SOLVING PROBLEMS IN DRUG THERAPY: CLINICAL PHARMACOLOGY
DOGS ARE NOT PEOPLE, CATS ARE NOT DOGS
Tara Bidgood, DVM, PhD, DACVCP

Introduction
Efficacy, safety, and pharmacokinetics of drugs can vary significantly among dogs, cats, and humans due to physiologic and anatomical differences. Today, drugs in several different therapeutic categories are approved for use in companion animals. If an approved animal drug for a specific indication does not exist, then veterinarians often use animal drugs or human drugs in an extra-label manner. Simply extrapolating human drug dosages for use in cats and dogs can lead to reduced efficacy or even toxicity. There are several examples where the absorption, distribution, metabolism, and/or elimination of drugs differs among species. Obtaining an understanding of these differences will enable veterinarians to make rational individualized drug therapy choices for their patients.

Within this manuscript, recommendations for medical treatment may be covered that are not labeled for use in dogs and cats. Whether these are products developed for use in humans, or are extra-label use of veterinary products, the recommendations are based on medically recognized standards of care.

Absorption
Oral administration of drugs is convenient and enables therapies for chronic conditions to be given by the pet owner. Oral absorption can differ between humans and companion animals due to differences in physiology, anatomy, and physicochemical properties of the drug.

Compared to humans, the gastrointestinal length is shorter and the gastric emptying time is longer in dogs (National Institute for Public Health and the Environment). These differences can affect the rate and extent of absorption of drugs. For example, in humans, enteric coated aspirin was designed to reduce stomach irritation by delaying absorption until the drug reached the small intestine. In a study where dogs were administered enteric coated aspirin, oral absorption was incomplete, gastric retention of tablets occurred, and partially digested tablets were found in the feces of some dogs (Nap et al. 1990). Many human sustained release preparations allow convenient dosing regimens such as once a day administration in people. Many of these preparations have been investigated for their potential use in companion animals; however, pharmacokinetic differences between species have shown that many of these sustained release preparations do not have 24-hour duration of efficacy in dogs. Immediate release (IR) tramadol has been used for the control of pain in dogs. Immediate release tramadol has been recommended to be administered every 6–12 hours. Interest has been generated over the use of the tramadol HCL extended release (ER) tablets to provide more convenient dosing regimens in dogs. In people, tramadol HCL ER tablets are labeled for one a day administration for management of moderate to moderately severe chronic pain (Ultram® ER package insert). Preliminary studies have been performed to determine the pharmacokinetics and in vitro dissolution of the tramadol ER tablets in dogs (Giorgi et al. 2008; Papich et al. 2008). Although the half life after administration of the ER formulation in dogs was longer than the IR formulation, the results did not support once a day administration in dogs (Giorgi et al. 2008; Papich et al. 2008). In addition, in vitro dissolution tests revealed that dissolving occurred within 30 minutes after breaking the tablet (Papich et al. 2008). Therefore, clinically, if a dog chewed the ER formulation it could result in rapid release of the drug and increase the potential for adverse effects (Papich et al. 2008).

Oral narcotics are frequently prescribed for human patients to control pain associated with chronic medical conditions. Dose recommendations for oral morphine can be found in many veterinary drug reference textbooks. However, little research has been performed to determine plasma concentrations that correlate with clinical efficacy in dogs. Pharmacokinetics and efficacy evaluation of several oral narcotics have been performed in dogs to explore the potential use in the management of chronic pain. Studies with morphine sulfate extended release tablets in dogs showed poor and erratic absorption after oral administration (Kukanich et al. 2005a). In addition, concentrations were below concentrations determined to be therapeutic in humans (Kukanich et al. 2005a). Studies with codeine (Findlay et al. 1979) and methadone (Kukanich et al. 2005b) have also demonstrated low bioavailability after oral administration. Based on these studies, clinical use of oral narcotics in dogs is limited.

Distribution
Many drugs used daily in clinical practice are highly protein bound. The clinical significance of protein binding displacement interactions, when two highly protein bound drugs are administered concurrently, is likely...
insignificant for the majority of drugs. It is the free (unbound) drug that is active and can cross capillary membranes and act at the target site. Drugs that are highly protein bound (> 70%), are extensively metabolized in the liver, administered parenterally, and have a low therapeutic index can exhibit changes in unbound drug concentrations with displacement interactions, and these changes may be clinically significant (Benet & Hoener 2002). Fortunately, very few drugs meet these criteria (Benet & Hoener 2002).

