3 Pharmacokinetics

Definitions

pharmacodynamics = what the drug does to the animal

pharmacokinetics = what the animal does to the drug or, the movement of drugs in the body. Sometimes called "toxikinetics" when the drug in question is a poison.

There are usually four components to pharmacokinetics

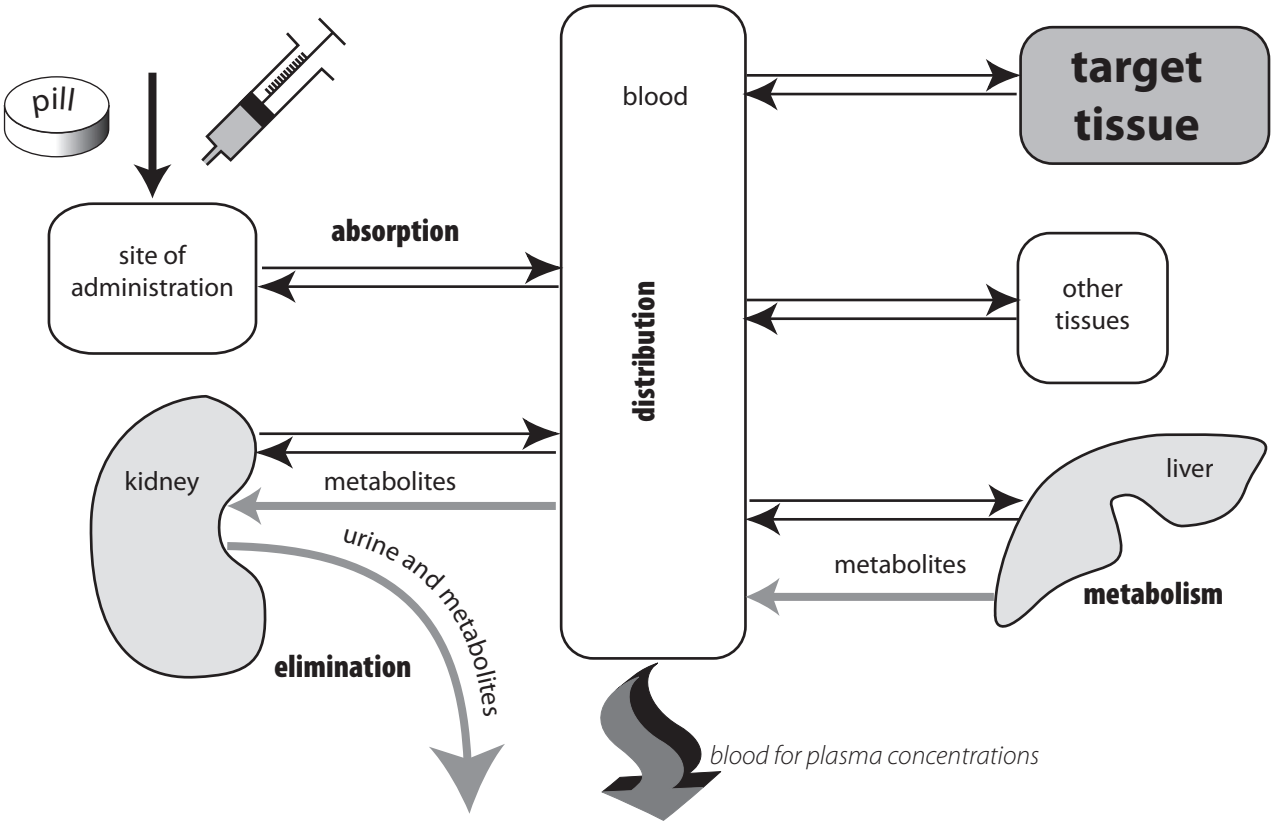
absorption from site of administration

distribution around the body including to the target tissue

metabolism to something which can be excreted more easily (although some drugs are excreted unchanged)

elimination from the body, usually via the kidneys and urine

These processes differ between animals of different species, age, sex, health status and size, and within an individual from time to time.



Movement of drugs in the body. Drug concentrations are usually measured in plasma (because it is easier) rather than the target tissue, which would be more useful. The liver is not the only organ which metabolises drugs, but it is probably most important for most drugs.

Understanding pharmacokinetics is important because unless the drug reaches a sufficient concentration at the target cells it will not work. If the concentration at other sites is high enough, you will get side effects. The effect is usually proportional to plasma concentration rather than dose (absorption can be very variable).

It is useful to think of the body as a number of compartments with barriers between them that the drug has to cross to get from the site of administration to the target tissue and then out of the body.

Consider a cat that has been bitten on the tail by another cat. These puncture wounds are usually infected with *Pasteurella* spp. and an abscess will form rapidly unless the bacteria are killed with an antibiotic (usually penicillin). To kill the bacteria, there must be a sufficient concentration of penicillin in the fluid bathing them for a sufficient length of time. It is not usually possible to apply the penicillin directly to the bacteria; the cat is usually given a tablet or injection which means that the penicillin has to get from the cat's stomach or the injection site to the extracellular fluid around the bite in the tail and stay there for long enough to kill the bacteria. In the meantime, the cat's kidneys will be doing their best to get rid of the penicillin into the urine.

The penicillin thus has to be absorbed from the stomach or injection site, distributed to the tail (and other tissues) and eliminated by the kidneys (penicillin is not metabolised to any great extent). Penicillin is a very safe drug so the simplest way of ensuring that the bacteria are killed is to overdose the cat. With most drugs however, overdosing will cause serious problems with side effects: getting exactly the right concentration of drug in the target tissue requires a knowledge of pharmacokinetics. It is largely a matter of giving the right amount of drug by the right route for that particular animal, and requires skill and judgement since no two animals are exactly the same.

Further reading

Journal of Veterinary Pharmacology and Therapeutics, 2004, (6). A special issue with review papers on various aspects of pharmacokinetics.

Absorption

This is the process that involves the drug moving from its site of administration into the blood. A major factor here is the route of administration. Once the drug is administered, it must dissolve in the body fluids to be absorbed. This step is manipulated by altering the formulation of the drug.

Administration

Possible routes of administration:

- *oral* (**po** = *per os*)
- *intramuscular* (**im**)
- *subcutaneous* (**sc** (SQ in USA))
- *topical*
  - epithelial surfaces
    - mammary gland
    - nasal mucosa
    - cornea
  - intact skin (pour on, ointments)
- *inhalation*
- *intraperitoneal* (**ip**)

- *spinal*
  - epidural
  - intrathecal (**it**)
- *rectal*
- *intratracheal*
- (*sublingual* - not usually practical in animals)

Intravenous (**iv**) administration bypasses the absorption process but other routes give rise to variation.

Effects of route of administration on absorption

As a very rough rule, iv injection has a peak plasma concentration in seconds, im in 15 mins, sc / po in 30 mins - 1hour. This will depend on many factors. Peak effect will usually occur several minutes after peak plasma concentration, depending on the drug.

Since it is usually desirable for drugs to be present at their site of action for a specified period, it is either necessary to repeat the dose often or give a large dose in such a way that the absorption is slow and the drug is being continuously released into the plasma. This can be done by using different routes of administration, by altering the formulation of the drug or by using a device which releases the drug slowly.

Intravenous

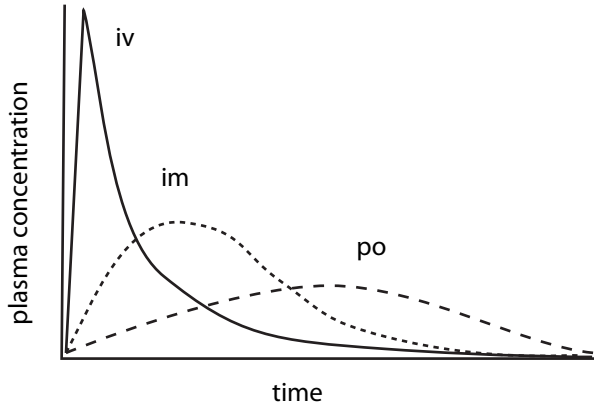
The "absorption" phase is the time it takes to inject the drug. Usually iv injections are made quickly so that the plasma concentration reaches an almost instantaneous peak and rapidly declines as the drug is distributed away to other tissues. However, intravenous injections can be made with an infusion pump so that the rate of "absorption" can be directly controlled. This is usually only necessary during anaesthesia or intensive care where potentially dangerous drugs are given to sick animals.

Intravenous injections are usually only used where the drug has to act rapidly (anaesthetics and sedatives), which have to be given in large volumes (fluids) or which are irritant (parenteral nutrition solutions).

Any superficial vein can be used: in dogs and cats the cephalic vein is usually used, although the lateral (dogs) or medial (cats) saphenous vein is also used. In large animals, the jugular vein is used. In pigs and rabbits, the marginal ear vein is used.

Oral

The surface area of gut available for absorption of the drug is the most important factor effecting the rate of absorption. Disease processes such as gastroenteritis, neoplastic infiltration or villus atrophy may significantly change the



Plasma concentration time curves after administration of the same dose of drug by different routes.

available absorptive surface area. This should be taken into account before the administration of an oral medication.

Dilution of the drug by administration with feed or with fluid would retard the rate of drug absorption since the drug diffuses down a concentration gradient. Some foods contain substances which bind to the drug, preventing absorption.

The concentration gradient is the main factor affecting the rate of drug absorption (rather than purely the drug concentration in the gut). Therefore, the drug concentration in the blood or extravascular fluid is also an important determinant of the rate of drug absorption. Factors which affect the drug concentration in the blood or extravascular fluid include the rate of distribution and the rate of elimination of the drug. More importantly, in the local environment of the absorptive process, the rate of blood flow and / or lymph flow determines to a large extent the steepness of the concentration gradient. Blood flow and lymph flow are dependent upon the timing of the drug administration with respect to meals, exercise and other variants of cardiac output.

Drug absorption can also be altered by alterations in the permeability of the gut wall. Diseases such as infiltrative neoplasia, inflammatory bowel disease and mucosal injuries by viruses, bacteria, parasites and caustic chemicals can all increase the rate of absorption of drugs. In addition increases in the permeability of the gut wall can result in the absorption of drugs not normally absorbed from the gut. Obviously, if the animal vomits its medication up, the drug will not be absorbed. Gastroenteritis usually results in a faster than normal passage of gut contents, the drug may not be there long enough to be fully absorbed. Therefore care needs to be taken in consideration of administration of all drugs to animals with gastrointestinal disease.

Intramuscular

Surface area can be altered by injecting a given dose in aliquots to multiple sites, thus increasing the rate of absorption.

The concentration of drug in the injection will also determine the steepness of the diffusion gradient for drug absorption. The concentration of the drug in the injection might be altered after injection due to a formulation which is not isosmolar. Drug concentration in the tissue fluid will also effect the diffusion gradient. Both the rates of lymph and blood flow vary from muscle to muscle and also vary dependent upon on exercise, cardiac output and catacholamine release.

The pH in the muscle may vary from one muscle to another as a function of exercise and tissue perfusion. Therefore difference in the rate of absorption of an intramuscular injection will vary dependent upon the formulation used and the injection site. The cranial third of the neck is the preferred site in food animals (both for better absorption and reduced residues in edible meat), the quadriceps or deltoid muscles in small animals (although im injections are not often used in small animals because they are painful).

There are only a few examples where the permeability of blood vessels in the area of an injection might significantly alter the expected rate of drug absorption. In particular, it is important to ensure that an injection is not made into an inflamed area where blood vessel permeability might be expected to have changed. The proximity of the injection to impermeable boundaries such as fascial planes and fat is an important determinant of the rate of drug absorption after intramuscular administration and is to some extent controllable by appropriate choice of injection site.

If an "intramuscular" injection actually goes into fat (easy with pigs) or between fascial planes (easy with cats), absorption will be variable but probably much slower than expected. If it goes into a vein, absorption will be much faster than expected, resulting in a relative overdose of organs with a high blood flow, and probably side effects.

Subcutaneous

The rate of absorption is likely to be similar / slower than an intramuscular injection but much more variable because of differences in the rates of blood and lymph flow to the skin due to species, gender, age, environmental temperature and body temperature. Care needs to be taken that the drug is not given into fat but is truly subcutaneous, since fat is poorly perfused. The usual site is over the ribs, or in the scruff in small animals.

Intramammary

In cows with mastitis, the usual route of drug administration is intramammary. The drugs either directly affect bacteria in the milk or cross into macrophages and mucosal cells where the bacteria are hiding. Significant systemic absorption can occur; with dry cow therapy, nearly all the drug is absorbed systemically and eliminated. Great care is needed to ensure that dirt on the end of the teat is not injected as well as the drug.

Other Routes of Administration

Transdermal patches containing drugs can be applied to hairless skin. The drug is absorbed either by simple diffusion (which is slow), by solvent carrier assisted diffusion (which can be faster) or by voltage assisted diffusion. Transdermal patches containing fenatanyl have potential for the administration of analgesia to animals both for chronic pain and for acute pain post-operatively. They are often used in people and have been used clinically in dogs, horses and pigs. There are species differences in absorption, but they usually take 24 hours to reach analgesic concentrations in the brain,

which limits their usefulness.

Other topically administered drugs may be absorbed transdermally also. Sometimes this absorption is by design and sometimes an accident, resulting usually from a breakdown of the cutaneous barrier. Breakdowns of the cutaneous barrier occur with disease processes such as inflammation and where wounds exist. Drugs used in this way include nitroglycerine (see cardiovascular notes) and many anthelmintics for large animals. Care is necessary as in some circumstances the skin can act as a reservoir of drug. It is worth bearing in mind that any drug designed to cross an animal's skin will also cross human skin.

Drugs applied topically to the eye or subconjunctivally in the treatment of ocular disease are frequently absorbed systemically. There have been cases of iatrogenic Cushing's syndrome being caused by steroid administration in topical preparations to the eye of the dog.

The administration of drugs by rectal suppository is not often used in veterinary medicine. Very little work has been done studying the pharmacokinetics of rectal suppositories in domestic animals. However, this route of administration may be appropriate for administering drugs to animals with upper gastrointestinal disease or with protracted vomiting.

In large animal practice drugs are sometimes administered in pessary form into the lumen of the uterus. Many drugs administered in this fashion are absorbed systemically - may be important with respect to drug withholding times for slaughter.

Some soluble drugs can be applied by nebulisation and inhalation of the resulting aerosol. These drugs are used mainly for local treatment of respiratory tract disease. Doses need to be calculated carefully because systemic absorption does occur through the mucosa. Drug classes which can be applied in this fashion include mucolytics, antibiotics and β adrenergic agonists. In emergencies, adrenaline is sometimes given intra-tracheally and is absored rapidly across the mucosa.

Volatile anaesthetics are administered by inhalation and absorbed very rapidly across the alveolar membranes (see anaesthesia notes).

Drugs applied to the nasal mucosa can be rapidly absorbed. This route is undergoing investigation in people for the administration of peptides, which would be broken down in the gut if given orally. Many new drugs are peptides, so this route may become more important in future.

The intraperitoneal (ip) route used to be used commonly. Now it is only used in laboratory animals with no or very small veins. Everything else should have drugs given iv.

Dissolution

The solubility of the drug is important in determining the rate of drug absorption. Solubility is a function of the molecular structure of the drug and the fluid surrounding it. Solubility can be altered by forming salts of the drug; eg, morphine chloride is more soluble than morphine sulphate and both are much more soluble than morphine base. For weak acids or weak bases the solubility of the drug varies with the drug's pKa and the environmental pH of the medium in which the drug is dissolved. This pH varies from site to site along the gastrointestinal tract and in similar sites between species (the rumen has a pH of about 8.5; the monogastric's stomach about 1.5). Exercise and inflammation can alter pH at injection sites.

The solubility of drugs might vary from one proprietary preparation to another since the formulations may have different excipients or a different pH. Many drugs are prepared as relatively insoluble salts to ensure a slow absorption and a prolonged effect. Some are suspensions of finely divided particles; these give a sustained release but will block arterioles if injected iv (eg lente insulin).

Formulation of the drug is very important for oral preparations. Some tablets are coated to protect them from acid in the stomach; they then dissolve in the intestine where the pH is completely different. The particle size will affect the rate of dissolution (bigger is slower), the excipient (often lactose) will affect how quickly the tablet breaks up. An extreme example is trace element supplements for ruminants, where the excipient is sometimes glass!

Some drugs are practically insoluble in water and are dissolved in lipid emulsions or other vehicles for injection. Some of these vehicles can be dangerous in some species, eg, polyethoxylated castor oil will cause massive histamine release in dogs (the same thing can happen in other species, but the risk is acceptably low). Oily injection diluents can act as depots from which the drug is slowly leached. The lipid solubility of the drug and the nature of the oil determine the absorption. Waxes are often used for situations such as dry cow intramammary preparations where a slow release of drug is required (typically 30 days). Where extremely slow absorption is required (100 days), such as growth promoting hormone implants, silicone rubber is used. A variety of plastics are used for intravaginal delivery of hormones in cattle and sheep, these implants usually have a string attached and are pulled out when they have finished delivering the drug.

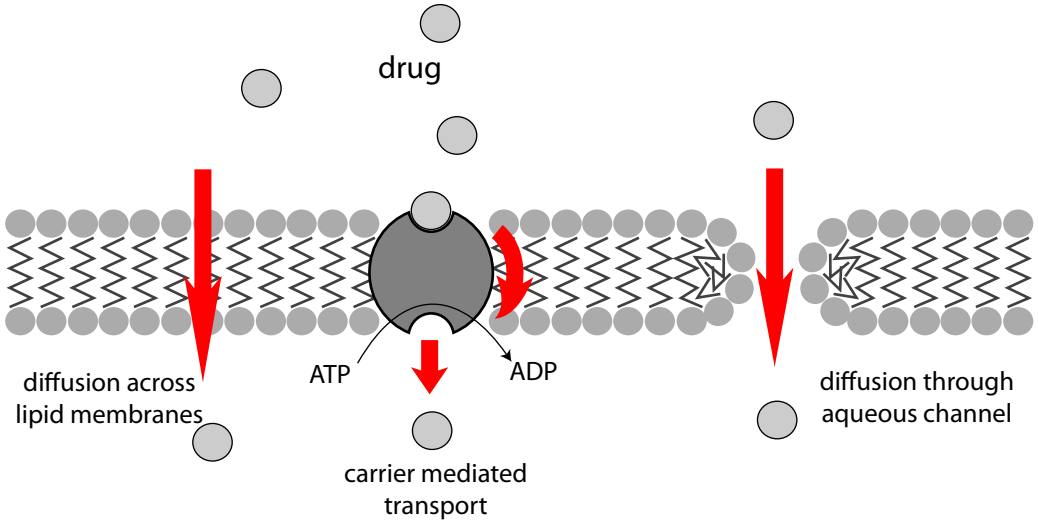
Mechanical devices such as osmotic pumps are occasionally used. These are capsules containing a compartment with a hypertonic solution and a semipermeable membrane open to the ECF. As fluid diffuses across the membrane the hypertonic compartment expands, pushing the drug out of the other end of the device. These give accurate drug delivery which can act over several months but are expensive. Similar pumps are used for slow delivery in the rumen of oral drugs such as anthelmintics and trace elements.

Implanting devices to release a drug a a precise rate in the right place is likely to increase in the future; pumps with electric motors are increasingly being used in people for insulin administration and have been tried in cattle for hormone manipulation.

Drugs for intravenous injection bypass the dissolution process so they must already be dissolved in water, or in a form which will quickly dissolve once injected. Relatively fat soluble drugs are usually in the form of an emulsion, so the drug is at least miscible with the plasma. Emulsifiers used like this can often cause side effects.

Drugs which are not in solution or in an emulsion of some sort should **not** be given iv.

Passage across membranes



For a drug to get from the site of administration to the blood, it has to cross cell membranes. (It also has to cross membranes to get from the blood to other tissues). Thus a drug given orally must cross into a mucosal epithelial cell, out the other side of the cell, across any connective tissue and through an endothelial cell or through a fenestration in an endothelial cell. There are two main ways that drugs can cross cell membranes:

diffusion through the lipid bilayer
transport by a carrier molecule

Rate of diffusion through membranes is largely determined by a drug's lipid solubility (molecular weight becomes important for large molecules). Lipid solubility is often expressed as oil - water partition coefficient because it is usually measured by shaking some drug up in a bottle with some water and some oil (often olive oil) and then measuring the concentration of drug in the water and the oil, and expressing this as a ratio.

Ionisation

An important complicating factor here is pH. Most drugs are either weak acids or weak bases and the degree of ionisation will depend on pH. The ionised form of the drug is usually insoluble in lipid so it will not cross membranes. The lipid solubility of the unionised form is a property of the drug but is usually much greater than that of the ionised form. The dissociation constant, pKa is an important concept. It is given by the Henderson - Hasselbalch equation:

for a weak base: $pK_a = pH \log_{10} \frac{[BH^+]}{[B]}$

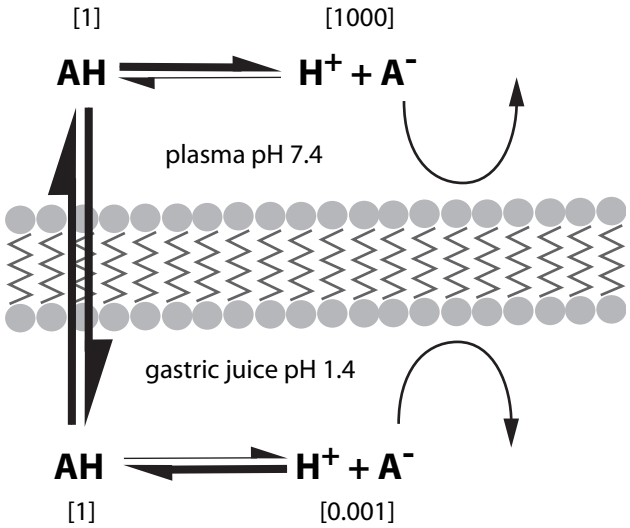
for a weak acid: $pK_a = pH \log_{10} \frac{[AH]}{[A^-]}$

ie, the pKa is the pH at which the drug is 50% ionised.

A weak acid usually has a low pKa eg aspirin - 3.5, a weak base usually has a high pKa eg pethidine 8.6. This has practical applications if the pH on each side of a membrane is different.

Ion trapping and pH partition

Inside a body compartment, the ionisation of a drug is determined by the pH and pKa. Where the pH varies across a membrane, eg plasma pH 7.4 and gastric contents pH 2, the degree of ionisation will be different. Since only the unionised form can cross the membrane, it will diffuse down the concentration gradient to the other side of the membrane where most of it will become ionised and thus



Ion trapping of a weak acid (pKa 4.4 to make the arithmetic simple) encourages movement across the gastric lining. This can be important with aspirin like drugs.

trapped. Thus a weak acid (such as aspirin) will move out of the gastric juice and into the plasma.

A weak acid will accumulate in a compartment with high pH, a weak base will accumulate in a compartment with low pH.

This can be useful to increase the concentration of drugs in various sites, eg milk pH 6.8, inflammatory exudate pH variable but acid, urine pH can be altered as required.

Carrier mediated transport

Many cells have carrier proteins which normally facilitate the transport of endogenous substances such as sugars, aminoacids, metal ions and neurotransmitters. Drugs which are analogues of these substances are often transported by the carriers. This process can be passive or require energy (active transport). It often involves exchange with other ions such as Na^+. These processes are important for transport in the kidney (particularly to pump weak ions into the proximal convoluted tubule) and blood brain barrier as well as absorption across the gut mucosa. These carrier processes are saturable, ie, once all the molecules are busy carrying drug, adding extra drug does not increase the rate of carriage.

These carrier molecules can also pump drugs out of cells, preventing them moving across the cell to get where they are supposed to go to produce a response. Glycoprotein P plays a major part in the blood brain barrier (as well as in drug resistant tumour cells and bacteria).

Effect of Alterations in Absorption Rate

A decrease in the absorption rate of a drug results in several changes to the plasma concentration time profile. These changes are of major clinical importance.

It is obvious from the graph that a decrease in the absorption rate results in a decrease and a delay to the maximum plasma concentration reached (lower C_{max} and T_{max}). In some cases this may be beneficial by reducing unwanted side effects (e.g.phenobarbitone), but in other cases it may prevent attainment of effective plasma drug concentrations (e.g. benethamine salts of penicillin G).

A more important effect of decreasing absorption rate is a prolonged time before the onset of drug action. In clinically acute situations this might be quite important and therefore in these situations a route of administration such as the intravenous route where absorption rate changes cannot occur would be more appropriate.

Depressed absorption rate may alter the duration of drug action by either shortening or lengthening it, depending on the particular drug's elimination kinetics and its minimum effective concentration.

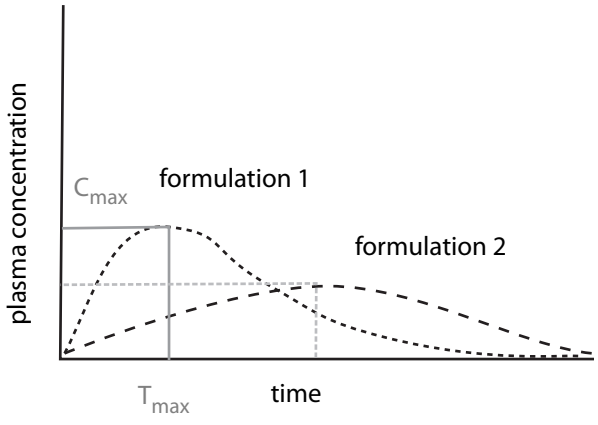
Bioavailability

The bioavailability of a drug is the fraction of the dose given which finds it way into the systemic circulation. It should be noted that this is not necessarily equal to the fraction of the dose which is absorbed, since a drug might be absorbed, for example across the gastrointestinal lumen, but removed from the portal blood by the liver by metabolism before reaching the systemic circulation. Similarly, for topically applied drugs the skin is an organ of drug metabolism and might biotransform a drug already absorbed before it reaches the circulation. The same of course is true for drugs administered by any route other than a simple intravenous injection.

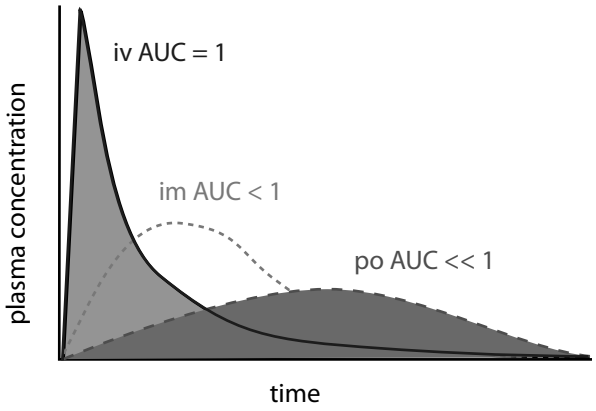
The bioavailability is calculated from the area under the plasma concentration / time curve and expressed as a proportion of the area under the iv curve, ie, if the area under the po curve is 20% of the area under the iv curve, the bioavailability is 0.2 or 20%.

Bioequivalence

Different formulations of the same drug are said to be bioeqivalent when they are absorbed to a similar extent and at a similar rate, ie, the C_{max}, T_{max} and AUC are similar. This technique is used when generic versions of drugs just out of patent are being licensed, to avoid having to carry out expensive efficacy and safety trials. Beware - some definitions of bioeqivalence only cover the extent of absorption and not the rate. For an antibiotic, for instance, if C_{max} does not rise above the MIC, it is unlikely to work. There is also a difference between "being similar" and "not being significantly different from". In the past, this sort of thing was only a



Effects of alterations in absorption rate.



The area under the plasma concentration / time curve after oral compared to iv administration.

concern to the licensing authorities, but under the new deregulated system you might have to make assumptions about bioequivalence yourself.

Absorption

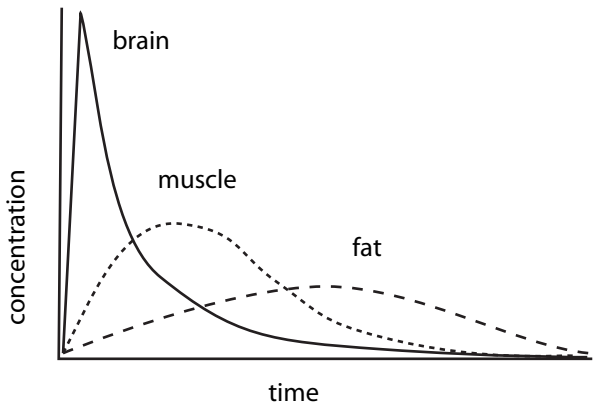
- pharmacokinetics consists of four processes: absorption, distribution, metabolism and elimination.
- most drugs must be absorbed to act.
- iv administration bypasses drug absorption
- absorption depends on lipid solubility and ionisation
- drugs are often formulated to provide delayed absorption
- bioavailability gives an indication of the extent of absorption

Distribution

Most drugs, apart from those appplied to the site of action, are distributed around the body by the blood. Tissues with high blood flow, such as the brain, will have more drug distributed to them initially than tissues with low blood flow such as fat. Disease can alter this, eg in heart disease, the blood flow to all tissues is reduced; inflammation usually increases the bood flow to the affected tissue.

Blood brain barrier

The brain is protected from many drugs by the blood brain barrier. This is both a physical barrier - there are tight junctions between the brain capillary endothelial cells so that a drug must be lipid soluble enough to cross the cells, and a physiological barrier - the endothelial cells contain P glycoprotein pumps whcih pump drugs out of the cells back into the blood. Occasionally these Pglycoprotein pumps are missing in some individuals which can let drugs get access tot he brain and cause unexpected side effects, eg, ivermectin gets into the brains of many collies and causes anaesthesia.



Distribution to different tissues depends on blood flow, among other things.

The blood placenta barrier is similar, and it is safe to assume that any drug which gets into the brain will also get into the foetus.

This means that drugs which must get into the brain to work, such as anaesthetics, are small, highly fat soluble molecules. Similarly, large, polar molecules do not usually get into the brain and can be chosen as a way of avoiding CNS side effects. However, in inflammation (meningitis) the blood brain barrier breaks down and these drugs can get in.

The blood brain barrier can be bypassed by giving drugs intrathecally or intracisternally, but it is very rarely necessary to do this. It is also highly dangerous.

Protein binding

Once many drugs get into the plasma, they bind to plasma proteins, especially albumin. Plasma albumin is particularly important in binding acidic drugs; basic drugs may be bound by β globulin and acid glycoprotein. Binding depends on:

drug concentration
affinity for the binding sites
protein concentration

There is usually a much larger number of binding sites than molecules of drug to bind to them, but this can change if there is a low concentration of albumin (liver disease) or if many of the binding sites are already occupied by another highly protein bound drug. This is clinically important since it is the free (unbound) proportion of the drug which can move into the target tissue and is thus active. If you give a drug which is normally 98% protein bound leaving 2% to produce the expected effects, if the binding sites are not available the amount of free drug may be dramatically different from expected and the effects may be much greater. This can cause embarassment if the owner is watching.

However, most modern drugs are so potent (ie, work at very low concentration) that displacement is rare. Old drugs such as sulphonamides and phenylbutazone can occupy clinically significant numbers of binding sites.

Protein bound drug is also unavailable for metabolism (but if the free drug is metabolised, some bound drug will quickly take its place, so this is not a limit on metabolism).

Compartments

Highly lipid soluble drugs will be partitioned into fat. Thus nearly all the administered dose of thipentone (fat : water partion coefficient 10:1) would be dissolved in fat at equilibrium. Fortunately, fat has such a poor blood supply that equilibrium never occurs, but fat can still be a significant reservoir for thiopentone. This then slowly leaches out and has a prolonged effect in much the same way as a depot injection dissolved in oil.

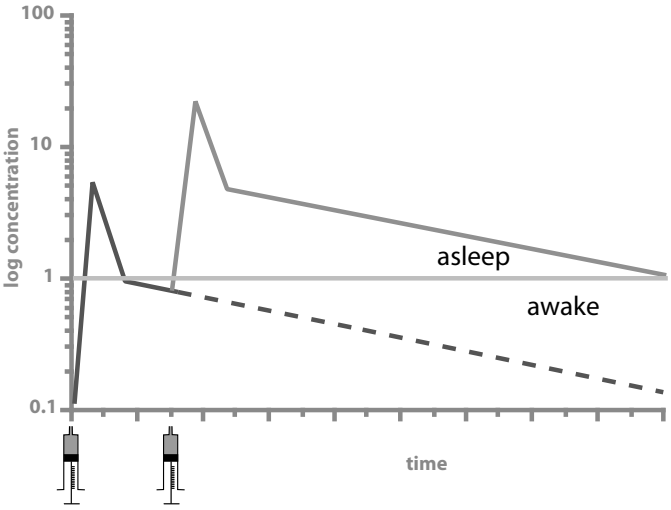
Ion trapping can also occur in tissues, eg, non-steroidal anti-inflammatory drugs tend to be trapped in inflamed tissue.

Volume of distribution

The body can be regarded as a number of fluid compartments:

plasma	5% body weight
extracellular fluid	20%
intracellular fluid	40%
CSF etc	2%
fat	20% (variable!!!)

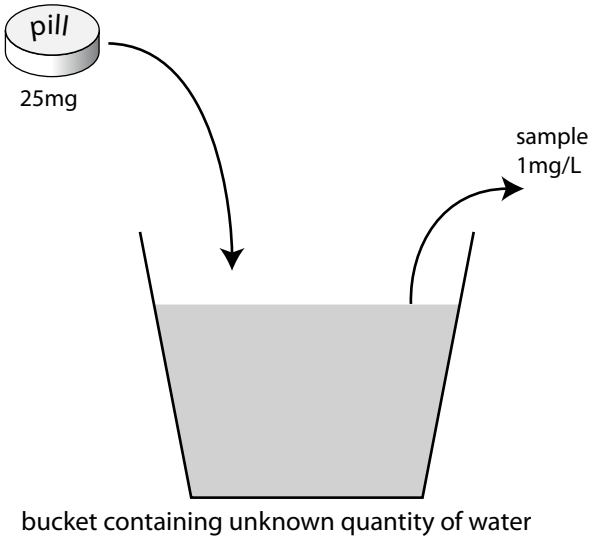
Some idea of where drugs go can be obtained from the apparent volume of distribution (Vd). This is defined as the volume of fluid required to contain the amount of drug in the body at the same concentration as that present in the plasma. Thus if the volume of distribution is the same as the plasma volume (c 0.05 L/kg), the drug is probably staying in the circulation, eg large protein bound molecules like heparin. If it is much greater than the volume of the total body water, or even of the body, the drug is being distributed to a reservoir somewhere, usually fat, eg morphine (c 5 L/kg).



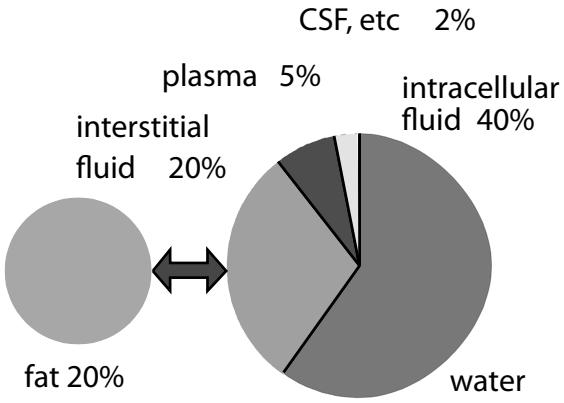
A drop in plasma concentration of a drug when it distributes to the tissues can have clinical effects, for instance when using thiopentone for induction of anaesthesia. A single dose gives a rapid wakening, but a top up dose can lst a long time!

Drugs with a large volume of distribution usually cross the blood brain barrier, which may be desirable, and also the placenta, which is usually not.

The volume of distribution is sometimes used to calculate the dose required to reach a target plasma concentration.



Volume of distribution: the Vd can be calculated if the amount put in (the dose) and the concentration are known. nb - animals are more complicated than a bucket of water!



Distribution

- drugs are usually distributed from the site of administration to the site of action via the blood.
- many drugs bind to plasma proteins and are unavailable for action or metabolism.
- drugs are not usually evenly distributed throughout the body.
- every drug has a volume of distribution which can be useful to know when calculating doses

Metabolism

The main route that the body uses to get rid of drugs is via the kidney. Lipophilic drugs are easily reabsorbed in the kidney, so drugs are usually metabolised to a more polar metabolite before elimination, although some drugs are eliminated unchanged, eg penicillin, which is a weak acid. Most metabolism takes place in the liver, but other organs such as the lungs and kidneys, and even the skin, can be important. Metabolism usually inactivates a drug; exceptions to this are prodrugs; these are inactive and have to be converted to the active metabolite to have an effect, for instance, the sedative chloral hydrate has to be converted to trichloroethanol before any effects are seen. Some active drugs also have active metabolites, eg, the sedative diazepam.

Modern drugs are sometimes given as lipid soluble prodrugs, then converted to the active drug at the site of action, and hopefully trapped there. Most angiotensin converting enzyme inhibitors given to dogs with heart failure are prodrugs.

Metabolism usually occurs in two phases:

Phase 1
- oxidative reactions
  - hydroxylation
  - dealkylation
  - deamination
- reductive reactions (rare)
- hydrolytic reactions

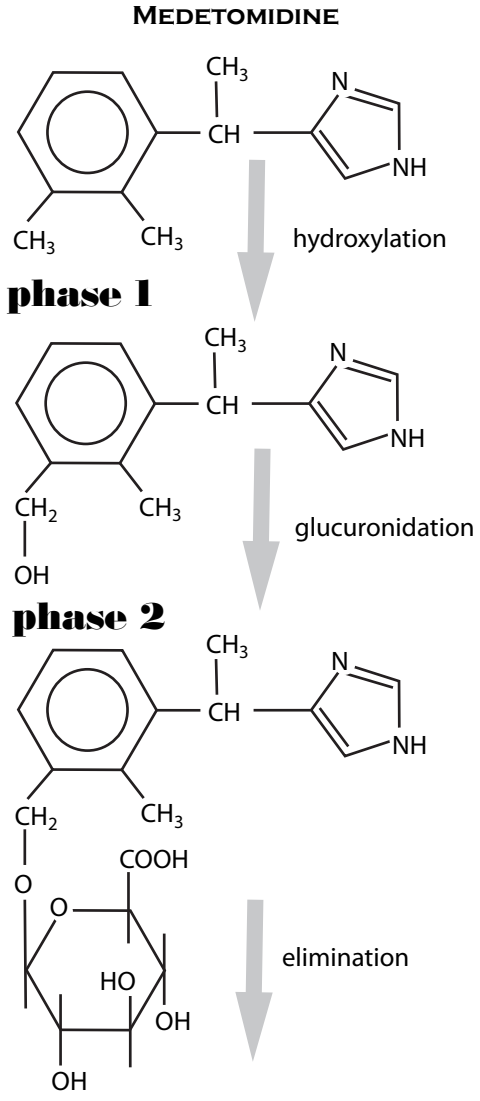
Phase 2
- conjugation with
  - glucuronide (not cats)
  - sulphate (not pigs)
  - methyl
  - acetyl (not dogs and cats)
  - glycine
  - glutamine (mainly man)
  - ornithine (birds only)

Phase 1

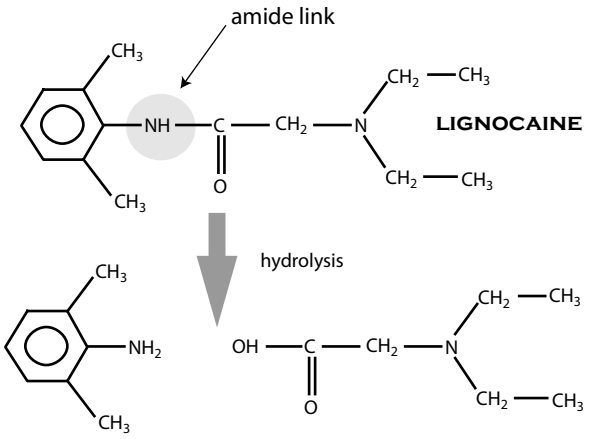
These reactions generally produce a more reactive molecule which can then conjugate with a polar molecule in phase 2. Occasionally these reactive intermediates are toxic (eg, paracetamol).

Most phase 1 reactions take place in hepatocytes (so lipid soluble drugs have better access) catalysed by enzymes attached to the smooth endoplastic reticulum (microsomal enzymes). The most important of these is the cytochrome P450 system of enzymes (mixed function oxidase system). Cytochrome P450 enzymes (CYP) usually carry out the first step of phase 1 which is then finished off by other enzymes. At least 50 different CYPs have been cloned in people and this work is starting to be carried out in dogs. They are grouped into different families depending on their homology, ie, CYP1, CYP2 etc. These are further divided into CYP2A, CYP2B etc, and then into CYP2A1, CYP2A2 etc. CYP3A4 and CYP2D6 are commonest in people. They are reasonably non-specific in what they will metabolise, but there are exceptions to this.

For many drugs in people, the specific enzyme in the P450 family which metabolises that drug is known. This can be useful to know if you also know that the person is deficient in that enzyme, which is fairly common. This also happens in dogs (and probably other species). For instance, celecoxib, an aspirin type drug, is metabolised in dogs by CYP2D15 (thought to correspond to CYP2D6 in people).



Main metabolic pathways of medetomidine, an α_2 agonist sedative and analgesic, in most species Several other pathways are possible.



The hydrolysis of lignocaine - a very rapid phase 1 reaction.

However, only 45% of dogs possess this enzyme and they metabolise celecoxib much faster than the rest.

Cytochrome P450s are also present in the intestinal mucosa, and can metabolise some drugs before they reach the systemic circulation.

Phase 2

These reactions occur when a molecule has a suitable reactive group for the attachment of a substituent group. Although the reactive group is usually put there by phase 1 reactions, some drugs can be conjugated without going through phase 1. These reactions also take place mostly in the liver.

Glucuronidation, the commonest reaction, is catalysed by glucuronyl transferase (except in cats which do not possess this enzyme); acetylation by acetyl coenzyme A and methylation by S adenosyl methionine.

There are major species differences in phase two reactions - see list above. There are probably also major individual differences (there certainly are in people).

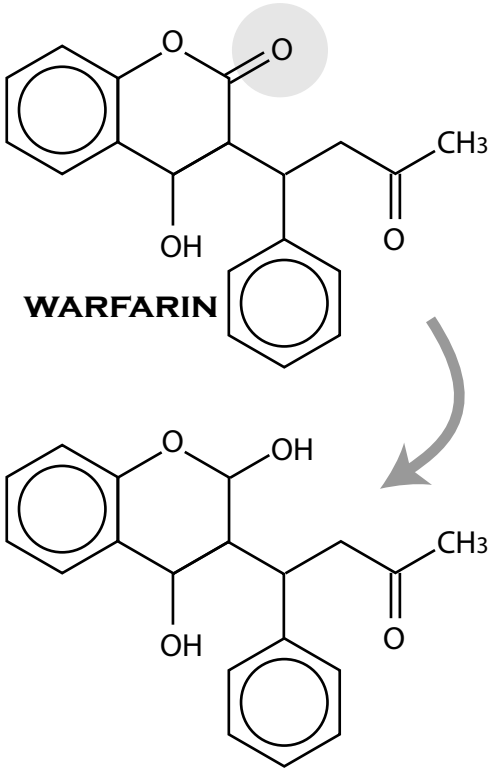
Phase 2 reactions can be reversed. Etorphine is conjugated with glucuronide in most species and a significant amount is excreted in the bile where it is exposed to the gut bacteria. These bacteria can lop off the glucuronide, allowing etorphine to be reabsorbed (and thus produce a second set of effects - in the case of etorphine this is sedation). This process is called **enterohepatic recirculation**.

Drugs are usually metabolised by several different pathways so the end result is a range of different metabolites.

Newborn animals do not possess many of the enzymes required for drug metabolism. This can be important, eg during caesarian section, anaesthetics will cross the placenta as well as the blood brain barrier; since the newborn animals have no enzymes to metabolise the anaesthetics, they may suffer from prolonged sedation which will not increase their chances of survival. (The answer is to use drugs which are eliminated without metabolism, such as inhalation anaesthetics.)

Older children usually metabolise drugs faster than adults, this has not been shown in animals (but no-one has looked).

Old animals and particularly animals with liver disease



Phase 1 reduction of warfarin. A rare but important reaction.

also tend to metabolise drugs slowly. Some individuals also lack the necessary enzymes - but this is usually discovered after the drug has been given!

Enzyme induction

The rate at which metabolism proceeds can be altered by drugs. Some drugs, such as phenobarbitone, cause a greatly increased synthesis of cytochrome P450 and glucuronyl transferase which means that the phenobarbitone (and other drugs) will be metabolised much more quickly (up to five times faster). This process is known as induction. It is of great clinical importance: many dogs are given phenobarbitone chronically for epilepsy, if they are then given some other drug the duration of action of the other drug may be much shorter than expected. Brassicas (rape, kale etc) also contain compounds which induce P450 enzymes. Grapefruit juice is a potent inhibitor of CYP3A enzymes in people, but it is not often drunk by animals! Ketoconazole, usually used as an antifungal drug, also inhibits CYP3A4, and is sometimes used to prolong the effects of expensive drugs in dogs. Macrolide antibiotics such as erythromycin and clarithromycin also inhibit CYP3A4 in people. Fluoxetine (an antidepressant) inhibits CYP2D6.

The rate of drug metabolism is also altered by changes in liver blood flow. These can occur in heart disease or shock, or can be caused by drugs.

Some drugs are metabolised so rapidly by the liver that they cannot be given orally. They are taken up by the portal system and most or all of the drug is metabolised by one passage through the liver so that very little or no drug appears in the systemic circulation. This is known as **first pass metabolism**. It is important for drugs like lignocaine (all removed) and morphine (about 80% removed).

Although most drug metabolism takes place in the liver, other organs (eg, skin, kidneys) are clinically important for some drugs. Intestinal lining cells may also be important in first pass metabolism.

Metabolism

• most drugs are metabolised in two phases - they have a "reactive handle" attached by a cytochrome P450 enzyme which is then conjugated with a water soluble molecule - usually glucuronide.
• some drugs will induce increased production of P450 which will increase the rate of metabolism.
• produgs have to be metabolised to produce their action.
• liver disease usually slows metabolism

Elimination

Most drugs and their metabolites are excreted in the kidney. Biliary excretion is also important for some drugs.

Most drugs (except those that are highly protein bound) are freely filtered in the glomerulus. There are also transporter systems in the proximal tubules which actively excrete some drugs (especially weak acids), even when they are protein bound. Competition can occur for these carriers and one drug can have a major effect on the excretion of another, eg probenecid has been used to block the excretion of penicillin.

Polar drugs and metabolites do not cross the tubule walls easily and are therefore concentrated in the urine as the water is reaborbed. pH and thus ionisation is important here - basic drugs are more rapidly excreted in an acid urine because they will be more highly ionised and thus not reaborbed. With acidic drugs the opposite is true. Since the urine pH can be altered with drugs, the concentration of some drugs in the urine can be altered. This can be important in treating urinary tract infections.

Some drugs such as frusemide, penicillins and digoxin are excreted unchanged by the kidney - they are polar enough without metabolism.

If the kidney is not working properly (common in old age) then drug excretion will be reduced.

Conjugates (usually glucuronides) can be subject to enterohepatic recirculation.

Clearance

Clearance (CL) is a measure of how quickly a drug is eliminated from the body. It is defined as the volume of plasma cleared of drug per unit time. It is sometimes divided into renal clearance, hepatic clearance etc but total clearance is probably a more useful concept.

Mathematical models

It is useful to be able to predict what a drug will do before you give it to an animal. If you have a computer with suitable software and are that way inclined you can have hours of fun fitting curves and deriving equations for plasma concentration / time curves of drugs which may help you to do this. There are a few clinically important concepts, however, which allow prediction of how long a drug is likely to stay in the plasma and thus how long it is likely to act.

There are several different ways of doing this, all of which can be taken to absurd levels of complexity. In stochastic models, drug molecules are assumed to move randomly as each is absorbed, distributed, metabolised and eliminated. Each molecule hangs around in the body for a finite length of time, thus the mean residence time (MRT) gives an idea of the time course of absorbtion and elimination. This approach requires few assumptions but the MRT is of limited usefulness.

Another approach is compartmental modelling. This requires more assumptions to be made, but if the assumptions are correct, the data is more useful. In the simplest model the animal consists of a single (purely theoretical) compartment in which drugs are quickly and evenly mixed. The volume of this compartment is the volume of distribution of the drug (Vd). The concentration of drug will fall as it is eliminated by metabolism and excretion. With most drugs, rate of elimination is directly proportional to concentration (first order kinetics). Some drugs rely on a saturable metabolic or excretion system; once this is saturated, adding more drug will make no difference, the system proceeds as fast as it can which is a fixed rate (zero order kinetics). Not many veterinary drugs do this at normal doses, phenlybutazone in the horse at some dose rates, paracetamol in the cat and phenytoin in the dog are the only obvious examples.

When a drug exhibits first order kinetics, its plasma concentration will decay exponentially. If a graph of plasma concentration is plotted on a logarithmic scale against time, the decay shows a straight line. The slope of the line is the elimination rate constant (k_{el}).

A more useful concept than k_{el} is the half life ($t_{1/2}$) which is inversely related to the elimination rate constant:

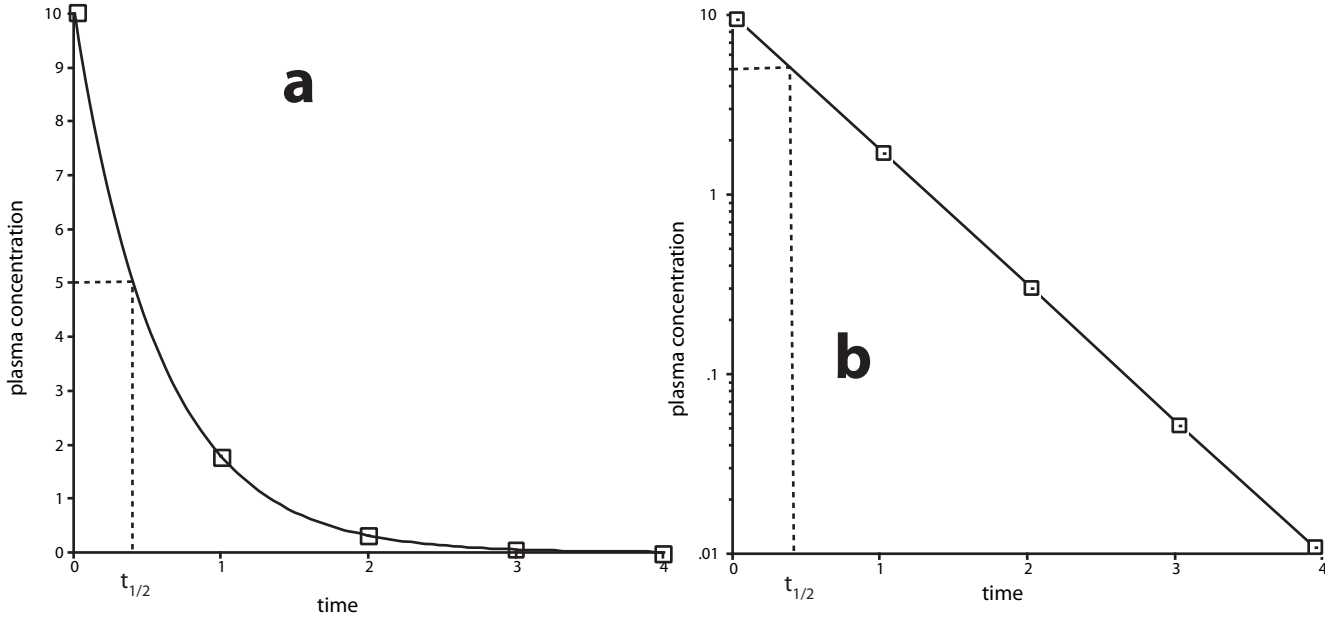
$$t_{1/2} = \ln 2 / k_{el}$$

or

$$t_{1/2} = 0.693 / k_{el}$$

The half life is the time taken for the drug concentration to be reduced to half the original concentration. This gives some idea of how long the drug remains in the plasma and thus its duration of action. (Drugs eliminated by zero order processes do not have fixed half lives.)

Thus:



***a**: plasma concentration / time curve, linear scale; **b**: plasma concentration / time curve, semilogrithmic scale. The slope of the line in **b** is the elimination rate constant. The time taken for the concentration to fall to half its original level is the half life ($t_{1/2}$).*

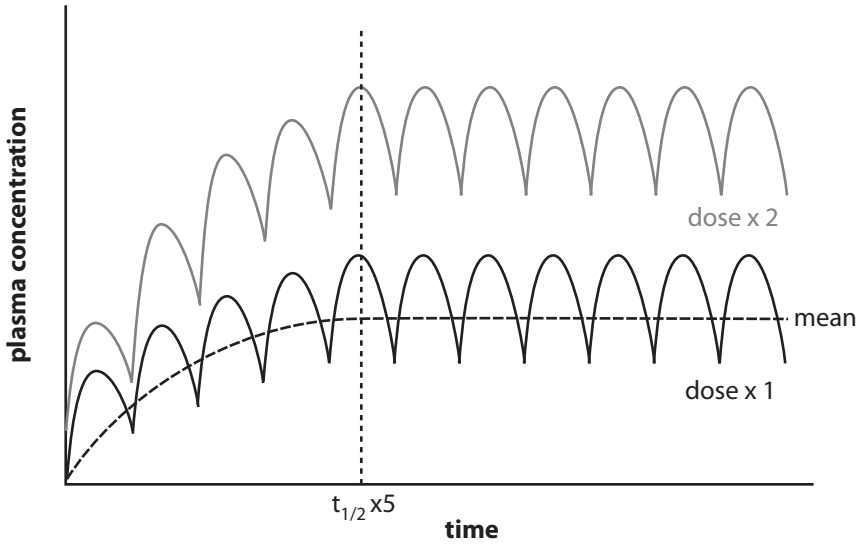
after	1 half life	50% of drug remains,
after	2	25%
	3	12.5%
	4	6.25%
	5	3.125%
	6	1.56%
	10	0.098%, ie 99.9% has been

eliminated.

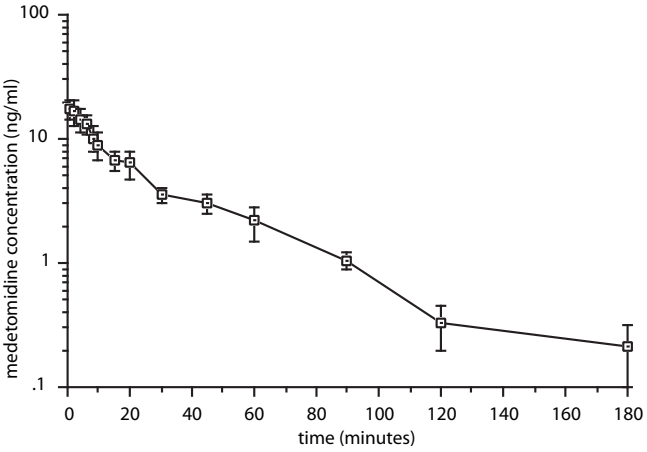
For practical purposes in clinical veterinary practice, a rule of thumb is that 5 half lives must pass before effectively all of the drug is eliminated (but this may not be enough to avoid residues, see below). Similarly five half lives must pass before a change in dose results in a new steady state plasma concentration. It can be seen therefore that the time one must wait before attaining a new therapeutic plasma concentration or before attaining complete elimination of a drug is a function solely of the half life of that drug. The dose rate and the dose interval do not effect the length of time necessary to wait for attaining a new steady state plasma concentration or complete elimination.

Two compartment models

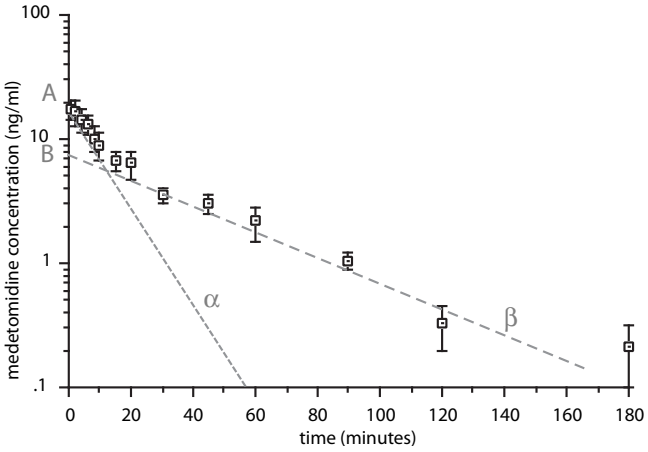
Many drugs' concentration/time curves are fitted to a two compartment model. Again, these compartments are purely theoretical, although they are sometimes called the central and peripheral compartments. In a two compartment model, the "curve" is fitted to two straight lines, corresponding to distribution from one compartment to the other, and elimination from the second compartment. These straight lines have slopes of α and β, and intercepts in the Y axis of A and B. These values are used in equations predicting plasma concentrations at any given time. The two lines each have



Concentration time curves for repeat dosing (wavy line) or infusion (mean). A steady state is reached after about five half lives no matter what the dose.



Plasma concentration of medetomidine in sheep after iv injection of 25µg/kg at time 0. n = 12, mean ± sem.



The same data fitted to a two compartment model.

a different half life, the distribution half life ($t_{1/2\alpha}$) and the elimination half life ($t_{1/2\beta}$).

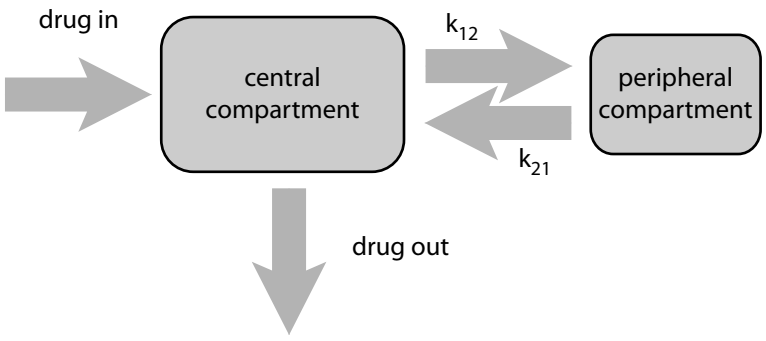
A WORD OF CAUTION

Multiple compartment models are possible. The body is obviously not a single homoeogeneous compartment: the line produced by a semilogarithmic plasma concentration / time plot is usually a curve and can be fitted by a series of straight lines representing different compartments. It is important to keep a sense of reality: this curve is a series of points with a line interpolated, even the points are an average of several animals or several experiments in one animal (and may be of dubious accuracy depending on the measurement method used). The graph above is a typical plasma concentration time curve obtained experimentally. It is obvious that a number of different curves could be fitted to these data. In this case, the computer decided that a two compartment model gave the best fit, and the parameters were worked out on that basis.

If the object of a knowledge of pharmacokinetics is to predict what is going to happen in another animal, all the (large) variables must also be taken into account. Clinical pharmacology is still an art rather than a science.

Elimination

- the plasma concentration of most drugs falls exponentially
- a drug's half life is the time for the drug concentration to fall by (to) half
- nearly all the drug is gone after 5 half lives (but this may not be enough to avoid residues)
- with repeated dosing, a steady state is reached after about 5 half lives
- some drugs show a biexponential decay corresponding to distribution and elimination



A two compartment open model which describes the behaviour of most drugs in the body.

Practical applications

Working out how much drug to give and when

If you know the target plasma concentration and the volume of distribution you can work out what the dose should be by multiplying the two (assuming 100% bioavailability). Obviously this does not take into consideration the elimination of the drug, so you need to know what the upper and lower limits on plasma concentration are to work out the dose schedule. You also need to know the half life of the drug. In clinical practice, these figures are not often known, and even if they are, you have to make the large assumption that the individual animal you are treating is the same as the animals in the literature. **Disease will alter pharmacokinetics!**

Very toxic drugs, eg anticancer drugs, are often given on body surface area rather than weight. This is because body surface area corresponds better with metabolic activity than weight. Small animals need relatively more than big animals. Body surface area (m^2) is given by:

$$bsa = k \times W^{0.67} \times 10^{-4}$$

where W is weight in g, k = 10.1 in dogs and 10 in cats.

Therapeutic Drug Monitoring

Therapeutic drug monitoring is appropriate as a clinical tool only under certain, well defined conditions:

- when the drug of interest has a narrow safety index (i.e. therapeutic plasma concentrations are very close to toxic plasma concentrations), e.g. gentamicin, digoxin
- when the therapeutic effect of the drug of interest is difficult or impractical to monitor, or would require an extended period of individual trial and dose adjustment, e.g. phenobarbitone for epilepsy
- when the drug's half-life or clearance is likely to change as a result of its use, or the co-admistration of other drugs, e.g. phenobarbitone, phenytoin
- when the drug's distribution or elimination cannot be predicted
  - (i)because of pre-existing or on-going disease, e.g. liver or kidney disease, or
  - (ii)because of 'unusual' physiology, such as in neonates or in pregnant animals
- when there has been a failure of the drug to induce the expected therapeutic results
- when there is the suspicion that the drug is not being administered as directed, i.e. breakdown of client compliance.

The usefulness of therapeutic drug monitoring in any of these situations is based on the assumption that the therapeutic efficacy or toxicity of a drug is a direct function of its plasma concentration. This assumption is fundamental, since it is the plasma drug concentration which is measured, but it does not hold true for all drugs, eg NSAIDs. The target plasma concentrations must be obtained from the literature (beware - human figures are often used and assumed to be valid for other species); a further assumption is that these are appropriate for the individual patient being treated. In the end you have to use your clinical skill and judgement!

Abbreviations

These are included for reference only - **do not try to memorise them**!

α = slope of the component of the plasma concentration / time curve attributable to distribution. Used for predicting C_t

A = the intercept of this line on the Y axis. Used for predicting C_t

AUC = area under the plasma concentration / time curve

$AUC_{0\text{-}inf}$ = area under the plasma concentration / time curve extrapolated to infinity

$AUC_{0\text{-}12}$ = area under the plasma concentration / time curve for the first 12 hours

AUMC = area under the moment curve. A theoretical concept used for deriving the MRT.

β = slope of the component of the plasma concentration / time curve attributable to elimination. Used for predicting C_t

B = the intercept of this line on the Y axis. Used for predicting C_t

bsa = body surface area. Corresponds more closely to metabolic rate than weight, especially important with drugs with a low therapeutic ratio. Used for extrapolating doses from big animals to small ones and vice versa.

C = C_p = plasma concentration of drug. Units usually µg/mL (M rarely used).

Css = Cpss = plasma concentration at a steady state, ie, the amount of drug going in is the same as the amount of drug going out.

CL = clearance = the volume of blood cleared of drug per unit time. Units usualy mL/min/kg

$CL_{systemic}$ = CL_{total} = the sum of $CL_{hepatic}$, CL_{renal}, etc

C_{max} = maximum plasma concentration reached after a dose of drug.

D = Q = dose or quantity, ie, amount of drug given.

F = bioavailability (fraction of dose reaching the systemic circulation).

k_a = absorption rate constant

k_{el} = elimination rate constant - slope of the plasma concentration / time curve in a single compartment model. Used in deriving the half life and other parameters.

Ln = natural logarithm

λz = slope of the terminal elimination phase in a multicompartment model (corresponding to k_{el} in a single compartment model)

MRT = mean residence time = $AUMC_{0\text{-}inf}$/ $AUC_{0\text{-}inf}$Gives some indication of how long a drug persists in the body. nb - covers absorption as well as distribution and elimination.

Q = amount of drug

$t_{1/2}$ = half life = the time it takes for drug concentration to fall by half.

$t_{1/2\alpha}$ = half life of the distribution phase

$t_{1/2\beta}$ = half life of the elimination phase

Vd = volume of distribution = the volume the drug would occupy if it was evenly distributed at the concentration found in the plasma. Gives some idea of where the drug goes.

Vd_c = volume of distribution of the central compartment

Vd_{ss} = volume of distribution at a steady state

$Vd_{\lambda z}$ = Vd_β = Vd_{area} = volume of distribution during the terminal elimination phase.

Drug residues

Definitions

maximum residue level (MRL) = maximum permitted level = maximum permitted tolerance = tolerance level = the maximum amount of drug allowed in food. nb. MRLs are different in different countries. At the moment, NZ uses different MRLs for domestic and export food, although this should change.

withholding time = withdrawal period = the minimum length of time between the last dose of drug and slaughter / milking. Also different in different countries, and for different formulations of the same drug.

acceptable daily intake (ADI) = the maximum amount of drug the average person could eat for the rest of their life without causing any effects

Introduction

After a drug has been administered and reached peak concentration, the amount of drug in the body usually declines exponentially.This means that most of the drug is removed fairly quickly, but the last bit takes a long time. (If the decline was truly exponential, the concentration would never reach zero.) Since most large animals will eventually be eaten, there is a danger of consumers ingesting some drug in their meat or milk.

International and domestic markets have a right to expect that the food animal products they are buying are safe, wholesome, and true to label. However, residue testing is being used more today to control access to markets than it is for food safety. Europe has led the way in this but the rest of the world is following. The general public has a grossly distorted perception of the relative risks that residues pose to their health.

What constitutes a food animal varies from country to country. Because the French eat horses, horses are classified internationally as a food species and are subject to the full range of regulation. (The same does not apply to Koreans and dogs - yet!)

One way of removing the problem of residues would be to test every animal slaughtered and the milk from every cow (at every milking) for all the possible drugs each animal may have had. This is obviously not possible, although that does not stop some people advocating this approach.

New Zealand relies on an "integrated quality assurance approach" (to use MAF speak). This includes having a registration process for veterinary medicines and agrichemicals which is geared towards international market requirements, well informed users (ie, vets and farmers), and some law on which to base enforcement activities. Rather than being a screen, residue testing in New Zealand is regarded as an audit of both the effectiveness of the controls put in place, and of farmer compliance with the relevant conditions of use. This system relies heavily on vets using drugs responsibly and making sure that farmers do the same.

Different foods are treated differently for historical reasons. Milk residues are usually dealt with by the dairy industry, Milk residues are usually dealt with by the dairy industry, most of the rest is covered by the Food Safety Authority, which is officially part of MAF but comes under the Minister of Health. This is still in the process of being sorted out.

Residues may also come from other sources, eg pesticides, environmental contamination (particularly heavy metals) and plant and fungal toxins. Problems can arise when a fungal toxin in pasture is the same thing as a drug produced by fungal cultures in a lab.

Maximum residue levels

Current analytical techniques (usually HPLC) are so sensitive that it is possible to detect some residue of a drug even years after its administration if you look hard enough. This means that there must be an allowable level of drug in food which is considered "safe". Since safety is rather subjective, it is not surprising that different countries choose different levels (and call them different things). Eventually, everyone may follow the World Health Organisation's Codex Alimentarius, but at the moment Europe and the USA have different but parallel systems to the WHO: Australia and NZ have a half way house where some levels are different again. The WHO and EU call the "safe" amounts of drug in food the maximum residue level (MRL). You must know about these, since exports from NZ must conform to Codex, or failing that, EU MRLs. These are also accepted for imported food. Food for the domestic market is currently subject to different MRLs. There are moves afoot to sort out this situation, but don't hold your breath.

How are MRLs calculated?

First the **acceptable daily intake** (ADI) value for each chemical is established. The ADI is calculated from chronic toxicology studies on at least two species of laboratory animals. These animals are given different doses of the drug and the highest dose which produces no effect is called the **no observed effect level** (NOEL). For antibiotics, the effects examined are changes in the gut flora, either the normal flora or axenic mice with human gut flora added.

For most chemicals the ADI is based on the amount the average human could consume for their entire life and still show no observable effect. This involves using the animal NOELs and multiplying by various fudge factors (usually 100) to increase safety. Drugs which are potentially carcinogenic cannot have an ADI since it is assumed that one molecule could be enough to start a tumour. This raises problems when those drugs are also naturally present in man and animals, eg oestrogen. Different countries deal differently with such drugs: they are banned in Europe, given very low MRLs in the USA, and generally ignored in NZ in the hope that they will go away.

The first principle of establishing MRL values is that they should be set low enough for each food type so that the ADI will never be exceeded by anyone eating a diet made up of foods which could conceivably contain these residues. The Ministry of Health (noe the NZ Food Safety Authority) has tables showing the "average" diet of different ethnic groups in NZ. The second principle currently applied is that they should be further restricted to that level which is required if they are used in accordance with 'good agricultural practice'. This term is not defined.

MRLs used in NZ can be found at:

`http://www.nzfsa.govt.nz/acvm/registers-lists/nz-mrl/index.htm`

European MRLs (and a brief explanation of how they were decided) can be found at:

`http://www.emea.eu.int/htms/vet/mrls/a-zmrl.htm`

American and Australian MRLs are more difficult to find.

Withholding times

Once the MRL for the active ingredient has been established (and officially approved), drug companies carry out pharmacokinetic tests with their product to see how long it takes for tissue levels to decline to the MRL. Another fudge factor is added on to allow for individual variation (and sometimes for the effects of disease) and that time becomes the withholding time. Since the pharmacokinetics of a drug will be different in different species, this process must be repeated for each species. This is expensive. nb, the withholding time calculated by a drug company is only valid for their formulation of the drug, a product containing the same active ingredient from a different company may require a different withholding time.

If you use the drug according to the instructions on the bottle and stick to the withholding time given, the chances of a residue above the MRL are very small (although not zero). If you vary the dose or route of administration, or give the drug to an animal for which it is not licensed, then you have to work out a new withholding period. There are several options.

If you have the full pharmacokinetic data and are into stats / suffer from masochistic tendencies you can use the same procedure as the drug companies (outlined in the FDA document at `http://www.fda.gov/cvm/fda/TOCs/guideline3pt6.html`

If you have data on the half life of the drug in milk or meat, and you double the dose, you can establish a new withholding time by adding on a half life.

If the drug is licensed overseas (EU or USA) for the use you intend, then you could use the overseas withhold-

ing periods. **Beware** - the MRLs may not be the same. You must also compare like with like - eg penicillin injections from different companies may have different formulations which affect their pharmacokinetics and thus withholding times. Information for products in the USA can be obtained from `http://www.farad.org/` Europe does not yet have much useful information on line, but the British data is published by NOAH in two annual publications: "Withdrawal Periods for Veterinary Products" and "Compendium of data sheets for veterinary products". It is also contained in the Veterinary Formulary.

You can use a "standard" withholding time. This is a (long) time calculated to avoid residues for most drugs. In the UK the figures are 28 days for meat, 7 days for milk and eggs and 500˚days for fish. The NZFSA has a set of very conservative default times for animals which have been in clinical trials (table). These have been advocated for drugs where the withholding time has not been established, but there is no legal or scientific basis for this recommendation.

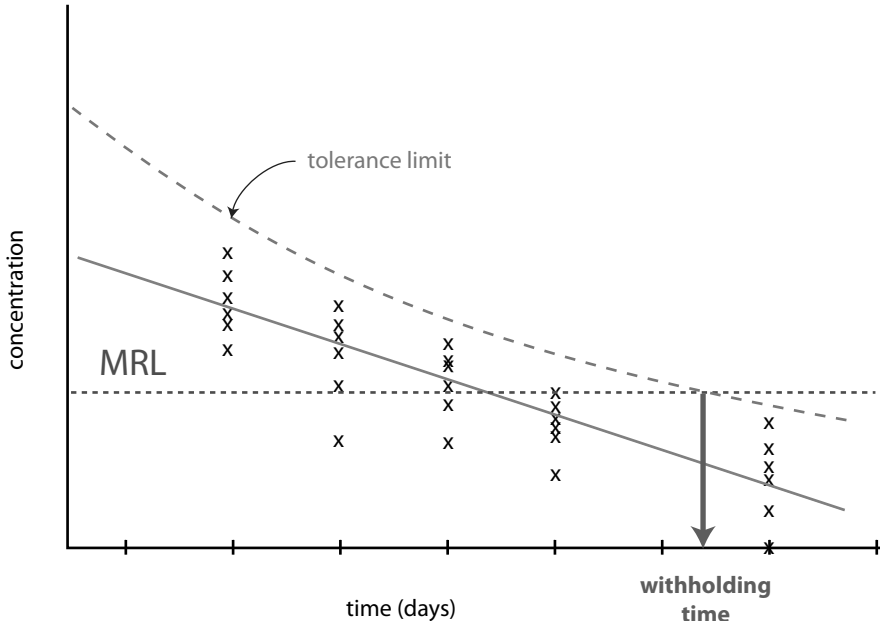
It is always wise to err on the side of caution, but bear in mind this will probably involve increased costs for the farmer.

The bottom line is that unless you know what you are doing, or there is absolutely no chance of the animal getting into the food chain, it is better to stick to the instructions on the bottle.

Problems arise with horses, which are classified as food animals (even in NZ) because of the barbaric habits of the French. It is illegal not to give an animal's owner information which will prevent residues in the meat, even though the average girl with a sick pony is unlikely to take kindly to being told not to eat her pet for the next four weeks. One way around the problem is to write "this horse must not be sold for human consumption for x weeks" in very small print at the bottom of the invoice.

Further reading

Riviere et al., (1998) Primer on estimating withdrawal times after extralabel drug use. *JAVMA*, **213**, 966 - 968



Withholding time calculation. The tolerance limit is the maximum concentration present in 99% of animals with 95% confidence. The withholding time is where this crosses the MRL (rounded up).

animal	meat	milk	eggs
ruminants	91	35	
pigs	63		
horses	180		
birds	63		10
camelids	63		
rabbits and hares	63		

Default withholding times in days. In the vast majority of cases, these will be excessively conservative. They are widely used in NZ but are not based on science or law.

Enforcement

How are excess residues prevented?

•Focus your farmers on the importance of withholding times

•Follow label instructions closely

•If you deviate at all then increase the withholding time

•Make sure treated animals are readily identifiable

•Leave a written record of all treatments and the withholding time

National Residue Monitoring and Surveillance (NRMS) programme

MAF is responsible for running New Zealand's National Residue Monitoring and Surveillance programme (NRMS) for meat and offal, and undertakes most of the enforcement activities. The analytical testing alone costs in the region of 2 million dollars a year with 117 chemicals specifically looked for, and approximately 70,000 analyses completed.

The NRMS programme consists of three different parts.

1. The random monitoring programme is designed to provide domestic and international assurances as to the overall effectiveness of New Zealand's residue controls in preventing consumers from being exposed to toxicologically significant amounts of residues. All animals sampled are randomly selected and this prograннne is essentially an audit of the effectiveness of the control measures the country has in place to prevent residues in excess of defined limits finding their way into the human food chain.

2. The surveillance targeted sampling programme targets suppliers and animals which for some reason have been identified as posing more of a risk. Previously identified non-complying farmers, sheep smelling of dip, and cattle with mastitic udders or injection site lesions are examples of reasons why certain animals or lines will be specifically targeted for more intensive sampling and analytical testing.

3. Surveys aimed at identifying potential problems are a way the MAF and the industry can be more proactive, and allow for early identification of possible future problems so that effective control measures can be implemented in advance. They also provide valuable data on which the Ministry can base a case against overseas markets trying to impose more testing on us.

Consequences of residues- NZ

- Condemnations
- Suspect listing
- Increased costs
- Black listing by processors
- Possible prosecution

If the NRMS programme detects residues above MRLs in any samples analysed then; firstly, a trace back is undertaken to ascertain which control system has failed to deliver. Secondly appropriate actions are taken to ensure the problem doesn't reoccur, and thirdly the number of analyses increases dramatically so we are able to provide additional assurances both domestically and internationally that any problem has indeed been rectified.

Where the supplier is found to be at fault, either through not complying with label directions or withholding periods, or through having inadequate management systems, then extra conditions of supply are placed on this farmer. These involve compulsory notification of the Inspector in Charge prior to sending any stock for slaughter so that the stock can be subjected to more intensive inspection and sampling, automatic condemnation of all offal, and/or retention of carcases until tested clear. Repeat offenders, or those blatantly disregarding the controls, can face prosecution and or movement control notices being served on them.

Where the product or its label directions are found to be a contributing cause, a formal request is put to the Animal Remedies Board for a prioritised review of the withholding period and label of the product.

Where there has been a failure in buyer / seller communication responsibility is put on the buyer to set up systems which prevent a reoccurrence. It is up to the buyer to initiate his/her own actions against the seller. Similarly, if a farmer claims his or her veterinarian failed to inform him or her of the relevant withholding period associated with the sale or administration of a prescription animal remedy (PAR) this is a civil matter between the farmer and this professional.

Consequences - overseas

- Consignment rejections
- Reduced credibility
- Increased costs
- Market access restrictions
- Consumer backlash

The reaction of the importing country depends to some extent on the chemical residue found and the type of product it is found in. At the very least an explanation is requested on how product containing residues above their specifications is being certified to their market. Most regard the presence of excess residues in exported produce as evidence of lack of effective control by the exporting country's controlling authority. Accordingly, they reject the consignment and demand assurances and evidence of what will be done to prevent a reoccurrence. In the interim, trade restrictions and increased rates of testing at port of entry may be imposed. In some situations market access for that product type will be blocked.

However, these are the government to government interactions. Increasingly, the real risk associated with residue detections is associated with the media coverage and the inevitable consumer backlash this causes.

Overview of the law

NZ law on residues is rather confusing since so many different acts of parliament and regulations made under those acts are involved. These are starting to be consolidated under the Animal Products Act, but there is still some way to go. The recently established NZ Food Safety Authority oversees all this, as well as the licensing of veterinary medicines (although there are different departments involved in each).

Agricultural Compounds and Veterinary Medicines Act (1997)

It is an offence for vets to fail to provide a client with information to prevent the occurrence of residues ($15,000 fine).

New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standards (2010) made under the Food Act (1981)

This is the list of MRLs for veterinary medicines and agricultural chemicals. It is updated regularly. Note that these MRLs are often different from those used in Europe and America (and the Codex). In these cases, it is effectively the overseas MRL which is used in NZ!

Dairy Industry Act (1952) and Dairy Industry Regulations (1990 / 290)

These mainly relate to quality and hygiene, but are written vaguely enough to cover drug residues as well. Dairy products must not be sold or exported if they are likely to endanger public health. Milk purchasers may take samples for analysis. Milk and dairy products must be fit for human consumptionion.

Animal Products Act 1999

This is supposed to replace the previous acts and regulations with mandatory food standards.

It is an offence to submit animals for slaughter with residues present greater than the MRLs or inside the withholding period.

The Director General of MAF may decree that animals treated with some groups of drugs must be permanently identified (currently hormonal growth promoters and Johne's vaccine) (it is also an offence to use officially sanctioned ear tags for anything else). It is illegal to use a drug to promote growth unless it is licensed for that.

Anyone selling a treated animal must tell the buyer.

MAF can control movement of animals.

Overseas information

The FDA (USA) publish MRLs and other useful information and the EMEA (Europe) publish MRLs and toxicity data. The urls keep changing, so check the pharmacology website for the latest link.

When looking at overseas information, remember that MRLs may be different from here, and that different formulations of the same drug may have different withholding times.

Banned drugs (food animals)

New Zealand a

chloramphenicol
β agonists
stilbenes
thyreostatics

Europe

chloramphenicol
chlorpromazine
dapsone
nitroimidazoles
nitrofurans
ronidazole

USA

chloramphenicol
clenbuterol
fluoroquinolones
dipyrone
phenylbutazone
glycopeptides
nitrofurans
nitroimidazoles
stilboestol
sulphonamides(cows)
thalidomide
gentamicin (voluntary)

New Zealand b

chloramphenicol
colchicine
chloroform
nitrofurans
nitroimidazoles
chlorpromazine
dapsone
phenylbutazone
dipyrone
arsenilic acid
nandrolone

Some drugs have been banned in food animals because of the risk of residues.

The method of "banning" varies from place to place: in NZ it is not illegal to give the drugs in table (a) but it is illegal for the farmer to move the animals or present them for slaughter when they contain the drugs. This gives rise to anomalies: clenbuterol is licensed for delaying parturition in cows, but as a β agonist is banned in food animals.

The drugs in table (b) are likely to be banned soon unless tracking and tagging programmes are instituted for them. These lists are contantly getting longer!!! Check `http://www.nzfsa.govt.nz/acvm/subject/vet/prohibited.htm`

Practice exam questions

Multiple choice questions

1. The speed of onset of clinical effects of an antibiotic may depend on
   - its rate of renal clearance ❑
   - the area under the plasma concentrqation / time curve ❑
   - the route of administration ❑
   - the virus being targetted ❑
   - the time of year ❑

2. The ability of a drug to cross cell membranes may depend on
   - the route of administration ❑
   - its lipid solubility ❑
   - the degree to which it is ionised at pH6 ❑
   - its potency ❑
   - the affinity of the drug for its receptors ❑

3. Speed of absorption of a drug after oral administration depends on
   - intestinal parasite burden ❑
   - splanchnic blood flow ❑
   - plasma protein concentration ❑
   - stomach contents ❑
   - liver function ❑

4. The apparent volume of distribution of a drug is
   - approximately the volume of total body water minus the volume of drug injected ❑
   - the volume required to contain the the drug at the same concentration as plasma ❑
   - equivalent to the plasma volume ❑
   - a theoretical concept of little clinical relevance ❑
   - the Vdss minus AUMC ❑

5. The elimination half-life of a drug
   - is inversely related to the volume of distribution ❑
   - varies with the bioavailability ❑
   - varies inversely with the clearance ❑
   - is the time taken to reach a steady state plasma concentration ❑
   - is 0.7/kel for drugs eliminated by a zero order process ❑

6. For a drug injected intravenously, if the plot of log plasma concentration against time can be separated into two linear components of decay
   - the initial phase is the absorption phase ❑
   - the existence of a 3 compartment model is suggested ❑
   - the 2nd phase indicates a zero order elimination phase ❑
   - the elimination rate constant is the Y intercept of the 2nd phase ❑
   - the distribution phase has 1st order kinetics ❑

7. In drug metabolism
   - phase one reactions are commonly performed by liver mixed function oxidases ❑
   - phase two reactions generally make drugs more lipid soluble ❑
   - the metabolite is always less active than the original parent compound ❑
   - liver enzymes may be induced by drugs such as ketoconazole ❑
   - the liver is the only organ involved in biotransformation ❑

8. In general, drugs which are highly lipid soluble
- have low oil water partition coefficients ❑
- have high apparent volumes of distribution ❑
- are not readily absorbed after oral administration ❑
- are readily excreted without being metabolised ❑
- have very short elimination half lives ❑

9. The blood brain barrier is easily crossed by
- quaternary ammonium compounds ❑
- inhalation anaesthetics ❑
- small polar molecules ❑
- proteins ❑
- macrocyclic lactones ❑

10. You give morphine sc to a dog which has a fractured leg after being hit by a car. After administration, you realise that the dog is in shock and the morphine is likely to be absorbed very slowly, if at all. The best course of action is to
- wait and see what happens ❑
- use a NSAID for analgesia instead ❑
- attempt to aspirate the morphine and give another dose iv ❑
- just give another dose iv ❑
- give a small dose of fentanyl iv ❑