

Veterinary Pharmacology in Human Health Discovery Research - The Use of Laboratory Animals in Pharmaceutical Research: Species Similarities and Differences in Pharmacokinetics

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Introduction

Pharmacokinetics not only support drug safety and efficacy evaluation during the drug development, but also play a very important role in the drug discovery. Many drug companies now include pharmacokinetics as part of their screening criteria. A drug is not worth developing even if it is the most potent compound in an *in vitro* pharmacological test, if it is poorly absorbed or is so rapidly eliminated that it shows no activity *in vivo*. Thus, the key criteria for the selection of a drug candidate are good oral absorption and a reasonably long biological half-life. At the early stage of drug discovery, there is usually a very small quantity of each compound available. This limits kinetics studies to one or two animal species. Therefore, the selection of animal species and experimental design of studies are important in order to provide a reliable prediction of drug absorption and elimination in humans. After clinical studies show a drug to be pharmacokinetically unsatisfactory, it is very costly to start again with a new compound.

The purpose of this review is to show some species similarities and differences in drug absorption, distribution, metabolism and excretion (ADME) with an attempt to address the question of whether animal data can be extrapolated to humans. Whenever possible, the underlying mechanisms responsible for these similarities and differences

will be discussed and examples given for illustration.

Allometry and Biological Similarities

Humans share with other mammals many similarities in anatomy, physiology and biochemistry (Economos, 1979). The most obvious differences are their size and shape. Many anatomic and physiological parameters can be described as exponential functions of body weight, using the allometric equation expressed as (Gould, 1966; Calder, 1984):

$$Y = aW^b \quad (1)$$

Where Y is an anatomical or physiological parameter, W is the body weight, a is the allometric coefficient, and b is the allometric exponent.

The allometric equation for liver weight (kg) as a function of total body weight (kg) is $0.037 W^{0.85}$ (Boxenbaum, 1980). The liver is 4.5% of the total body weight in a 250 g rat and 2% in a 70 kg man. Similarly, the allometric equation for kidneys (g) as a function of total body mass (g) is $0.021 W^{0.85}$ (Adolph, 1949). The kidneys are 0.9% of total body weight in a 250 g rat and only 0.4% in a 70 kg man. Since both the liver and kidney play important role in the elimination of drugs, the concept of relative organ size must be taken into

consideration when species differences in drug elimination are compared. The relative organ size decreases as animal size increases. Furthermore, the relative amount of hepatic enzymes (such as cytochrome P-450) and the relative number of nephrons are higher in small animals than in humans. Thus, we would expect small animals to eliminate drugs more rapidly than human beings.

Physiological functions also change as a function of total body weight in an allometric manner. For example, the allometric relationship between the blood circulation time (sec) and total body weight (kg) is $21 W^{0.21}$ (Stahl, 1967). The blood circulation time is 15 sec in a 250 g rat and 50 sec in a 70 kg man. This means that a drug molecule circulates the body four times every minute in the rat and only once per minute in man. Similarly, both relative hepatic and renal blood flow (ml/min/kg) decrease as the animal size increases. The exponent values are 0.89 for hepatic blood flow (Boxenbaum, 1980) and 0.77 for renal blood flow (Edwards, 1975). Thus, the smaller species deliver drugs more frequently and faster to the eliminating organs, and eliminate the drugs, particularly those with high clearances, more rapidly. However, some physiological parameters, such as body temperature (36-38°C), hematocrit (40-45%) and serum albumin (3-4 g/dl) are relatively constant among animals and are independent of animal size (Davies & Morris, 1993).

