Interspecies allometric analysis of the comparative pharmacokinetics of 44 drugs across veterinary and laboratory animal species

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The purpose of this study was to apply the method of allometric analysis to a study of the comparative disposition of veterinary drugs using the Food Animal Residue Avoidance Databank (FARAD) as a source of the comparative pharmacokinetic data. An initial filtration of the FARAD data was performed in order to exclude drugs for which no pharmacokinetic data were available, in at least four species the route of administration was other than intravenous, and the matrix was different from blood, plasma or serum. This process restricted the study to a total of 44 candidate drugs. The primary pharmacokinetic parameter selected for study was half-life ($t_{1/2}$). As this parameter is a composite of clearance (Cl) and volume of distribution (Vd), it was considered to be the most robust for interspecies scaling. Volume of distribution at steady state ($V\mathrm{d}_{ss}$) and clearance showed weak allometric correlations with weight across species. The relationships between body weight and elimination half-life ($t_{1/2\beta}$) were determined for this selected group of drugs by using the empirically determined function $Y = a\ W^b$. The function Y represents the parameter of concern (half-life), a is a coefficient typical of every drug (intercept), W is the species average body weight, and b is the scaling exponent. A total of 11 drugs (tetracycline, oxytetracycline, chlortetracycline, erythromycin, diazepam, prednisolone, cephapirin, ampicillin, gentamicin, apramycin and carbenicillin) showed statistically significant correlations and consequently are excellent candidates for interspecies extrapolation of pharmacokinetic parameters (half-life) in species of relevance to veterinary medicine. The remaining 33 drugs were divided into two groups which showed various degrees of lack of correlation. Many of the drugs that showed no allometric correlation were low hepatic extraction drugs. However, some other drugs demonstrated equivocal results which could either be due to a true lack of allometric correlation, or be inconclusive due to the lack of quality data or excessive variability due to the multi-laboratory origin of the FARAD data. The results of this study show that interspecies scaling is applicable to certain veterinary drugs. The experimental determination of the coefficients of the allometric equation for relevant pharmacokinetic parameters (clearance and volume of distribution) could be an important tool in estimating dose in species where the drug has never been studied. This could have important consequences in terms of avoiding the use of dose-titration studies in Phase I of drug development, for drugs that are experimentally 'well behaved'.

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INTRODUCTION

Interspecies scaling has been advocated as a practical way to ascertain the pharmacokinetic profile of drugs in a particular species, once the pharmacokinetic characteristics of that drug have been determined in a series of reference species (Boxembaum & D'Souza, 1990). This is based on the universality of anatomical characteristics and biochemical reactions (Davidson *et al.*, 1986) and on the empirical observation that certain physiological functions such as renal glomerular filtration rate,

oxygen consumption, heart and respiratory rate, cardiac output, basal metabolic rate, etc. may be scaled across species as a function of body size, according to a power function or its log-transformed linear equivalent (Adolph, 1949).

Historical background

Almost half a century ago, Adolph found that as many as 34 anatomical, physiological and biochemical parameters correlated with body weight across species (Adolph, 1949) according to the following allometric equation:

$$Y = a\,W^b$$

where Y is the parameter under study, a is an allometric coefficient (intercept) that is constant for a drug, W is the species average body weight and b is the allometric exponent. This exponential function turns into a linear function after logarithmic transformation, so that estimates of the intercept a and the slope b can be computed by linear regression according to the following equation:

$$\ln Y = \ln a + b\,(\ln W)$$

The wealth of empirical data available suggests that for most physiological processes, the allometric exponent b is 0.67–1.0. Classically, physiologists have used $b = 0.67$ when parameters are believed scaled to body surface area. However, there is no concrete evidence that this number is an universal constant. When the parameter is an inverse function of a physiological function (as happens with the elimination constant (k) that is an inverse function of clearance), the exponential term will be 1-b. The Environmental Protection Agency has used $b = 0.67$ (surface area) for risk assessment purposes (U.S. Environmental Protection Agency, 1984).

As most pharmacokinetic parameters are dependent upon physiological functions, it is possible to consider scaling across species based upon the aforementioned general allometric relationship. The relationship between body size and pharmacokinetic parameters was first noted with methotrexate (Dedrick *et al.*, 1970). Dedrick designed a graphical representation of this relationship by plotting in the y-axis of a semilog graph the serum concentrations from several species after the administration of a certain drug (adjusting for the dose), and in the x-axis the time multiplied by $B^{0.25}$, where B represents the body weight. This results in a single concentration–time (C–T) profile that is applicable to all species. The rationale for the conversion of time is based on the fact that energy turnover times and turnover times for endogenous substrates and endogenous processes are proportional to $B^{0.25}$. As a result of this procedure the chronological time, that is identical for all species, is converted to physiological time, that is specific for every species (Boxembaum, 1982a).

In many cases the drug action is related to some parameter describing the C–T profile (area under the concentration–time curve (*AUC*), clearance (*Cl*), volume of distribution (*V*d), half-life ($t_{1/2}$)). Allometry may be performed on any of these parameters, although the composite parameter half-life is most often studied.

As practical as this method may be for estimating pharmacokinetic parameters (and consequently dose regimen) in a species in which there is limited kinetic information on a drug, we cannot assume that this kind of relationship will hold for all drugs. There are cases in which interspecies extrapolations may not be feasible. The following peculiarities of drug disposition might prevent one from easily scaling pharmacokinetic parameters (and consequently dosages) across species.

