9

Comparative Veterinary Pharmacokinetics

Akos Jerzsele
Szent Istvan University-Faculty of Veterinary Science,
Department of Pharmacology and Toxicology
Hungary

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 adiministration), 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 continous 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 conspicouos, 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.

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

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 parvovirosis) 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 parvovirosis (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 anthelminthics. 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 (Agerso&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 form 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 anthelminthic 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 anthelminthics 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 anthelminthics. 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

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.

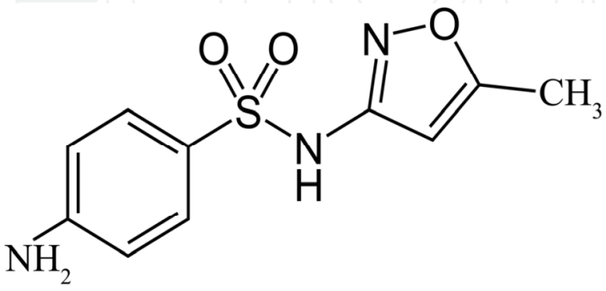


Fig. 4. Sulfametoxazole, an antibacterial agent with an aromatic amino group

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 inhibiton 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, inducive 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 CYP_{450} 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 CYP_{450} 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 CYP_{450} 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 concomittantly 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 alkalinization 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.

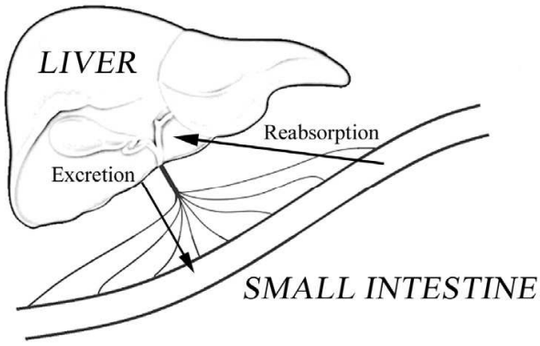


Fig. 5. Enterohepatic circulation of drugs

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-salycilic 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 posioning 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 sulfamethoxasole 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.

7. Acknowledgement

I would like to express my gratitude to Dr. József Lehel and Dr. Melinda Donka-Jerzsele for the thorough and critical supervision of this chapter.

8. References

Aderounmu, AF, Fleckenstein, L. (1983). Pharmacokinetics of chloroquine diphosphate in the dog. *Journal of Pharmacology and Experimental Therapeutics.* 226. pp. 633-9.

Agerso, H, Friis, C. (1998). Bioavailability of amoxycillin in pigs. *Journal of Veterinary Pharmacology and Therapeutics.* 21. pp. 41-46.

Anfossi, P. et al. (2002). Relative oral bioavailability of microgranulated amoxicillin in pigs. *Journal of Veterinary Pharmacology and Therapeutics.* 25. pp. 329-334.

Arancibia, A. et al. (1988). Dose-dependent bioavailability of amoxycillin. *Journal Of Clinical Pharmacology Therapy And Toxicology*. 26. pp. 300-303

Baggot, JD. et al. (1988). Clinical pharmacokinetics of metronidazole in horses. *Journal of Veterinary Pharmacology and Therapeutics.* 11. pp. 417-420.

Brown, SA. et al. (1991) Ceftiofur sodium: disposition, protein-binding, metabolism, and residue profile in various species. *Acta Veterinaria Scandinavica.* 87 (suppl). pp. 97–99.

Cagnardi, P. et al. (2010). Cefoperazone sodium preparation behavior after intramammary administration in healthy and infected cows. *Journal of Dairy Science.* 93. pp. 4105-4110.

Capece, BPS. et al. (2001). Effect of ruminal microflora on the biotransformation of netobimin, albendazole, albendazole sulfoxide, and albendazole sulfoxide enantiomers in an artificial rumen. *Journal of Animal Science*. 79. 1288-1294.

Carretero, C. et al. (2002). Pharmacokinetics of marbofloxacin in mature horses after single intravenous and intramuscular administration. *Equine Veterinary Journal.* 34. pp. 360-365.