Physiological and Allometric Models

Two well known methods, the physiological and allometric models have been employed to predict the pharmacokinetics in man from data in animals. The physiological model offers a mechanistic approach where organs of interest are arranged according to organ size and blood flow to each organ (Bischoff *et al.*, 1971; Lin *et al.*, 1982; Lin *et al.*, 1984). Biochemical parameters, such as plasma protein binding, enzymatic kinetic parameters and excretion clearance determined *in vitro* and *in vivo*

are often incorporated into the model. Using this approach, the kinetic behaviors of drugs in humans can be predicted. In contrast, the allometric approach is more empirical, examining the relationships between body size, time and kinetic parameters without necessarily understanding the underlying mechanisms (Chappell & Mordeanti, 1991; Boxenbaum & D'Souza, 1990). A linear regression of log-log plot of the kinetic parameters *vs.* the body weight of the animal species produces an allometric relationship from which a particular kinetic parameter in the human can be calculated.

Although both physiological and allometric methods are of academic interest, they are not practical and have only limited use in drug discovery and development. The former approach tends to be costly and time-consuming, with frequent failures in obtaining all the parameters needed. The latter is also costly and time-consuming since it requires the kinetic data from at least four or five species in order to properly define the allometric relationship. Often, these kinetic parameters are not available before the initial clinical studies, which is the time when an accurate prediction of human pharmacokinetics data is needed.

In practice, the selection of a drug candidate for further development in humans relies heavily on the limited information of pharmacokinetics obtained from one or two animal species and on earlier experience gained from similar drugs. Thus, an understanding of the underlying mechanisms for the species differences in pharmacokinetics is important for the interpretation of data.

Species Similarities and Differences in Pharmacokinetics

Absorption

Absorption is a very complicated process. Among the factors that can influence the rate and extent of absorption are gastric and intestinal transit time and pH, aqueous solubility and lipophilicity of the drug. Gastric emptying times in

laboratory animals are related to their stomach volume and body size. During the fasting state, the half-life of gastric emptying for drugs in solution is about 10 min for the rat, 30 min for the rabbit, 1 hr for the dog and 2 hr for the human (Watanabe *et al.*, 1977; Mizuta *et al.*, 1990; Dressman, 1986; Wilson & Washington, 1989). Transit time of the small intestine also varies among species. It is not surprising that the species dependent gastric emptying and intestinal transit times may result in differences in the rate and/or extent of drug absorption. Furthermore, species differences in gastric and intestinal pH may also contribute to the differences in drug absorption. Humans, rabbits and rats have a lower gastric pH ranging from 1 to 3, and monkeys and dogs have a higher pH ranging from 4 to 5 (Wilson & Washington, 1989; Smith, 1965). When the solubility of a drug is pH-dependent, species differences in absorption of the drug is expected. L-735,524 is a good example.

L-735,524, a potent and specific inhibitor of HIV protease, is currently under investigation for the treatment of AIDS. The aqueous solubility is pH-dependent, 60 mg/ml at pH 3.5 and 0.3 mg/ml at pH 5. When L-735,524 was given orally as a suspension in 0.5% methylcellulose (pH 6.5) at a dose of 10 mg/kg, the bioavailability was 18% for the rat and 16% for the dog. When the same dose of L-735,524 was given as a solution in 0.05 M citric acid (pH 2.5), the bioavailability was 75% in the dog and 20% in the rat. The blood clearance of L-735,524 was 79 and 11 ml/min/kg for rats and dogs, respectively. From the clearance data, an extensive first-pass effect is expected in rats, but not in dogs. In a separate study, the hepatic first-pass extraction in rats was estimated to be about 67% by comparing the concentrations in the systemic circulation during portal or femoral vein infusions at steady state. It was concluded that the low bioavailability in rats was mainly attributed to an extensive first-pass effect. After correction for the hepatic first-pass effect, the extent of absorption of L-735,524 in the rat was estimated to be at least 60%.

The high bioavailability (75%) in dogs for the citric acid solution supports the argument that there was no extensive first-pass effect in this species. The difference in bioavailability in dogs between the citric acid solution and methylcellulose suspension may be attributed to the higher gastric pH and to the pH-dependent solubility of the drug. Because the gastric pH in dogs is high (>pH 4), the majority of the drug in the stomach was not dissolved when dosing in a 0.5% methylcellulose suspension, which in turn resulted in low absorption. No significant difference was observed in the bioavailability in rats receiving the citric acid solution and methylcellulose suspension because the gastric pH in rats is low (<pH 3), and most of the drug was dissolved in the stomach even when given as a methocel suspension.