Biotransformation. If a drug is eliminated primarily by 'capacity limited' hepatic biotransformation, total body clearance would be related to intrinsic clearance which is dependent upon the intrinsic ability of that species and individual to metabolize the drug. Numerous studies have demonstrated a great deal of heterogeneity in both Phase I and Phase II drug metabolism processes (Paine, 1995). For example, dogs are known to be deficient acetylators, pigs are deficient in sulfation capacity and cats are deficient in glucuronidation. If a drug is metabolized by one of these Phase II pathways and the resulting change in disposition has pharmacological or toxicological impact, extrapolation will not work. However, if the only result is to produce a sulfated rather than acetylated inactive metabolite, and C-T profile of the parent drug and active Phase I metabolites are not affected, allometry may still work.

The largest and most important source of interspecies variability relates to differences in cytochrome P450 isoenzymes. Although P450 content scales to body size, species differences in isoenzymes confound one's ability to make predictions. A substantial amount of progress has been made in studying which genes are responsible for controlling specific P450 isozyme expression. For example, the P450 IIIA gene expresses isoenzymes in the rat, dog (Ciaccio & Halpert, 1989) and humans which show similar substrate specificity and inhibitor selectivity, with sex differences only being expressed in the rat (Gonzalez *et al.*, 1986; Eberhart *et al.*, 1991; Murray, 1991). If one knew *a priori* that the drug in question was metabolized by an isoenzyme under control of this gene, then allometry should work on extrapolating such drugs (flunisolide, cyclosporine, dihydropyridine Ca^{++} channel blockers). However, the data base for which these data are available is sparse at best, and outside of the dog contains no other veterinary species. Additionally, some of these compounds may also be metabolized by isoenzymes controlled by the P450 IIC gene which, depending on relative substrate specificities between IIIA and IIC isoenzymes, will produce a different profile of Phase I metabolites. The situation gets very complicated when other genes are considered and non-cytochrome P450 enzymes are also considered.

At the present time and for the foreseeable future, it will not be possible to precisely predict the interspecies disposition of 'capacity limited, low extraction' drugs. If the hepatic clearance is 'flow limited', there should be no problems using allometry as metabolic clearance will now be correlated to hepatic blood flow, a scaleable parameter. The only exception would be if the compound were also cleared by another route or if a specific enzyme were required to activate a drug, and our species of

interest (the one we try to extrapolate the pharmacokinetic profile to) were deficient in that enzyme.

Protein binding. Protein binding is almost impossible to extrapolate across species. Differences in protein binding would be expected to affect *Cl*, *V*d and the fraction of a dose that is able to interact with receptors (only free fraction is available). Protein binding would also affect bioavailability after oral administration of a drug with a high extraction ratio. In this situation the degree of protein binding in portal flow will affect the extent of first-pass effect, and consequently the bioavailability. In many cases, this problem can be avoided if pharmacokinetic parameters based on free drug concentration are employed (Riond & Riviere, 1989).

Saturation. If the effective dose in some of the species (or the species of interest) produces concentrations that saturate elimination mechanisms, nonlinear pharmacokinetics will result making allometric approaches difficult. This would not be a problem for most pharmacological doses, except in species such as cats in which a normally glucuronidated drug cannot be eliminated.

Genetic polymorphism. Although this feature has not been extensively studied in veterinary medicine, the presence of unidentified genetic differences in drug disposition within a species for a certain drug, could lead to extreme intraspecies pharmacokinetic variation and consequently preclude an adequate interspecies extrapolation of pharmacokinetic parameters. If the polymorphism affects the pharmacodynamics of the drug, doses could still be extrapolated across species but the effects of the drug in the species affected by such polymorphism would be very variable.

Drug induced alterations in physiology. Up until this point we have considered drugs to be pharmacologically inert. If the drug alters physiological parameters that, in turn, affect its disposition (e.g. renal function, hepatic blood flow) in one species and not in another then the allometric relation of physiology to body weight will be broken and interspecies scaling will not work. This situation should be rare.

Interspecies differences in entero-hepatic circulation. If a considerable part of a drug is cleared via bile and there are important interspecies differences in the fraction that is reabsorbed back into the systemic circulation, the pharmacokinetic parameters might not be amenable to interspecies extrapolation.

Tubular reabsorption sensitive to urinary pH. The half-life of a drug that undergoes tubular reabsorption can be influenced by the pH of the urine. The extent of this effect would depend on the degree of ionization and concentration of the drug in the tubular lumen. Carnivores tend to have more acidic urine than herbivores. If a drug is reabsorbed from the renal tubuli to a significant extent and its degree of ionization (determined by the acid/basic nature of the drug, pKa, and pH of the environment) in carnivore urine is very different to that in herbivore urine, variations in clearance may take place between different species that are not correlated to the species weights. Weak organic acids with pKa values ranging from 3.0–7.2 may have a decreased half-life when the urine is alkaline as a consequence of a considerable reduction in tubular reabsorption. The converse would apply to the excretion of weak organic bases.

Despite the potential usefulness of allometric scaling using a common value of the exponential coefficient *b* for many drugs, it would be optimal that whenever possible, the exponent *b* were experimentally estimated for the drug of interest in relevant species and utilizing a broad range of individual body sizes. Currently a comprehensive review of drugs and species and their interrelationships is lacking in the scientific literature. Such information could allow a more accurate determination of the exponential term (*b*) of the allometric equation. By doing so, pharmacokinetic parameters (clearance and volume of distribution) could be more accurately extrapolated across species for the purpose of defining the effective dose of drug to be used in clinical efficacy and safety trials.

The objective of this paper is to study the relationship between half-life and body size across different species for a large number of drugs, to determine the scaling coefficients in those cases were significant relationships are found and to consider the reasons why certain drugs may not be scaled. The pharmacokinetic data used in this study are derived from the information compiled in the Food Animal Residue Avoidance Databank (FARAD) (Riviere *et al*., 1991; Craigmill *et al.*, 1994; Sundlof *et al.*, 1996). This database (although obviously not containing all the existing pharmacokinetic information) constitutes the most extensive and accessible compilation of pharmacokinetic data for veterinary drugs available to date.