Cox, SR. et al. (2010). The pharmacokinetics of mavacoxib, a long-acting COX-2 inhibitor, in young adult laboratory dogs. *Journal of Veterinary Pharmacology and Therapeutics.* 33. pp. 461-70.

Costa, LG. (2006). Current issues in organophosphate toxicology. *Clinica Chimica Acta.* 366. pp. 1–13.

Davis, JL. et al. (2002). Pharmacokinetics of azithromycin in foals after i.v. and oral dose and disposition into phagocytes. *Journal of Veterinary Pharmacology and Therapeutics.* 25. pp. 99-104.

Dawidowicz, A. et al. (2000). The Role of Human Lungs in the Biotransformation of Propofol. *Anesthesiology*. 93. pp. 992-997.

De Boever, S. et al. (2005). Pharmacokinetics and oral bioavailability of pentoxyfylline in broiler chickens. *Journal of Veterinary Pharmacology and Therapeutics*. 28. pp. 575-580.

Duffee, NE. et al. (1997). The pharmacokineitics of cefadroxil over a range of oral doses and animal ages in the foal. *Journal of Veterinary Pharmacology and Therapeutics*. 20. pp. 427-433.

Ehinger, AM. et al. Tissue distribution of cefquinome after intramammary and "systemic" administration in the isolated perfused bovine udder. 2006. *The Veterinary Journal*. 172. 1. pp. 147-153.

El-Sooud, KA. et al. (2004). Comparative pharmacokinetics and bioavailability of amoxycillin in chickens after intravenous, intramuscular and oral administrations. *Veterinary Research Communications*. 28. pp. 599-607.

Ensink, JM. et al. (1996). Bioavailability of pivampicillin and ampicillin trihydrate administered as an oral paste in horses. *Veterinary Quarterly*. 18. pp. 117-20.

Ensink, JM. et al. (1992). Bioavailability of oral penicillins in the horse: a comparison of pivampicillin and amoxicillin. *Journal of Veterinary Pharmacology and Therapeutics*. 15. pp. 221-230.

Fink-Gremmels, J. (2008). Implications of hepatic cytochrome P_{450}-related biotransformation processes in veterinary sciences. *European Journal of Pharmacology. 585. pp. 502-509.*

Frey, HH, Löscher, W. (1980). Clinical pharmacokinetics of phenytoin in the dog: a reevaluation. *American Journal of Veterinary Research*. 41. pp. 1635-1638.

Gemer, O. et al. (1983). Absorption of orally administered gentamicin in infants with diarrhea. *Pediatric Pharmacology*. 3. pp. 119-123.

Geyer, J. et al. (2009). Brain penetration of ivermectin and selamectin in mdr1a,b P-glycoprotein- and bcrp- deficient knockout mice. *Journal of Veterinary Pharmacology and Therapeutics*. 32. pp. 87-96.

Giguere, S. et al. (2006). *Antimicrobial therapy in veterinary medicine*. 4th Edition. Blackwell Publishing. Ames, Iowa.

Gokbulut, C. et al. (2006). Plasma disposition and faecal excretion of netobimin metabolites and enantiospecific disposition of albendazole sulphoxide produced in ewes. *Veterinary Research Communications*. 30. 791-805.

Guengerich, FP. (1997). Role of cytochrome P_{450} enzymes in drug–drug interactions, *Advances in Pharmacology.* 43. pp. 7–35.

Hustace, JL. et al. (2009). Pharmacokinetics and bioavailability of metformin in horses. *American Journal of Veterinary Research*. 70. pp. 665-668.

Jerzsele, A. et al. (2011). Oral bioavailability and pharmacokinetic profile of the amoxicillin-clavulanic acid combination after intravenous and oral administration in turkeys. *Journal of Veterinary Pharmacology and Therapeutics.* 34. pp. 202-205.

Jerzsele, A. et al. (2009). Oral bioavailability and pharmacokinetic profile of the amoxicillin-clavulanic acid combination after intravenous and oral administration in broiler chickens. *Journal of Veterinary Pharmacology and Therapeutics.* 32. pp. 506-509.

