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Comparative Veterinary Pharmacokinetics

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1. Introduction

In veterinary clinical practice the sensitivity of a given animal species to a certain drug can be attributed to pharmacodynamic and pharmacokinetic variations. In contrast to human medicine where individual differences are of primary importance, interspecies and also inter-breed distinctions are crucial in comparative veterinary medicine. Pharmacokinetics describes the behaviour of the drug in the body. Similarly to human nomenclature, the ADME process describes the absorption (other than IV administration), the distribution, the metabolism and the elimination of certain drugs. To produce a systemic effect, the drug must be absorbed and distributed to attain therapeutic concentration at the site of action. If the target site is the GI tract, then no absorption is needed after oral application. Significant variations can be seen in the extent of absorption and distribution, the rate and the manner of metabolism and elimination between animal species. Because of pronounced interspecies variations extrapolation of parameters from pharmacokinetic data of human or other animal origin is inappropriate and can be hazardous in case of several drugs. Lack of pharmacokinetic data however, necessitates the empiric application of extrapolated human dosages in many cases. This chapter concentrates on the variations in the ADME process between animals of different species, breed and age.

2. Administration routes in veterinary practice

Administration routes in the veterinary medicine are mainly similar to those in the human medicine with minor differences. Major application routes include intravenous (IV), intramuscular (IM), subcutaneous (SC), oral (PO), topical, intramammary and inhalational administration. *Intravenous (IV) administration* is frequent in all animal species. Drug action is the fastest when applied IV because no absorption is necessary. Drugs applied as an intravenous bolus achieve high plasma levels and produce a quick, immediate action and usually a pronounced effect. Drugs can also be applied IV as a continuous infusion with which the surgeon can easily govern the effects of the substance as the concentration and the rate of infusion determines plasma steady state levels. It is a common way of applying intravenous anaesthetics like propofol. Although the IV route has many advantages, it is probably the most toxic way of administration. Drugs administered IV have to be applied slowly and observe the patient for potential side effects. *Intramuscular (IM) and subcutaneous (SC) application* is very frequent in the veterinary medicine. It is common in ruminants, swine, horse, dogs, cats and rabbits. Rate of absorption is determined principally by the

administration route, the vascularity and area of the region, the concentration and the ionization of the drug. There are also differences in the localization of the injection. For example, suprascapular IM injection is frequently applied in small animals, as it results in much faster absorption when compared to the gluteal muscles because of better vascularity and the proximity of the periosteum. Depending on the injection site, peak plasma concentrations are usually achieved 20-40 minutes after administration. There are several drugs that are formulated as sustained release preparations. Ampicillin and amoxicillin trihydrate, procaine and benzathine penicillin are antibiotics frequently formulated as depot injections resulting in prolonged absorption and effective plasma levels. These preparations are usually applied with 2-3 day intervals that is a great advantage in food producing animals where restraint is an important and avoidable stress factor. Bioavailability is generally higher or equal to oral administration and it is infrequently 100%. Inactivation or precipitation at the injection site and damage of the tissues are common contributing factors to low IM bioavailability values, like in case of diazepam. *Oral administration* is the most frequent mode of application in animals as food producing animals are primarily treated via this route. In poultry and swine drugs are commonly dissolved in the drinking water or mixed into the feedstuff to treat a large number of animals. Boluses, drenches, oral gels and oral pastes are common dosage forms for the oral treatment of ruminants and horses. Tablets, capsules, oral solutions and suspensions are the primary oral dosage forms in companion animals. Differences in oral bioavailability between animal species are conspicuous, detailed comparative aspects are discussed in the "Absorption of drugs" Chapter. *Topical administration* also raises several comparative pharmacokinetic issues that are discussed in the "Absorption of drugs" Chapter. *Intramammary application* is an important veterinary application route in the treatment and prevention of mastitis in cattle.

3. Absorption of drugs

Once the drug has been administered by any route other than IV it has to be absorbed into the bloodstream to exert its systemic effect. The extent of absorption is termed *bioavailability*, and defined as the ratio of AUC (area under the curve) after extravascular and intravenous administration.

$$F (\text{bioavailability}) = AUC_{\text{extravascular}}/AUC_{\text{intravenous}}$$

Depending on the administration route we can talk about oral, intramuscular, subcutaneous, topical etc. bioavailability. As the greatest interspecies differences occur after oral administration, this chapter concentrates on this application route. The extent and rate of absorption depends mainly on the lipophilicity, molecular weight and degree of ionization of the substance at the site of administration. Weak acids (like most of the NSAIDs) are mainly in nonionized form in the acidic environment of the stomach thus their absorption starts in the proximal regions of the GI tract resulting in lower T_{max} values. Weak bases are mainly in ionized form in the stomach, thus their T_{max} values are usually higher. Oral bioavailability can also be influenced via biotransformation by intestinal epithelial cells or by the liver. This is called the "first pass effect". Many drugs are inactivated via this mechanism, examples include lidocaine, diazepam, xylazine, detomidine, medetomidine, morphine or cimetidine. In case of prodrugs, like codeine, cefuroxime-axetil or pivampicillin first pass metabolism is essential in activating the substance. To avoid first pass metabolism the drug can be applied parenterally or rectally as the rectum is not connected to the portal vein. Pharmaceutical formulations can also significantly alter the rate of absorption.

Modified release or coated tablets can delay dissolution of the substance in the gastrointestinal (GI) tract thereby protract absorption. Some examples for these preparations are retard tablets and capsules containing potassium, phenytoin, azythromycin, NSAIDs, sedatives and water soluble vitamins. Oily solutions, emulsions and suspensions can be used for the formulation of depot injections which - if injected subcutaneously or intramuscularly - can provide delayed absorption of the active substance. Chemical modifications are also used to prolong absorption. Ceftiofur is a veterinary third generation cephalosporin that has three different formulations for use in swine and ruminants. Ceftiofur sodium and ceftiofur hydrochloride are rapidly absorbed after intramuscular administration, while the free crystalline acid form have a protracted absorption resulting in approximately 150 hours effective plasma levels against certain respiratory pathogens, like *Pasteurella multocida* or *P. haemolytica*. Additional important factors that affect drug absorption include physical or chemical interaction with feed constituents, increased gastrointestinal motility or inflammation of the GI tract and disruption of GI epithelium. An example for the former phenomenon are the tetracyclines that are well known about their ability to form insoluble complexes with calcium and magnesium ions. Thus, feedstuff containing these ions in a high amount (e.g. milk products) should not be administered together with these antibiotics. Diseases with inherent increased GI motility will result in decreased absorption of the administered drugs. Inflammation of the GI mucosa and disruption of the GI epithelium (e.g. canine or feline parvovirus) will result in increased absorption of the active substances. Aminoglycosides that are practically not absorbed from the intact GI tract can have much higher bioavailability and can exert systemic toxic effects (ototoxicity and nephrotoxicity) in animals with parvovirus (Gemer et al., 1983, Riviere&Papich, 2009).