These results suggest that the gastric pH may play an important role in the absorption of L-735,524. To test this hypothesis, the drug was given orally to dogs as a 100 mg capsule 1 hr after feeding or without food. Both C_{max} and AUC were higher in the fed state than in the fasted state by a factor of 3 to 4. The increased absorption of L-735,524 in dogs is believed to be due to the stimulation of gastric acid secretion by the food and the consequent lowering of pH and enhancement of the solubility of the drug. After understanding the underlying mechanisms for the low bioavailability in rats and dogs, we predicted that L-735,524 would be well absorbed in humans, because humans normally have a low gastric pH, and that the first-pass effect of the drug would be insignificant in man. As expected, when L-735,524 was given orally to AIDS patients (600 mg; ~10 mg/kg), the plasma profiles were similar to those in dogs receiving the same dose (10 mg/kg) in citric acid. The C_{max} and AUC in humans were 10 μ M and 19 μ M·hr, respectively and the corresponding values for dogs were 11.5 μ M and 12.5 μ M·hr.

Another appropriate example is L-365,260, a potent CCK_B receptor antagonist currently under investigation for the treatment of anxiety. This drug has poor aqueous solubility (~2 μ g/ml) and when

given orally as a suspension in 0.5% methylcellulose, bioavailability was 14% for the rat, 9% for the dog and 2% for the monkey (Chen, *et al.*, 1992). The poor bioavailability in all species studied could be attributed to poor absorption and/or extensive first-pass metabolism. To examine the underlying mechanism, an i.v. study was carried out to determine the elimination clearance. Because the blood clearance of L-365,260 in all species was small in relation to the hepatic blood flow, about 15 ml/min/kg, an extensive first-pass metabolism is not expected. Thus, the limited bioavailability of L-365,260 is more likely to be attributable to its poor absorption as a result of its poor aqueous solubility. When L-365,260 was given orally as a solution in PEG 600 to dogs, the bioavailability was increased 8 to 9-fold (~80%). With this information at hand, L-365,260 was dosed in capsules containing PEG 600 in the subsequent clinical studies. The dose-normalized C_{max} and AUC were comparable in the dog and man. When the same dose (50 mg) of L-365,260 in PEG capsules was given orally to dogs (12 kg) and normal volunteers (70 kg), the C_{max} and AUC were 2.3 $\mu\text{g/ml}$ and 450 $\mu\text{g}\cdot\text{min/ml}$ for the dogs and 0.50 $\mu\text{g/ml}$ and 148 $\mu\text{g}\cdot\text{min/ml}$ for normal human subjects. These results suggest that the dog is a useful model for dosage form testing of this drug.

Drugs pass the gastrointestinal lumen into the blood stream *via* two routes: (1) transcellularly, in which the drugs are transported into and through epithelial cells into the bloodstream, and (2) para-cellularly, in which drugs reach the bloodstream *via* the tight junctions between the epithelial cells. These junctions are permeable to water, electrolytes and small molecules (<150 dalton) (Madara & Pappenheimer, 1987). Alendronate, an antiosteolytic agent under investigation in the treatment of a number of bone disorders, is poorly absorbed after oral administration. The bioavailability was 0.9% for the rat, 1.8% for the dog and 1.7% for the monkey (Lin *et al.*, 1991). The poor absorption is most likely attributed to its poor lipophilicity which prohibits transcellular transport

across the epithelial cell membrane, and to its relatively large molecular size (250 dalton) which hinders paracellular transport. The octanol/buffer partition coefficient of alendronate was estimated to be 0.0017 and independent of pH values ranging from 2 to 11. Alendronate has 5 pKa values (0.8 - 12.2) and is completely ionized at this pH range. Since the anatomical structure of epithelial cells is similar in animals and man, and since alendronate can only be absorbed by paracellular transport, one would anticipate that the absorption of alendronate in humans will be very low. As expected, the bioavailability of orally administered drug was less than 1% in normal healthy volunteers.