Jerzsele, A., Semjén, G. (2006). The usage of the amoxicillin-clavulanic acid combination in the veterinary practice. Magyar Állatorvosok Lapja. 7. pp. 419-426.

Kampmann, J. et al. (1972). Effect of some drugs on penicillin half-life in blood. *Clinical Pharmacology and Therapeutics.* 13. pp. 516-519.

Kappers, WA. (2001). Diazinon is activated by CYP2C19 in human liver, *Toxicology and Applied Pharmacology.* 177. pp. 68–76.

Kaukinen, H. et al. (2010). Bioavailability of detomidine administered sublingually to horses as an oromucosal gel. *Journal of Veterinary Pharmacology and Therapeutics.* 34. pp. 76–81.

Kietzmann, M. et al. (2010). Tissue distribution of cloxacillin after intramammary administration in the isolated perfused bovine udder. *BMC Veterinary Research.* 6. 46.

Kluge, K, Ungemach, FR. (1999). Investigation of ampicillin plasma concentration after oral application in dogs. Are recommended dosages sufficient? *Tierarztliche Praxis Ausgabe Kleintiere Heimtiere.* 27. pp. 150-154.

Kung, K. et al. (1993). Pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin after intravenous and oral administration of enrofloxacin in dogs, *Journal of Veterinary Pharmacology and Therapeutics.* 16. pp. 462–468

Kung, K., Wanner, M. (1994). Bioavailability of different forms of amoxycillin administered orally to dogs. *The Veterinary Record*. 135. pp. 552-554.

Kung, K. et al. (1995). Effect of the interval between feeding and drug administration on oral ampicillin absorption in dogs. *Journal Of Small Animal Practice.* 36. pp. 65-68.

Kuroha, M. et al. (2002). Effect of multiple dosing of ketoconazole on pharmacokinetics of midazolam, a cytochrome P-450 3A substrate in beagle dogs. Drug Metabolism and Disposition. 30. pp. 63-68.

Le Traon, G., et al. (2009). Pharmacokinetics of cimetidine in dogs after oral administration of cimetidine tablets. *Journal Of Veterinary Pharmacology And Therapeutics.* 32. pp. 213-218.

Lu, C., A. Li. (2001). Species comparison in P450 induction: effects of dexamethasone,omeprazole, and rifampin on P450 isoforms 1A and 3A in primary cultured hepatocytes from man, Sprague-Dawley rat, minipig, and beagle dog. *Chemico-Biological Interactions*. 134. pp. 271-281.

Masubuchi, N., Okazaki, O. (1997). An evaluation of the CYP1A induction potential of pantoprazole in primary rat hepatocytes: a comparison with other proton pump inhibitors. *Chemico Biological Interactions*. 107. pp. 63-74.

Matot, I. et al. (1993). Pulmonary uptake of propofol in cats. Effect of fentanyl and halothan. *Anesthesiology*. 78. pp. 1157-1165.

Meyer, S, et al. (2009). Pharmacokinetics of intravenous ceftiofur sodium and concentration in body fluids of foals. *Journal Of Veterinary Pharmacology And Therapeutics.* 32. pp. 309-316.

Montesissa, C. et al. (1989). Comparative microsomal oxidation of febantel and its metabolite fenbendazole in various animal species. *Xenobiotica*. 19. 97-100.

Musulin, SE., et al. (2011). Diazepam pharmacokinetics after nasal drop and atomized nasal administration in dogs. *Journal of Veterinary Pharmacology and Therapeutics*. 34. pp. 17–24.

Nakamura, M. et al. (1994). Induction of cytochrome P-450 isozymes in rat renal microsomes by cyclosporin A. *Biochemical Pharmacology*. 48. 1743–1746.

Nebbia, C. et al. (1999). Oxidative metabolism of monensin in rat liver microsomes and interactions with tiamulin and other chemotherapeutic agents: evidence for the involvement of cytochrome P-450 3A subfamily. *Drug Metabolism and Disposition*. 27. pp. 1039-1044.