The volume of distribution quantifies drug distribution in the body. A drug with a high volume of distribution indicates the drug is distributed to fluids other than plasma. Drugs that are highly lipophilic often have high volume of distribution because they are able to cross cell membranes. Some antimicrobial drugs have been promoted as being highly lipophilic and able to attain high tissue concentrations. However, drugs that are highly lipophilic are not necessary superior for treating bacterial infections. Most bacterial infections are extracellular, and achieving adequate concentrations in the extracellular fluid (ECF) of tissues is necessary for therapeutic success. A drug does not need to be lipophilic or have a high volume of distribution to achieve adequate ECF concentrations. In a study comparing fluoroquinolones, the higher lipophilicity and volume of distribution of enrofloxacin did not result in superior ECF antimicrobial distribution compared to marbofloxacin (Bidgood & Papich 2005). Penicillins and cephalosporin drugs also have low lipophilicity, but they attain good ECF concentrations.

**Metabolism**

Generally, after absorption drugs are eliminated as the parent compound or are metabolized to various metabolites before elimination. Metabolism offers a way to increase the solubility of drugs and therefore increase their excretion from the body. Extrapolation and prediction of drug metabolism mechanisms between species is difficult, and species differences in metabolism are a major source of variation in drug activity and toxicity. There are several examples of drug metabolism differences between species and within a species. For example, dogs metabolize benzodiazepines more rapidly than humans (Lin 1995), and the half life of most NSAIDs is longer in cats than in dogs (Taylor et al. 1996; Gassel et al. 2006).

Mutations in the MDR 1 gene coding for p-glycoprotein has been identified in collies and related breeds (Mealey et al. 2001). As a result these breeds were shown to be more sensitive to the neurotoxicity side effects of avermectins (hypersalivation, mydriasis, ataxia, muscle tremors, depression, and coma) (Mealey et al. 2001; Mealey 2006). Other breeds that have been identified as having mutations in the MDR-1 gene include the Australian shepherd, English shepherd, Shetland sheepdog, Old English sheepdog, longhaired whippet, and silken windhound (Neff et al. 2004; Mealey 2006). Dogs with the MDR-1 mutation may also show side effects with other drugs, including acepromazine, butorphanol, vincristine, doxorubicin, and digoxin (Mealey et al. 2003; Mealey 2006). The Clinical Pharmacology laboratory at Washington State University College of Veterinary Medicine has the ability to test for the presence of the MDR-1 mutation in dogs.

Greyhounds have shown differences in efficacy and toxicity of drugs compared to other breeds. Greyhounds have shown differences in the metabolism of thiobarbiturates (Sams et al. 1995), propofol (Court et al. 1999), midazolam (Kukanich et al. 2008a), and amikacin (Kukanich et al. 2008b) compared to other breeds. Studies have suggested the difference in drug disposition seen with greyhounds may be attributed to a decrease in CYP mediated drug metabolism and/or differences in body composition (percent body fat, muscle mass). Dose selection and/or dose adjustment may be required for these drugs when administered to greyhounds.

Prednisone is metabolized by the liver to the active metabolite prednisolone. Both prednisone and prednisolone are available as commercial formulations. In dogs similar area under the curve parameters for prednisone or prednisolone are achieved when either drug is administered orally. When cats were administer 10 mg oral tablets of prednisone or prednisolone in a crossover study, lower concentrations were achieved after administration of prednisone compared to prednisolone (Graham-Mize & Rosser 2004).

Phase II enzymes are responsible for conjugation reactions (glucuronidation, sulfation, methylation, acetylation, glutathione conjugation, glycosidation), and species differences exist in phase II metabolism. The classic example has been the reduced ability of cats to conjugate drugs with glucuronic acid for some drugs (e.g., acetaminophen). In dogs the acetylation pathway is absent, and a decreased N-acetylation activity can result in toxicity of some drugs (sulfonamides, procainamide, hydralazine) (Trepanier et al. 1997).
Elimination
Compared to hepatic metabolism, differences in renal elimination in dogs and cats are relatively minor. Gabapentin is a human drug that has been used incorporated into a multimodal approach to manage chronic pain in dogs. In humans there is no biotransformation of gabapentin in the liver, and it is primarily excreted in the urine (Vollmer et al. 1986). In dogs, gabapentin is metabolized to N-methyl-gabapentin (up to 34% of the dose). Both the parent compound and the metabolite are excreted in the urine, but up to 32% of the administered dose is excreted in the feces of dogs (Vollmer et al. 1986).

References