3.1 Differences in oral and parenteral absorption in different animal species

Discriminating monogastric and ruminant, herbivorous, omnivorous and carnivorous animal species is essential when defining comparative pharmacokinetics. Although there are notable differences in the whole ADME process, perhaps oral absorption and metabolism phases show the greatest distinctions. The length and volume of the GI tract in ruminants and horses is much more pronounced when compared to the other important domestic species (poultry, swine, dog and cat). This will result in longer passage time and usually delayed absorption after oral application of drugs. An example for this are the benzimidazole class of anthelmintics. A single oral dosage of these substances (e.g. albendazole, fenbendazole) can provide a protracted duration of action in horses, cattle, sheep and goats to eliminate the most important parasitic worms. In other animal species, multiple oral administration is usually necessary to eliminate the GI parasites. Dogs, cats and swine usually resemble in the rate and extent of oral absorption and these parameters are usually similar to humans. There are several exceptions however, that necessitate pharmacokinetic investigations in the certain species and need to arise precautions when extrapolating dosages or dosing intervals to humans or other species. Namely, oral bioavailability values show pronounced differences between animal species. The frequently applied broad spectrum aminopenicillin, amoxicillin shows an oral bioavailability of 5% in horses (Ensink et al., 1992), 28-33% in swine (Agero&Friis, 1998), 59-68% in poultry (El Sooud et al., 2004, Jerzsele et al., 2009, Jerzsele et al., 2011) and 60-80% in dogs and cats (Küng et al., 1994).

In *horses*, oral bioavailability of a large number of drugs show great individual variations. Absorption of most antimicrobial agents is significantly hindered by feeding, thus 2-4 hours fasting is essential before applying these drugs. Even in these cases systemic availability can show wide variations between individuals, as in case of metronidazole between 60 and 90% (Baggot et al., 1998). Bioavailability of several drugs can be very low compared to other domestic species. Examples include several antibiotics, like ampicillin and amoxicillin that have 0-1% and 5% oral bioavailability, respectively (Ensink et al. 1992, Ensink et al. 1996). This phenomenon can result in severe dysbacteriosis because of the low extent of absorption and accumulation of the substance in the intestinal lumen. Pivampicillin, an ester of ampicillin can be used to overcome this problem, as the oral bioavailability of this drug is 31-36% (Ensink et al. 1992). In foals *per os* absorption is usually more pronounced, oral bioavailability and age being frequently in a negative correlation. Cefadroxil shows approximately 100% oral bioavailability in neonatal foals that decreases to 15% until 5 months of age (Duffee et al. 1997). Metformin, an antidiabetic substance has also very low oral absorption compared to humans (Hustace et al., 2009). Absorption of drugs from the oral mucosa can be quite significant. Detomidine, a frequently applied veterinary α_2 -agonist has significant first pass metabolism resulting in low oral bioavailability if ingested. If applied sublingually however, absorption from the oral mucosa eventuates 22% bioavailability (Kaukinen et al., 2010) which is clinically useful. In horses, subcutaneous injection of drugs is infrequent, intramuscular application is more common. Bioavailability values are similar after these administration routes, although IM administration usually produce lower T_{max} values indicating faster absorption. As IM injections can cause sterile abscesses, IV administration is prevalent, in this case no absorption of the drug is necessary.

In *ruminants* the presence of the reticulorumen has some important clinical consequences. Large volume of the ruminal fluid (60-70L in cattle) dilutes the drugs and decreases their rate of absorption delaying the effect of orally applied medicines. Ruminal microbial flora restricts the oral usage of most antibacterial agents in adult individuals. As calves do not possess a mature ruminal microflora, antibiotics can also be applied orally. The bacterial flora plays an important role in the biotransformation of certain substances, like the already banned chloramphenicol. In several cases, however, ruminal microflora can transform a less active substance to a more active/toxic one. For instance, urea is almost nontoxic to monogastric animals, while highly toxic to ruminants as urea is rapidly transformed to ammonia by the bacterial urease enzyme. Netobimine, an inactive prodrug of the anthelmintic molecule albendazole is converted to its active form, albendazole and albendazole sulfoxide in the rumen (Capece et al., 2001). Anthelmintics as one of the most commonly used medications in ruminants can be administered orally to young and adult ruminants alike. In ruminants, sustained release boluses represent an important group of formulations. These preparations often contain anthelmintics which are released slowly and/or intermittently from the product resulting in excellent activity against gastrointestinal endoparasites. These formulations are retained in the reticulorumen and release the substance for months resulting in a very long withdrawal period.

In *swine* oral administration of drugs via feedstuff or drinking water is a common practice. Pharmacokinetic investigations are frequently conducted, especially in case of antibiotics and anthelmintics. In infectious diseases where bacteria are localized mainly in the GI tract antibiotics with no or very low oral bioavailability have an important role. Colistin and the aminoglycosides are frequently applied in these cases as they have excellent activity against

Enterobacteriaceae, mainly *E. coli* and *S. enterica* and retained in the intestinal lumen. Apramycin is an important exception however, it has 25-30% availability, thus it can also be used for the treatment of systemic or urinary tract infections. Oral bioavailability of amoxicillin is approximately half when compared to those in poultry, dogs and cats. The exact explanation is not yet known, but it can be attributed to acid-catalysed hydrolysis, intestinal enzymes or a carrier mediated uptake mechanism, that can be saturated (Reyns et al., 2007). Thus, increasing dosage decreases oral bioavailability, as described in humans (Arancibia et al., 1988). When using an microencapsulated granule formulation, bioavailability is significantly increased to nearly 100%, that might be an explanation as microencapsulation protects amoxicillin from enzymatic degradation (Anfossi et al., 2002).

Dogs and cats are carnivorous animals, they do not possess basal secretion of hydrochloric acid in the stomach, thus the gastric pH varies in fasted and fed animals. In animals with empty stomach gastric pH can reach values of 5-6, while in fed animals it is declined to 1-2. This phenomenon has clinical pharmacological consequences in some cases. As an example, proton pump inhibitors (like omeprazole) as they need a strongly acidic pH to be activated should be administered along with food. Certain NSAIDs, like the newly developed long acting veterinary coxib, mavacoxib should be administered together with food. The oral bioavailability of mavacoxib in fasted animals is approx. 46.1%, while being 87.4% in fed animals (Cox et al. 2010). Other examples that have greater systemic availability when applied with feeding include doxycycline or ketoconazole. Ketoconazole also needs acidic pH in the stomach to be absorbed thus it should to be given with food (Giguere et al, 2006). In contrast, several substances should be applied to fasted animals, as feeding significantly decreases absorption. Examples are ampicillin (Kung et al., 1995, Kluge et al., 1999), oxytetracycline, chlortetracycline (Giguere et al. 2006) or cimetidine (Le Traon, 2009). Drug formulations can also influence oral bioavailability. In case of amoxicillin oral availability was 77%, 68% and 64% after oral suspension, oral drops and tablet administration, respectively (Küng et al., 1994).

In *poultry* the main administration route of drugs is oral application via drinking water or feedstuff. Oral bioavailability values are mainly similar than those in humans. Infectious diseases where bacteria are localized mainly in the GI tract are less frequent compared to swine as *E. coli* and salmonellae frequently penetrate into the bloodstream. Combinations including colistin (that has a very low bioavailability) and an other antibiotic with good absorption helps inhibiting and destroying bacteria systemically and lumenally alike. Intramuscular administration of drugs is uncommon, but it comes into question when valuable breeding animals must be treated. IM bioavailability values are similar to oral. In case of marbofloxacin in ducks, oral and IM bioavailability was 87% and 81%, respectively. In case of amoxicillin in broiler chickens, oral and IM bioavailability was 61% and 77%, respectively. Although veterinary products licensed for poultry frequently have two or more target animal species, pharmacokinetic profile and thus dosage can show significant differences. Clavulanic acid has an IM bioavailability of 76% in turkeys and 87% in chickens. The oral bioavailability of the lactamase inhibitor is 61% in turkeys and 66% in chickens.

3.2 Percutaneous absorption after topical administration

Percutaneous absorption consists of three distinct phases. The drug must be dissolved, penetrate the stratum corneum and the epithelial layer and finally enter the bloodstream.

Lipophilicity is a major determining factor. Several substances have excellent transcutaneous absorption, e.g. the ectoparasiticidal amitraz, avermectins and the organophosphates, lipophilic glucocorticoids, omega fatty acids etc. Absorption can be enhanced by formulation, namely surfactant or organic solvents, like dimethyl sulphoxide (DMSO). These auxiliary substances help penetration of the substances through the outer layer of the skin. Percutaneous absorption is also enhanced by inflammation or excoriation of the skin. It is important to note that there are pronounced differences between animals. Cats have relatively thin skin compared to other domestic species thus absorption from the skin can be more significant. This fact together with the metabolic deficiencies in this species contributes to several important toxicological occurrences in cats. Therefore spot on preparations containing pyrethroids are highly toxic to cats, because of pharmacokinetic and pharmacodynamic peculiarities.

3.3 Intranasal absorption

Intranasal application is uncommon in the veterinary practice, although there is an increasing number of medicines that are to be applied via this route. The notable advantage of this method is to avoid first pass metabolism and thereby increasing bioavailability. Oxytocin can be applied intranasally to induce labor, promote milk letdown and for the adjunctive treatment of mastitis mainly in swine. Absorption is variable however, IM or SC administration is more common. Another example is diazepam, a frequently applied anticonvulsive benzodiazepine. Nasal bioavailability of diazepam is 41-42% in dogs (Musulin et al., 2011), providing an alternative route next to rectal administration in *status epilepticus*.

3.4 Intramammary absorption

Intramammary application of antibiotics, antiinflammatories and other substances is a common practice in dairy cattle. The large inner surface of the mammary gland provides opportunity for the extensive absorption of lipophilic substances. In mastitis inflammation enhances intramammary absorption as described about cefoperazone (Cagnardi, 2010), probably because of disturbances in epithelial cell lining. Florfenicol, a small, lipophilic molecule has 54% intramammary bioavailability compared to 38% when applied IM (Soback et al., 1995). This phenomenon worth considering as drug residues will be present also in the milk and the edible tissues raising a public health issue if the animal must be slaughtered. Less lipophilic substances are absorbed usually in a negligible amount, especially in healthy animals as proved about cloxacillin *in vitro* by Kietzmann et al. (2010)

4. Drug distribution

After the drugs are absorbed or applied intravenously they are distributed in the body. Certain drugs reach and are retained only in extracellular fluids, some are also penetrating cell membranes and distributed intracellularly and extracellularly alike. Finally, the drug reaches the target cell or tissue and/or its receptor sites. Tissue concentration achieved primarily depend on penetration across capillary membranes. Drug distribution is mainly influenced by the lipophilicity, the molecular weight and the degree of ionization of the substance and tissue blood flow rates. Generally, the more lipophilic, the smaller and less ionized the molecule, it is more completely distributed in the body. Distribution shows

significant differences between domestic species, breeds and individuals of a certain breed. This can be attributed to distinctions in body composition. For instance highly lipophilic barbiturates are much more dangerous in greyhounds as they do not possess large volume of fat tissue where the drug could be redistributed. Some substances have such high plasma protein binding or large molecular weight that they are retained in the bloodstream after IV administration. Mannitol in a 5-25% concentration is applied intravenously to treat or prevent pulmonary edema, life threatening acute renal failure and reduce intracranial pressure. As it remains in the intravascular space it establishes an osmotic gradient between intravascular and extracellular compartments resulting in rapid decline in extracellular fluid amount.

For quantitating the extent of drug distribution, the *volume of distribution* (V_d) term need to be introduced. V_d is the volume that would be necessary for the drug to be distributed in the body according to its plasma concentration. Thus, V_d can be described as

$$V_d (\text{volume of distribution}) = A(t)/C_p$$

where $A(t)$ is the amount of drug in the body, C_p is the plasma concentration and t is time. According to this definition, the larger the V_d , the more extensive the drug distribution with higher tissue concentrations. The above mentioned mannitol has a very low V_d as it does not leave the intravascular space. Thus, V_d is practically equivalent with the blood volume, which is 0.08 L/kg. Drugs with V_d values of 0.3-0.8 L/kg (e.g. penicillins) are distributed in the body and achieving concentrations in tissues similar to the plasma. Drugs with moderate to high V_d are for instance marbofloxacin with a V_d of 1.2 L/kg in the horse (Carretero et al., 2002), or pentoxifylline in chickens (De Boever et al., 2005). These drugs achieve much higher concentrations in the tissues than in the plasma. Chloroquine has extremely high V_d values in all species including humans. The substance has a V_d of 53.3 L/kg in dogs (Aderounmu et al., 1983) representing an almost complete penetration from the plasma to the tissues.

After distribution, *redistribution* occurs when administering certain drugs. Ultrashort acting, highly lipophilic barbiturates (e.g. thiopental) is applied IV, is rapidly distributed, crosses the blood brain barrier and causes general anesthesia. Meanwhile, the drug is quickly redistributed in high blood flow tissues, mainly the voluntary muscles causing a rapid decline in plasma drug levels. As plasma levels decrease, brain concentrations also decline resulting in awakening of the animal. The substance - as being highly lipophilic - is then accumulated in the fat tissue for a certain amount of time. Thus, readministration of thiopental after awakening is prohibited as the tissues featured in redistribution are already saturated. As mentioned above, animals with low amount of fat, like starving animals, or greyhounds are exposed to risk when applying the thiobarbiturates.

Certain drugs are liable to *accumulation* in different regions of the body. Aminoglycosides for instance have very high affinity to the cortical regions of the kidney, probably because of high phospholipid content of this area as the cationic aminoglycosides have high affinity to these anionic molecules. Certain antifungal agents (e.g. griseofulvin, ketoconazole) can be accumulated in the stratum corneum of the skin achieving high concentrations and providing excellent activity against dermatophytosis and onychomycosis. The pK value of the molecule largely influences its ability to accumulate in certain regions of the body. In

case of weak acids pH values above the pK_a result in accumulation in regions with higher pH, while in contrast weak bases tend to accumulate at lower pH values than the pK_a . The clinical relevance of this phenomenon is widely accepted. Alkaline drugs are accumulated in the reticulorumen in ruminants (pH 5.6-6.5), the milk (pH 6.5-6.8) or the intracellular environment (pH~7.0) - regions that have lower pH values compared to the plasma - if they are lipophilic enough to penetrate these membranes. This phenomenon is called „ion trapping”. Thus, lipophilic, alkaline drugs, like erythromycin, azythromycin, clarythromycin, clindamycin, minocycline or florfenicol have important clinical role (Davis et al., 2002, Yamazaki et al., 2008) in the treatment of infections caused by intracellular pathogens (*Mycoplasma spp.*, *Chlamydia spp.*, *Rhodococcus equi* etc.) or mastitis.

Plasma protein binding decreases the extent of distribution as it limits capillary membrane transport of the molecule. Drugs are primarily bound to plasma albumin reversibly, maintaining an equilibrium between bound and free molecules. As the concentration of the free drug declines (because of metabolism, redistribution or excretion) the protein bound ratio acts as a reservoir thereby protracts elimination and increases half-life of the drug. A newly developed third generation cephalosporin, cefovecin has 96-98.7% plasma protein binding in dogs and 99.5-99.8% in cats resulting in long half-lives and prolonged action. Desfuroylceftiofur, the metabolite of ceftiofur, another third generation cephalosporin is highly protein bound and has a moderately long, 10 hour half-life in cattle (Brown et al., 1991) and 8 hour in the horse (Meyer et al., 2009), uncommon to other beta lactams. If the drug is extensively bound to plasma proteins, it raises also toxicological issues. If such kind of drugs are applied together (like NSAIDs with anticoagulants) the competition for albumin results in higher free drug concentrations and more pronounced pharmacological effects, and finally, toxicosis. The same phenomenon can be observed in hypoalbuminaemia. It was reported that anesthesia achieved with propofol, a highly protein bound injectable anesthetic increases free fraction of propranolol by approx. 6% compared to untreated control (Perry et al., 1991). Competition for plasma albumin is one of the most frequent cause of pharmacokinetic interactions in the veterinary medicine. Some examples for drugs extensively protein bound can be found in Table 1.

Drug	Protein binding (%)
Cefovecin	98-99.8 (dog, cat)
Ceftiofur	~65% (cattle)
Digitoxin	~88% (dog)
Phenytoin	~78% (dog)
Phenylbutazone	~99% (horse)
Furosemide	~95% (dog)
Propranolol	~92% (dog)
Propofol	95-99%
Warfarin	96.5% (cat)

Table 1. Examples of drugs with extensive plasma protein binding

In the course of distribution drugs are able to penetrate certain *physiological special barriers* in a lesser or higher degree. Clinically relevant barriers include the blood brain barrier (BBB), blood milk, blood prostate, blood testicle and blood placenta barriers. Diffusion through

these barriers is mainly affected by lipophilicity, molecular weight, ionization of the substance and the presence of inflammation. Inflamed meninges, mammary gland tissue or prostate markedly increases drug concentration in these areas. Acute or chronic nature of inflammation influences penetration of antibiotics across these barriers. Most of the beta lactams (like penicillin or ampicillin) achieve only low concentrations in the cerebrospinal fluid (CSF), the milk or the prostate. In acute meningitis, mastitis or prostatitis, however, penetration is significantly increased and can achieve inhibitory concentrations. In healthy tissues or those with chronic inflammation this diffusion is worse, and need emerges for the administration of more appropriate antibiotics, like third generation cephalosporin ceftriaxone or the phenicols. In modern veterinary practice usually the latter substances are used in the first line treatment of meningitis (Giguere et al., 2006). Another clinically relevant aspect is the sensitivity of some dog breeds to certain drugs including ivermectin. Ivermectin is a highly lipophilic endectocidal agent that readily crosses the BBB, but a P-glycoprotein mediated efflux mechanism helps to pump out the molecule from the CSF (Schinkel, 1999). Some dog breeds (Collie, Sheltie, Australian Shepherd) however, carry a mutated MDR-1 gene encoding a false P-glycoprotein (Roulet et al., 2003) thereby causing disturbances in this efflux mechanism in sensitive individuals. Selamectin, a derivative of ivermectin is tolerated better thus can also be used in MDR-1 mutant dog patients (Geyer et al. 2009). Other substances for P-glycoprotein are loperamide, domperidone or doxorubicine. Penetration of the blood milk barrier is important in the antibacterial therapy of acute mastitis in cattle. Although inflammation increases the level of antibiotics in the milk, only a limited number of substances is able to achieve therapeutic concentrations in this region. Penethamat, a narrow spectrum penicillin is a drug with excellent penetration is appropriate for intramuscular treatment of Gram-positive mastitis. In contrast, intramuscular injection of ceftiofur resulted in tissue and milk concentrations below detectable limits (Owens et al., 1990). In conclusion it can be pronounced that given parenterally, most of the beta lactams licensed for the treatment of mastitis are usually inappropriate in the sole treatment of the disease, but they do potentiate the efficacy of intramammary applied antibiotics (Ehinger et al., 2006, Owens et al., 1990). Certain lipophilic and alkaline substances however, can reach high concentrations in the mammary tissue and the milk because of excellent lipophilicity and the ion trapping mechanism (see above). For comparison, milk:plasma level ratios are 0.1-0.3 in case of penicillins and first generation cephalosporins, while 4.6 and 8.7 in case of spiramycin and erythromycin, respectively (Giguere et al., 2006). In conclusion it should be emphasized that among certain physiological barriers the BBB is the less permeable and is protected also by pump mechanisms, like P-glycoprotein. For comparison, fluoroquinolones can attain 2-3 times higher concentrations in the prostatic fluid than in the serum, while only 25% of serum levels can be achieved in the CSF (Giguere et al., 2006).

5. Drug metabolism

Metabolism or biotransformation involves a series of reactions that will render the xenobiotic (drug) available for excretion. These enzymatic processes decrease lipophilicity and increase polarity and hence water solubility of the parent molecule which can be eliminated via one of the excretion mechanisms present in the organism. Metabolism immediately begins after absorption and runs parallel with further absorption, distribution and excretion. Biotransformation generally takes place in two phases (Figure 1).

Phase I – or non-synthetising phase - involves chemical reactions that „prepare” the xenobiotic for Phase II, namely oxidative processes (oxidation or reduction), dealkylation or hydroxylation that are prerequisites for conjugation in Phase II. Functional groups converted or attached to the molecule in this Phase are future targets of conjugation. During Phase I the molecule can be inactivated or on the contrary, attain activity. Diazinon, a frequently applied organophosphate in dogs is metabolised into diazoxon in the liver that is more active and more toxic than the parent molecule (Kappers et al., 2001., Costa, 2006). Certain antibiotics can be metabolised into an other active form, like the veterinary enrofloxacin to ciprofloxacin in dogs (Kung et al., 1993) or ceftiofur to desfuroylceftiofur. Those drugs that attain activity after biotransformation are called *prodrugs*. Ramipril and enalapril, two frequently applied angiotensin-convertase enzyme inhibitor is metabolised into active ramiprilat and enalaprilat to exert their pharmacological effects. Febantel, a frequently applied benzimidazole anthelmintic achieves activity when it is metabolised to fenbendazole. Fenbendazole is further converted into oxfendazole, a metabolite with higher activity (Montesissa et al., 1989). Netobimine, an other benzimidazole prodrug is transformed to active albendazole which is rapidly metabolised to albendazole sulfoxide (Gokbulut et al., 2006). In most of the cases however, drugs are converted to an inactive form, like phenobarbital to hydroxy-phenobarbital.

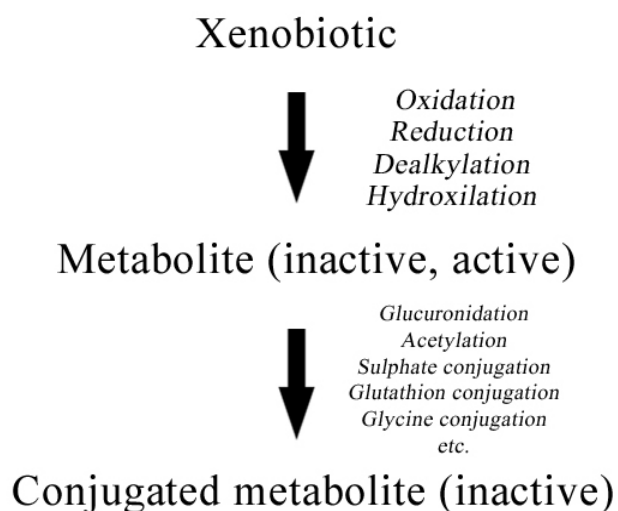


Fig. 1. Summary of Phase I and Phase II metabolic reactions

Phase I metabolic reactions are catalyzed by microsomal enzymes, mainly by the cytochrome P₄₅₀ (CYP₄₅₀) superfamily. The cytochrome P₄₅₀ enzyme family is located in the smooth endoplasmic reticulum. When the cells are homogenized, these cell organs form vesicles known as microsomes, thus the nomenclature *microsomal enzyme* garniture. Microsomal CYP₄₅₀ enzymes are monooxygenases that account for approx. 70-80% of Phase I metabolic reactions in animals and can be divided into CYP₄₅₀ families and subfamilies. In humans, 18 families are distinguished. There are great differences in activity of the distinct CYP₄₅₀ families in animals and humans. In humans, the largest and widely investigated enzymes belong to the CYP3A1 family. In laboratory animals CYP2E1, CYP1A2 have the

highest activity, but CYP4A, CYP2D and CYP3A subfamilies also play important role in metabolic processes (Guengerich, 1997, Fink-Gremmels, 2008). In dogs, CYP1A2 is expressed the most, while CYP2B11 is unique to dogs and account for approx. 20% of CYP₄₅₀ metabolic activity in this species. In chickens, CYP2H1 and CYP3A37 have the highest activity. Not only the presence of certain enzymes but also their activity show great differences between animals. For instance, the highest overall CYP₄₅₀ activity was measured in rabbits (1.77 nmol/mg protein), the lowest in chickens (0.25 nmol/mg protein) (Nebbia et al., 2003, Fink-Gremmels, 2008).

In addition to microsomal CYP₄₅₀ monooxygenases, several enzymes play role in the biotransformation of drugs in animals. Alcohol and aldehyde dehydrogenases, monoamino oxidase (MAO) and enzymes responsible for conjugation in Phase II are also participate in drug metabolism.

Phase II - or synthesising phase - results in conjugation of the molecule with a polar substance, primarily glucuronic acid (glucuronidation), acetic acid (acetylation), less frequently sulphate, glutathion or glycine. This process results in a water soluble, almost exclusively inactive metabolite that can be excreted. In comparative veterinary pharmacokinetic differences in metabolic processes mainly affect Phase II reactions and are discussed in details in the next Chapter.

The primary organ of metabolism is the liver, but several organs have metabolic activity. It is reported in cats (and humans) that propofol is extensively metabolized in the lungs next to the liver making it relatively safe also in patients with hepatic failure (Matot et al., 1993, Dawidowicz et al., 2000). The intestinal tract also has metabolic activity, as several drugs are transformed into active or inactive forms in the intestinal wall. For instance, pivampicillin is hydrolysed to active ampicillin, or cefuroxime-axetil is converted to active cefuroxim. The kidney has also large metabolic capacities. Vitamin D for instance achieves activity in the proximal tubules where it is converted to active dihydroxy-cholecalciferol. Cyclosporin, an immunosuppressive agent is metabolized by renal cytochrome P₄₅₀ enzymes and also causes enzyme induction (Nakamura et al., 1994).

5.1 Comparative veterinary aspects of metabolism

Several domestic animal species show defects in certain metabolic reactions. Phase I reactions show relative similarity among domestic animal species, the clinical relevance of these, usually only quantitative distinctions is not known. Defects in Phase II conjugation reactions, however, result in the clinically most relevant consequences. The most important metabolic pathway is glucuronidation which is present at low levels in cats rendering this species highly sensitive to several substances.

In *cats* glucuronide conjugation is very slow as this species has a low activity of the enzyme glucuronyl transferase. This metabolic defect is known for long to be responsible for the high sensitivity of cats to several drugs (Weisburger et al., 1964). Feline species are one of the most endangered species from a toxicological aspect, drugs potentially toxic to cats include paracetamol (acetaminophen), most of the NSAIDs, especially salicylates, morphine or phenobarbital. Paracetamol toxicosis is a frequently fatal, common household and malicious poisoning in cats. Paracetamol is primarily metabolised by glucuronidation or

sulphate conjugation, and in less amount by microsomal enzymes into reactive intermediers, mainly N-acetyl-p-benzoquinone-imine (NAPQI) (Figure 2). In cats however, in the absence of glucuronic acid conjugation, NAPQI is accumulated (Figure 3) and causes methemoglobinaemia, liver necrosis leading to death.

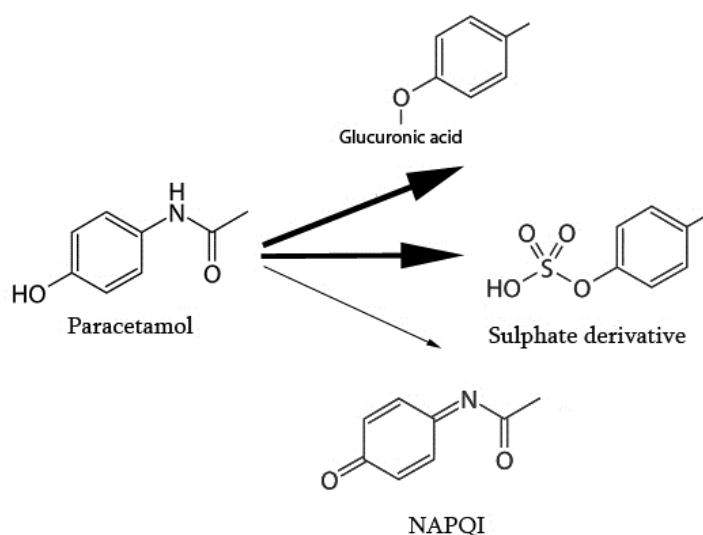


Fig. 2. Paracetamol metabolism in humans and animal species excluding the cat

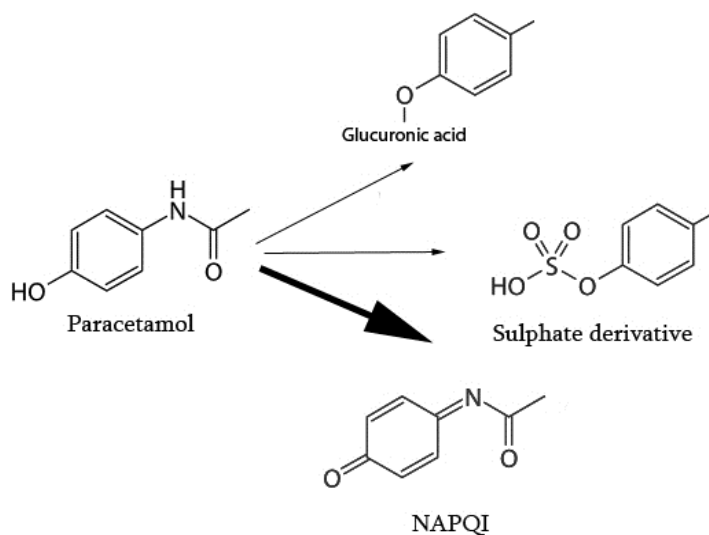


Fig. 3. Paracetamol metabolism in cats

Non-steroidal antiinflammatory drugs like aspirin, ibuprofen, naproxen, diclofenac, phenylbutazone or piroxicam are also conjugated with glucuronic acid in most of the mammalian species. Slow glucuronidation in cats results in long elimination half-lives and consequent gastroduodenal ulcers and renal damage associated with NSAIDs. Diazepam and its several metabolites are also conjugated to glucuronic acid in the liver. Half-lives of diazepam are 2.5-3.2 h and 5.5 h in dogs and cats, and half-lives of nordiazepam (the primary metabolite of diazepam) is 3 h and 21.3 h in dogs and cats, respectively, indicating significant differences between the two species (Plumb, 2005).

In *dogs*, Phase II acetylation reactions are absent, but this has much less importance in veterinary medicine compared to the deficiencies in the cat. These reactions occur when conjugating aromatic amino groups (Williams, 1967), for instance in case of most sulfonamides (Figure 4.). This defect in dogs has an advantage however, as acetylated sulfonamides are less water soluble than the parent compounds and are precipitated in kidney tubules causing renal damage in humans and several animal species. In dogs, however, this side effect is less frequent according to the lack of acetylated metabolites.

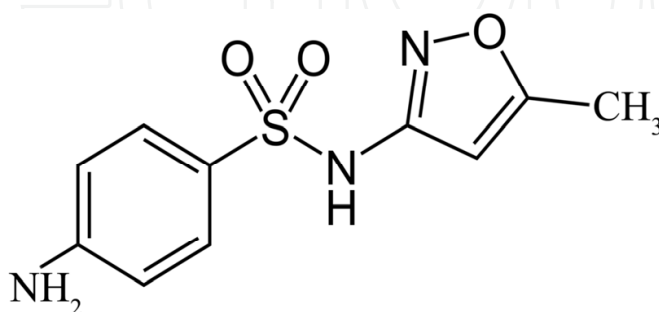


Fig. 4. Sulfamethoxazole, an antibacterial agent with an aromatic amino group

In *pigs*, sulphate conjugation is present only in a low extent, but as this pathway is primarily an alternative to glucuronidation, the latter mechanism overcomes this deficiency, resulting in no known clinical importance in the veterinary practice.

5.2 Induction and inhibition of enzymes involved in metabolism

Enzyme induction and enzyme inhibition are the most important factors affecting drug metabolism. Additional factors include decrease in plasma protein binding or decrease in hepatic blood flow.

Enzyme induction in humans has been experienced for instance in case phenobarbital, phenytoin or rifampin. In animals, inductive capabilities are different. In rats, for instance phenobarbital has much lower while rifampin has negligible effect on CYP3A enzymes (Lu et al, 2001). The most thoroughly studied inducer of CYP₄₅₀ enzymes is phenobarbital, a frequently applied antiepileptic sedative in dogs and cats. In humans it is a potent inducer of CYP3A4, CYP2B6 and CYP2C19. As this medication is given long term (usually lifelong) to veterinary patients, the phenomenon has significant clinical consequences. Phenobarbital accelerates metabolism and thus decreases duration of action of drugs given in conjunction with the barbiturate and metabolised on inducible CYP₄₅₀ enzymes. Examples include amitriptyline, benzodiazepines, phenothiazines, tramadol or fentanyl. As phenobarbital also induces CYP2C19, the enzyme responsible for its own metabolism, the half-life of phenobarbital is subsequently decreased. Therefore, in animals receiving phenobarbital, plasma phenobarbital levels should regularly be checked and dosage adjusted to attain therapeutic levels. Phenytoin is another antiepileptic, that has pronounced enzyme inducer activity. Clinically it is useless in dogs, as it is a strong inducer of microsomal enzymes and therapeutic concentrations can only be achieved in the first days of treatment, after that autoinduction decreases plasma levels rapidly (Frey et al., 1980).

Enzyme inhibition is peculiar to several drugs, like cimetidine, omeprazole, macrolide antibiotics (erythromycin, clarithromycin), ketoconazole, certain fluoroquinolones or chloramphenicol. Omeprazole and lansoprazole are known inhibitors of the human CYP1A subfamily, while pantoprazole has the lowest inhibitory action among the proton pump inhibitors (Masubuchi et al., 1997). These drugs increase half-life of numerous drugs leading to potential side effects. Erythromycin and clarithromycin increases risk of toxicity in case of terfenadine or theophylline. Azithromycin seems to have little potential of CYP₄₅₀ induction. Cimetidine and some fluoroquinolones also increase theophyllin plasma levels by inhibiting CYP1A2 in dogs (Fink-Gremmels, 2008). Ketoconazole increases midazolam plasma levels by interacting with CYP3A4 (Kuroha et al., 2002). One of the most significant metabolic interaction is observed in case of macrolides or pleuromutilins and the ionophore antibiotics. Namely, administration of erythromycin, tiamulin and valnemulin concomitantly with anticoccidial ionophores (monensin, salinomycin, narasin) causes significant increase in mortality, mainly because of decreased elimination of the latter substances. The most frequently investigated interaction is between monensin and tiamulin. According to these data it can be pronounced that tiamulin inhibits biotransformation of monensin on CYP3A subfamily, and very low margin of safety associated with monensin can increase mortality (Nebbia et al., 1999, Szucs et al., 2004).

6. Drug excretion

In the course of metabolism the primary purpose of biotransformation is to increase water solubility of drugs making them capable of elimination. Certain drugs are polar and hydrophilic enough to be excreted unchanged. Examples include the penicillins or the aminoglycosides, that are excreted with the urine in an active form. In point of fact elimination consists of metabolism and excretion, but polar drugs are eliminated mainly by excretion only. Excretion of xenobiotics follows usually first order kinetics, a certain ratio of a drug is eliminated in a certain amount of time. In some cases however, elimination follows zero order kinetics, and only a certain amount of drug is eliminated in a certain amount of time. This happens, when the excretion mechanisms become saturated, for instance in severe renal insufficiency.

Renal excretion is the most important route of elimination. Polar, hydrophilic drugs can be eliminated via the urine and this includes several unchanged (not metabolised) substances. In case of antibiotics it is of great importance, whether the drug is excreted in an active or inactive form when treating urinary tract infections. Antibacterial agents, like penicillins, most of the cephalosporins and aminoglycosides are practically not metabolised, short acting tetracyclines and fluoroquinolones are metabolized in a low extent, but eliminated mainly with the urine. All of the before mentioned substances are effective in the treatment of urinary tract infections, but certainly pharmacodynamic considerations must also be considered. Renal excretion involves passive glomerular filtration and active tubular secretion, mainly in the proximal tubule. The latter requires energy and carrier molecules („organic anion transporters”), and the process can be saturated. As active secretion plays an important role in the excretion of several substances, like most of the beta lactams, inhibiting the process significantly reduces elimination, thus increases half-life of these medicines. Probenecid, a substance inhibiting these carrier mediated transport mechanisms played an important role in prolonging the effect of penicillin (Kampmann et al., 1972).

Probenecid is still used concurrently with several medicines (carbapenems, antiviral agents) to increase their half-life.

Glomerular filtration is a passive process and is significantly hindered by extensive (>80%) plasma protein binding. For instance, cefovecin, a third generation veterinary cephalosporin has over 95% protein binding in dogs and cats, therefore half-lives in these species are very long, 133 h and 166 h, respectively.

Reabsorption in the distal tubule plays an important role in prolonging half-life of drugs. Nonionized, lipophilic substances can diffuse passively from the tubular fluid back to plasma. As several drugs are weak acids or bases, pH of the urine has top priority when predicting tubular reabsorption of these substances. Acidification of the urine increases ionization of weak alkaline substances, while alkalization increases ionization of weak acids, and these polar molecules are ion trapped in the tubular fluid. This fact helps to govern the elimination of some potentially toxic substances via urine. Excretion of alkaloids, like atropine or caffeine can be enhanced by urine acidifiers. Elimination of acidic substances, like most of the NSAIDs or the barbiturates can be accelerated by alkalizing the urine.

Biliary excretion of xenobiotics is less decisive, than renal excretion and mainly depends on molecular weight. Molecules larger than 500D are usually excreted with the bile in all animal species and humans. Dogs, rats and chickens are „better” biliary eliminators, in these animal species smaller (300-400D) molecules are also excreted via this route. The nature of the xenobiotic largely influences the route of excretion. Certain drugs, like erythromycin, lincomycin, clindamycin, chloramphenicol, ketoconazole, griseofulvin or the methylxanthines are primarily excreted with the bile. Conjugated forms of these substances can be deconjugated in the small intestine by bacterial β -glucuronidase enzymes and can be reabsorbed. This enterohepatic circulation (Figure 5.) can significantly increase half-life of certain drugs, like the xanthine derivatives. Thus, administration of activated charcoal in theophylline or theobromine (chocolate) toxicosis in dogs and cats is highly effective in reducing half-life by binding to intestinal portions of the substance and hindering its reabsorption.

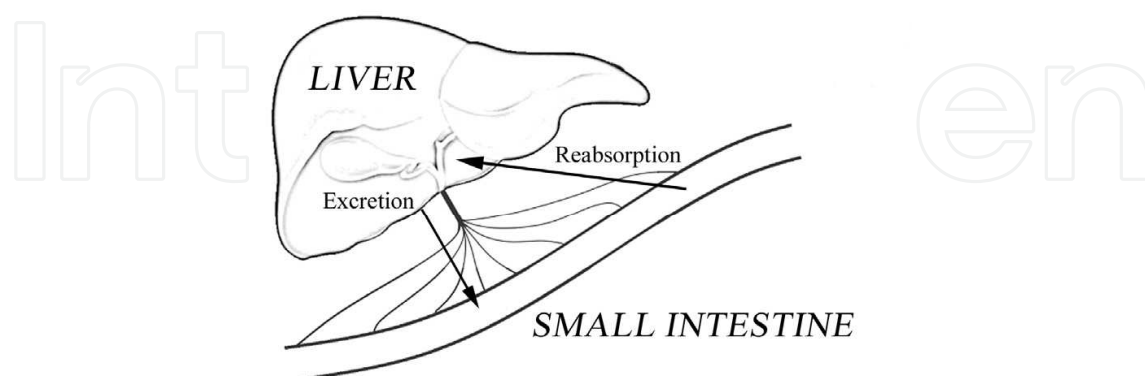


Fig. 5. Enterohepatic circulation of drugs

Elimination via milk and eggs is also important in the veterinary medicine. Several lipophilic drugs are excreted partly with the milk. As an example, 3.8% and 6.8% of the dosage of

erythromycin and spiramycin, two lipophilic macrolide antibiotics is excreted via the milk, respectively (Giguere et al., 2006). Penethamat can also attain high concentrations in the milk after intramuscular administration. Relatively high drug concentrations in the milk necessitate caution when determining and observing withdrawal time for these substances. Elimination via the eggs is of high practical importance in laying hens. For instance, several anticoccidials, like robenidine must not be applied to egg producing animals, as drug reaches high concentrations and gives an unpleasant taste to the egg.

6.1 Half-life of drugs

Elimination half-life ($t_{1/2}$) is the time when plasma levels of the drug decline to half and is an essential parameter when comparing elimination of drugs between species. The half-life is usually independent from the dosage, as elimination generally follows first order kinetics, and a certain ratio is eliminated from the body in a certain amount of time. As the dosage is increased and excretion capacity becomes saturated, the elimination will show zero order kinetics, and half-lives will be significantly longer. An example for this is acetyl-salicylic acid (aspirin) in cats. Because of this phenomenon, aspirin is usually administered with 48-72 hour intervals to cats if less toxic drugs are not available or not appropriate for the disease condition. As half-life of drugs show pronounced differences, it is crucial in determining dosage and dosing interval and to predict toxic effects in animals. Theobromine for instance that has approx. 7 hours half-life in humans is very slowly eliminated in dogs and cats (dog $t_{1/2}$ is 17.5 h), and frequently causes poisoning when chocolate is given to these species. Sulfonamides and trimethoprim are good examples to demonstrate differences in half-lives among species. Trimethoprim for instance has 1.25 h half-life in cattle, 3.2 h in horses, 4.6 h in dogs and 10.6 h in humans. Its partner sulfamethoxazole has 2.3 h half-life in cattle, 4.8 h in horses and 10.1 h in humans. Differences in these parameters necessitate the adaptation in drug dosing in the different species. Similar half-life of sulfonamides and trimethoprim in humans makes it an excellent combination pharmacodynamically and pharmacokinetically. In animals, however, half-life of the sulfonamides and trimethoprim is infrequently similar, thus efficacy of the combination is less pronounced and needs correction in the ratio of the substances in veterinary products. An other important group with pregnant differences are the NSAIDs. Aspirin for instance has 7.5 h elimination half-life in dogs and 37.6 h in cats. This necessitates the prolongation of the dosage interval in cats, as described above. In conclusion it can be stated that half-life of drugs is essential when determining dosage and dosage intervals in each animal species, and prolonged half-lives of certain drugs play a crucial part in evoking toxicoses in animals, especially in those with defects in elimination, like cats.

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