Although oral absorption is expected to be different among species due to their differences in gastrointestinal physiology, the prediction of absorption in humans has been reasonably successful after appropriate application of pharmacokinetics and careful examination of the underlying mechanisms. In a survey, Clark & Smith (1984) have shown that the extent of absorption of a large variety of drugs is remarkably consistent between animals species and man; however, the bioavailability differs substantially among species. The canine model is particularly popular for oral dosage form testing. The use of dogs in bioavailability studies has been reviewed by Crouthamel and Bekersky (1983) and Dressman (1986). Although the dog is believed to be a useful model, there is still a large discrepancy in bioavailability of drugs in dogs and humans in some cases as the example of L-735,524. Generally, the rat has a high hepatic drug metabolizing activity. If the rat is used as a model, it is important to distinguish whether the low bioavailability is due to poor absorption or to an extensive first-pass effect.

Protein Binding and Tissue Distribution

It has long been known that the extent of binding of drugs to plasma proteins is species-dependent and differs considerably between animal species. The observed species differences in plasma binding may

reflect differences in protein concentrations, and the affinity and/or the number of binding sites on the protein molecule. Differences in plasma binding can independently affect both distribution and elimination of the drug, particularly for those with low clearance, such as MK-571 and MK-417.

Plasma binding of MK-571, a potent leukotriene D₄ antagonist has been studied in 12 mammalian species (Lin *et al.*, 1990). The binding of MK-571 enantiomers to plasma protein is extensive, stereoselective and species dependent. In some species, the S-enantiomer binds to a greater extent than the R-enantiomer, in some, the R-enantiomer binds more extensively and in other species there is no stereoselectivity. For both enantiomers, the unbound fraction in plasma differs by a factor of 8 among the species studied. Further studies with serum albumin suggest that this protein is the major component for MK-571 enantiomer binding, and that the species differences in stereoselective binding which are due to differences in association constants are linked to structural differences in the albumin molecule. The R-enantiomer of MK-571 is bound to rat plasma to a greater extent than the S-enantiomer, while in dog and monkey plasma the reverse is the case. The elimination clearance of the enantiomers is related to the stereoselective plasma protein binding; that with the greater unbound fraction being cleared more rapidly (Tocco *et al.*, 1990). In human plasma, the unbound fraction of R-enantiomer is higher than the S-enantiomer. Thus, it is anticipated that the R-enantiomer will be cleared more rapidly in humans.

MK-417 binding to carbonic anhydrase is another example where clearance can be effected. Carbonic anhydrase, a zinc metalloenzyme, is extensively distributed in red blood cells of all mammals, accounting for more than 90% of the enzyme in the body. MK-417 is a potent investigational carbonic anhydrase inhibitor as a topical ocular hypotensive agent for the treatment of glaucoma. The pharmacokinetic parameters of MK-417 remained unchanged when the dose was

increased from 0.05 to 0.2 mg/kg, whereas the blood clearance and apparent volume of distribution increased substantially when the dose exceeded 2 mg/kg (Lin *et al.*, 1990; Lin *et al.*, 1991). The dose-dependent pharmacokinetics of MK-417 is due to the saturation of protein binding of the limited carbonic anhydrase in blood cells.

The binding of MK-417 to erythrocytes is extensive and species-dependent. The dissociation constant (K_d) is 0.51 μM for the rat, 0.28 μM for the rabbit, 0.073 μM for the dog and 0.023 μM for humans (Lin *et al.*, 1992; Lin *et al.*, 1991). Under linear conditions, the elimination kinetics are also species-dependent. Both blood clearance and half-life were roughly related to their binding affinity, greater K_d values being associated with enhanced elimination. However, the binding data alone cannot quantitatively explain the species differences in the elimination kinetics of MK-417. For example, the difference of K_d between rats and dogs was only 7-fold, and the differences in CL (1.29 ml/hr/kg *versus* 0.038 ml/hr/kg and t_{1/2} (46 hr *versus* 1859 hr) were 33- and 40-fold, respectively. Other factors, such as metabolism, may also contribute to the overall species differences in the elimination kinetics.