Nebbia, C. et al. (2003). Comparative expression of liver cytochrome P450-dependent monooxygenases in the horse and in other agricultural and laboratory species, *Veterinary Journal.* 165. pp. 53–64.

Owens, WE. et al. (1990). Determination of milk and mammary tissue concentrations of ceftiofur after intramammary and intramuscular therapy. *Journal of Dairy Science*. 73. pp. 3449-3456.

Perry, SM, et al. (1991). Effect of i.v. anaesthesia with propofol on drug distribution and metabolism in the dog. *British Journal of Anaesthesia*. 66. pp. 66-72.

Plumb, DC. (2005). *Plumb's Veterinary Drug Handbook*. 5th Edition. Blackwell Publishing. Ames, Iowa.

Reyns, T. et al. (2007). Disposition and oral bioavailability of amoxicillin and clavulanic acid in pigs. *Journal of Veterinary Pharmacology and Therapeutics*. 30. pp. 550-555.

Riviere, JE., Papich, MG. et al. (2009). *Veterinary Pharmacology and Therapeutics*. 9th Edition. Wiley-Blackwell Publishing. Ames, Iowa.

Roulet, A. et al. (2003). MDR1-deficient genotype in Collie dogs hypersensitive to the P-glycoprotein substrate ivermectin. *European Journal of Pharmacology*. 460, pp. 85-91.

Schinkel, AH. 1999. P-glycoprotein, a gatekeeper in the blood–brain barrier *Advanced Drug Delivery Reviews*. 36. pp. 179-194.

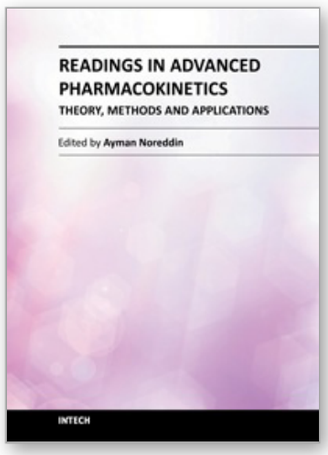
Soback, S. et al. (1995). Florfenicol pharmacokinetics in lactating cows after intravenous, intramuscular and intramammary administration. *Journal of Veterinary Pharmacology and Therapeutics*. 18. pp. 413-7.

Szucs, G. et al. (2004). Biochemical background of toxic interactions between tiamulin and monensin. *Chemico Biological Interactions*. 147. pp. 151-161.

Weisburger, JH. et al. (1964). The metabolism of N-2-fluorenylacetamide in the cat: Evidence for glucuronic acid conjugates. *Biochemical Pharmacology*. 13. pp. 469-475.

Williams, RT. (1967). Comparative patterns of drug metabolism. *Federation Proceedings.* 26. pp. 1029–1039.

Yamazaki, T. et al. (2008). The intracellular accumulation of phagocytic and epithelial cells and the inhibitory effect on Chlamydophila (Chlamydia) pneumoniae of telithromycin and comparator antimicrobials. *Journal Of Chemotherapy*. 20. pp. 428-430.



Readings in Advanced Pharmacokinetics - Theory, Methods and Applications

Edited by Dr. Ayman Noreddin

ISBN 978-953-51-0533-6
Hard cover, 378 pages
Publisher InTech
Published online 20, April, 2012
Published in print edition April, 2012

This book, "Readings in Advanced Pharmacokinetics - Theory, Methods and Applications", covers up to date information and practical topics related to the study of drug pharmacokinetics in humans and in animals. The book is designed to offer scientists, clinicians and researchers a choice to logically build their knowledge in pharmacokinetics from basic concepts to advanced applications. This book is organized into two sections. The first section discusses advanced theories that include a wide range of topics; from bioequivalence studies, pharmacogenomics in relation to pharmacokinetics, computer based simulation concepts to drug interactions of herbal medicines and veterinary pharmacokinetics. The second section advances theory to practice offering several examples of methods and applications in advanced pharmacokinetics.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen