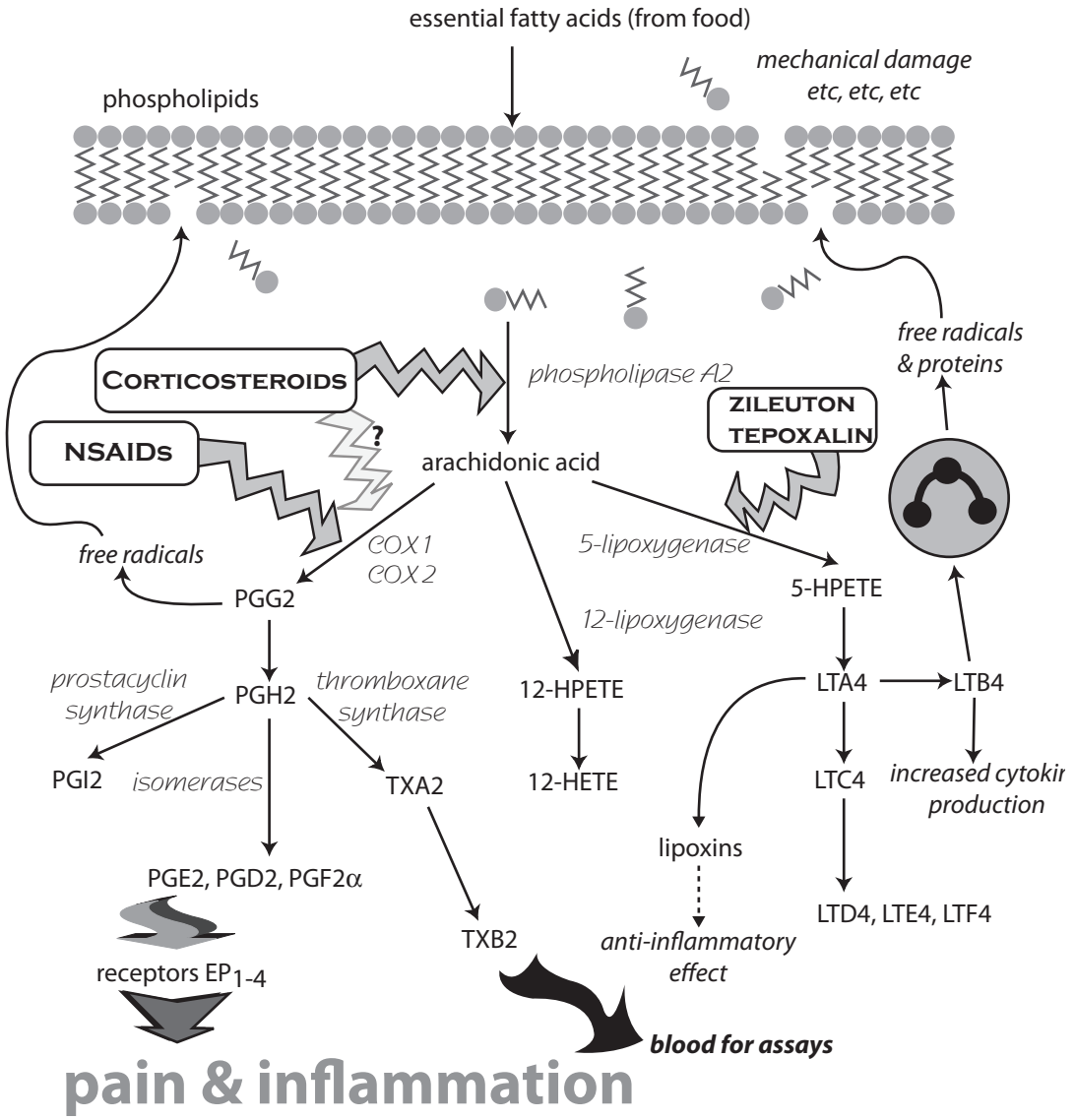
NSAIDs are not as effective as anti-inflammatory agents as corticosteroids. They do not delay healing in the way that steroids do.

Analgesic actions

See CNS notes

Anti thrombotic actions

NSAIDs bind to the cyclo oxygenase enzyme in platelets inhibiting their production of thromboxane A_2 (TXA_2). Low doses of aspirin can preferentially inhibit the production of TXA_2 relative to PGI_2 by irreversibly acetylating the platelet cyclo oxygenase and can thus be used therapeutically



The arachidonic acid cascade.

to decrease the likelihood of development or growth of a thrombus e.g. cats with ileal thrombosis, dogs with heartworm disease. Low dose aspirin is used therapeutically for this purpose since it covalently acetylates cyclooxygenase. Platelets have no nucleus and thus no protein synthesis machinery so thromboxane production is inhibited for the life of the platelet (about 7 days), whereas cyclooxygenase in other cell types can be replaced.

Although TXA_2 generation is only part of the clotting process, the increase in blood clotting times may have affect aspirin's use in post trauma situations where internal haemorrhage is a consideration. The other NSAIDs are less effective anti-thrombotics and do not prolong bleeding time significantly.

Antipyretic actions

The use of NSAIDs will not affect normal body temperature (except in cases of toxicity) nor will they affect exertionally induced hyperthermia. They will reduce pyrexia associated with pyrogens circulating in the plasma. Bacterial endotoxins can cause the release of interleukin 1 which stimulates the generation of PGE_2 in the endothelium of the hypothalamic vasculature, which is thought to be the mechanism responsible for changing the bodies normal thermostatic control setting.

Anti-endotoxic actions?

Bacterial endotoxins (lipopolysaccharides) are thought to produce some of their effects through prostaglandin production. There is no good evidence that NSAIDs are beneficial, although they are often used.

Clinical Uses

Arthritis

Useful in acute joint inflammation to reduce pain and inflammation and allow use of joint. Care must be exercised if their use encourages overuse of structurally compromised joints.

The progression of chronic cases of arthritis is probably not affected by the use of NSAIDs. However most chronic joint conditions have acute inflammation associated with them to varying extents and it is the acute inflammatory processes responsible for much of the associated pain.

High concentrations of NSAID will suppress synthesis of cartilage matrix but it is unlikely that the concentrations

necessary for this suppression are achieved in most clinical situations. Prostaglandins appear to be involved in the activation of chondrocyte mediated degradation of cartilage matrix and it is more likely in the short to medium term situation that most NSAIDs are potentially chondroprotective when therapeutic concentrations are achieved. However, the possibility exists that some NSAIDs could result in a significant suppression of matrix synthesis if used at high concentrations for extended time periods.

In people, chronic use of most NSAIDs reduces blood flow to the joints, which is thought to accelerate cartilage degeneration.

Soft tissue inflammation

Used to reduce the acute inflammatory response and to leave the animal more comfortable while natural healing of the tissue injury occurs. The efficacy of NSAIDs is not 100%, therefore the inflammatory process necessary for healing is unlikely to be greatly retarded. Evidence that NSAID use improves outcomes exists for few diseases, e.g. bovine shipping fever

Analgesia

(see CNS notes)

Endotoxaemic syndromes

NSAID use in endotoxic shock is controversial. NSAID toxicity is significantly increased by a compromised circulation. Combining NSAIDs with high doses of corticosteroids further increases potential for toxicity. NSAIDs have been used for treatment of acute bovine coliform mastitis, colitis X syndrome in horses, agalactia/hypogalactia syndrome in sows and parvoviral diarrhoea in puppies.

Colic

Some NSAIDs offer profound visceral pain relief in the horse. Flunixin will give analgesia for 4 - 6 hours and ketoprofen will give similar analgesia for 2 - 3 hours. NSAIDs also relax smooth muscle in the gut; flunixin appears to be most potent. There is a certain amount of evidence that suggests lower dose rates may offer some therapeutic benefit without affecting diagnosis. There have been some cases where the analgesia provided by flunixin was potent enough to hide severe ischaemic damage to the gut which should have been treated surgically. It is probably best to use shorter acting analgesics (pethidine, xylazine) until you have decided that the colic is definitely medical or surgical. Remember the potential for toxicity when large doses are being repeated frequently.

Pharmacokinetics

The desired site of action is usually the peripheral tissues rather than the plasma. Penetration into and clearance from inflamed tissues where the circulation is compromised shows kinetics markedly different from those of plasma.

Absorption

Bioavailability is generally good in all species. Absorption after oral administration is usually rapid. Phenylbutazone binds to hay and this reduces its absorption and presents more phenylbutazone to the large intestine and may alter the pattern of gut effects.

Distribution

Inflammation inhibits NSAID distribution to peripheral tissues, but then delays their clearance from these tissues. This is especially true where the proximity of the microcirculation is reduced such as in areas of bruising,

drug	dog	cat	horse	cattle	pig	sheep	man
salicylate (aspirin)	9	**22-38**	3	0.5	6		3
carprofen	8 (4.5-18)	19	17 - 43	44 - 65		30	12
deracoxib	3						
dipyrone	6						7
etodolac	10 - 15		3				6 - 8
firocoxib	8	9-12	30-40				
flunixin	2.5-4	0.7-3	1.5 - 3	6		2.5	
ibuprofen	4						3
ketoprofen	2 - 5	3-5	0.8 - 1.5	0.4			1.8
ketorolac	4 - 5					0.25	3 - 7
meclofenamate			1				3
meloxicam	24	21	3-8	13	3.4		20
naproxen	**74-92**		5-8		5		14-24
paracetamol	2		2-2.5				2
phenylbutazone	4		6	**40 - 55**	4	18	72
rofecoxib	4						17
tolfenamate	6.5		4.2 - 6	2.5 - 13.5			2.1
vedaprofen	13		6-8				

Elimination half lives (hours) for selected species and NSAIDs.

necrosis and edema.

The NSAIDs are extensively protein bound so total plasma concentration does not reflect the concentration of free drug at the site of action, binding variability may influence CNS penetration and they can be displaced by other protein bound organic acids administered at the same time, leading to toxicity. They also bind to muscle leading to long witholding times in food animals.

They are all anionic and subject to ion trapping in areas of inflammation which are usually acidic. However, they do not cross into milk to any great extent.

Metabolism

Most are extensively metabolized by both Phase I and Phase II enzyme systems. The particular CP450 used varies between NSAID chemical classes. Species differences in metabolism are responsible for many of the inter species variations in rate of elimination.

Elimination

Plasma half lives can vary enormously. You cannot extrapolate dose rates and intervals from one species to another! The plasma half life of aspirin is very short (minutes) and most of its other anti inflammatory effects are due to its metabolite salicylate.

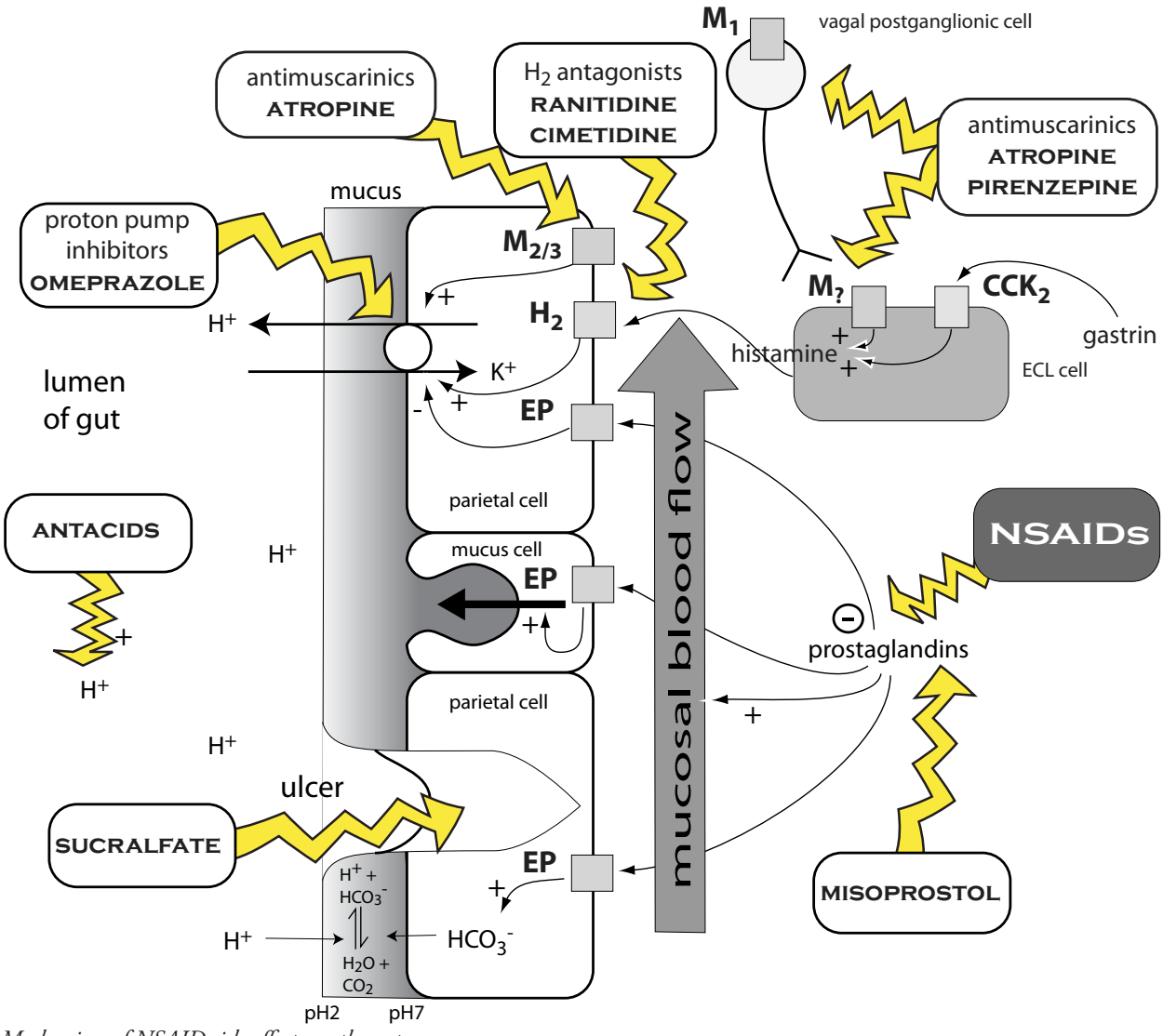
Selection of appropriate drugs

There are lots of drugs on the market but none are perfect. They are widely used for arthritis in people and most drug companies produce drugs for this very lucrative market.

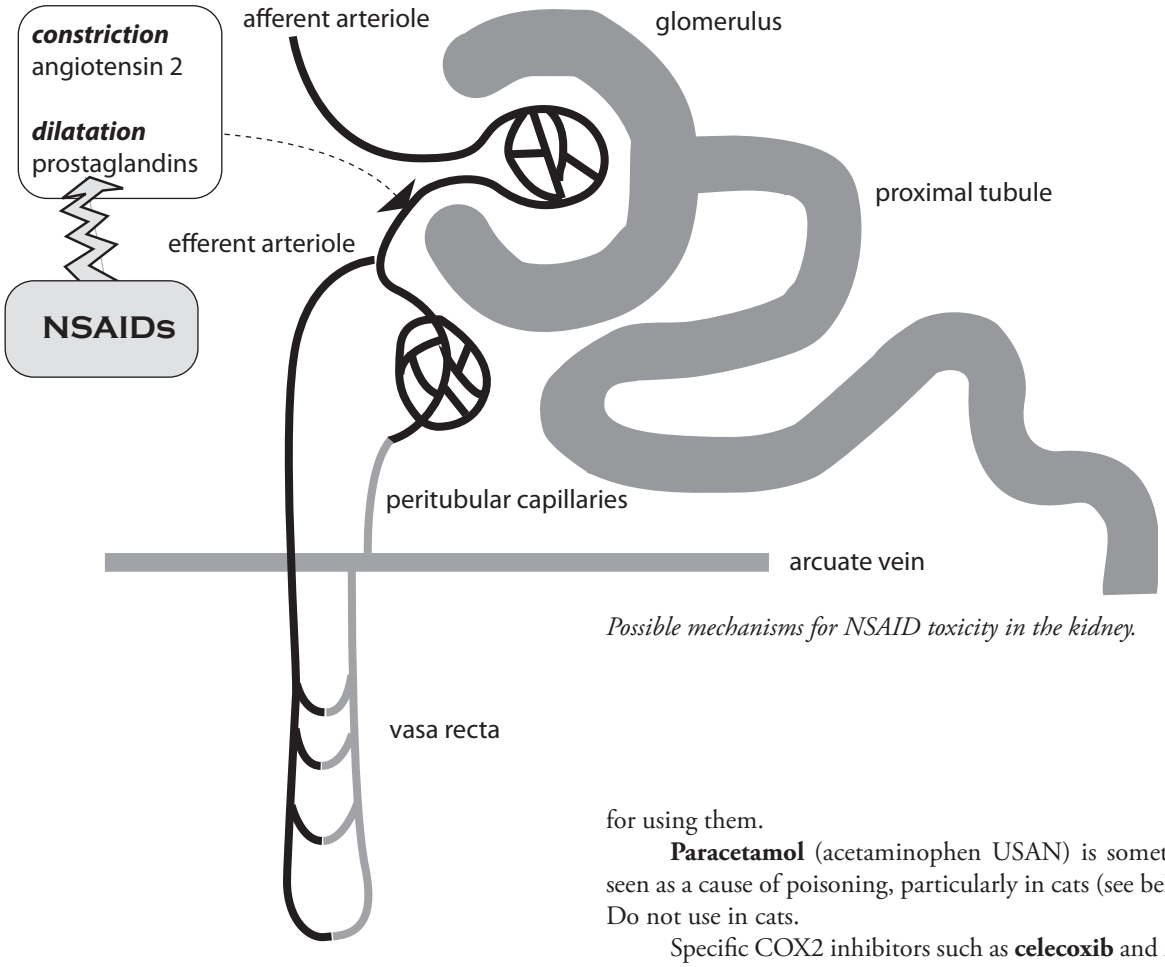
There are huge individual, species and age variations in both efficacy and toxicity for all NSAIDs. Some of the newer drugs claim to have a much higher potencies. However, it is their potency relative to the incidence and severity of side effects which is important. To date, all studies examining NSAIDs in dogs have shown gut pathology after a single dose at the recommended rate, except perhaps carprofen.

Aspirin (acetylsalicylate) has been around for a long time in the form of willow bark. It is deacetylated as soon as it gets into the plasma and most of the anti-inflammatory effects are caused by salicylate. Since aspirin is not very soluble, injectable forms are usually the sodium or copper salt of salicylate. Cheap, not very potent but good at producing ulcers. Cats metabolise it very slowly - it is probably best not to give more than one dose to a cat.

The pyrazolones, **phenylbutazone**, **dipyrone** and **isopyrin** have been around since the 1950s. They are no longer used in people since they very occasionally cause fatal blood dycrasias (possible in dogs too), but are still widely used in horses. Phenylbutazone has the reputation of being



Mechanism of NSAID side effects on the gut.



Possible mechanisms for NSAID toxicity in the kidney.

less analgesic and more anti-inflammatory than the others (dipyrone is the other way around), but the main reason for using them is that they are cheap. Isopyrin is only available mixed with phenylbutazone in Tomanol (they inhibit each other's metabolism and so prolong the anti-inflammatory effect). Phenylbutazone has an unexpectedly long half life in cattle.

Flunixin is very widely used. It is a very potent analgesic, anti-inflammatory and ulcerogenic drug.

A variety of propionic acids are used in human and veterinary practice. **Ketoprofen** is used in man and animals, and is similar to, but perhaps less potent than flunixin. **Carprofen** has been used in most species, it is a good analgesic but not so good an anti-inflammatory. **Ibuprofen** and **naproxen** are widely used in people. Naproxen has a very long half life in the dog and has killed several; ibuprofen is much better at producing ulcers in dogs than in people.

The fenamates have been used in man and horses for many years. Amongst others they include **mefenamate**, **meclofenamate** and more recently **tolfenamate**. They may have some prostaglandin receptor antagonist activity as well as inhibiting cyclo-oxygenase. Clinically similar to ketoprofen.

The oxicams, **meloxicam**, **piroxicam** and **tenoxicam**, are widely used in people and dogs for arthritis.

There are lots of other drugs used in man but not commonly in animals. Indomethacin was for years the most potent cyclo-oxygenase inhibitor available so you may see it mentioned in papers. It is rarely used. The quinolines, cinchophen, quinine and chloroquine are sometimes used in animals because they are cheap - there is no other reason for using them.

Paracetamol (acetaminophen USAN) is sometimes seen as a cause of poisoning, particularly in cats (see below). Do not use in cats.

Specific COX2 inhibitors such as **celecoxib** and **rofecoxib** have recently come on the human market, although rofecoxib has since been withdrawn as there is an increased risk of heart attacks with long term use. **Valdecoxib** and **parecoxib** are also available in NZ. Metabolism in dogs varies markedly with breed with celecoxib, so these drugs may be difficult to use clinically. They may also impair bone healing.

Dual COX and LOX inhibitors such as **tepoxalin** and pure LOX inhibitors such as **zileuton** are starting to be used overseas in people.

Contraindications

glucocorticoid therapy
anti coagulant therapy or poisoning
severe renal disease
severe hypotension

Precautions

Anything which causes ulcers or kidney disease: mild renal disease, hepatic impairment, hypoproteinemia, late pregnancy, gastro intestinal ulceration, dehydration

Adverse effects and toxicity

Toxic doses and effective doses usually overlap. Major side effects include gut ulceration which is common but rarely serious - at any rate in animals. Dogs seem to be more prone to the gut side effects of NSAIDs than most species, possibly because many of the NSAIDs undergo entero hepatic cycling in the dog, but death from gut ulceration following NSAIDs

is almost unknown (1200 people a year die from this in the UK - no figures for NZ).

The other major side effect is kidney failure. Inhibition of prostaglandin synthesis in the kidney of a healthy, well hydrated animal is of little consequence, and some predisposing factors (hypovolaemia, pre-existing renal insufficiency, old age, urinary tract obstruction, sodium retention eg congestive heart disease) has to be present.

(see CNS pharmacology notes).

Although some drugs have specific hepatotoxic effects, idiosyncratic reactions sometimes take this form in dogs. This is probably an immune mediated problem, but is too rare to have been studied properly in dogs. Carprofen has been implicated in some cases of liver failure in dogs in the USA (5.2 cases / 10,000 doses).

Paracetamol produces specific hepatotoxic metabolites, particularly in cats. These toxic metabolites are usually mopped up by glutathione, but liver glutathione reserves can be quickly used up and liver damage results. Acetylcysteine can be given as a source of glutathione but prevention is better than cure - paracetamol is best avoided in both cats and dogs.

For minor side effects see NSAIDs section of CNS notes.

Drug interactions

NSAIDs are highly protein bound and can displace other drugs from plasma proteins, eg warfarin, other NSAIDs and anaesthetics eg thiopentone. Frusemide inhibits some NSAID excretion; some NSAIDs inhibit digoxin excretion.

Recommended reading

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

`http://www.bmj.com/cgi/content/full/323/7323/1236`

A useful review of NSAID induced ulcers and management in people. Remember species differences!

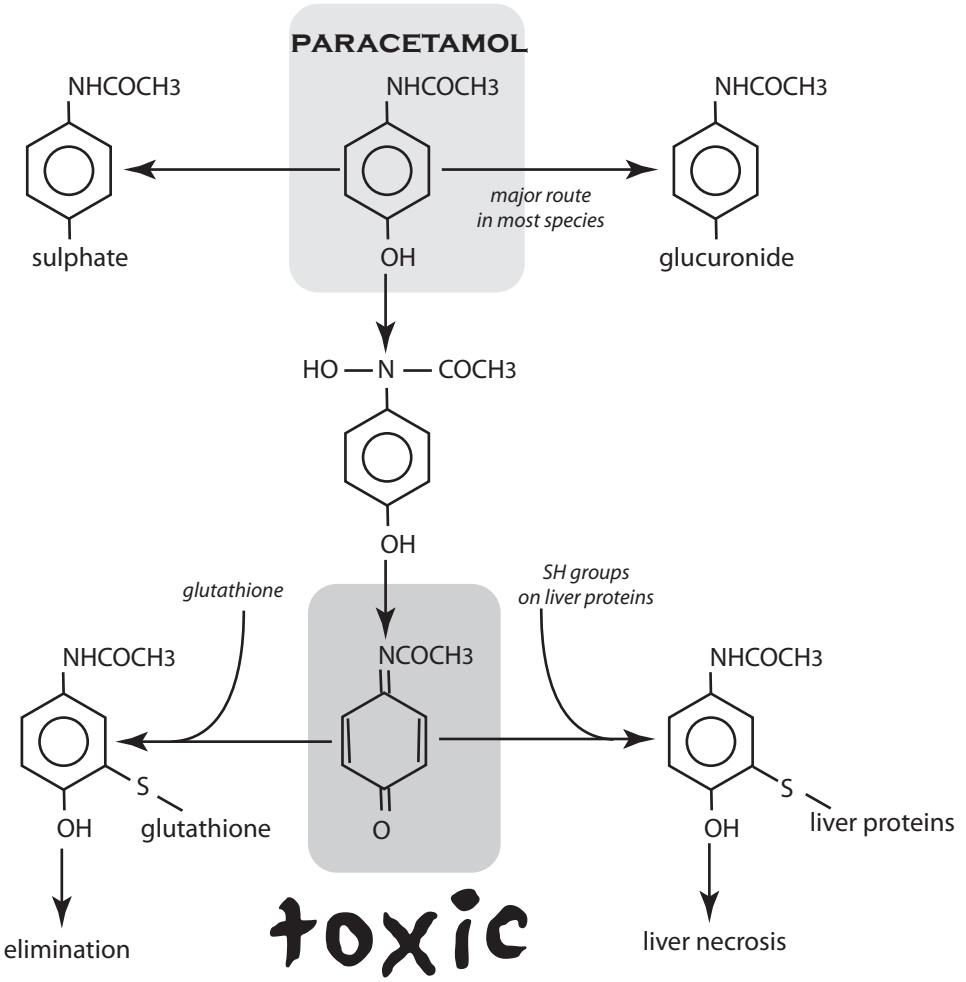
Hinz B. Brune K. (2002) Cyclooxygenase-2--10 years later. Journal of Pharmacology & Experimental Therapeutics. 300:367-75

The future??

Prostaglandin receptor antagonists are likely to be important in the long term, but the physiology is complex and not well understood at the moment.

Several new human NSAIDs have been designed as non acidic prodrugs. This reduces the severity of gastric ulceration but does not eliminate the problem.

There is lots of money going into research on COX 2 inhibitors and this will probably throw up some useful drugs in the near future. These may get round the major



The metabolism of paracetamol.

side effects.

Cases to Think About

Cow

What is the role for NSAIDs in the treatment of endotoxemic mastitis? What proposed mechanisms of action would be of benefit?

Dog

You are treating a nine year old dog with degenerative joint disease of the stifles using phenylbutazone 10 mg/kg twice daily, but the dog has not responded after three days of therapy. What are the possible reasons for this lack of response? What is your plan to deal with this therapeutic failure?

Cat

Describe the various manifestations of NSAID toxicity in the cat. Make sure you consider paracetamol.

Horse

You choose to refer a thoroughbred filly with acute, severe colic to an equine surgeon 3 hours driving from your practice. How would you choose a NSAID for analgesia (NB: you could also consider α_2 adrenergic agonists such as xylazine or opioids such as butorphanol for this purpose).

commonly used drugs

aspirin
carprofen
flunixin
ketoprofen
meloxicam
phenylbutazone
tolfenamic acid

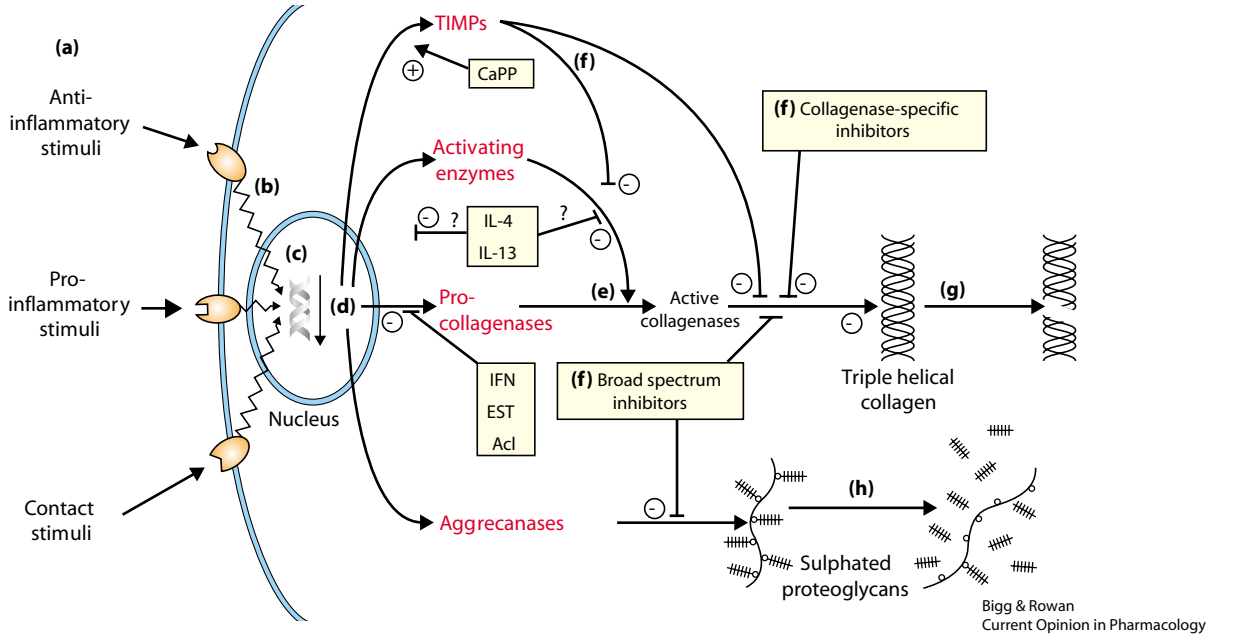
NSAIDs

- widely used in all species for minor pain and injury
- gastric ulceration limits long term use
- care required where kidney perfusion is less than optimal
- beware paracetamol in cats
- use corticosteroids if potent anti-inflammatory effects are required

clinical use

- indications - pain, minor tissue damage, minor inflammation
- horses - phenylbutazone for sprains, flunixin for colic
- cattle - flunixin, ketoprofen, tolfenamate for pain (short / zero milk WHT, long meat WHT)
- dogs & cats - many drugs used for arthritis

Anti-arthritis drugs



The control of cartilage extracellular matrix degradation. (a) Chondrocytes and synovial cells are stimulated by anti-inflammatory and pro-inflammatory cytokines, mechanical stress and cell–cell and cell–matrix contacts through a variety of cell-surface receptors. (b) These stimuli are transferred to the nucleus via intracellular signalling and mechanotransduction pathways and (c) result in activation of gene transcription. (d) Synthesis and secretion of enzymes and inhibitors that modulate matrix turnover then occur. (e) Activation of pro-collagenases to the active forms is mediated through activating enzymes that may themselves require activation. (f) Inhibition of active collagenases and other metalloproteinases by TIMPs and synthetic inhibitors prevents matrix degradation. An excess of active enzymes compared with inhibitors results in the destruction of triple helical collagen (g) and sulphated proteoglycans (h). Points of intervention where potential therapeutic agents either promote (+) or inhibit (–) biological processes are indicated in yellow boxes. Possible points of intervention are denoted '?'. Acl, aceclofenac; CaPP, calcium pentosan polysulphate; EST, esculetin.

Articular cartilage is made up of large aggregating proteoglycans held together by strings of type 11 collagen with the odd chondrocyte here and there. The chondrocytes are continuously breaking down and synthesising the matrix. Arthritis pushes this dynamic equilibrium towards degradation. Proteoglycans are easily lost and rapidly replaced, collagen loss is slower and probably irreversible.

Matrix metalloproteinases (MMPs) break down the matrix; they are usually in balance with tissue inhibitors of metalloproteinases (TIMPs), which irreversibly block MMPs. Although MMPs can break down proteoglycans, aggrecanases are thought to be mainly responsible. Control of these systems is only starting to be elucidated and offers lots of scope for new drugs as well as understanding how some old ones work (see diagram).

Glycosaminoglycans

A variety of high molecular weight, long chain mucopolysaccharides which mimic normal components of cartilage are used to treat arthritis in dogs and horses. Most of these are polysulphated glycosaminoglycans. They include various **chondroitin** sulphates (eg "Adequan", not available in NZ), **pentosan** polysulphate (not strictly a polysulphated glycosaminoglycan but very similar- it is a semisynthetic pentasaccharide derived from beech wood shavings and present in many grains) and **hyaluronic acid** (a normal constituent of synovial fluid and cartilage matrix). **Heparin** is very similar, and most of the synthetic drugs started life as heparin - type anticoagulants in the 1950s.

All these drugs have a wide range of effects and it is not clear at the moment which effects are most important. For instance, pentosan given icv is the only drug shown to affect the course of variant Creuzfelt Jacob disease in people.

The effects in arthritis also appear to be dose related. All work best in mild, early joint disease without destructive changes, although good clinical trials of these drugs are lacking.

Mechanism of action

Limit cartilage degradation by inhibiting enzymes causing proteoglycan degradation

Support cartilage matrix synthesis by increasing proteoglycans synthesis

Improve the quality of synovial fluid by stimulating the synthesis of hyaluronic acid and has an anti-prostaglandin effect

Improve circulation to the tissues of the joint because of anticoagulant activity

Inhibit fibroblast growth factor and other cytokines. Fibroblast growth factor is required for neovascularisation and for growth of some types of tumour; pentosan is undergoing clinical trials as an anticancer drug in people at the moment.

Hyaluronic acid may also increase the viscoelasticity of synovial fluid.

Probably indirectly affect many aspects of proteoglycan turnover via cytokines

Indications

adjunct therapy to correct the cause of osteoarthritis (cruciate or intra articular fracture)

chronic osteoarthritis

primary osteoarthritis

degenerative joint disease

Duration of soundness after treatment increases with the molecular weight of the product from about 50 days to about 160 days.

They are usually given intra-articularly, although they may work after im injection too. They are broken down in the gut, so are not much use orally (see below).

Contraindications

•infection

•animals with clotting defects or traumatic haemorrhage

•liver or kidney disease

Side effects

Local reaction post-injection when given intra-articularly

Extreme care must be taken to avoid introducing infection when making repeated intra-articular injections.

Heparin like clotting problems and immune mediated hypersensitivity have occurred in people.

These drugs are not cheap.

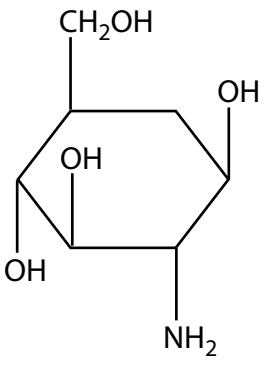
Glucosamine

Glucosamine is the basic building block of GAGs. It is normally made from glucose by chondrocytes, but is preferentially taken up if available, and stimulates the production of GAGs (glucosamine availability is the rate limiting step).

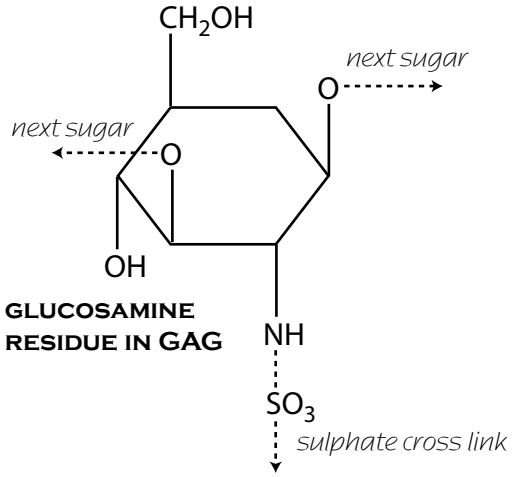
Glucosamine is completely bioavailable from the gut and is practially non toxic, so is sometimes included in horse food.

It has a wide range of useful effects in vitro, and appears to have a small beneficial effect in osteoarthritis in rats and people. It modifies the progress of the disease rather than providing analgesia, so it takes several months for improvements to be seen in people. There are no clinical trials in dogs or horses, but as it probably has a beneficial effect and is unlikely to cause harm, it is becoming more widely used.

Glucosamine is currently being investigated for vCJD in people.



GLUCOSAMINE



GLUCOSAMINE RESIDUE IN GAG

Other drugs

Extracts of **green lipped mussels** (*Perna canaliculus*) have some anti-inflammatory effects. This is probably produced by a large glycoprotein similar to the other anti-arthritis drugs, but it may also be caused by the copper in the mussel's blood. Many organic copper compounds have a mild anti-inflammatory effect, probably because copper is an essential part of the enzyme superoxide dismutase, which mops up superoxide ions before they can damage tissue. Copper has been a traditional treatment for arthritis in people and is now being sold for use in dogs. Published evidence of efficacy is lacking.

A wide variety of other drugs are used in people to treat rheumatoid arthritis and are sometimes tried in dogs. These include **penicillamine**, **chloroquine** (also used as an antimalarial), **sulphasalazine** (see gut notes) and **gold** compounds (see immunosuppressive drugs). Tetracyclines (especially **doxycycline**) and **nicotinamide** are sometimes used as immunosupressants / anti-inflammatories in dogs. Their mechanism is unknown.

Phosphodiesterase 4 is involved in inflammation, and its inhibitors can have a useful anti-inflammatory effect, but they also cause vomiting. They are being investigated for asthma in people. A variety of non specific PDE inhibitors are used in animals, which may have some anti-inflammatory effect. The most widely used non specific PDE4 inhibitor used in people is **oxpentifylline** (pentoxifylline USAN) and it is occasionally used in animals.

There are many μ opioid receptors on macrophages in inflammatory lesions for some reason, and opioids have an anti-inflammatory effect in these sites. Morphine is occasionally injected into joints after surgery as an analgesic and anti-inflammatory.

Suramin, used to treat sleeping sickness in people, is an effective inhibitor of fibroblast growth factor, and has been used in people for this effect. It is a nasty drug and best avoided.

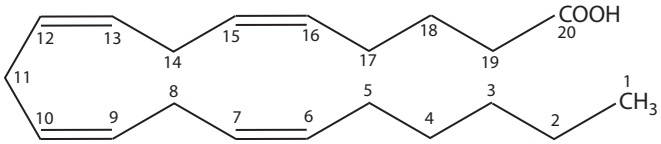
Antioxidants

Various free radicals, often superoxide ions, are released in inflammation. These are very effective at damaging cell membranes, releasing phospholipids and activating the arachidonic acid cascade. A variety of substances act as antioxidants, **vitamin E** and **glutathione** are common examples. Many plants produce compounds to mop up free radicals (they are produced during photosynthesis but also damage plant cells) so many herbal medicines have a mild antioxidant effect. Many also have NSAID compounds present which add to the effect. Plants also produce corticosteroids, and many "antioxidant" herbal medicines produce their anti-inflammatory effect through steroids, either natural or added during adulteration.

Essential fatty acids

A variety of polyunsaturated fatty acids derived from plants and sea fish have been used as dietary supplements. γ-linolenic acid from evening primrose oil or borage oil is popular in dogs, as is oil from cold water fish (eicosapentaenoic acid and docosahexaenoic acid) in people. These have an anti-inflammatory effect by being converted to abnormal prostaglandins and leukotrienes, which do not have such a pro-inflammatory effect. There are a large number of products of COX and 5-LOX which affect inflammation (and many other processes), and the optimal mix of fatty acids is not known.

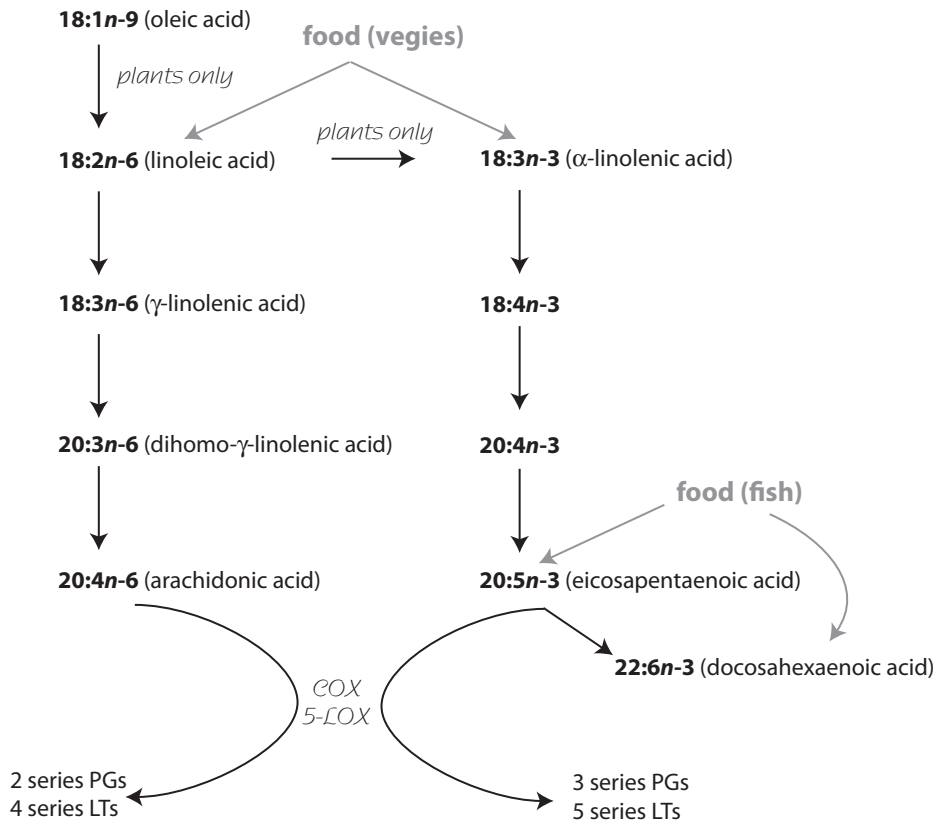
The effect of polyunsaturated fatty acids is small, but can be clinically important, for instance in skin disease in dogs.



The nomenclature of fatty acids is confusing. This structure is usually known as arachidonic acid (eicosatetraenoic acid, 20:4n-6). It has 20 carbon atoms and 4 double bonds which start from carbon 6.

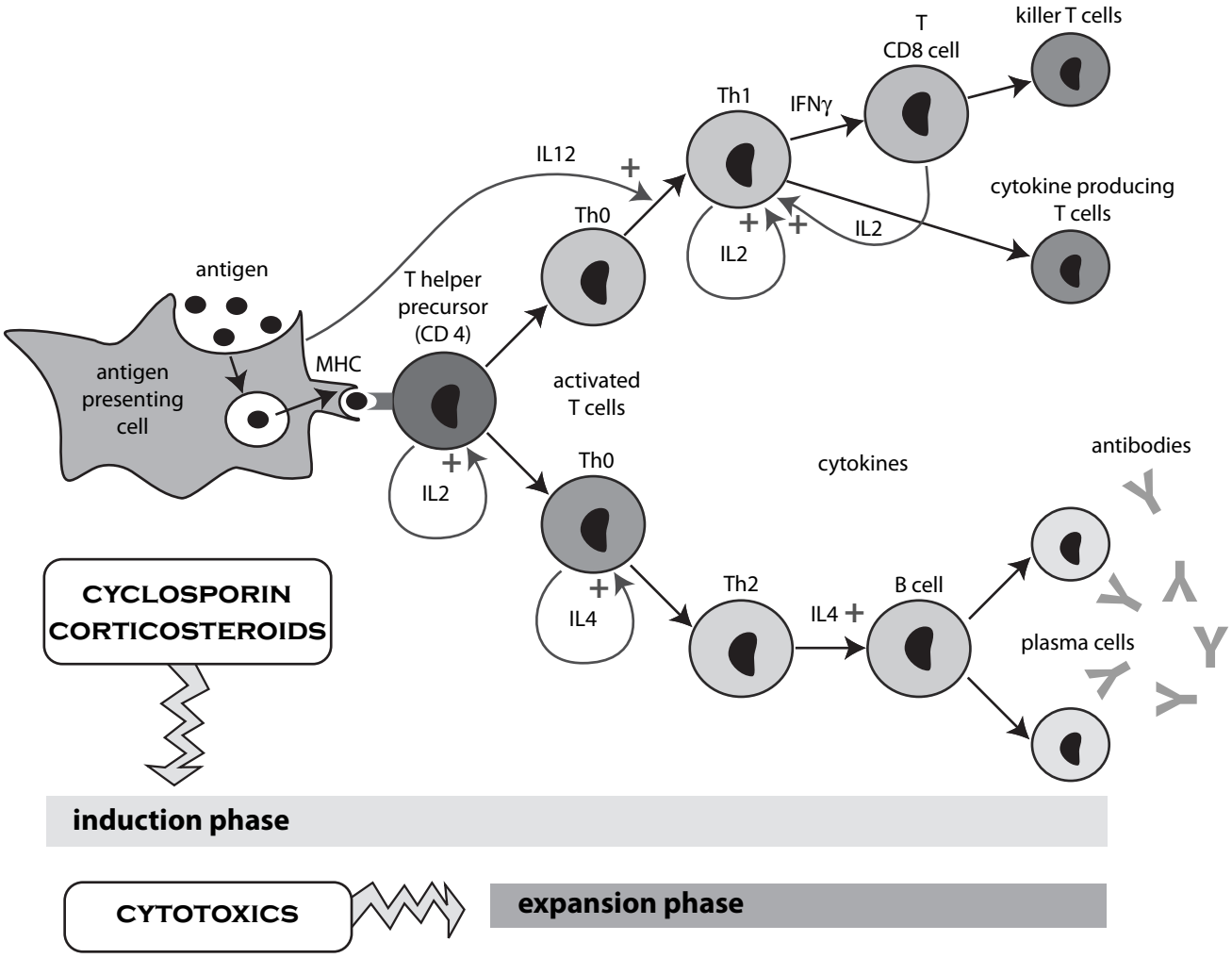
clinical use

- most of these drugs have only a small effect and are used as dietary supplements for arthritis in dogs and horses
- horses - PSGAGs for sprains
- dogs - many drugs used for immune mediated disease to supplement steroids and allow reduction in dose, EFAs for skin disease



Essential fatty acid metabolism.

Immunosuppressive drugs



Sites of action of immunosuppressive drugs

Immunosuppressive drugs suppress function of the cells of the immune system. The same drugs are used for the treatment of most immune-mediated diseases but there are certain types/patterns of drug use that maximize therapeutic success and minimize side-effects in the different immune mediated conditions. These drugs suppress the signs of immune mediated disease, they do not cure it. This means that they usually have to be given for life so chronic side effects are important.

Collectively, immune-mediated diseases are common - particularly in small animal practice. They affect all body systems. The most common immune-mediated diseases are allergic conditions (eg atopy, flea allergic derinatitis, food allergy), autoimmune skin diseases (eg pemphigus foliaceous), gastrointestinal hypersensitivities (eg inflammatory bowel disease), haematopoietic diseases (eg autoimmune haemolytic anaemia, autoimmune thrombocytopaenia), glomerulonephritis, and respiratory diseases such as bronchitis and allergic rhinitis.

The drugs used in veterinary practice to treat immune-mediated diseases in order of importance are glucocorticoids, antihistamines, azathioprine, and miscellaneous others (see anticancer drug notes).

Glucocorticoids

Very commonly used in small and large animal veterinary practice as immunosuppressives at higher doses than used for anti-inflammatory effects (nb, there is still a small immunosuppressant effect at low doses). Duration of action varies greatly. **Prednisone**, **prednisolone** (probably the most commonly used immunosuppressants) and **triamcinolone** are of medium duration of action whereas **dexamethasone** and **betamethasone** are long acting. The duration of action of these drugs is further influenced by the chemical form of the glucocorticoid in the preparation. (see corticosteroid notes). Generally, prednisolone (or prednisone) is used for twice daily dosing (at about five times the anti-inflammatory dose), or dexamethasone for daily / alternate day dosing. The dose is

tapered down to what works in that individual.

Immunosuppressive properties include:

•depression of antibody production especially of new antibodies or inappropriate (eg autoimmune) antibodies
•depression of migration of immune cells
•depression of cytokine release
•may be lympholytic in high doses
•decreased uptake of antigen by reticuloendothelial cells
•at massive doses glucocorticoids inhibit mitosis by stopping cell cycle in M phase

Side-effects in dogs

(see corticosteroid notes)

Effects on laboratory values

•stress leukogram (neutrophilia without left shift, lymphopaenia, eosinopaenia)
•elevated serum alkaline phosphatase (SAP) (dogs only)
•elevated ALT
•lipaemia
•increased blood albumin

Other drugs

Antihistamines are mainly used for management of allergic conditions (H_1 -blockers) of the skin. Most commonly used as glucocorticoid-sparing agents as they are not usually effective by themselves. Most modern antihistamines are designed to be non sedative (in people) but sedation is often useful in dogs so older drugs, mostly phenothiazines such as **acepromazine**, **promethazine** and **trimeprazine**, tend to be used. Second generation drugs such as **chlorpheniramine** are also useful in dogs. There are dozens of more modern drugs, most of which have not been assessed in dogs and cats.

The only licensed drug in NZ is **tripelennamine** but it is not recommended as an antihistamine. When given iv to ruminants, it appears to block H3 receptors in the CNS increasing arousal / making them convulse. Has been used to get downer cows up but not recommended!

Cyclosporin (cyclosporine USAN, ciclosporin INN) is a potent inhibitor of T lymphocyte activation halting the immune response. Its main use has been to prevent graft rejection (in man); its main use in vet medicine is topical treatment of keratoconjunctivitis sicca as an eye drop, but it is also used for anal furunculosis and atopic skin disease.

It is too expensive for routine use in other immune-mediated diseases, and therapeutic drug monitoring is advisable if it is used systemically. Kidney toxicity is a problem in people, but does not seem to occur in dogs and cats. It has been given with P450 inhibitors such as ketoconazole to reduce metabolism, and thus dose and cost.

Newer, homologues such as **tacrolimus** are starting to come onto the human market. Both bind to numerous receptors in the brain as well as interfering with steroid receptor binding. Tacrolimus crosses intact skin better than cyclosporin and ahs been used for anal furunculosis in dogs.

Gold, as an organic salt, eg **aurothioglucose**; **aurothiomaleate** (= aurothiosuccinate USAN) is sometimes used by intramuscular injection in the dog and cat. Its mechanism of action is not known but appears to "normalize" immune function and decrease phagocytic activity. Its main use in veterinary medicine is chronic arthritis and feline idiopathic gingivitis-pharyngitis. Gold's most common side-effect is thrombocytopaenia. It is expensive.

Cytotoxic drugs

A variety of cancer chemotherapeutic drugs are used when potent immunosuppression is required. **Azathioprine** (Imuran) is the least toxic and most commonly used in dogs (often in combination with steroids). It is a prodrug for mercaptopurine, a synthetic purine which interferes with DNA and RNA formation, resulting in inhibition of antigen-induced lymphocyte transformation and a slow decline in antibody levels

Azathioprine is mainly used in dogs when long term, moderately potent immunosuppression is needed, but is often used when long term prednisone is resulting in unacceptable side effects. The addition of azathioprine to the treatment regimen usually allows the prednisone dose to be at least halved and sometimes eliminated.

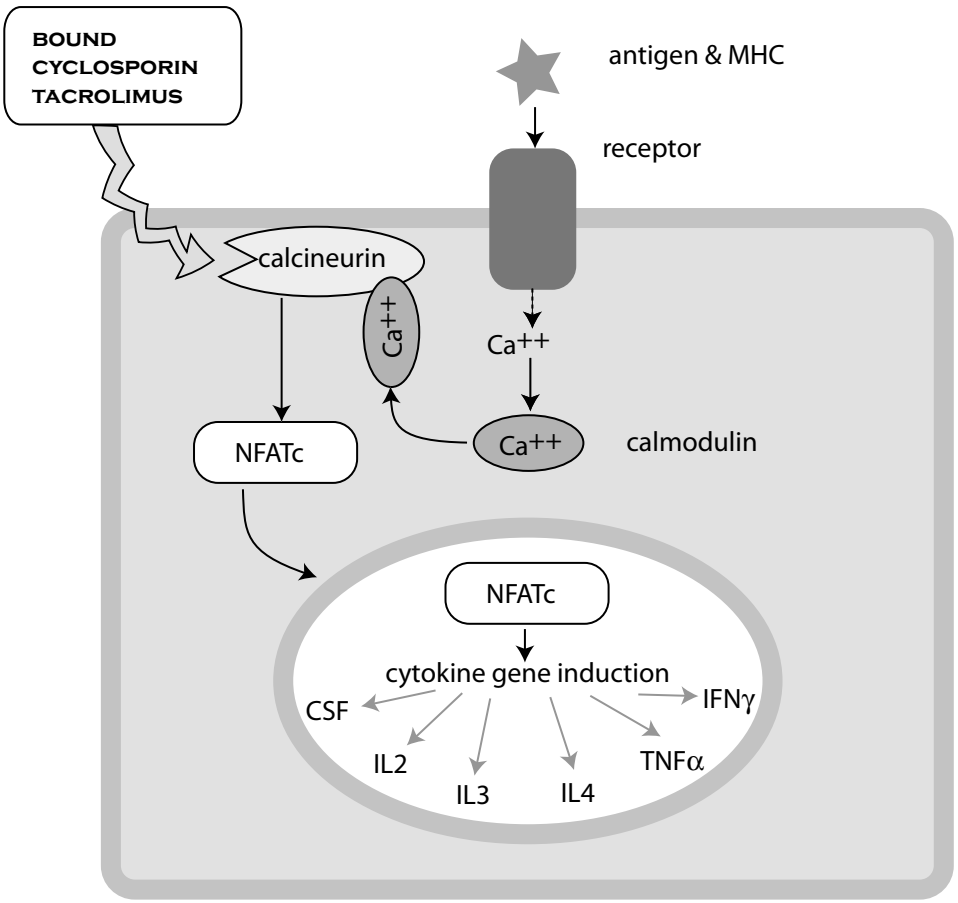
A lag effect of several weeks should be expected before the beneficial effects of azathioprine become apparent.

The most important side effect is bone marrow suppression. Mild suppression is common with this drug and of little concern. Severe depression is rare, is most often seen early in the treatment protocol, is more common in cats than in dogs, and is usually reversible on discontinuation of therapy. A complete blood count should be performed every 10- 14 days for the first 2-3 months of therapy and should be repeated at monthly to bimonthly intervals thereafter. Treatment with azathioprine should stop if marked neutropaenia or thrombocytopaenia develop.

If more potent immunosuppression is required, other anticancer drugs are used, eg. **cyclophosphamide**, **chlorambucil** (see below for more detail). Newer drugs such as **mycophenolate** are being used in people as immunosuppressives because they are relatively specific for T and B cells, but there is no information on their use in animals yet. IL2 receptor antagonists such as basiliximab and daclizimab are occasionally used in people but are mind-bogglingly expensive.

commonly used drugs

prednisolone
azathioprine



Cyclosporin switches on genes affecting many aspects of inflammation.

Anti-cancer drugs

The options for treatment of cancer in veterinary practice are fairly limited:

- •euthanasia
- •palliative treatment then euthanasia
- •surgery (then euthanasia)
- •radiotherapy
  - X rays
  - γ rays
  - electrons
  - microwaves
  - light
- •chemotherapy

None of these options is ideal, and the last three are not cheap. **Current anticancer drugs are some of the nastiest drugs available and are not to be used lightly.** For this reason, this chapter aims to give you an overview of the subject rather than specific instructions on how to use these drugs.

Treatment Philosophy

Treatment of cancer is appropriate provided the animal's quality of life can be preserved during treatment. Cure is often not the goal - rather extension of useful life (cure requires the removal of every single cancer cell). Provided quality of life is preserved, extending life of the patient by as little as a few months may be very worthwhile. This allows the owner to come to terms with their pet's impending death (quality time is quality time even though it is destined to be short). For some tumours, particularly those maintained by sex hormones, or thyroid tumours, response to treatment can be dramatic.

If quality of life is not preserved, treatment of cancer is inappropriate. Oncology is not about prolonging a pet's dying. Thus judgement of quality of life is of paramount importance. It requires both vet's and owner's assessment but some simple rules help: if the pet is not eating, is inactive and is not responsive to its owner, its quality of life is unsatisfactory; if the animal is in pain its quality of life is poor (painful cancers - bone tumours; bone metastases; rapidly expanding organ masses, spinal tumours, some peripheral nerve tumours)

Chemotherapy protocols used in veterinary medicine are purposefully not aggressive to minimize side effects and preserve quality of life during treatment. Veterinarians cannot sit down with their patients and explain that short term pain will provide long term gain. Unfortunately, the trade off of less aggressive protocols is shorter remission times.

Owner concerns

Is the pet suffering as a result of the cancer?

Owners assume all animals (and people) with cancer are in excruciating pain. They must be reassured that this need not be the case and that if the animal appears to be suffering you would recommend euthanasia. It is very important for you to convey this point to the owner least they think the animal's well being is not paramount in your mind. Otherwise the client may become suspicious your recommendation to treat is based on your wish to earn money or "experiment" on the pet.

Will the pet suffer as a result of the treatment?

Most owners believe chemotherapy will cause their pet to become very ill and lose its fur. They need to be reassured that the chemotherapy protocols used in veterinary medicine are purposefully designed to minimize such complications. Be careful of some drugs, however. For instance, many dogs vomit after methotrexate and cisplatin. Also, dog breeds with wire-haired, curly or "woolly" coats (such as Old English sheepdogs, poodles, Afghans and some terriers) may lose their hair.

How long will the animal live?

Median survival time for the particular tumour type can be quoted but it is very important to emphasize and reemphasize that some animals will live for shorter and some longer than the median time. That way, if a pet comes out of remission much earlier than expected there is no recrimination. Moreover, the fact that a small number of patients will survive a long time following treatment for tumours such as lymphoma seems to be the incentive many owner's need to elect to treat.

How much will it cost?

Have an estimate ready for the first 3, 6 or 12 months of treatment including all anticipated costs (chemotherapy agents, administration costs, blood work, hospitalization). For example, treatment of a dog for lymphoma for a year at Massey University costs approximately $2000. Providing an "all up" estimate like this better allows the client to budget and avoids unexpected charges arising from such things as blood work.

Formulating a treatment plan

Incisional or excisional biopsies are essential before treatment can be considered. Biopsy is necessary for diagnosis of the tumour and greatly assists prognosis (the pathologist should grade the malignancy of the tumour). Following excision of a mass, biopsy is necessary to determine if the tissue sample is free of tumour (clean margins). (See surgical oncology notes)

If the tumour can be removed in its entirety or "debulked" then surgery is usually indicated. Many publications in recent years have dealt with successful aggressive surgical techniques for removal of tumours (eg mandibulectomy for oral tumours and hemipelvectomy for pelvic tumours). The primary aim of the surgery is to remove as much of the tumour mass as possible. Complete removal offers the chance of a cure. Debulking of tumour is valuable because it reduces the

number of cells resistant to chemotherapy and may stimulate dormant cells into cycling (and hence chemosensitivity). Surgery is also used for pain relief (eg osteosarcoma).

Adjuvant radiation therapy is indicated if not all visible tumour was removed at the time of surgery or if histopathology reveals dirty surgical margins or a type of tumour with a high rate of local recurrence (eg fibrosarcoma). For instance, adjuvant radiation therapy is often required for cutaneous mast cell tumours. Radiation therapy is rarely justified if systemic spread of the cancer can be demonstrated. Some of the most radioresponsive tumours in dogs and cats include lymphoma, mast cell tumours, and acanthomatous epulides. Adjuvant chemotherapy may also be helpful if clean margins are not obtained.

If the cancer is multicentric or has metastasized, systemic treatment is required. The primary systemic therapy is chemotherapy.

Chemotherapy

The main problem with using drugs to kill cancer cells is that cancer cells are not much different from normal cells and most of the drugs kill lots of normal cells as well as the diseased ones. Some important cancers are dependent on sex hormones (and are usually treated by removing the hormones - castration or spaying) but the only distinguishing feature of most cancer cells is that they grow more rapidly than most normal cells. Most anticancer drugs aim to disrupt cell division in some way. They usually kill all rapidly dividing cells, hopefully including the cancer cells.

Anticancer drugs are usually divided into several different groups:

- •antimetabolites
- •alkylating agents
- •anticancer antibiotics
- •microtubule inhibitors
- •odds & sods
- •hormones

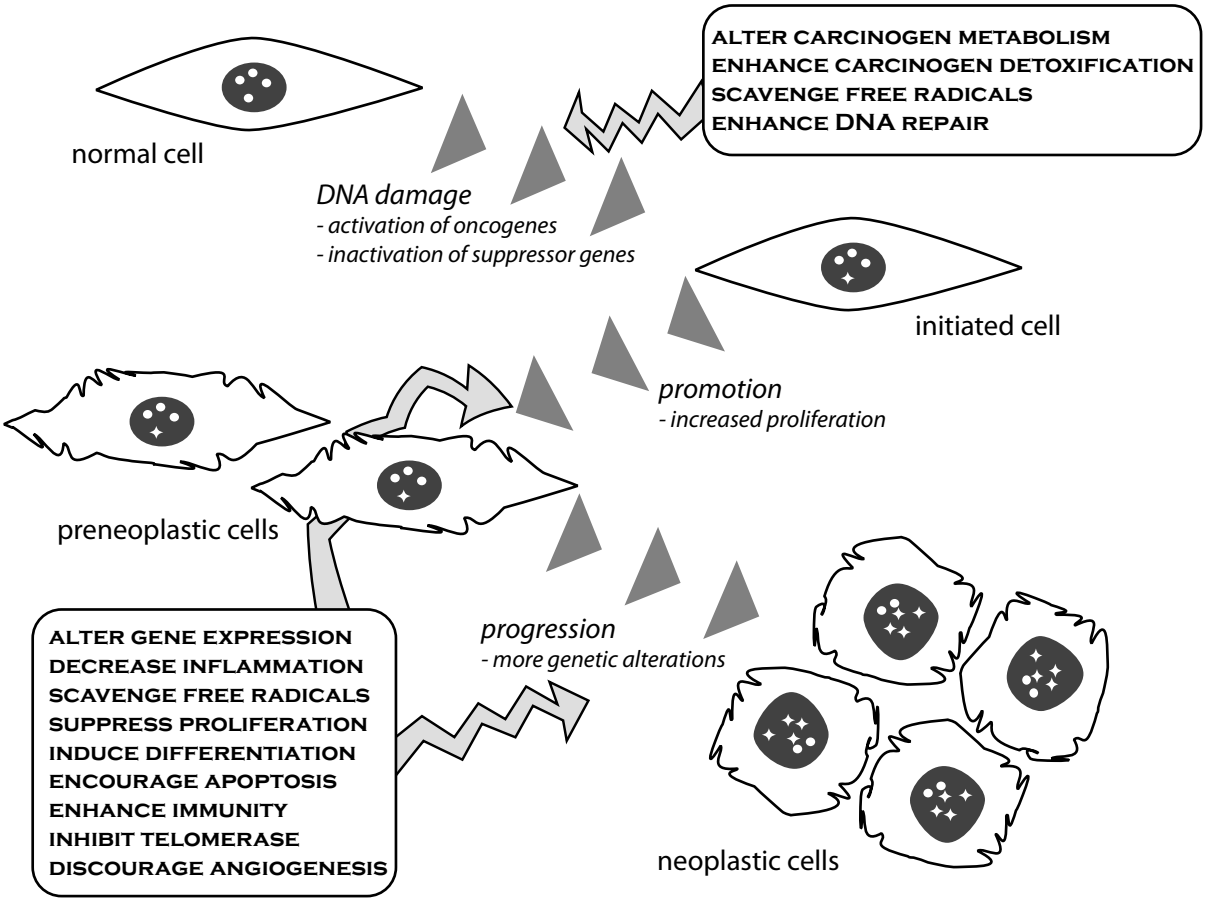
Indications

Chemotherapeutic drugs are primarily used for the treatment of cancers that have metastasized to distant sites in the body or are localized but non-resectable. They are also used when potent immunosuppression is required for immune-mediated diseases (see immunosuppressives notes).

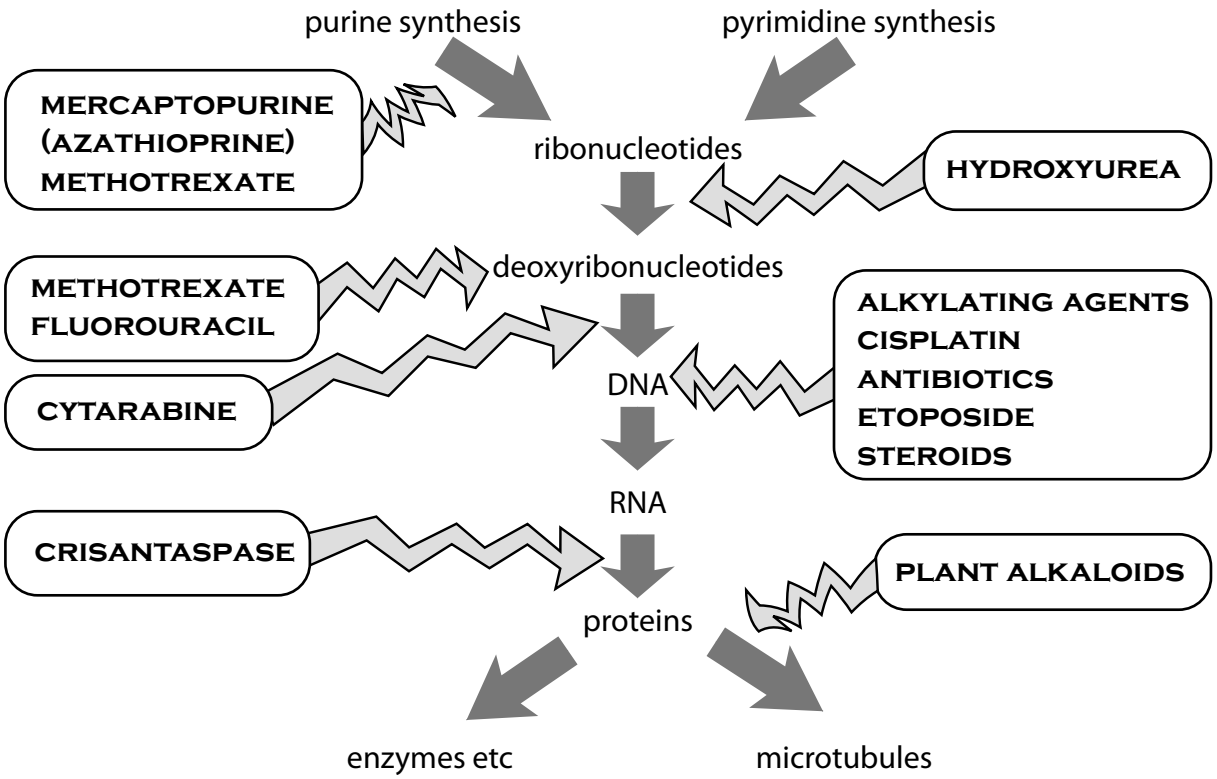
Specifically, chemotherapy is indicated in the following circumstances:

- •Palliative therapy for a non-resectable or disseminated tumour
- •Adjuvant to radiotherapy and/or surgery for local control
- •Delay/prevent development of metastatic disease
- •"Rescue" of relapses following radiation or surgical failure

Chemotherapeutic drugs selectively kill rapidly dividing cells because they interfere with protein or DNA synthesis which is more rapid in such cells. The cells most susceptible to chemotherapeutic drugs are therefore cancer cells, cells of the haematopoietic and lymphopoietic systems and gastrointestinal mucosal cells. Fortunately, normal cells have a more rapid recovery from chemotherapeutic drug in-



General stategies for treating cancer.



Sites of action of cytotoxic drugs.

jury than neoplastic cells. Obtaining a fine balance between kill rate of host cells (toxicity) and recovery rate of tumour cells (failed therapy) is the daily challenge for vets administering chemotherapeutic drugs.

Side effects

gut upset (vomiting, diarrhoea, colitis)

•bone marrow depression (especially thrombocytopaenia and neutropaenia)

•alopecia (especially woolly coated breeds)

•slow wound healing / infection

and miscellaneous other toxicities more specific to each drug

Dosages

Doses of chemotherapeutic drugs are usually based on body surface area because they are so toxic that the minimum effective dose must be given (metabolic rate and therefore drug pharmacokinetics and toxicity are more closely related to body surface area than body weight - see pharmacokinetics notes). You will still find some chemotherapy doses for cats listed on a per kg basis. This is acceptable because the body-weight range (and therefore body surface area) is very small in cats in comparison to dogs. Body surface area is usually calculated from tables or use the formula:

$$\text{body surface area } (m^2) = \frac{\text{wt in kg}^{0.67}}{10}$$

Chemotherapeutic protocols

The same pharmacological principles apply to treatment of all neoplastic diseases, however, there are certain patterns (protocols) of drug use that maximize therapeutic success and minimize side-effects in the different neoplastic conditions. A variety of standard protocols exist for the treatment of small animal cancers. A typical protocol for the treatment of canine and feline lymphoma is included below. Intermittent dosing is preferred to continuous dosing to allow normal cells to recover.

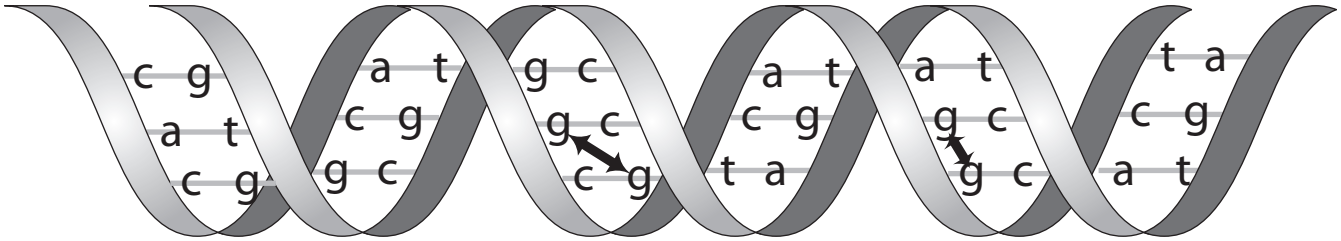
Standard chemotherapy protocols may not suit an individual animal for a variety of reasons such as cost, idiosyncratic drug reactions, side effects, impractical administration etc. For this reason, you may have to individualise a chemotherapy protocol for an animal. Therefore you need to have some grasp of the reasoning behind chemotherapy drug protocols.

Single drug protocols are not in fashion because of resistance and efficacy with the exception of doxorubicin. It is used in cats for convenience and seems quite effective for lymphoma

Multiple drug protocols are more effective because they decrease the chance of a drug-resistant or partially resistant clone of tumour cells escaping the chemotherapy. The drugs chosen should have activity against the particular tumour (preferably proven in previously reported single-drug trials) and preferably affect cells at different stages of the cell cycle or be non-cell cycle specific (ie affect cells in all stages of the cell cycle) eg. combination of two drugs affecting the cell only during mitosis is likely to be less effective than combination of a drug that affects the cell at mitosis and a drug that strikes during DNA synthesis.

They should also have a different mode of action, not have overlapping toxicities eg. adding two markedly bone marrow suppressive drugs into the same protocol is undesirable (but sometimes necessary)and should not interact.

Another consideration is the likelihood of tumour cross-resistance. For instance, if a tumour is resistant to cyclophosphamide it will also often be resistant to chlorambucil,



Cross linking of guanine residues is the mode of action of the alkylating agents and platinum compounds. Dactinomycin is thought to work in a similar way. The DNA damage triggers apoptosis.

a closely related alkylating agent

Multiple drug resistance

Rapidly dividing cells exposed to anticancer drugs are under a lot of selection pressure. The main mechanism of resistance is to express P (permeability) glycoprotein on the cell surface. This actively pumps drugs out of the cell (it is a major component of the blood brain barrier) before they can cause damage. Cross resistance to the various classes of drugs occurs. Ivermectin is one of the most potent inhibitors of P glycoprotein and is undergoing trials to reverse multidrug resistance in people.

Supportive treatment

Analgesia - usually NSAIDs, especially for bone pain
Bone marrow stimulants - anabolic steroids
Appetite stimulants - benzodiazepines or steroids
Nutritional support - gastrostomy tubes

Choosing drugs

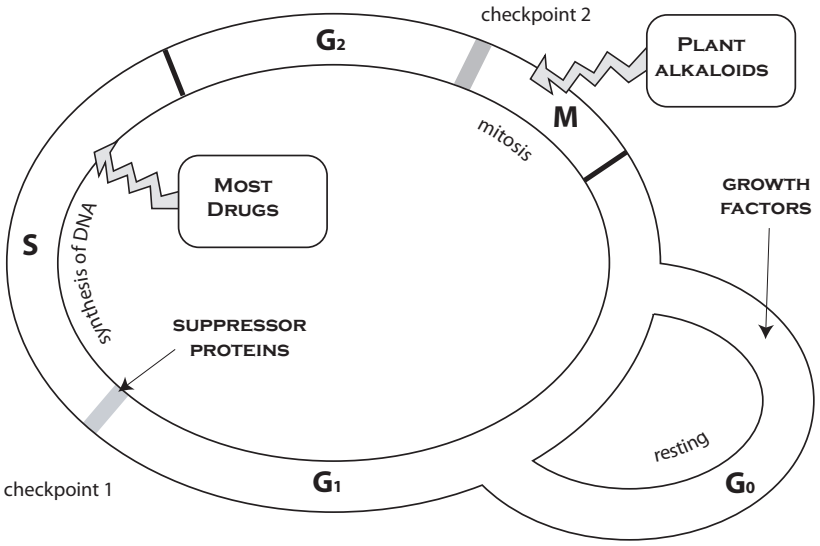
The range of tumours which animals can get is vast; most of the few which are treated, are treated empirically. Protocols (based on human protocols, which are also empirical but of which there is much more experience) have been established for some tumours (particularly white cell tumours), but often it is a matter of trying drugs or protocols which have been reported to work in a small number of cases and tailoring the treatment to the response.

Alkylating agents are probably the most commonly used group of drugs in small animals. They include **cyclophosphamide** - a prodrug for one of the nitrogen mustards. These are closely related to the sulphur mustard gases used for chemical warfare in WW1. Cyclophosphamide is not a pleasant drug. Although it is cheaper than some of the other drugs and works well in some lymphomas and leukaemias, a metabolite can cause haemorrhagic cystitis (as well as all the general side effects of cytotoxic drugs). A similar drug without this effect is **chlorambucil** (similar indications). Both drugs are sometimes used as potent immunosuppressives. The other alkylating drug occasionally used is **melphalan**. **Cisplatin**, and its less toxic analogue **carboplatin**, act in a similar way to the alkylating agents and are used for a variety of solid tumours. Cisplatin in particular is nephrotoxic and should not be used in cats (carboplatin can be used in cats).

The main antimetabolites used are **methotrexate** (used for lymphoma) and cytarabine (= **cytosine arabinoside**) (used for lymphoma, leukaemia and myeloproliferative disease). Resistance develops quickly to cytarabine.

A number of antibiotics are in human use but the only one much used in animals is **doxorubicin** (Adriamycin). This is effective in a broad range of cancers and is used for carinomas and sarcomas as well as lymphoma and leukaemias. It has a broad spectrum of side effects too, including cardiotoxicity, allergic reactions and nephrotoxicity (cats). It is also very irritant when injected perivascularly.

Plant alkaloids are a growth area for human drugs but the only ones in veterinary use are **vincristine** and **vinblastine** (from the periwinkle, *Vinca rosea)*. Vincristine in particular is not as myelosuppressive as most drugs, although it does produce some unique side effects such as peripheral neuropathies. Both are used in combinations (usually with



Stages of the cell cycle at which drugs act.

Typical lymphoma treatment (COP) protocol (dogs and cats)

This protocol is included here to give some idea of the complexity of treatment - check on the latest recommendations before treating any animals!

Induction therapy

Vincristine 0.7mg/m^2 iv on day 1
Cyclophosphamide 50mg/m^2 po on days 1,2 3, & 4
Prednisone1mg/kg po twice daily
Repeat induction therapy for 8 weeks. Precede each vincristine injection with a WBC and platelet count. Skip a week's treatment if WBC count is below $3x10^9$/L, neutrophil count is below $2x10^9$/Lor platelet count is below $100x10^9$/L. Start prophylactic trimethoprim / sulphonamide if neutrophil count is below $1x10^9$/L.

Maintenance therapy

Vincristine 0.7mg/m^2 iv every 3 weeks
Chlorambucil 2 - 4mg/m^2 po on days 1,2,3 & 4 every week
Prednisone 1mg/kg po every second day
Continues until the 52nd week of treatment or until the lymphoma comes out of remission.

Rescue or late intensification therapy

When the animal comes out of remission (usually due to tumour resistance) a change of drugs is required to regain remission. The second period of remission is usually shorter than the first period. The treatment required to obtain a second remission is usually more expensive. An alternative approach is to use late intensification of therapy after sucessful induction but before tumour recrudescence. Late intensification has some theoretical support as an effective strategy. It is also practical in veterinary medicine because by the time the owner is asked to consider more expensive and potentially more toxic drugs, much of their fear of chemotherapy has evaporated. Consider the following drugs for rescue or late intensification. Doxorubicin is the most effective rescue drug.

Doxorubicin 30mg/m^2 iv every 3 weeks for 3 - 6 treatments (max 8 treatments) or cytarabine 100mg/m^2 iv on days 1,2,3 & 4 repeated every 3 weeks for 2 - 3 treatments or vinblastine 2.5mg/m^2 iv every week for 6 treatments

Given with or without asparaginase 400iu/kg sc or ip weeky for 1 - 3 treatments

doxorubicin and cyclophosphamide) for lymphmomas and some sarcomas and are very irritant perivascularly. Taxanes such as **paclitaxel** (Taxol) are effective in people but are too expensive for use in animals at the moment.

Miscellaneous cytotoxic drugs include crisantaspase and colaspase - types of **asparaginase**. Some tumour cells require exogenous asparagine, asparaginase breaks this down and stops the tumour cells making protein. It is used for lymphoma but can cause anaphylaxis and is expensive.

Many tumours are started or maintained by sex hormones. In veterinary practice, these are usually treated by castration (prostate cancer, anal adenoma) or spaying (mammary tumours). In people, and rarely in animals, drugs are used. **Tamoxifen** is an antioestrogen used for breast cancer in women which is also effective in dogs but too expensive to use. **Anastrozole** blocks oestrogen production and is more effective in women. **Delmadinone** is a progestagen which acts as an antiandrogen and is sometimes used in dogs. Stilboestrol used to be used as an antiandrogen, but is no longer available.

Risks to people

Paradoxically, repeated exposure of people to low doses of chemotherapeutic drugs can predispose them to neoplasia. In addition, chemotherapeutic drugs are teratogenic and toxic. Exposure can occur via absorption through skin or mucous membranes, inhalation of vapours or ingestion through contamination of food or cigarettes.

Common situations in which exposure occurs:

•aerosol formation when reconstituting or removing liquid drugs from a pressurized vial
•expulsion of air from drug-filled syringes
•spills during transfer of drug between containers
•leakage of catheters, iv lines or bags
•self-inoculation when recapping needles
•crushing or breaking tablets
•handling urine or faeces from treated animals

Precautions required:

•wear latex gloves; +/-protective eyewear and a disposable gown when administering drugs or handling waste
•pet owners should be instructed to wear gloves when administering tablets.
•prepare drugs in a low-traffic, draught-free but well ventilated area
•if possible wear a respirator or dust mask when preparing drugs (often more practical to buy the drugs reconstituted from a local hospital)
•avoid recapping needles or pressurizing vials
•wrap an alcohol-dampened swab around needles before withdrawing them from vials
•evacuate air bubbles from drug-filled syringes into

alcohol-dampened gauze

•use disposable plastic-backed table covers to minimize contamination of tables with spilled drug

•never eat or drink in areas where cytotoxics are used

•consider altering oral drug dosing frequency to allow use of whole tablets rather than tablet fragments

•never allow pregnant women (including owners) to handle drugs or handle excreta from treated animals

•think very carefully (and discuss with the owner) before sending an animal home to a household with a pregnant woman or children

•be familiar with routes of excretion so that contaminated urine or faeces are safely disposed of. This is particularly important with the urine from cisplatin-treated dogs.

•if skin contact occurs, wash hands thoroughly with soap and water

•all materials used in the injection of a chemotherapeutic should be placed in a plastic bag, sealed and then placed in a clearly labelled, leak-proof container for disposal by incineration.

Protocol to follow if a vesicating drug is injected outside the vein

1) Do not remove needle but aspirate forcefully while needle remains in place.

2) If doxorubicin has been extravasated immediately flood area with 5 mL of 8.4% sodium bicarbonate.

3) Aspirate the area with a 25 SWG needle.

4) Infiltrate affected area with small volumes of normal saline and repeat aspiration (use 3-5 mL with vincristine and 15-30 mL with doxorubicin).

5) Infuse dexamethasone 4mg.

6) Cold pack for 15 minutes

7) Use a DMSO roll-on three times daily for 5 days.

Prevention is better than cure - use a catheter.

Large animals

The only tumours treated medically are sarcoids in horses. When these grow around the eyes it is difficult to resect them or use cryosurgery, so cisplatin in oil is sometimes injected into the tumours. It requires high pressure to inject oil into a solid tumour, so use Luer lock syringes and wear goggles.

The future??

The unsatisfactory state of chemotherapy (in people) has prompted a huge amount of research. This has taken several directions: new drugs are the most obvious. Lots of plants and sedentary animals such as sponges make toxins to stop themselves being completely eaten, so the jungles and seabeds are being scoured for suitable drug candidates. (Sponges are handy because they will grow in a stream of sea water - the drug just needs to be extracted at the other end of the pipe.) Expect some new drugs soon.

Another approach has been to target the cancer cells more directly, rather than zap all dividing cells. One way is to use some drug which is preferentially taken up by the cancer cells but requires activation by / sensitises the cells to radiotherapy (ideally relatively innocuous radiotherapy such as laser light). This approach is already in use in people.

Another way is to use biochemical markers which are more specific for cancer cells (usually specific types of cancers) and attach the drug (either cytotoxic or activator) to antibodies for these markers. These markers are being well characterised for human cancers, but do not expect much useful work in animals.

Yet another way is to interfere with the tumour's blood supply and starve it to death. A rapidly growing tumour needs a rapidly growing blood supply - new vessels are under the control of various growth factors which can be blocked by drugs such as the anti-arthritis drug pentosan. Thalidomide is also being tried - it will never be used in animals, but newer, safer analogues are also available. The tumour's blood supply often does not keep up with demand and the tumour becomes hypoxic. Injecting anaerobic bacteria into such tumours to kill the hypoxic cells has shown some success.

New drugs are currently coming onto the market (overseas) at the rate of about one every six weeks, so do not regard this study guide as the last word on cancer chemotherapy!!!

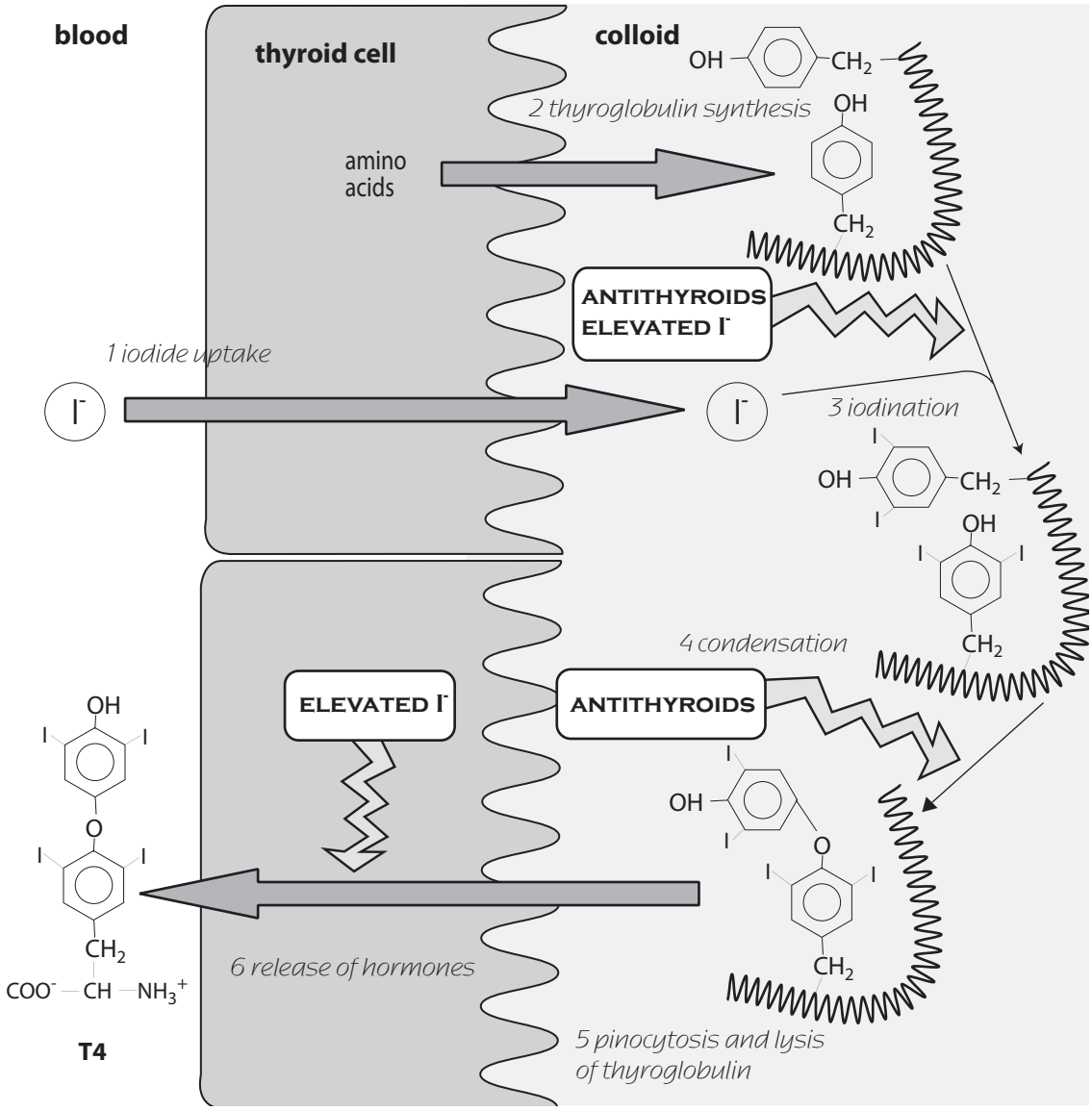
Further down the line, insertion of tumour suppression genes looks hopeful if problems with the viral vectors are sorted out. New Zealanders will probably have to go overseas for this. A number of genes have been identified in people which predispose to cancer.

Cancer is the number one killer of humans, so there is plenty of incentive to find the definitive cure, quickly!

Further reading

Dobson, J.M. and Gorman, N.T. (1993) Cancer chemotherapy in small animal practice. Blackwell

The thyroid



Disorders of thyroid function are common in small animals; usually hypothyroidism in dogs and hyperthyroidism in cats. In large animals, the problems are usually external, either iodine deficiency or plant toxins which interfere with iodine utilisation (particularly plants of the cabbage family - see toxicology notes).

Thyroid Physiology

The hypothalamus releases thyrotropin releasing hormone in response to environmental stessors such as cold or trauma. Thyrotropin releasing hormone acts on the anterior pituitary to increase the release of thyrotropin. This in turn stimulates the thyroid to produce thyroid hormones. Several of these steps can be manipulated with drugs but this is not done clinically.

Thyroid hormone production

see diagram.

The thyroid gland makes four times as much **thyroxine** (T4, levothyroxin INN) as **liothyronine** (T3, triiodothyronine) but T3 is four times as active as T4 in the tissue. T4 has more control over thyrotropin releasing hormone secretion.

Thyroid hormones are highly protein bound in circulation. Free T4 makes up 0.1 - 0.3% of the total T4. Thyroxine-binding globulin is the major transport protein for both thyroid hormones.

T4 has a half life of approximately 10-16 hours in the dog (nb the half life in man is much longer - about 6 days - beware if reading the human literature). It is converted to T3 or reverse T3 (rT3) by deiodinase enzymes. There are two

types of enzyme - type 1 found in the liver, kidney, skin and muscle (highest activity in the liver and kidney) and type 2 found in the CNS and brown adipose tissue. T3 is quickly deiodinated, then broken down in the liver and excreted in the faeces (predominantly) or urine.

Actions of thyroid hormones

T4 is converted to the active T3 in cells. T3 binds to a specific receptor similar to the steroid receptor. The T3/receptor complex activates transcription of a variety of proteins (the unbound receptor will reduce transcription). These proteins result in an increase in metabolic rate and oxygen consumption, and thus temperature, mainly by an increase in gluconeogenesis and glycogenolysis. Effects on the heart are most obvious - tachycardia and possibly arrhythmias. Thyroid hormones are also necessary for growth and maturity.

Hypothyroidism

This is the most common endocrinopathy in dogs; occuring in middle aged dogs of medium to large breeds, particularly Dobermanns. It is uncommonly diagnosed in cats - most often secondary to treatment for hyperthyroidism.

Causes

primary hypothyroidism - destruction of the thyroid gland by lymphocytic thyroiditis

-idiopathic follicular atrophy

-congenital - dyshormonogenesis, Iodine deficiency, thyroid dysgenesis

-iodine deficiency/excess

-destruction of gland by tumour / infection

-secondary hypothyroidism -eg pituitary tumour

Clinical signs of hypothyroidism

large range may be seen, including:

cold and exercise intolerance

bradycardia

hypothermia

depression / lethargy

symmetrical alopecia, hyperpigmentation, lightening of the coat colour, "rat tail', but sometimes increased thickness of the coat, recurrent pyoderma

polyneuropathy

polymyopathy

anaemia

reproductive failure

Drugs

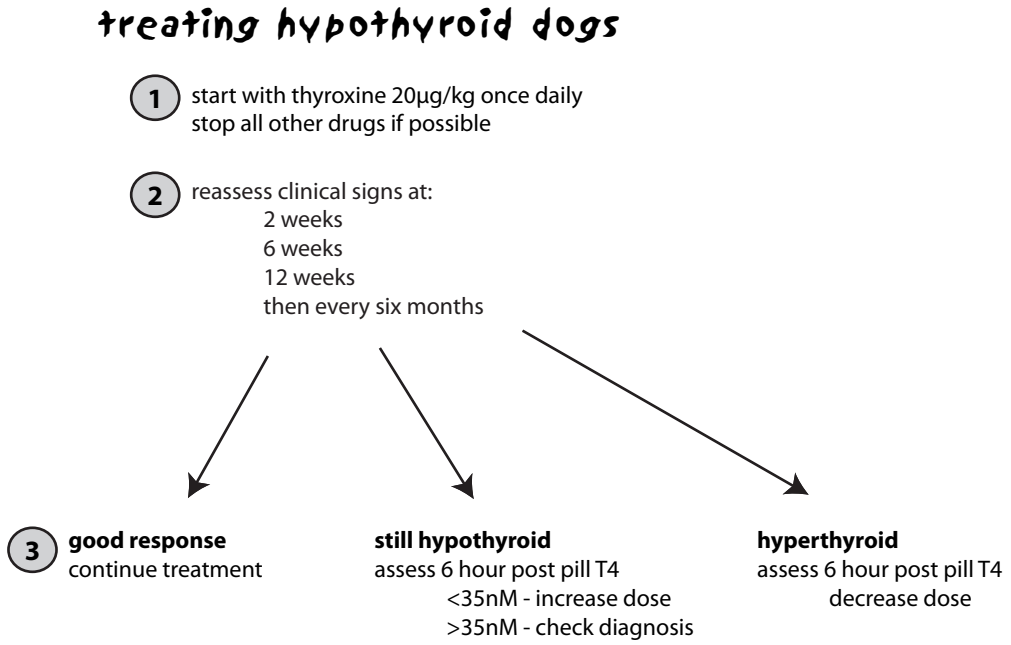
The aim of treatment is to approximate the secretion of thyroid hormones in a normal dog. Levothyroxine is the treatment of choice as it mimics the normal physiological situation. It is rapidly converted to T3 and has a half life of 10-16 hours, but the biological effect lasts longer than this - it is usually given once daily. The peak plasma concentration is reached in 4-12 hours. It is cheap.

Synthetic liothyronine is also available. It has a short half life (5 - 6 hours) so needs to be administered every 8 hours, so is not often used. It is only given if a T4 to T3 conversion defect is diagnosed or if thyroxine is poorly absorbed, but neither of these conditions has been reported in dogs. Some tissues rely on circulating T3 for their source of intracellular T3, so when T3 is given you can get hyperthyroid signs in the heart, but the brain may be euthyroid or hypothyroid. Peak plasma levels occur 2-5 hours after administration.

Dessicated thyroid is now obselete.

Dose

Start with a low dose, particularly if there is cardiac disease, diabetes mellitus or hypoadrenocorticism. It was usual to start with a moderate dose for three months and then decrease, but recent work shows that this is unnecessary. Hy-



poadrenocorticoid animals will need supplementary cortisol due to increased metabolic demands by the increased T4.

Reduce dose in liver or renal failure.

Higher doses more often are necessary in dogs than humans, as the bioavailability of T4 is low due to poor absorption and the first pass effect.

Monitoring

Resolution of clinical signs: mental state/alertness should improve in 1-3 weeks; skin and weight improve in weeks to months.

Absorption and pharmacokinetics vary between animals so therapeutic drug monitoring may be necessary. Routine post pill testing may not be necessary if clinical response is good, and there are no thyrotoxic signs.

Monitor plasma concentration if response is poor after 6-8 weeks of T4 supplementation or if thyrotoxic signs develop - tachycardia, polyuria ± polydipsia, weight loss, diarrhoea, pyrexia, pruritus, anxiety. Take a 4-8 hour post-pill serum for total T4 measurement - it should be high normal. If the T4 is high, but there are no signs of hyperthyroidism, it is not necessary to lower the dose. T3 concentrations are not helpful in monitoring T4 therapy. If the T4 appears adequate but there has been no clinical improvement consider: wrong diagnosis or antibodies to thyroid hormones.

Drug interactions

Corticosteroids, phenytoin, salicylates, frusemide and androgens enhance the elimination of T4 by decreasing protein binding. T4 increases the actions of catecholamines, ketamine will cause tachycardia and hypertension when used in patients receiving T4 and the therapeutic effect of digoxin may be reduced by T4. Phenobarbitone increase metabolism of levothyroxine and may require a higher dose to be given. Levothyroxine enhances the effects of warfarin type anticoagulants.

Avoid giving thyroid hormones with other drugs.

Hyperthyroidism

Is a common problem in middle aged to old cats and is usually a benign tumour of thyroid. It rarely occurs in dogs - associated with thyroid carcinoma

Clinical signs

polyuria and polydipsia
weight loss
polyphagia
vomiting
alopecia/overgrooming
heart murmur, tachycardia, gallop rhythm

Treatment options

surgery - thyroidectomy
radioactive iodine
antithyroid drugs - carbimazole

Radioiodine (radioactive ^{131}I)

A single iv or sc injection (or even an oral dose) is effective in 90-95% of cases - first time failures usually respond to a second dose. No immediate adverse side effects have been reported, although occasionally cats may become hypothyroid. They may show clinical signs of lethargy, bradycardia, thick coat. Supplement T4 for life.

Disadvantages - radiation hazard and need for hospitalisation. A licence is required to posess radioactive materials. Before using, read the Code of safe practice for the treatment of cats for thyroid disorders with iodine-131, issued by: The National Radiation Laboratory, PO Box 25-099, Victoria Street, Christchurch

Recommended reading

Radioiodine treatment of hyperthyroid cats. BR Jones, J Cayzer, EA Dillon, KP Smidt (1991) *NZVJ* **99** 71-74 .

Antithyroid drugs

Mechanism of action: block incorporation of iodine into thyroglobulin, prevent coupling of mono- and diiodotyrosine into T4 and T3 and direct interaction with thyroglobulin molecule. They do not interfere with the ability of the thyroid to trap inorganic iodide and do not block the release of stored thyroid hormone into the circulation.

Methimazole (thiamazole INN) (only available as a transdermal formulation in NZ) and its prodrug **carbimazole** (tablets), which is rapidly converted to methimazole in the body, are most commonly used. Most side effects, vomiting, anorexia and depression, occur in the first two weeks and are mild and transient. Stopping treatment is usually not required. Other uncommon side effects may include hepatopathy, thrombocytopaenia and leukopaenia: monitor the white cell and platelet count every 2 weeks for 3 months. There is usually an improvement in about two weeks, when the dose is reduced (and ideally titrated against T4 levels). Remember that treating the hyperthyroidism may unmask other problems such as kidney failure.

Propylthiouracil is no longer recommended due to high incidence of anorexia, vomiting, lethargy, immune mediated haemolytic anaemia and thrombocytopaenia. It has been used (illegally) to promote growth in cattle.

commonly used drugs

hypothyroidism
thyroxine
hyperthyroidism
carbimazole (NZ & UK)
methimazole (USA)

The pancreas

Definitions

Diabetes mellitus is a chronic metabolic disorder characterised by high blood glucose caused by insulin deficiency or insulin resistance. It can be:

Type 1 - insulin dependent (dogs) - absolute deficiency of insulin from autoimmune destruction of B cells

Type 2 - non-insulin dependent (horses, cats and people) - relative insulin deficiency and insulin resistance

Diabetes insipidus is caused by an absolute or relative deficiency of antidiuretic hormone, and is usually treated with thiazide diuretics. It is rare.

Physiology

Insulin is a complex protein made and stored in the B cells of the islets of Langerhans in the pancreas. The amino acid sequence of the protein differs slightly between species. Insulin is produced initially in the form of preproinsulin, a single chain precursor. This is converted to proinsulin, and then insulin and is packaged in granules ready for release by exocytosis. Increased blood glucose increases insulin secretion via increased ATP in the B cells which blocks ATP-sensitive K^+ channels and depolarises the cells. This causes Ca^{++} influx and exocytosis of insulin. Other stimuli for insulin release include gastrin, secretin, cholecystokinin and glucagon-like peptide - all released by eating. Vagal stimulation will do the same. α_2 adrenoreceptor agonists (including adrenaline and noradrenaline) reduce, and antagonists increase insulin release, probably by an action at the imidazoline I_3 receptor.

Insulin is degraded in the liver, kidney and muscles.

Insulin stimulates the uptake and metabolism of glucose, amino acids and fatty acids in fat and muscle. It inhibits hepatic glycogenolysis and gluconeogenesis, and the catabolism of protein and fat. It is also anabolic, especially in the foetus.

Treatment strategies

Treatment involves a combination of dietary and exercise management, and either oral hypoglycaemics or insulin.

A high fibre, high complex carbohydrate diet is desirable in dogs. Avoid foods containing simple sugars, which will be rapidly absorbed from the gastrointestinal tract and elevate blood glucose. **Acarbose** is sometimes used in diabetic people to slow sugar absortion. Fibre slows carbohydrate absorption and dampens the post prandial rise in blood glucose.

Cats should be given a high protein diet. Slow weight loss is needed in obese cats. At least two meals a day is advisable.

Diabetic patients classically present with polydipsia, polyuria, polyphagia and weight loss. There are several different situations you will have to manage:

•the fat diabetic cat - diet & insulin, or, if owner unable to give injections, diet & oral hypoglycaemics

•the thin, sometimes ketotic, diabetic cat - diet & insulin

•diabetic dogs - diet & insulin

•insulin resistant cases - ?

•diabetic ketoacidosis - soluble insulin iv infusion

•diabetic coma - soluble insulin by iv infusion

•insulin overdose - hypoglycaemic seizures/coma - iv glucose

Oral hypoglycaemics

These drugs are not often effective in dogs but sometimes are in cats. The two main groups of drugs are the sulphonylureas (**glipizide** (best in cats), **glibenclamide**, **gliclazide**, **chlorpropamide** (rarely used now) and **tolbutamide** (most widely used in vet medicine)) and biguanides (**metformin**). A promising new group of drugs (glitazones) includes **rosiglitazone**, **pioglitazone,** ciglitazone and troglitazone (since withdrawn - worked in diabetes but caused liver failure), which are thought to decrease insulin resistance.

Sulphonylureas work by direct stimulation of insulin secretion by the B cells by binding to the ATP-sensitive K^+ channels and blocking them. In the longer term, they also cause increased tissue sensitivity to circulating insulin by an unknown mechanism.

Biguanides do not require functioning B cells. Their exact mechanism of action is unknown but they cause inhibition of hepatic glycogenolysis and increased peripheral glucose utilisation.

Indications

Non insulin dependent diabetes

Approximately 25% of cats will respond to these drugs, so insulin may not be required.

Side effects

•hypoglycaemia

•vomiting shortly after administration - usually subsides with time

•increased hepatic enzymes (but clinical liver disease has not been reported)

Sulphonylureas may contribute to the progression of type 2 diabetes. The response isusually slow, and in the meantime, hyperglycaemia can cause B cell death. Glipizide can also cause cats to deposit more amylin (co-released with insulin) in their pancreas, also resulting in B cell death.

In people side effects reported include cytopaenias, nausea and vomiting, cholestasis and hypersensitivity. Sulphonylureas can promote weight gain.

Insulin

Most animals with diabetes mellitus will require insulin. A variety of insulin formulations are available in NZ but all except one are human recombinant insulin. The other is pig insulin marketed for dogs - nb, it is 40iu/mL as opposed to the standard human 100iu/mL.

Insulin has traditionally been conjugated with a number of adjuvants to alter its solubility and thus speed of onset and duration of action. A newer approach is to alter the protein itself to change its duration of action. Beware; the nomenclature is confusing!

insulin lispro is an insulin analogue in which a lysine and a proline residue have been swopped. It is the most rapid and shortest acting. **Insulin aspart** is similar. These are relatively new and there is not much information on effects in animals.

soluble insulin (crystalline / neutral / regular insulin) is rapid acting, short duration and is used iv in emergencies, onset of action - minutes, maximum effect 30 mins - 2 hours, duration 1 - 4 hours (prolonged to 4 - 10 hr if given sc)

isophane insulin (NPH insulin) (complexed with protamine) is intermediate acting, only given sc - onset 30 min - 3 hr, duration 4 - 24 hr depending on preparation

insulin zinc suspension is a mixture of soluble and amorphous crystals complexed with zinc chloride. Small lumps / crystals are absorbed slowly (**lente insulin**), big lumps / crystalls are absorbed more slowly (**ultra lente insulin**). These are only given sc and last about 24 hours.

Mixtures of these are also sold to get a fast onset and long duration. The insulin in these preparations is the same; the formulation is merely adjusted to alter its rate of release.

insulin glargine is another longer acting analogue (24 hours in people). It also has rearranged amino acids. It has become the drug of choice in cats.

The price of insulin is approximately $50 for 10 mls of a 100 IU/ml suspension. Insulin must be given parenterally as it is inactivated by proteolytic enzymes.

An animal's requirement for insulin will vary throughout the day, depending on feeding and exercise. Once the animal has stabilised on insulin (usually about a week) it is usual to measure blood glucose every 1 - 2 hours and plot a glucose curve for 24 hours to reasess the dose. A single blood glucose can be misleading.

Insulin resistant cases

Insulin resistance is defined as persistent hyperglycemia, glucosuria and clinical signs, despite receiving more than 2.2 iu of insulin/kg per injection. Possible causes include the Somogyi overswing, problems with insulin administration/storage/mixing of different insulins, concurrent disease such as hyperadrenocorticism, acromegaly and urinary tract infections, the development of antibodies to insulin. The first step is to evaluate the glucose curve and assess the owner's technique (see medicine notes).

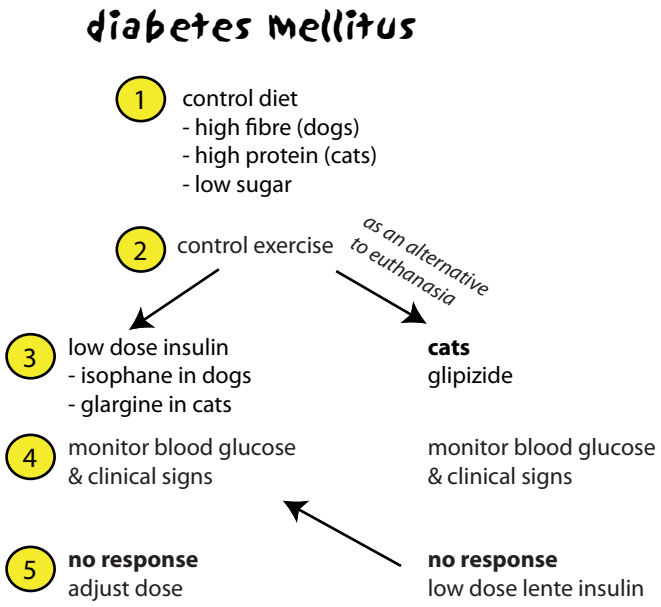
Diabetic Ketoacidosis

These animals are always dehydrated and usually have intercurrent disease. Glucose spilling over into the urine causes an osmotic diuresis and consequent sodium and potassium depletion, so these animals have hyperosmolality, hypovolaemia, metabolic acidosis and prerenal azotaemia.

Correct fluid and electrolyte deficits (0.9% NaCl with added potassium (40mmol/L)) and monitor ECG. Give soluble insulin (0.1iu/kg/h in fluids) to reduce the ketone bodies, avoiding a rapid decline in blood glucose. Check blood glucose every hour and give iv gluccose if necessary. Then correct acid base imbalance (give bicarbonate) if pH is low. Phosphate supplementations may also be necessary (potassium phosphate iv), but this can cause hypocalcaemia.

Diabetic Coma

Depression and coma result from intracellular dehydration of neurones due to increased osmolality. A vicious cycle is set up as depression leads to reduced water intake, further hypovolaemia and hyperosmolality. Treatment is as for ketoacidosis but the animal should be given lots of fluid



One approach to the treatment of diabetes.

first as insulin will result in potassium and water moving into the cells.

Treat circulatory collapse with fluids as an emergency. Replace sodium and fluid deficits with 0.45% NaCl plus potassium. Slowly correct the glucose as above - start after 6 hours fluid therapy. Once the animal has improved (blood glucose 10mM), begin stabilisation with isophane insulin.

Hypoglycaemic seizures / coma

These can occur with insulin overdose or unusually strenuous exercise. In these situations, severe hypoglycaemia may occur.

If the animal is at home get the owner to rub or pour sugar syrup onto the gums. Once the animal regains conscious a small meal should be fed and the pet should be taken to the vet clinic. 50% dextrose should be administered iv **slowly** to effect (2-15 mLs), preferably added to an infusion, and the animal should respond in approximately 2 minutes. If inappetance is a problem the animal should be maintained on a 5% dextrose iv drip.

The future?

A lot of work is going into ways to deliver insulin orally, but there is nothing nearing commercial release yet. Insulin sprays for inhalation or absorption across nasal or buccal membranes are in clinical trials in people. These would be difficult to use in animals. Transdermal delivery is another possibility.

An artificial pancreas is still some way off - present implantable glucose detectors are not reliable enough.

Some zinc complexes mimic the effects of insulin and are being investigated.

An islet neogenesis gene associated protein has been found which makes islet cells regrow. This has possibilities in the distant future.

Exocrine pancreatic insufficiency

This occurs mainly in German Shepherds. It is usually treated by providing a highly digestible diet (low fat and fibre) and giving pancreatin, which contains a mixture of protease, lipase and amylase enzymes. The most effective form is a powder or granules which are sprinkled on the food. It may be necessary to give a H_2 blocker such as cimetidine to stop acid breakdown of the enzymes in the stomach.

Growth promoters

There are a variety of ways of making animals grow faster using drugs; the two commonest classes of drugs used for this are hormonal growth promoters and antibiotics (fed continuously at a low level (euphemistically called "production enhancers") - see antibiotic notes).

Hormonal growth promoters, also known as anabolic steroids, are only widely used in cattle, although several preparations are sold for horses and dogs. They are all derivatives or analogues of sex hormones, usually testosterone.

The use of growth promoting agents in food producing animals is a political hot potato. They were banned in Europe in the late 1980s after (illegally used) stilboestrol was found in veal flavoured baby food in Italy. (There is still an enormous black market for them in Europe, particularly Belgium and Italy.) Europe has refused to accept any imports of meat produced using anabolic steroids since then, although there is more complete toxicity data for this class of drugs than for any others used in food animals. Recently, the USA has taken Europe to the World Trade Organisation and won its case that Europe's restrictions on imports are a barrier to trade that is not justified on scientific grounds. Europe has appealed but is likely to lose. As far as NZ is concerned, any animals treated with anabolic steroids must be clearly marked, and records kept, so that there is no chance of them getting into a consignment of beef to Europe. (For details of the red tape involved, check the NZVA website `http://www.vets.org.nz/`)

Advantages of anabolic steroids include increased growth rate, food conversion efficiency and carcase quality; disadvantages include potential animal welfare problems and the attention of the food scare industry.

Anabolic steroids are also occasionally used in small animals, particularly old animals recovering from surgery and those with chronic kidney failure, with or without bone marrow depression and anaemia. There are several preparations licensed for use in horses; **they should not be administered to competition horses**.

The anabolic steroids abused by human athletes are often veterinary preparations (particularly nandrolone), and vets have been struck off for supplying the human black market. Think hard before supplying these drugs to anyone.

Anabolic steroids are usually androgens. However, in cattle, the highest growth rates are achieved when there is a balance of androgens and oestrogens (including those produced by the animal).

In the USA, recombinant **growth hormone** (somatotropin, BST) is sometimes used as a growth promoter in cattle, usually in combination with anabolic steroids since their effects seem to be additive. BST also increases milk yield, which is its main use there. It is banned in NZ. Equine recombinant somatotropin has recently been approved here. It will probably be abused in racing animals but may be useful to promote tendon repair. Porcine somatotropin is also used to promote growth

Clenbuterol, and occasionally other adrenergic β_2 agonists, are sometimes used illegally as "partitioning agents". They do not seem to promote growth but ensure that any growth is of muscle rather than fat.

Thyreostatics have been used as growth promoters but they make animals fat rather than promoting muscle growth. They are now illegal.

It is important to realise that animals will not grow without an adequate supply of good food. **Anabolic steroids are not a substitute for good feeding.**

Mechanism of action

Most of the hormonal growth promoters appear to increase nitrogen retention in muscle cells and reduce catabolism; muscle cells grow faster than fat cells. Exactly how the drugs do this is not clear.

Androgens have a direct effect on muscle cells, block corticosteroid catabolism and enhance thyroxin's effects. **Nandrolone**, **ethylestrenol**, **stanozolol** and **methandriol** are used in dogs, horses (and man); **testosterone** and **trenbolone** are used in cattle.

Oestrogens cause increased growth hormone release from the pituitary, enhance the effects of insulin (or insulin like growth factor?) and thyroxin. Recently, oestrogen receptor subtypes have been found which may shed more light on the mechanism of action. Oestrogen is only used in cattle. **Oestradiol** (natural oestrogen precursor) and **zeranol** (not strictly a steroid but binds to oestrogen receptors) are used. Zeranol is derived (via zearalenone) from a fungus (various *Fusarium* spp) which grows on clover, residues are frequently found in cattle in NZ, presumably from eating mouldy clover (see toxicology notes for details). Caterillars can concentrate the zearalenone to an extent that can cause serious problems if they are eaten by grazing animals: this caused an epizootic of abortions in mares in Kentucky in 2001. Stilbenes such as stilboestrol are banned as they may cause cancer when given in high doses (as may the endogenous oestrogens).

Progestagens' main effects are probably to increase appetite and reduce bulling behaviour leaving more time for eating. They may also bind to testosterone receptors and elevate oestrogen levels. **Progesterone** is the only progestagen used in NZ, **melengestrol** is used in America.

Useful effects

Most drugs will increase the rate at which cattle gain weight by 10 - 15% and the cattle are bigger at slaughter. Under some circumstances, some drugs (especially androgens) will increase food conversion efficiency. The effects on carcase quality are more controversial. While the muscles are usually bigger, they contain less fat (which may or may not be a good

thing, depending on the market) and are usually tougher.

Horses and small animals are usually given anabolic steroids in an attempt to speed recovery from debilitating diseases, or in chronic renal failure. The aim is to reduce protein breakdown, which means that protein is converted to muscle and the kidney has less work to do excreting urea. Since they stimulate erythropoiesis, they are sometimes used in anaemia (see cardiovascular pharmacology notes).

Side effects

Inappropriate administration of sex hormones will interfere with breeding. Since none of the drugs promote growth in bulls, they should not be used. Bull calves given anabolic steroids are unlikely to be of any use for breeding. In heifers destined for breeding, anabolic steroids will increase their size (and possibly pelvic size) at the first oestrus, but reduce the chances of pregnancy. Oestrus cycles will be irregular. If given to pregnant heifers, everything from abortion to reduced milk yield is possible. In all animals behavioural changes will be seen, especially an increase in mounting behaviour, this often leads to injury. Other effects are rectal and vaginal prolapses, ventral oedema, teat and udder development (oestrogens).

Practical use

Cattle seem to grow best with the testosterone levels of a bull and the oestrogen levels of a young cow, however, none of the drugs have much effect on growth rates of bulls. Bulls generally grow about 10% faster than steers, this is about the same increase as anabolic steroids produce.

There is only consistent evidence of a beneficial effect in steers and prepubertal calves, but nearly all the published work relates to cattle fed on grain; there is very little information on the usefulness of these drugs in a New Zealand situation. The drugs are most effective when the animals are growing quickly.

Current use in NZ

steers

The main group in which these drugs are used: oestradiol then oestradiol + trenbolone usually gives a 5 - 30% (typically 10 -12%) increase in weight gain over controls.

bulls

do not use if the bulls are for breeding, zeranol may have some effect on others and may also be useful to control behaviour.

breeding heifers

do not use

store heifers

oestradiol / oestradiol + progesterone at weaning then oestradiol + testosterone Gains are less impressive than with steers.

Most animals are implanted at a young age to take advantage of the longer growth period, then re-implanted with the same or a shorter acting product for finishing. Re-implanting with trenbolone is not recommended as carcase quality suffers.

Remember that growth promoters are not a substitute for good husbandry and feeding.

Administration

Most anabolic steroids come in the form of a silicone rubber implant (to provide a depot with very slow release). Some preparations are in the form of pellets; care is needed not to crush these which could result in a faster than expected release of drug. These implants are deposited between skin and cartilage on the outside of the middle third of the ear using specially designed applicators like large syringes. The ear is used as it will be discarded when the animal is slaughtered and there is no danger of anyone eating a depot of drug.

A good implanting technique is important. The animal must be restrained in a head bail. The ear must be pulled straight, and with the bevel of the applicator needle a nick is made in the skin cranial to the dorsal ridge of the ear. This entry point should be quite close to the tip of the ear. With a fast action, the entire length of the needle is pushed forward under the skin towards the base of the ear, making sure to stay clear of the dorsal ridge (in this area, the skin is firmly attached to the cartilage and there is an artery). It is important not to penetrate the cartilage of the ear. When properly inserted, the implant can be clearly seen or felt just before the area of loose skin at the base of the ear. The implant is then secured in place by the thumb and the needle withdrawn. Check that only one implant is delivered. The animal must receive a specially designed ear tag at the same time. After administration, the hormone is released from the implant in a controlled manner over a certain number of days, which varies depending on the product used.

To reduce the possibility of infection, and thus the potential loss of the implant, hygienic and antiseptic procedures must be followed during implantation. The ear must be clean and dry When ears are wet or contaminated with soil, urine or faeces, the skin must be cleaned with an antiseptic soap and dried prior to implanting.

The needle of the applicator must be kept sharp and clean. To reduce possible transmission of disease or local infection, the needle must be disinfected before each implantation (between animals).

Controls on the use of anabolic steroids

Controls on the sale and use of these drugs are mandatory for access to European markets (at the moment, anyway). Basically, Brussels wants to know that we have a system to clearly separate the animals which have been implanted so that they do not get to Europe.

The use of "hormonally active substances for the purpose of promoting growth" is restricted to veterinary surgeons. They can only be administered by a vet or a trained technician under veterinary supervision after a consultation. It is illegal for vets to sell hormonal growth promoters to farmers. They are for use in cattle only. Every implanted animal must be identified with a special ear tag, as well as two other identifying ear tags (MAF do not seem to realise that cattle only have two ears). Auditable records on special forms must be kept in triplicate of all cattle implanted and of supplies of drugs kept. One copy of these forms has to be sent to MAF within 10 days after implantation. Records must be retained for at least five years. There are huge fines for failure to comply with these regulations. Before implanting any cattle, check

the latest regulations at http://www.maf.govt.nz/animalproducts

MAF routinely audit the compliance of veterinarians and their clients with the above conditions of use of HGPS. Identified "flagrant" non-compliances, abuses, or missuses will result in consideration of either a formal complaint being laid before the veterinary council or prosecution as appropriate. Veterinary delegations from the EU also make random checks on HGP product licensees, wholesalers and retailers, as well as random on-farm inspections of treated cattle to see that those using HGPs have indeed complied with the requirements for the use of HGPs in cattle.

Animal welfare

Problems can arise from:

The method of administration (implants). When done properly, implanting HGPs under the skin of the ear of cattle restrained in a head bail does not appear to cause much distress to the animal. After release, animals do not shake their head and often start grazing straight away. It is important to use the correct technique and to work quietly and quickly.

The purpose of use. Growth promoters are no substitute for inadequate feeding.

The occurrence of side effects. Behaviour problems such as excessive bulling and fighting, which are occasionally seen after implantation, must be managed properly. They may be associated with increased absorption from a damaged implant - remove the implant. Cases of rectal and vaginal prolapse or distressed ridden animals must receive veterinary attention.

Human safety

Residues in the meat. Anabolic steroid implants are designed to release very small amounts of drug slowly. For instance, "Compudose 200" contains 24mg oestradiol designed to be released over 100 - 200 days; a cow in late pregnancy produces several hundred mg oestradiol per day! The concentrations reached in meat are much lower than those of endogenous hormones. This, combined with the depot of drug being in an inedible part of the animal, mean that there is no witholding time for these drugs. There were initial concerns about persistence of the synthetic compounds zeranol and trenbolone, but these have been shown to be groundless. This assumes that the drugs have been used correctly; implantation into muscle could result in serious residues (common practice in the European black market - no detectable pellet in ear). The risk to people eating meat is further reduced as most steroids are rapidly broken down in the stomach or on first pass through the liver.

Carcinogenic potential. Oestrogen can both start and maintain tumours. However, most women in developed countries eat oestrogen containing contraceptive tablets every day without obvious problems. The EU has argued that oestrogen has not been shown to be safe in prepubertal girls, but it has not been shown to cause problems either. Many plants contain phytoestrogens, to which we are all exposed anyway. Sex hormones in laboratory animals can turn on a number of oncogenic viruses which can go on to cause various cancers. It is theoretically possible that anabolic steroids could turn on such viruses in farm animals and that these viruses could be transmitted to people. Another potential food scare? Alterations in sex hormone concentrations in people have been statistically correlated with altered incidence of a variety of tumours - in most cases the alteration in incidence after therapeutic (large) doses is small. Prostate cancer in men has been associated with increases in IGF 1.

Contamination of pasture and soil over the long-term. Administration of exogenous substances to animals may result in their passage into the environment via faeces and urine. In theory, this could lead to accumulation of these substances or their metabolites in plants or drinking water subsequently consumed by humans. Oestrogens are excreted by the animal in faeces and urine, but are degraded by soil bacteria into biologically inactive compounds and are then lost into the ground. Contamination from implants is infinitesimally smaller than from industrial pollution with oestrogenic compounds such as polychlorinated biphenols; or endogenous phytoestrogens common in clovers and beans. Most of our rivers receive sewage high in oestrogens from the urine of women on the pill.

Human abuse. There is a black market for anabolic steroids for use in human athletes. Only androgens work in people, it is usually the drugs marketed for horses such as nandrolone, stanozolol and ethylestrenol which are abused. Keep them somewhere secure.

The future?

Very heavily muscled cattle, such as Belgian Blues, have a defect in the gene responsible for making the protein myostatin. It appears that myostatin normally regulates (stops) muscle growth; if an antagonist for myostatin could be found it would be a potential winner as a growth promoter. Anabolic steroids tend to increase the size of muscle fibres, which usually makes the meat tougher, Belgian Blues have bigger muscles because they have a bigger number of muscle fibres, so the meat is more tender. Work on this is going on at Ruakura, ERMA permitting.

Further reading

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Growth promoters may be starting to get a better press...

BMJ 2001;322:203 (27 January)

Science commentary

Insulin-like growth factor and cognitive function

Insulin-like growth factors (IGFs) are peptides that regulate the growth, metabolism, survival, and differentiation of cells and are regulated by growth hormone. Both IGF-I and IGF-II consist of small peptides that share about 50% homology with proinsulin and are produced chiefly by the liver. IGF-I is an important cell growth regulator, but the role of IGF-II is less clear. IGF-II acts mainly via IGF-I receptors; IGF-II receptors do exist, but their role is believed simply to mop up IGF-II, rather than act as signalling receptors.

In contrast with other peptide growth factors, there is considerable evidence indicating that the IGFs play a critical role in determining overall (somatic) body growth in addition to contributing to local tissue regulation. A great deal of associative data show that IGF and IGF receptors, and growth hormone and growth hormone receptors, are located in the parts of the brain that are responsible for learning and memory (such as the hippocampus). It is feasible that early in life, IGFs and growth hormone play a role in the development of these areas of the brain, which could then explain associations between body size and subsequent measures of cognitive functions.

There has also been much speculation that relative IGF-I or growth hormone deficiency could contribute to the deterioration of cognitive functions observed in elderly people. Several studies in the United States have shown that giving growth hormone to elderly people reduces their body fat and increases lean body mass, but these same studies have produced equivocal data about memory function, and the methodology of the studies has been much criticised. Other studies have shown that giving growth hormone to adults with growth hormone deficiency does improve memory and is also associated with greater levels of circulating IGF-I, but controversy remains about what happens to cognitive function when growth hormone is given to children with growth hormone deficiency.(1)

On the basis on these observations, it has been suggested that circulating levels of IGF are related to cognitive function and that the administration of growth hormone may promote better cognitive function. But although IGFs may play a role in brain development early in life, it is much more difficult to come up with a mechanism that could explain how circulating IGF-I and cognitive function are connected in later life.

Abi Berger, science editor.

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Sex hormones

Human health risks

Most drugs with reproductive effects have the same actions in people. For example, prostaglandins will lyse corpora lutea, cause uterine contractions and therefore have the potential to cause abortion in pregnant women. Progestagens can cause cessation of cyclicity in women.

Some drugs have potentially life threatening effects in people. A prime example is prostaglandin $F_{2\alpha}$ and analogues. Prostaglandins have a more severe effect on the respiratory tract in people than in many animals, causing bronchoconstriction and respiratory distress. People with respiratory disease (including asthma) need to be particularly careful. These drugs can be absorbed across intact skin in large enough quantities to cause major problems.

You need to know the physiology of reproduction in order to make sense of what these drugs do.

Sex steroids

Ostrogens

Oestradiol 17-β is the natural hormone; oestradiol esters such as the cypionate or benzoate are often injected. Oestradiol is rapidly metabolised when given by mouth, so **ethinyloestradiol** is used orally. Stilboestrol (diethylstilboestrol, DES) is no longer available in NZ.

Natural sources are ovarian follicle and corpus luteum, testes, placenta, adrenal gland.

Therapeutic uses

behavioural receptivity
embryotoxic effects
anabolic effects (ruminants)
feedback effects on gonadotropin release
increased resistance of the female genital tract to infection
mammary gland development
abortion
maintenance of normal urethral muscle tone in small animals
epidermal effects - sex hormone responsive dermatoses in small animals

Adverse effects

feminization
behavioural receptivity
mammary gland development
abortion
negative feedback effects on gonadotropins (ovarian cysts, cessation of cyclicity)
increased uterine gland activity (CEH)
bone marrow suppression and aplastic anaemia
carcinogenic and teratogenic

Antioestorgens such as **tamoxifen** and oestrogen production inhibitors such as **letrozole** and **anastrozole** are sometimes used in women but are expensive.

Progestagens

Progesterone is the natural hormone; there are numerous synthetic progestagens: **altrenogest** (**allyltrenbolone**), **megestrol**, **proligestone**, **medroxyprogesterone**, **hydroxyprogesterone**, **flugestone** and **norgestomet**

Natural sources are the ovary and corpus luteum, placenta in some species, adrenal gland.

Therapeutic uses

feedback effects on gonadotropins (largely negative)
inhibits expression of oestrus behaviour
pregnancy maintenance
mammary gland development (together with oestrogens)
CNS calming effect
Thermogenic (body temp drop used as a predictor of impending parturition)

Adverse effects

increased risk of CEH and pyometra in bitch and queen, especially when coupled with increased oestrogens.
increased appetite and weight gain
decreased activity
personality changes
mammary gland enlargement, milk production and neoplasia
increased growth hormone secretion - acromegaly, protein synthesis and growth; insulin resistance, increased blood glucose levels, pancreatic exhaustion and eventually diabetes mellitus.
adrenocortical suppression: mainly seen in cats on progestagens with adrenal atrophy and Addison's syndrome which may occur within 1-2 weeks of beginning therapy in cats.

Androgens

Testosterone is the natural hormone. It is used in as various esters. Other androgens (usually described as anabolic steroids) include: boldenone, stanozolol, nandrolone, methandriol, ethylestrenol, etc

Natural sources are: gonads - testes primarily, ovaries (mainly as a precursor to oestrogens), placenta and adrenal gland.

Therapeutic uses

male sexual behaviour

negative feedback on gonadotropins

anabolic effects - appetite stimulant, RBC production, nitrogen retention etc

epidermal effects - sex hormone responsive dermatoses in small animals

urinary bladder urethral muscle maintenance in male castrates

Adverse effects

Masculinization and aggressive behaviour

negative feedback on gonadotopins (cessation of cyclicity and of spermatogenesis)

chronic use of high doses and different drugsin people has been associated with severe effects on general health including cardiovacular disease, mental disorders, neolpasia etc.

Delmadinone is a progestogen which is used as an antiandrogen.

Gonadotrophins

Follicle Stimulating Hormone

Natural source is the anterior pituitary gland.

Currently made by extracting hormone from anterior pituitary glands mostly from sheep or pigs (oFSH = ovine, pFSH = porcine). All products are contaminated to some extent with other hormones such as LH. Newer techniques have resulted in greater purity. LH contamination is generally considered to be undesirable since it makes the response of the ovary more unpredictable. Synthetic FSH products are being developed. Biological half life is about 6 hours and therefore twice daily injections required to achieve results.

Therapeutic uses

stimulation of follicle growth and development for oestrus induction and superovulation.

Adverse effects

excessive stimulation of follicle production resulting in ovarian cysts, endometrial hyperplasia, hyper-oestrogenism.

Luteinizing hormone

Natural source is the anterior pituitary gland. LH products are also made from pituitary extracts and are generally available only for research purposes. Other products are used commercially for their LH like actions (hCG and GnRH).

Therapeutic uses

Induction of ovulation

Equine Chorionic Gonadotropin (eCG)

Formerly known as Pregnant Mare Serum Gonadotropin (PMSG) and still marketed under this name in some regions. The natural source is endometrial cups in pregnant mares between days 40-120 of pregnancy. Produced commercially by extracting eCG from serum of pregnant mares or ponies.

Therapeutic uses

In the mare, eCG has a primarily LH like action. It binds to LH receptors and results in resurgence of the primary CL of pregnancy and formation of secondary CLs. It has no application in equine reproduction because such massive doses appear to be required to have any effect at all in mares. In other species, eCH binds to both LH and FSH receptors and has a long half life and therefore has become useful in stimulating the development of follicles and ovulation. It is widely used in domestic species other than the mare (sheep, cow, pig) to stimulate development of multiple follicles (superovulation) and to induce oestrus and ovulation in non-cycling animals (pigs).

Long half life (72 hours) and therefore used as a single injection.

Adverse effects

eCG has a long duration of action and therefore even a single dose can result in excessive stimulation of ovarian follicular development, resulting in cystic follicles, poor superovulatory response, hyperoestrogenism. Recently researchers have developed an anti-eCG antibody and have administered it 2 days after eCG to stop the adverse effects associated with its prolonged activity. This appears to make the product more effective as a superovulatory drug for domestic species.

Human Chorionic Gonadotropin (hCG)

Comes from human early blastocyst and placenta - appears in early pregnancy. Commercial product made from the urine of pregnant women.

Actions

LH like effect primarily and involved in women in CL support and pregnancy maintenance. In other species it is used for its LH effect primarily, for example ovulation induction, challenge testing, treatment of cryptorchidism.

hCG is a relatively large molecule and is capable of inducing an antigenic response in animals since it represents

foreign protein.

Gonadotropin Releasing Hormone (GnRH)

Comes from the hypothalamus. GnRH is a very small molecule (decapeptide) which is easily synthesized and numerous synthetic formulations are available. There is no risk of antibody stimulation and therefore very safe to use. It appears to be replacing hCG in most applications for these reasons.

Actions

Stimulation of LH and FSH release and therefore stimulation of ovarian and testicular activity.

induction of cyclicity and ovulation (cystic ovaries in cows, ovulation in all species)

increased spermatogenesis ?

increased libido?

challenge or diagnostic testing.

Injectable products have been available for years. Recently a biodegradable implant was released for use in horses to cause ovulation.

Prostaglandins

Prostaglandin$F_{2\alpha}$ (**dinoprost** - not to be confused with dinoprostone = PGE_2) is produced by all tissues. Numerous synthetic analogues, such as **cloprostenol**, **luprostiol** (= prostianol) and **etiproston** are used as well as the natural compound.

Therapeutic uses

corpus luteum regression - oestrus synchronization, abortion, induced parturition

smooth muscle contraction - uterus

cervical relaxation

Adverse effects

corpus luteum regression as above (abortion)

Smooth muscle contraction - vasoconstriction, bronchoconstriction, salivation, sweating, vomiting, diarrhoea, abdominal pain, micturition, pruritis, erythema, ataxia, increased vocalization, tail movement, tachycardia, fever, anxiety, pupillary dilation or constriction.

Signs in horses are mainly sweating and abdominal pain.

Side effects in animals generally appear within minutes of administration of drug and last for 15-30 minutes. Animals become accustomed to the drugs with repeated usage and side effects tend to diminish in intensity and range.

People: **women of child bearing age, pregnant women, people with asthma or other respiratory complaints must use extreme caution when handling $PGF_{2\alpha}$.** Prostaglandin analogues are readily absorbed through the skin (wear gloves) or as a vapour via the respiratory tract (be careful not to spray it around).

Case examples

Progesterone assays for timing of breeding in the bitch

Average bitch has pro-oestrus lasting 7-9 days and oestrus lasting 7-9 days and ovulates on about the 3rd or 4th day of standing oestrus. A traditional recommendation from breeders is to breed an oestral bitch on the 13th day after the beginning of pro-oestrus.

However, there is tremendous variation in both the length of pro-oestrus and oestrus and the timing of ovulation in bitches of normal fertility. Behaviour and vaginal cytology are not very accurate at determining when a bitch will ovulate. The bitch appears to be unique amongst domestic animals in that peripheral blood progesterone concentration rises prior to ovulation. It can therefore be measured and used as a predictor of impending ovulation. In all other species of domestic animals, progesterone does not rise until after ovulation.

In addition, the bitch ovulates a primary oocyte which takes about 2 days after ovulation to mature and become ready for fertilization (different to other species as well).

Event	*Progesterone conc*
pro-oestrus & early oestrus	very low (<3nmol/l)
time of LH surge	6-9nM (2-3 ng/ml)
day of ovulation	12-25nM (4-8ng/ml)
optimal time of breeding	28-80nM (9-25ng/ml)

The optimal time to breed a normal bitch is about 2 days after ovulation.

A suggested protocol is take a blood sample at about the 3rd to 4th day of pro-oestrus and measure progesterone concentration. If very low, take a second sample 2-4 days later. Continue sampling until an increase is seen. Then:

If you have identified a change from <3 to 6-9 nmol/l, consider breeding the bitch 1-2 days later and again 1-2 days after the first breeding. Consider measuring progesterone at the time of the second breeding to document the rise, confirm ovulation and determine whether further testing is necessary.

May wish to continue taking daily samples until you reach about 25 nmol/l and then breed the bitch. This approach is more commonly followed if using frozen semen.

Diagnosis of ovarian remnant syndrome in the bitch

ORS describes the bitch who has a history of being speyed and who now is showing signs consistent with oestrus. Signs include vulval swelling, serosanguineous vulval discharge, attraction to males, mammary gland development. Signs are suggestive of oestrogenism.

Primary differentials for oestrogenism are oestrogen secreting neoplasia, adrenal gland activity and a remaining remnant of ovarian tissue. Other differentials should be included for vulval discharge: urinary tract disease, vaginitis, uterine stump infection etc).

Diagnostic workup: complete physical, vaginal cytology, urinalysis, vaginoscopy, abdominal ultrasound/radiography.

Challenge testing: take a pretreatment blood sample for oestradiol and progesterone concentration. Admininster hCG (100-500 iu by im or iv injection) or GnRH (25-100 ug). 2-3 weeks later, repeat physical examination and blood testing. Look for changes consistent with ovulation and formation of luteal tissue. If changes are consistent with the presence of ovarian tissue, schedule surgery. If not continue diagnostics eg adrenal gland suppression testing.

Diagnosis of cryptorchidism in horses

Animals with a history of castration but which are now showing signs of male behaviour. A cryptorchid testicle can be retained within the abdomen or just outside the abdomen in the inguinal region. A detailed physical examination including palpation/ultrasound of the inguinal and scrotal regions and transrectal palpation/ultrasound should be performed.

Challenge testing should be considered for equivocal cases. Take a baseline blood sample and then administer hCG (2500 to 5000 iu iv). Take follow up blood samples. There is considerable debate about the best time to take follow up samples. Some labs suggest a second sample 2 hours after the injection. I prefer to wait longer and take follow up samples at 6-12 hours and occasionally at 24 hours. Look for a 2-fold increase in testosterone concentration. If this does occur it is highly likely there is testicular tissue present.

it is also possible to measure oestrone sulphate concentration in blood. In animals older than 3 years of age, oestrone sulphate concentration in a single sample (no challenge) is often sufficient to diagnose a cryptorchid (levels are low in geldings and very high in cryptorchids and stallions).

Challenge testing for cryptorchidism may also be performed in dogs and other species.

Medical treatment for pyometra in the bitch

Case selection: younger than 6 years of age, with a primary breeding function.

Stabilise systemic signs of illness associated with the disease eg fluid therapy

Once stable begin prostaglandin $F_{2\alpha}$ treatment: older recommendations used high doses: 250µg/kg sc twice daily, more recently, lower doses are suggested, down to as low as 20µg/kg sc three times daily

It is best to begin at a reasonably low dose(100-150µg/kg sc twice daily) and work up to a dose of 250µg/kg sc twice daily.

Beware: side effects do occur, success rate is not 100%, pyometra tends to recur and treatment is expensive.

Duration of treatment is variable and depends on response. Older recommendations suggested 5-8 days of prostaglandin therapy. Newer approaches suggest that the bitch be monitored by ultrasound and treatment continued until at least 1 day after the uterus is observed to be free of luminal fluid on ultrasound (can take 10-14 days).

Breed on the next heat period. Consider treating the bitch with systemic antibiotic during oestrus and spey the animal as soon as her breeding function is finished (as soon as the desired number of pups are achieved).

Misalliance in the bitch

There are two drug choices: antiprogesterones and oestrogens. Aglepristone (antiprogesterone) has taken over from oestrogens as it is safer and more effective. In early pregnancy, it prevents changes in the uterus required for implantationof the egg, while in later pregnancy it antagonises the effects of progesterone necessary for maintenance of pregnancy. This causes expulsion of the foeti.

Oestradiol benzoate injection is registered for mismating. However, oestrogens have potentially serious side effects in the bitch:

i) bone marrow suppression: life threatening aplastic anaemia. Very difficult to treat successfully. Fortunately this is a rare side effect unless large doses or very long acting analogues are used.

ii) cystic endometrial hyperplasia (CEH): CEH appears to be a common side effect of oestrogen therapy and is often followed by pyometra. Oestrogens potentiate the effect of progesterone on the uterus and together the two hormones increase the risk of CEH. The presence of CEH, progesterone dominance (luteal phase of the cycle) and contaminating bacteria is highly likely to result in pyometra.

The risk of pyometra appears to be highest when oestrogens are administered to a bitch in early dioestrus (high progesterone).

No dose of oestrogen has been shown to be both effective and safe.

Suggested protocol when presented with a bitch with a history of misalliance:

Physical examination: is the bitch in oestrus?

Vaginal cytology: is she in oestrus, can you see sperm?

Options:

1) do nothing and let the bitch whelp if she is in fact pregnant

2) ovariohysterectomy

3) do nothing initially and pregnancy test the animal at about 25-30 days and consider aborting the bitch using $PGF_{2\alpha}$ injections ± dopamine agonists at this stage (preferred option). Mifepristone would be better but is not available in NZ.

4) aglepristone

5) oestrogen as a last resort. Counsel the owner that treatment will make the bitch receptive to males for a further period of time (7-10 days), it is not 100% successful and may have serious side effects.

Treatment regimes

Aglepristone

10mg/kg sc as two injections 24 hours apart up to day 45 of pregnancy. Massage injection site to prevent pain and inflammation.

Oestrogen

0.3 mg/kg up to maximum of 10 mg, as a single im or sc injection, given 1-4 days after mating. Should only be administered if the bitch is still in oestrus as determined by vaginal cytology.

10µg/kg on days 3, 5 and 7 after mating. Does use a lower dose and is reported to be less likely to prolong behavioural receptivity or lead to bone marrow suppression but is more likely to result in elevated oestrogen concentrations in early dioestrus.

Inhibition and prevention of signs of oestrus in the bitch

In NZ, progestagens are the primary drug used for controlling the oestrous cycle of the bitch. An alternative drug which appears to be safer (mibolerone - an androgen) is available overseas.

suppression: means treatment initiated in early pro-oestrus to inhibit signs of behavioural receptivity. Generally requires higher levels of progestagen and is also associated with higher risk of side effects since it means using higher levels of progestagen on top of elevated levels of oestrogen.

postponement: means beginning treatment in late anoestrus to postpone the next pro-oestrus. This is considered to be safer, since it avoids any association with elevated oestrogen and usually allows the use of lower doses of progestagen.

General cautions for progestagens in bitches:

Use with caution in animals with a primary breeding future

Read the manufacturer's recommendations, particularly contra-indications

Advise the owner of possible side effects.

Abide by the manufacturer's recommendations for treatment protocols.

In decreasing order of safety, the progestagens available in NZ for oestrous control are: proligestone, megestrol, medroxyprogesterone (MPA)

Medroxyprogesterone acetate was withdrawn from the small animal market for oestrous control in the USA by a voluntary deal from the manufacturer in 1966 due to the high incidence of uterine abnormalities in treated bitches. In an Australian study (AVJ 70:249-250, 1993) 45% of treated bitches were found to have uterine lesions at subsequent spay compared to 0.05% of control bitches. As a result it is suggested that you avoid using MPA for oestrous control in bitches where ever possible since safer alternatives are available.

Greyhounds are a special case. Progestagens are associated with side effects which are undesirable for performance animals: weight gain, lethargy, reduced athletic ability. Most greyhound owners and trainers prefer to have racing bitches on some form of oestrus suppression but they usually use anabolic steroids .

Oestrus synchronizationin heifers using progestagens

Usually combined with other drugs such as oestrogens, PGF2alpha and PMSG (eCG).

There are currently two main products available in NZ for delivering progestagens to cattle. One is the CIDR-B (vaginal implant impregnated with progesterone) and the other is an ear implant impregnated with a synthetic analogue (Crestar implants which contain norgestomet).

There are many different treatment programmes with the variations mostly in how long the devices are left in place (ie, duration of progestagen therapy) and when to administer other drugs. Continued advances are being made each year in the design of these programmes. Therefore it is best to contact prodct manufacturers for the latest regime when you are in practice. Recommendations will vary depending on the type of cattle you are treating eg heifers versus cows, beef cattle versus dairy.

i) Early recommendations were to treat with progestagen only for a length of time equal to the normal CL lifespan (15-17 days). This ensured adequate time for any endogenous CLs to have regressed during treatment. Synchronization of oestrus was quite good but fertility was poor and it was subsequently found that longer durations of progestagen therapy reduced fertility.

ii) Next step was to shorten the duration of progestagen treatment and add $PGF_{2\alpha}$ treatments to lyse any CLs which were present. Regimes came down to about 7-10 days of progestagen with PGF added close to the end of the progestagen treatment. Oestrogens were also administered at the beginning of treatment and helped to lyse CLs as well as having a synergistic effect with progesterone inhibiting gonadotropin release and follicle development during treatment, which helps to produce better synchrony when treatment ends.

iii) The latest development has been the addition of a low dose of oestradiol given 1-2 days after cessation of progestagen treatment. This helps to stimulate overt displays of oestrus behaviour for oestrus detection and also helps to trigger the LH surge to induce ovulation.

Examples of two standard programmes for heifers:

Ensure all animals are in fact cycling prior to treatment.

1. Insert ear implant norgestromet (Crestar)

Inject with oestrogen at the time of insertion

Inject with $PGF_{2\alpha}$ on day 7-8

Remove ear implant on day 9-10

Inject with PMSG at time of implant removal .

Breed heifers based on oestrus detection or by timed breeding (48 hours after implant removal).

2. Insert CIDR-B and CIDIROL capsule (capsule contains oestrogen and fits into a slot in the CIDR-B) into the vagina.

Remove CIDR-B on day 7.

Inject with $PGF_{2\alpha}$ at time of CIDR removal.

Inject with oestradiol benzoate (1 mg) 24-48 hours after implant removal.

Breed based on oestrus detection.

Oestrus synchronization in heifers using prostaglandin $F_{2\alpha}$

The bovine corpus luteum is not susceptible to exogenous PGF until five days or more after ovulation. You should ensure all animals are cycling prior to beginning the programme. Generally do this by tail painting animals and watching for activity.

Again there are several different programmes:

1. Treat all animals with a single injection of PGF. Inseminate based on oestrus detection. Animals which respond will come into oestrus about 2-3 days later.

2. Palpate heifers and only administer PGF to those heifers which have a palpable CL on rectal palpation. Inseminate based on oestrus detection.

3. For the first 6 days of the programme, perform daily oestrus detection and breed animals based on oestrus detection. Then on day 6, inject all animals which have not been bred with PGF and continue oestrus detection and breeding.

4. Administer 2 injections of PGF separated by 11 days. At the time of the second injection, almost all animals should be responsive to PGF. May inseminate on oestrus detection or by timed insemination (heifers bred about 60-70 hours after second injection).

Reproductive Toxicities

Cypress trees- isocupressic acid (ICA)

Sources

Cypress *Cupressus* spp - Macrocarpa (*Cupressus macrocarpa*) and other related trees

Pine *Pinus radiata* (and other related trees such as *Pinus ponderosa*) – anecdotal reports of abortions after ingesting radiata pine needles. The amount of ICA in radiata is so variable that it is conceivable that some trees may contain enough to cause abortions.

Toxic principle

Isocupressic acid was identified in Ponderosa pine in 1994. Macrocarpa was shown to contain ICA in 1995.

Cupressus species and Pinus ponderosa contain quite variable quantities of isocupressic acid and abietane diterpene acids.

The mechanism of action is unknown.

Clinical Signs

Malaise and **abortion** in cattle during last trimester. Retained foetal membranes.

Severe depression/illness may lead to death.

Treatment

No specific treatment, use of antihistamines reported to be beneficial if given early.

Cases

A farmer has a herd of pregnant dairy heifers. While on a call to the farm you recognise a stand of macrocarpa next to the pasture where the heifers are grazing. What are the potential problem(s) of this situation?

Practice exam questions

Multiple choice questions

1. Parturition may be induced in dairy cows using
   - clenbuterol ❑
   - dexamethasone ❑
   - flunixin ❑
   - zearalenone ❑
   - calcium borogluconate ❑

2. Prostaglandins in cattle are not involved in
   - inflammation ❑
   - the febrile response ❑
   - parturition ❑
   - rumination ❑
   - bronchodilatation ❑

3. Non-steroidal anti-inflammatory drugs
   - inhibit cyclo-oxygenase 1 & 2 ❑
   - block the release of substance P from nociceptors ❑
   - prevent vasodilatation caused by CGRP ❑
   - increase the pain caused by bradykinin ❑
   - block phosphokinase C in dorsal horn neurones ❑

4. Paracetamol
   - kills dogs ❑
   - causes gastric ulceration ❑
   - causes liver necrosis in overdose ❑
   - overdose may be treated with methylene blue ❑
   - is safe in cats ❑

5. Hydrocortisone
   - is synthesised in the adrenal medulla ❑
   - is effective when swallowed ❑
   - has purely mineralocorticoid activity ❑
   - can be antagonised by spironalactone ❑
   - very rarely causes side effects when used for a long time ❑

6. Corticosteroids with mainly glucocorticoid activity
   - include fludrocortisone ❑
   - are free of actions in the CNS ❑
   - have anti-inflammatory actions ❑
   - do not suppress hypothalamic - pituitary - adrenal function ❑
   - include aldosterone ❑

7. Levothyroxine
   - is synthesised in the anterior pituitary ❑
   - is effective when swallowed ❑
   - can act as a growth promoter ❑
   - synthesis is reduced by glipizide ❑

reduces oxygen consumption in most tissues ❑

8. Prolactin
- is secreted from the anterior pituitary ❑
- secretion is inhibited by dopamine receptor antagonists ❑
- secretion is increased by bromocriptine ❑
- inhibits the release of growth hormone ❑
- is used to treat infertility ❑

9. Insulin
- is synthesised in the α cells of the islets of Langerhans ❑
- is effective orally when combined with zinc ❑
- can be antagonised by potassium ❑
- has actions opposite to glucagon ❑
- is potentiated by non selective β adrenoceptor blockers ❑

10. Hyperthyroidism in the cat
- causes alopecia ❑
- results in an increase in body weight ❑
- can be treated with tritium ❑
- is characterised by a decrease in thyrotrophin ❑
- can result in congestive heart failure ❑