Based on the binding data in human erythrocytes and the kinetic parameters from laboratory animals, one would expect that MK-417 would be cleared very slowly, similar to that in the dog with a prolonged half-life of 2 to 3 months. After instillation of MK-417 (0.04 mg/kg) into the eyes of patients, the t_{1/2} was only about 2 weeks, much shorter than expected. For low clearance drugs, such as MK-417, the elimination clearance and t_{1/2} are dependent not only on the plasma or blood binding but also on metabolic activity. Thus, it is difficult to predict the elimination in man from animal data when protein binding and metabolism are involved in the elimination.

Fichtl *et al.* (1991) reported that there were striking species differences in plasma protein binding and volume of distribution (V_d) of propranolol. The values for the V_d varied by more than 20-fold, being

lowest in monkeys and highest in rabbits. However, the distribution volume of unbound drug (V_f) was virtually the same in all species. Consistent with this, Sawada *et al.* (1984) reported that the V_f values of 10 basic drugs are quite similar among species including humans. By definition

$$V_f = V_d / f_p = \frac{V_p}{f_p} + \frac{V_t}{f_t} \text{ (where } V_p \text{ and } V_t$$

are the plasma volume and the tissue volume, and f_p and f_t are the fraction of unbound drug in plasma and tissue, respectively); thus, a change in f_t has a greater effect than f_p on V_f because V_t is considerably larger than V_p (Fichtl *et al.*, 1991). The similarity of V_f suggests that tissue binding of propranolol does not vary markedly among species. Evidence of species similarity in tissue binding has been presented by Fichtl and Schulmann (1986). For a series of 44 drugs differing widely in their physicochemical properties, when binding to rat, rabbit and human muscle tissues was compared and the binding ratios (i.e. ratio between bound and unbound concentration) were plotted, a close correlation between binding to muscle tissue of different species was found. If this holds true for all drugs, it is to be anticipated that the V_f should be similar in humans and other species. With the knowledge of V_f from laboratory animals and f_p from human plasma protein binding, one can estimate the V_d in human prior to the initial clinical studies. Unfortunately, this approach is not valid for all drugs. Boxenbaum (1982) compared the pharmacokinetic parameters for 12 benzodiazepines in dogs and humans. Eight of the twelve benzodiazepines had quite different V_f values between the dog and humans, the difference being as much as 7-fold. The large species differences in the V_f values were also reported for β -lactam antibiotics (Sawada *et al.*, 1984).

Metabolism

After ingestion, drugs are excreted either unchanged or chemically modified. Drug metabolism is generally divided into phase I and phase II reactions. Phase I metabolism generally adds or exposes polar

functional groups on lipophilic drugs, and phase II metabolism occurs when a functional group reacts with an endogenous substrate to yield a conjugated metabolite that is readily excreted from the body.

From an evolutionary standpoint, it is not surprising that similarities occur in drug metabolizing enzymes across species. Not only are there frequently identical enzyme systems, but also primary sequence similarity between species for specific enzyme proteins. Examples of this include cytochrome P450 and UDP-glucuronosyltransferase isozymes. During the past 10 years, greater insight has been obtained about the species similarity of the enzyme systems, however an extensive discussion of species differences in cytochrome P450 and UDP-glucuronosyltransferase is beyond the scope of this paper. The reader is referred to the excellent review of these topics (Guengerich, 1987; Coughtrie, (1992). In spite of the high degree of structural homology, the orthologous isozymes show subtle differences in a small number of amino acid residues. These small changes in the primary amino acid sequence can result in profound differences in substrate specificity (Lindberg, 1989).

The *in vitro* metabolism of MK-954 (Dup 753), a potent nonpeptide angiotensin II receptor antagonist has been studied in incubations with liver slice preparations from rats, monkeys and humans (Stearns *et al.*, 1992). Metabolism of MK-954 was qualitatively and quantitatively different among the species. In the rat, the primary route of metabolism was oxidative, leading to either monohydroxylated or oxidized (carboxylic acid) metabolites, whereas in monkeys, glucuronidation of the tetrazole moiety predominated. The metabolism of MK-954 by human liver slices, however, was not dominated by a single metabolic pathway, as with rats and monkeys, but was characterized by an approximately equal distribution of both oxidized and glucuronidated metabolites. The investigators suggest that the observed short duration of action of the drug in the monkey may be due to the low formation rate of a

carboxylic acid metabolite in this species. This pharmacologically active carboxylic acid metabolite has much longer $t_{1/2}$ than the parent drug in all species studied.

Stevens *et al.*, (1993) recently compared phase I and phase II hepatic drug metabolism activities using human and monkey liver microsomes. Of the eight P450-dependent activities measured, only N-nitrosodimethylamine N-demethylase activity was not significantly different in the two species. Coumarin 7-hydroxylase activity was greater in the human than in the monkey; whereas erythromycin N-demethylase, benzphetamine N-demethylase, pentoxyresorufin O-dealkylase, ethoxycoumarin O-deethylase, and ethoxyresorufin O-deethylase activities were significantly greater in monkey microsomes. Of the seven microsomal and cytosolic phase II activities measured, only 17α -ethynyl estradiol glucuronidation was significantly higher in the human. These results clearly show that the metabolic capacities of the human and Rhesus monkey drug metabolizing enzymes are different.

The pharmacokinetic parameters, disposition half-life and metabolic clearance of 12 benzodiazepines were compared in dogs and humans (Boxenbaum, 1982). All benzodiazepines were metabolized more rapidly in dogs than in humans. The differences in metabolic clearance between these two species ranged from 3-fold for triazolam to 72-fold for nordiazepam.

It is clear that extrapolation of drug metabolism from animals to man is the most difficult one of the ADME processes. Fortunately, the recent availability of human livers and the advanced knowledge of human drug metabolism have permitted the use of *in vitro* studies to predict the *in vivo* metabolism of drugs in man even prior to the initial clinical studies. Over the last several years, a body of research has evolved using human tissue for earlier drug metabolism studies.

Under certain well-defined conditions; it may be possible to extrapolate *in vitro* metabolism to *in vivo* situations (Hanano *et al.*, 1987; Sugiyama *et al.*, 1989). There are many examples of good correlation

between *in vitro* and *in vivo* drug metabolism, not only in qualitative but also in quantitative aspects. The antipyretic agent, ethoxybenazamide is exclusively metabolized to salicylamide by rat hepatic microsomes. The *in vitro* enzymatic kinetic parameters, V_{max} and K_m values of 3.46 $\mu\text{moles}/\text{min}/\text{kg}$ and 0.378 mM are in good agreement with those (3.77 $\mu\text{moles}/\text{min}/\text{kg}$ and 0.192 mM) obtained *in vivo* by application of a two compartment model (Lin *et al.*, 1978). Felodipine, a calcium channel blocker, is primarily metabolized to its pyridine analogue in rats, dogs and humans. The hepatic intrinsic clearance (V_{max}/K_m) of the drug obtained from *in vitro* studies with liver microsomes was 16 l/hr for the rat, 39 l/hr for the dog and 259 l/hr for the man, and agreed well with those observed *in vivo*; the corresponding values were 6.2 l/hr, 88 l/hr and 321 l/hr (Bäärnhielm *et al.*, 1986). Similarly a good *in vitro* and *in vivo* correlation of cytarabine hydrochloride has been reported by Dedrick *et al.* (1972).

Excretion

Drugs and their metabolites are usually eliminated from the body *via* the urine or bile or sometimes both. The relative contribution of biliary and urinary excretion to the overall elimination of drugs depends on the nature of the drug and the animal species. Generally, biliary excretion predominates in drugs with a relatively large molecular weight (>300) (Smith, 1971). Studies with organic anions and cations reveal that hepatic carriers preferentially recognize lipophilic drugs with a charged or a hydrophilic group (Meijer *et al.*, 1983). Although it is clear that molecular size, polarity and structural features are important determinants in biliary excretion of drugs, the relative importance of these factors is unclear. One striking feature of many drugs excreted in bile is that their structures are amphipathic in character, i.e., they contain both polar and non-polar groups. Many lipophilic compounds are excreted into bile at a higher rate after conjugation with glutathione or glucuronic acid, presumably because the reaction not

only increases molecular weight but also adds a polar group.

The amount of an organic chemical that is excreted in bile varies widely among species. In general, the mouse, rat and dog are good biliary excretors and the rabbit, guinea pig, monkey and human are relatively poor. However, the species differences become less marked when the molecular size exceeds 700. The underlying mechanism for the species difference is at present obscure. Species differences in hepatic blood flow and bile flow do not appear to correlate with biliary excretion of compounds (Smith, 1973).

The GFR values vary considerably among species ranging from 1.8 ml/min/kg for humans to 9 ml/min/kg for rats. The species differences in GFR are mainly attributable to their relative number of glomeruli (or nephrons) (Renkin & Gilmore, 1973). The relative numbers for rats and humans are 2.9×10^5 and 0.29×10^5 nephrons/kg body weight, respectively. Since it is generally believed that the GFR accurately reflects the renal function, one can predict the renal clearance of drugs in humans by using the ratio of the GFR values in animals to that in humans. In other words, the ratio of GFR should reflect the ratio of renal clearance of drugs between animals and man.

Famotidine, a H_2 -receptor antagonist, is mainly excreted by the kidneys in rats with a renal clearance of 28 ml/min/kg (Lin *et al.*, 1987). The renal clearance in humans can be predicted to be about 6.2 ml/min/kg, as the GFR is 4.5-fold greater in rats than in humans. The predicted value is in good agreement with the observed value of 4.44 ml/min/kg (Lin *et al.*, 1988). Enalaprilat and lisinopril, angiotensin-converting enzyme inhibitors, are exclusively excreted by the kidneys. Their renal clearance in rats are 18 and 11 ml/min/kg, respectively (Lin *et al.*, 1988). With the same approach, the renal clearance for these two drugs in humans expected to be 4 and 2.4 ml/min/kg which are also in good agreement with the observed data (3.1 and 1.7 ml/min/kg). Sawada *et al.* (1984) have compared the renal clearance of six β -lactam antibiotics

in six different species including human. Again, the prediction of renal clearance of unbound drug (CL_{ur}) from rats to humans is reasonably good with the exceptions of cefmetazole and cefazolin. The ratios of CL_{ur} between rats and humans for cefmetan, cefoperazone, moxalactam and cefpiramide are 2.2, 6.0, 4.8 and 3.3, respectively as compared to the GFR ratio of 4.5. These results suggest that for many drugs it may be possible to extrapolate the renal excretion data from animals to man.

Conclusion

Although pharmacokinetics have advanced greatly in recent years, it is not yet possible to predict all the pharmacokinetic parameters of a drug in man from animal studies. Nevertheless, under certain well-defined conditions, it may be possible to make reasonably accurate predictions. For example, the intrinsic absorption of a given drug to cross the wall of the gastrointestinal tract is probably similar among species since the nature of the biomembrane of epithelial cells is similar in mammals and since the absorption process is basically an interaction between the drug and biomembrane. However, the rate-limiting steps and factors, such as pH-dependent solubility and first-pass metabolism which affect the absorption, may be different from species to species resulting in species differences in absorption. It is, therefore, important to consider all factors which may affect absorption/bioavailability in explaining differences among the species.

Predicting the renal excretion of drugs in man has been relatively successful after applying corrections for differences in GFR. Similarly, if the elimination of a drug is by the liver and the rate of elimination is limited by hepatic blood flow, one could predict the clearance of the drug in man by correcting for the hepatic blood flow. Propranolol is a good example. The CL was 90 ml/min/kg for the rat, 34 ml/min/kg for the dog and 18 ml/min/kg for the monkey (Evans *et al.*, 1973), indicating that the elimination of the drug is limited by hepatic

blood flow. Thus, the CL in humans will be predicted to be close to the hepatic blood flow. The observed CL value in humans was 15 ml/min/kg which is in good agreement with the hepatic blood flow of 20 ml/min/kg.

However, protein binding and drug metabolism are less predictable. These parameters vary considerably among species. Fortunately, *in vitro* methodology has replaced animal studies in predicting plasma protein binding and enzymatic biotransformation of drugs in man.

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The Relationship Between Veterinary Pharmacology and Human Therapeutics

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To appreciate the extent to which veterinary drug development and regulation can influence human therapeutics, we first must examine the economics driving each of these two systems. In comparing recent reports published by the Animal Health Institute (AHI) and the Pharmaceutical Manufacturers Association (PMA), the latter representing both human and veterinary pharmaceuticals, it is evident that the financial foundation of the human and the veterinary drug industries are enormously different. These differences are expressed both in terms of sale revenues and research and development (R&D) allotments (Table 1). With the vast proportion of research funds being appropriated for human therapeutics, it's not surprising that veterinary pharmacology has had little opportunity to impact upon the progress of human medicine. Nevertheless, as technologies evolve and Guidelines are revised, new and valuable opportunities for research and regulatory harmonization are emerging.

Nearly half of all chemical entities approved for veterinary use also are approved for use in human patients (1993 FDA Approved Animal Drug Products; 1993 Physicians Desk Reference). The majority of this overlap involves anti-infective compounds. Of the nearly 300 chemical entities approved by the Center for Veterinary Medicine (CVM), over 21% can be classified as antimicrobials. Of these, approximately 60% are also the subject of approved human drug applications.

Both CVM and the Center for (human) Drug Evaluation and Research (CDER) generally require similar toxicology packages to verify product safety. However, CVM may request additional chronic toxicology data if an application is for use in a food-producing animal. Implementation of any additional requirements would be based on the perspective that drug residues contained within the edible tissues of food-producing animals act as chronically

administered, unintentional food additives (Somogyi, 1984).

CDER does not require chronic toxicity or carcinogenicity testing unless the drug is intended for chronic or chronic-intermittent administration (Goldenthal, 1968). In contrast, CVM requires chronic toxicity testing if the proposed level of residue in edible tissues exceeds 3 micrograms per ml. CVM requires carcinogenicity testing if the parent compound or any of its metabolites is a suspect carcinogen (CVM, 1986). Firms also voluntarily may provide chronic toxicity data if they wish to obtain a more liberal tolerance level for residues (thereby reducing their product's withdrawal time). Thus, CVM can be a repository of toxicology information which would be accessible to CDER in the event of unanticipated patient adverse reactions or when a firm seeks a chronic use indication for a drug previously approved solely on the basis of an acute exposure.

The science of veterinary pharmacology also can provide a wealth of information regarding the dose-response relationship of numerous anti-infective compounds. Of particular advantage in this regard is that a study involving naturally occurring infections bypasses many of the uncertainties associated with the extrapolation of data from animal models to human therapeutics (Barza, 1978). Such animal models often are employed during the preclinical phase of human drug development to help ascertain the biological activity of a drug against a targeted disease, to provide data for toxicity and safety evaluation and to provide the kinetic and dynamic data needed to assist in human dosing regimen evaluation and dose escalation strategies (Peck, *et al.*, 1992). Therefore, if the veterinary drug development data generated over a wide variety of diseases and animal species