MATERIALS AND METHODS

Data collected from the kinetics files of the FARAD database were analysed in three phases. In Stage I, data on 419 generic drugs (10,300 records) were reviewed. A list of 79 drugs (1,724 records) resulted using the following criteria:

(1) Only drugs administered by the intravenous route were considered;

(2) The matrices of interest in this study were serum, plasma or blood;

(3) For each particular drug, at least three species categories were available. Species category could be either a biological species or a species subset of different body weight and pharmacokinetic makeup;

(4) For each particular drug, at least one kinetic parameter had been reported (V_{ss}, V_{area}, *Cl*, $t_{1/2}$)

In Stage II, species groupings were adjusted to reflect body weight and/or pharmacokinetic differences. Individual records were examined and then deleted for any one of the following reasons: extremely high or low doses, abnormal disease conditions which apparently adversely affected the pharmacokinetic parameters or the mention of co-administered drugs. The final result was 61 drugs (1,221 records).

Stage III involved manipulating the individual records to obtain species means. These were first averaged within a citation and then all citations averaged for a given species. Both means and number of animals are composites of numerous replicates per citation as well as multiple citations. Thus if there was only one citation and one replicate, the kinetic parameter represents a single value as opposed to a mean.

Body weights were taken from the available data in the kinetic file and corresponded well with published body weights. Three new parameters to better characterize the ensuing analysis were created:

(1) # species = number of data points used in the regression analysis. Each data point represents the species average for the pharmacokinetic parameter.

(2) # citations = number of unique citations that contributed to the analysis.

(3) body weight ratio = the log of the ratio of the largest body weight to the smallest body weight as a measure of the 'robustness' of the regression, i.e. by spread of body weights. This number ranges from 0.51 (monkey:rabbit) to 9.77 (dairy cattle:mouse).

Fourteen drugs were deleted at this time due to having data only from three species. A minimum of four species was deemed necessary for a proper analysis. The remaining 44 drugs which serve as the basis of this paper were plotted as log $t_{1/2}$ vs. log body weight and individual records of 45 outlier data points scanned to determine if there were some justification for deleting the record. Thirty-six additional record deletions resulted in a final tally of 44 drugs (Tables 1 & 2). Regression analysis was performed at the logarithmic scale using SAS software (SAS Institute, Cary, NC, USA) to study the correlation between weight and half-life. Initially, the pharmacokinetic parameters of interest were Vd_{ss}, *Cl*, and half-life. A preliminary regression analysis of each pharmacokinetic parameter vs. weight (double logarithmic scale) led us to consider half-life as the most robust parameter for further analysis. The reason was the scarcity of significant allometric correlations found between weight and either volume of distribution or clearance. As half-life is a composite of *V*d and *Cl*, the explanation for its apparent higher 'robustness' for allometric scaling could be based on its insensitivity to occasional differences in volume of distribution and clearance, attributable to sources other than interspecies variation (e.g. excessive interstudy variability). Clearly, the multisource nature of the data contained in the FARAD database prevented us from an adequate allometric study of either volume of distribution or clearance. Under these circumstances, half-life seems to be robust enough so as to be used as an indicator of interspecies allometric relationships in pharmacokinetic parameters.

Coefficients of determination and *P*-values were computed for each correlation under study. This analysis did not break out age or sex or other co-treatments or diseases if they did not affect the 'species' mean.

Double logarithmic plots of body weight in several species vs. half-life were constructed to show the significant correlations. After the results were available, drugs were assigned to three groups according to their coefficients of determination and level of significance of the regressions. Group A included drugs with significant regressions ($P < 0.05$) and r^2 values between 0.74 and 0.99. Both groups B and C included drugs with non-significant correlations ($P > 0.05$). Group B consisted of drugs with r^2 values between 0.38 and 0.80 and Group C included drugs with r^2 values of 0.26 or less. This division was arbitrary and was only adopted to analyse possible reasons why drugs in Groups B and C would not scale significantly.

A close analysis was made of the drugs which did not show a significant correlation to shed light on the reasons for the lack of correlation.

RESULTS

Table 1 shows the results of the regression analysis conducted on the logarithm of half-life vs. logarithm of body weight, for the 44 drugs under study. Table 2 shows a comparison between the three groups in terms of data quality and results obtained.

A total of 11 drugs (25%) were included in Group A. Their half-lives correlated significantly with interspecies body size. For this group, the exponent term *b* ranged between 0.1 and 0.415, with an average of 0.236 ± 0.09. Roughly 65% of the *b*'s were between 0.19 and 0.32 (the general value mostly cited in the literature for this exponent term is 0.25). The average number of species per study in this group was 6.2 ± 2.2, the median value was 6, and in 91% of the cases it ranged from 4 to 8 (the exception was gentamicin with 11 species). The coefficients of determination (r^2) ranged from 0.74–0.99. The average was 0.87 ± 0.09, and for 65% of the cases the value was 0.85 or higher. The log body weight ratio ranged from 4.81–9.77. The average ratio was 8.1 ± 2.1, and 73% of the time it was included between 7.65 and 9.77. Finally, the average number of citations in this group was 10.7 ± 11.9 and the median was 6.

Group B included 14 drugs (32%). The average log body weight ratio in this group was 5.7 ± 1.8 with 71.5% of the values being between 5.16 and 7.65. The average number of species was 4.8 ± 1.1 and the average number of citations for this group was 7.5 ± 8.0 with a median value of 5.

Group C included the remaining 19 drugs (43%). The average log of body weight ratio in this group was 5.2 ± 2.0 with 73.7% of the values being between 4.36 and 9.64. The average number of species was 7.0 ± 2.5 and the average number of citations for this group was 11.3 ± 8.2 with a median value of 9.

Figures 1–11 show the allometric plots obtained for the drugs in Group A.

DISCUSSION

For Group A, 82% of the drugs are antibiotics. Allometric scaling of antibiotics is very convenient as their effectiveness is basically dependent on the concentrations of drug present in the extracellular fluid. This suggests that as there are likely not pharmacodynamic differences involved between species, their efficacy depends almost exclusively on reaching a determined

Table 1. Results of the interspecies analysis for the drugs included in the study

Log $t_{1/2}$ vs. log body weight							
Drug	Citations	Species	B/W ratio	Slope	Intercp.	r^2	*P* value
Tetracycline	8	6	9.8	0.249	2.8	0.97	0.0003
Erythromycin	6	8	9.8	0.15	1.1	0.79	0.003
Oxytetracycline	27	8	5.2	0.227	2.6	0.74	0.006
Cephapirin	4	4	9.6	0.135	0.4	0.97	0.01
Diazepam	5	6	9.6	0.415	1.6	0.81	0.005
Apramycin	3	4	4.8	0.32	0.6	0.94	0.03
Chlortetracycline	3	4	9.8	0.31	2.1	0.94	0.03
Gentamicin	40	11	7.7	0.191	0.9	0.86	0.00003
Prednisolone	7	6	7.7	0.272	0.5	0.74	0.03
Carbenicillin	4	4	9.8	0.226	0.4	0.99	0.0023
Ampicillin	11	6	5.0	0.1	0.7	0.85	0.009
Phenylbutazone	31	8	7.7	0.24	3.8	0.38	0.08
Tylosin	6	5	7.7	0.171	0.7	0.66	0.1
Phenytoin	4	4	7.5	0.247	2.4	0.80	0.11
Levamisole	4	4	2.4	0.668	0.4	0.77	0.12
Quinidine	7	4	6.3	0.505	1.8	0.75	0.13
Theophylline	18	6	7.5	0.097	5.0	0.47	0.13
Xylazine	2	5	3.4	0.18	0.3	0.52	0.17
Amoxicillin	3	4	5.0	0.119	0.6	0.64	0.2
Meperidine	5	5	5.1	−0.142	0.9	0.47	0.2
Ticarcillin	5	4	3.5	0.127	0.6	0.59	0.23
Flunixin	11	5	4.9	0.441	0.8	0.40	0.25
Acetaminophen	5	4	7.5	0.083	1.1	0.55	0.26
AM-833	1	5	6.3	0.17	3.0	0.38	0.27
Tinidazole	3	4	4.9	−0.148	8.6	0.52	0.28
Sulfamethazine	27	11	5.2	0.19	2.8	0.21	0.15
Antipyrine	18	11	7.5	0.122	1.3	0.20	0.16
Sulfadimethoxine	12	9	5.0	0.078	6.8	0.26	0.16
Amphetamine	1	7	4.4	−0.229	3.5	0.20	0.31
Amikacin	6	6	5.0	0.077	1.0	0.23	0.33
Cephalothin	7	6	9.6	0.105	0.3	0.20	0.37
Penicillin	11	6	3.5	0.133	0.5	0.17	0.42
Morphine	11	6	7.5	−0.05	2.1	0.14	0.47
Trimethoprim	14	8	7.5	0.053	1.4	0.05	0.59
Kanamycin	4	6	5.0	0.063	1.4	0.07	0.6
Cefazolin	5	5	5.0	0.076	0.5	0.07	0.66
Oxyphenbutazone	3	4	2.8	0.217	0.9	0.11	0.66
Chloramphenicol	26	13	5.2	0.052	1.9	0.02	0.67
Ketamine	9	5	4.7	0.101	0.8	0.07	0.67
Fentanyl	8	6	1.5	0.248	1.0	0.03	0.75
Lidocaine	28	9	7.5	0.03	0.8	0.01	0.79
Cefamandole	3	4	3.1	−0.032	0.8	0.03	0.82
Digoxin	13	6	5.0	0.022	15.5	0.01	0.89
Sulfathiazole	8	5	2.8	−0.006	1.7	0.00	0.97

Group	Weight ratio	Avg # spec	Avg # citations	*b*	r^2
Group A	8.1 (2.1)	6.2 (2.2)	10.7 (11.9)	0.24 (0.09)	0.87 (0.09)
Group B	5.7 (1.8)	4.8 (1.1)	7.5 (8.0)	– – –	0.56 (0.14)
Group C	5.2 (2.0)	7.0 (2.5)	11.3 (8.2)	– – –	0.11 (0.09)

Table 2. Data associated with the 'robustness' of the regression for the three groups of drugs. The amount in parenthesis represents the s.d.

MIC (minimal inhibitory concentration), independently of whether the particular antibiotic effect is concentration-dependent or time-dependent. In essence, the efficacy of these drugs should be well correlated to the plasma or serum concentrations and because of this their scaling properties should be fairly straightforward. For these drugs, there should be no problems of unique physiology or species-specific receptors, and consequently adjusting for species differences in pharmacokinetic parameters (clearance and volume of distribution) we should derive the optimal dose. Pharmacokinetic parameters of these

TETRACYCLINE

SPECIES	WEIGHT	HLIFE
Avian	3	2.76
Beef Cattle	370	12.9
Dairy Cattle	525	12.8
Human	70	8.2
Sheep	49	8.5
Mice	0.03	1.31

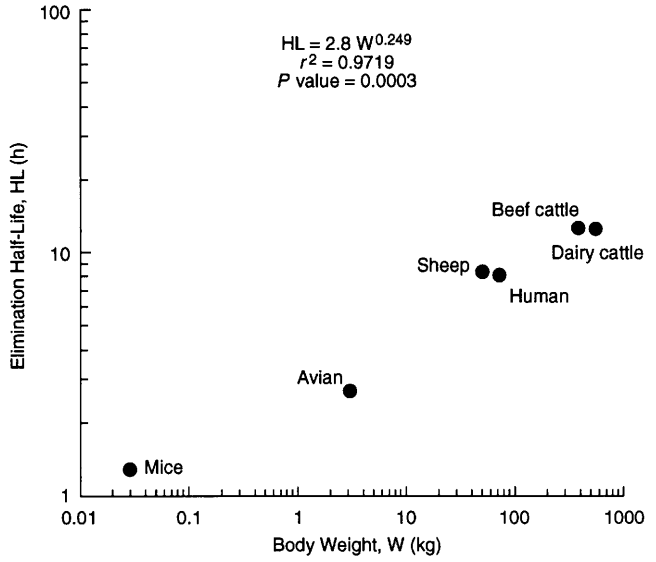

Fig. 1. Allometric plot obtained for tetracycline based on six species (beef and dairy cattle were considered separately). The allometric equation that best characterizes this relationship is $t_{1/2} = 2.8\ W^{0.249}$. The coefficient of determination (r^2) equals 0.97 and the P value is 0.0003.

OXYTETRACYCLINE

SPECIES	WEIGHT	HLIFE
Avian	3	2.53
Beef Cattle	370	7.47
Dairy Cattle	525	9.61
Goat	34	6.4
Horse	460	11.69
Dog	16	6.017
Sheep	49	9.24
Swine	32	4.65

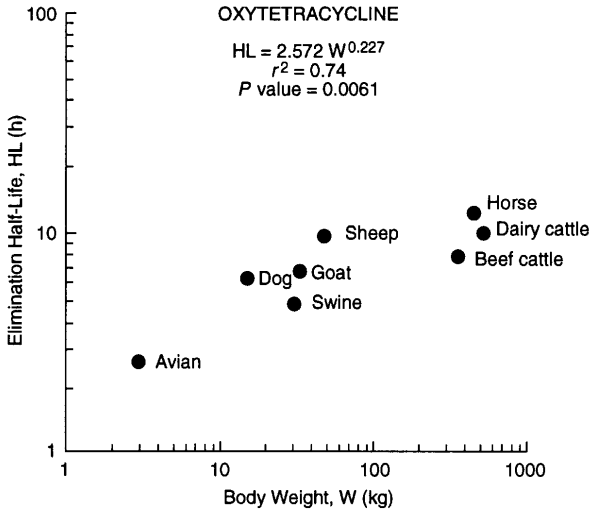

Fig. 3. Allometric plot obtained for oxytetracycline based on eight species (beef and dairy cattle were considered separately). The allometric equation that best characterizes this relationship is $t_{1/2} = 2.6\ W^{0.227}$. The coefficient of determination (r^2) equals 0.74 and the P value is 0.006.

ERYTHROMICIN

SPECIES	WEIGHT	HLIFE
Avian	3	0.9
Beef Cattle	370	3.61
Dairy Cattle	525	3.157
Rat	0.25	1.27
Human	70	1.48
Dog	16	1.72
Rabbit	3	1.4
Mice	0.03	0.65

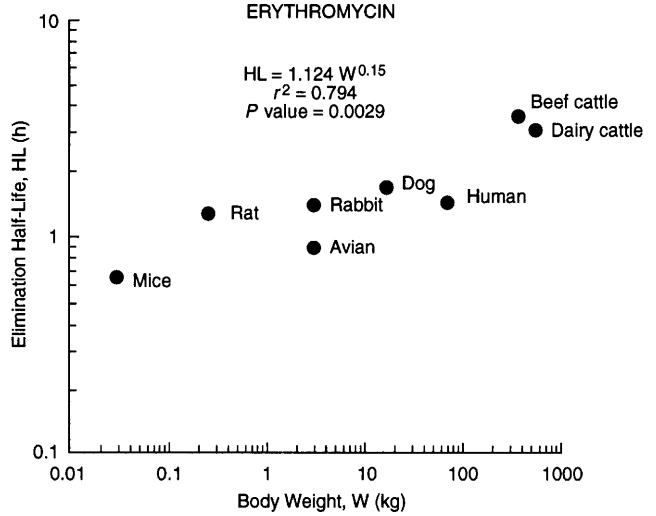

Fig. 2. Allometric plot obtained for erythromycin based on eight species (beef and dairy cattle were considered separately). The allometric equation that best characterizes this relationship is $t_{1/2} = 1.1\ W^{0.15}$. The coefficient of determination (r^2) equals 0.79 and the P value is 0.003.

CEPHAPIRIN

SPECIES	WEIGHT	HLIFE
Beef Cattle	370	0.83
Horse	460	0.92
Human	70	0.56
Mice	0.03	0.235

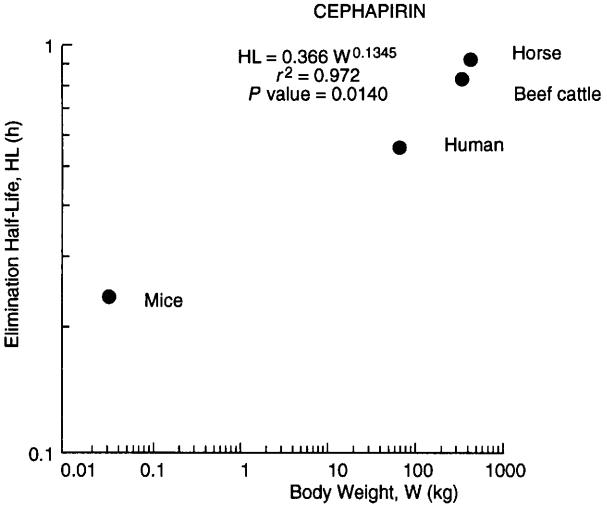

Fig. 4. Allometric plot obtained for cephapirin based on four species. The allometric equation that best characterizes this relationship is $t_{1/2} = 0.4\ W^{0.135}$. The coefficient of determination (r^2) equals 0.97 and the P value is 0.01.

DIAZEPAM

SPECIES	WEIGHT	HLIFE
Rat	0.25	0.86
Horse	460	12.75
Guinea Pig	0.29	2.4
Dog	16	4.36
Rabbit	3	2.7
Mice	0.03	0.14
Cat	4	4.97

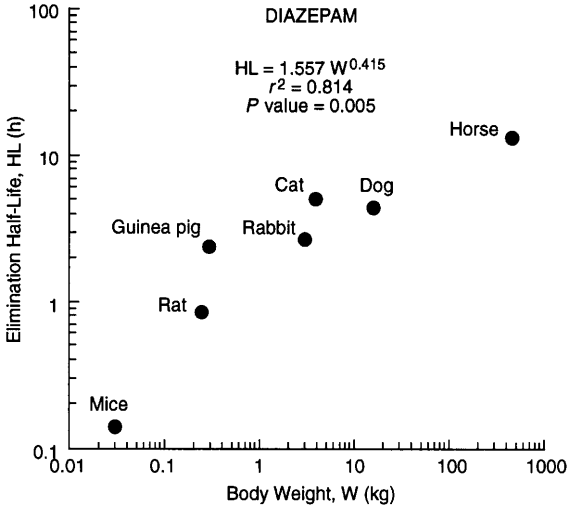

Fig. 5. Allometric plot obtained for diazepam based on seven species. The allometric equation that best characterizes this relationship is $t_{1/2} = 1.6\ W^{0.415}$. The coefficient of determination (r^2) equals 0.81 and the P value is 0.005.

APRAMYCIN

SPECIES	WEIGHT	HLIFE
Avian	3	0.918
Beef Cattle	370	4.41
Sheep	49	1.52
Rabbit	3	0.8

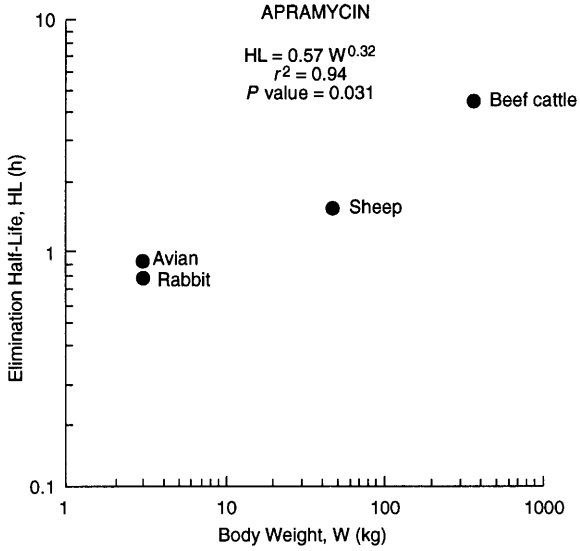

Fig. 6. Allometric plot obtained for apramycin based on four species. The allometric equation that best characterizes this relationship is $t_{1/2} = 0.6\ W^{0.32}$. The coefficient of determination (r^2) equals 0.94 and the P value is 0.03.

CHLORTETRACYCLINE

SPECIES	WEIGHT	HLIFE
Dairy Cattle	525	11.2
Sheep	49	11.2
Swine	32	5.49
Mice	0.03	0.66

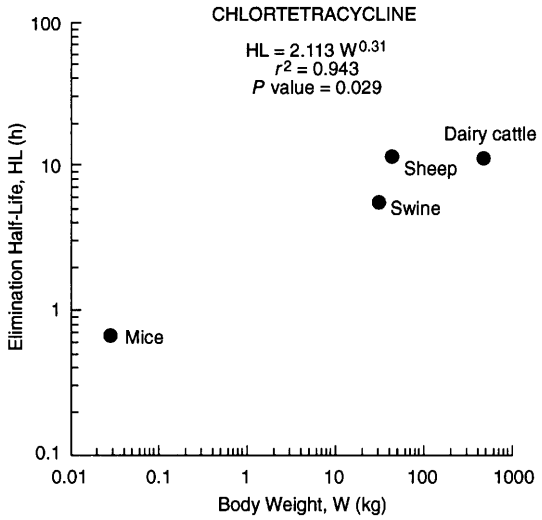

Fig. 7. Allometric plot obtained for chlortetracycline based on four species. The allometric equation that best characterizes this relationship is $t_{1/2} = 2.1\ W^{0.31}$. The coefficient of determination (r^2) equals 0.94 and the P value is 0.03.

GENTAMICIN

SPECIES	WEIGHT	HLIFE
Beef Cattle	370	3.5
Dairy Cattle	525	1.53
Horse	460	2.33
Dog	16	1.28
Sheep	49	1.92
Swine	32	2.65
Rat	0.25	0.61
Cat	4	1.23
Guinea Pig	0.29	0.91
Human	70	1.99
Rabbit	3	1.04

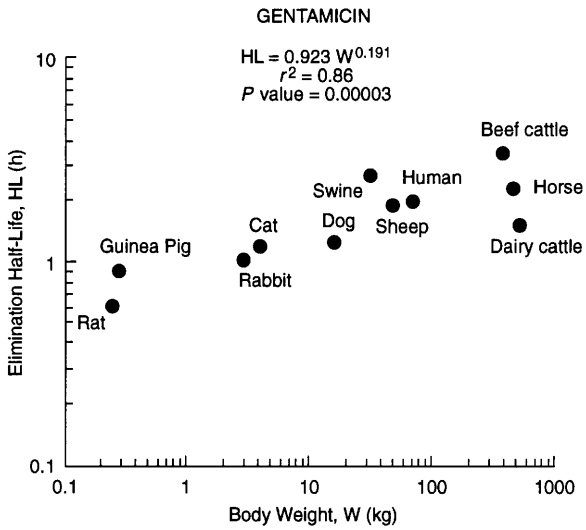

Fig. 8. Allometric plot obtained for gentamicin based on eleven species (beef and dairy cattle were considered separately). The allometric equation that best characterizes this relationship is $t_{1/2} = 0.9\ W^{0.191}$. The coefficient of determination (r^2) equals 0.86 and the P value is 0.00003.

PREDNISOLONE

SPECIES	WEIGHT	HLIFE
Dairy Cattle	525	3.61
Rat	0.25	0.33
Horse	460	1.65
Human	70	2.92
Dog	16	1.33
Swine	32	0.73

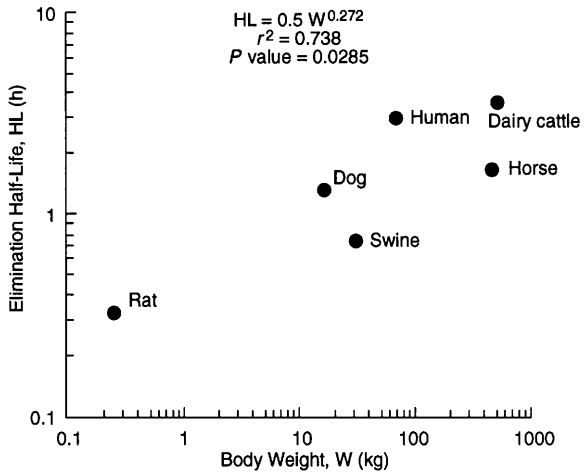

Fig. 9. Allometric plot obtained for prednisolone based on six species. The allometric equation that best characterizes this relationship is $t_{1/2} = 0.5\ W^{0.272}$. The coefficient of determination (r^2) equals 0.74 and the P value is 0.03.

CARBENICILLIN

SPECIES	WEIGHT	HLIFE
Dairy Cattle	525	1.83
Human	70	1.27
Dog	16	0.778
Mice	0.03	0.206

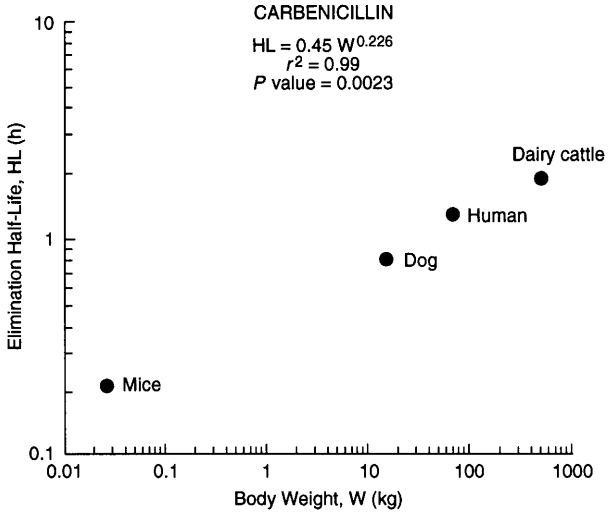

Fig. 10. Allometric plot obtained for carbenicillin based on four species. The allometric equation that best characterizes this relationship is $t_{1/2} = 0.5\ W^{0.22}$. The coefficient of determination (r^2) equals 0.99 and the P value is 0.0023.

drugs (like gentamicin or ampicillin) have been previously reported to have good scaling properties (Riviere *et al.*, 1983; Kirkwood & Merriam, 1990; Lashev & Pashov, 1992).

AMPICILLIN

SPECIES	WEIGHT	HLIFE
Avian	3	0.79
Goat	34	1.01
Sheep	49	1.18
Swine	32	0.921
Horse	460	1.27
Human	70	1.105

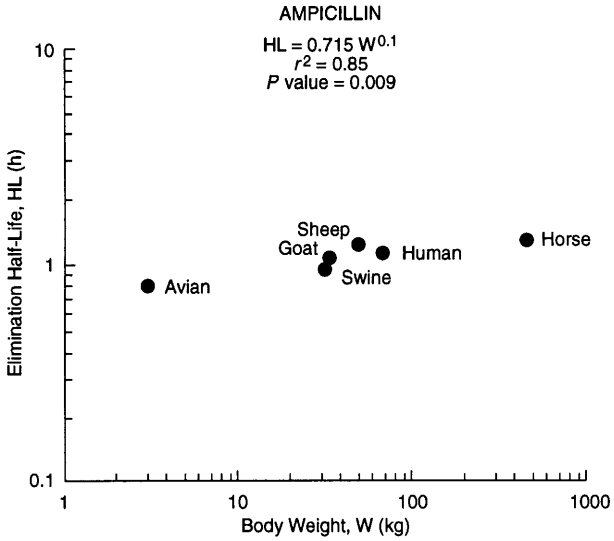

Fig. 11. Allometric plot obtained for ampicillin based on six species. The allometric equation that best characterizes this relationship is $t_{1/2} = 0.7\ W^{0.1}$. The coefficient of determination (r^2) equals 0.85 and the P value is 0.009.

The elimination half-life in the group of tetracyclines (oxytetracycline, chlortetracycline and tetracycline) scales significantly across species, as could be expected of drugs eliminated primarily by renal glomerular filtration, and which undergo minimal metabolism. Their exponential terms are, respectively, 0.227, 0.309 and 0.249. Up to 40% of the total amount of tetracyclines in the body is excreted unchanged into the bile (Kunin & Finland, 1961). From the gastrointestinal tract they are partially reabsorbed via entero-hepatic circulation. The significant allometric correlation observed for the tetracyclines in this study, would suggest that the fraction of the dose undergoing recycling is either similar between the species looked at, or too small to account for significant differences in half-life. The results for oxytetracycline presented here are in agreement with previous studies (Kirkwood & Widdowson, 1990).

Diazepam is an interesting case. With an r^2 value of 0.81 and P value of 0.005 it seems to be a good candidate for interspecies scaling. Yet, this drug is mostly cleared by the liver, has a variable degree of protein binding across species (usually high), and is a low hepatic extraction drug. Its clearance is dependent on the degree of protein binding and on the hepatic intrinsic clearance, factors both basically driven by species-specific characteristics. In fact, the extraction ratio of this drug is highly sensitive to changes in protein binding. These changes have greater influence on the extraction ratio than the hepatic intrinsic clearance (if the fraction unbound of diazepam were large, this drug would be a high extraction drug in humans). Consequently, large differences in clearance across species could

arise from changes in the unbound fraction. For example, if the free fraction in one species were 10% and in another 1%, the difference in clearance would be 10-fold. Nevertheless, this difference would not be paralleled by a similar change in half-life. Presumably the larger volume of distribution in the species with larger unbound fraction would partially offset this difference. A review of the pharmacokinetic data available for diazepam shows a high degree of variability in disposition both within and between species. In the absence of liver disease, changes in volume of distribution alone have been reported to significantly affect the disposition of this drug. In obese human subjects, the half-life of diazepam may increase more than three times as a consequence of an increase in the volume of distribution. Likewise, changes in volume of distribution related to age have been reported to account for variability in the half-life of this drug in people of different ages. On the other hand, this drug is partially metabolized (hydroxylated) by the CYP2C19 isoenzyme. In humans, this isoenzyme is polymorphically expressed, with 5% of Caucasians and 16% of Orientals being poor metabolizers. Consequently, although the results for diazepam are in agreement with previous studies (Boxembaum, 1982b), it could be considered relatively paradoxical that this drug demonstrates scaling properties for veterinary species, as such behaviour is not expected from a drug that has high interindividual (even intraspecific) variability.

The 14 drugs included in Group B did not show a significant interspecies correlation between body size and half-life. In fact, for some of these drugs this result would be expected, according to their disposition characteristics (low extraction drugs with high protein binding). On the other hand, the conclusions should not be definitive for all the drugs in this group. This analysis has been done with data derived from multiple sources and consequently it is subject to a considerably higher degree of variability than an analysis in which the data had a common origin (an almost impossible task considering the number of drugs). Our laboratory previously conducted such a study with doxycycline in calves, dogs, cats and pigs (Riond & Riviere, 1990). In that study a tight scaling could only be demonstrated when free drug concentration was employed.

The log body weight ratio, a parameter that can be empirically considered indicative of the 'robustness' of the allometric analysis is significantly higher in Group A than in Groups B or C (P-values equal 0.007 and 0.001, respectively). Table 2 shows some of the differences in the data quality between groups. The data contained in this table do not necessarily provide the reason for the lack of correlation (particularly in Group B). They are only intended to highlight the possibility that the lack of data quality or the excessive variability in the data could account, at least partially, for the lack of correlation observed with some drugs. This variability derives from summarizing data from numerous laboratories using different analytical techniques, not weighting for number of citations or animals, and having merged some production groups in order to obtain better species estimates. Experimental allometric studies for some of these drugs individually, could reveal an ability to scale across species that the present study is unable to detect. For example, the half-lives of drugs such as amoxicillin or antypirine have been reported to scale across species as a function of body size (Boxembaum & D'Souza, 1990). The half-life of tylosin has also been shown to scale across species with an exponent term $b = 0.18$ (Duthu, 1985).

For some of the 19 drugs in Group C the lack of correlation seems to be more clear. Again, even in this group, some other factors related to the lack of representative data or the integrity of the original study from which the data were extracted, could account partially for some of the lack of correlation. For example, it could be expected that the half-life of drugs like kanamycin or amikacin would allometrically correlate with weight across species (as happens with gentamicin and apramycin), as their elimination is almost exclusively dependent on renal filtration processes. Glomerular filtration rate is a reflection of cardiac output and basal metabolic rate, and these physiological processes have been empirically shown to scale with exponential terms between 0.67 and 0.75 (half-life would scale to 1-b, assuming that b is the exponent for these physiologic parameters).

Drugs such as sulfathiazole, digoxin, cefamandole, lidocaine, fentanyl, ketamine, chloramphenicol, oxyphenbutazone, trimethoprim, morphine and amphetamine seem not to be eligible for interspecies scaling.

In humans, cefamandole is excreted unchanged in the urine. Only four species were considered for the allometric analysis of this drug and the log of the body weight ratio was fairly small (3.1). Consequently, the results for this drug should be taken with caution.

Lidocaine, fentanyl, ketamine and morphine are eliminated in general by 'flow-limited' hepatic mechanisms. Theoretically, this should make them good candidates for interspecies scaling. The data on fentanyl were collected from studies in humans, goats, sheep, dogs and pigs. Allometric techniques are more effective if there is a wide range of body weights (because of the logarithmic transformation involved). The log body weight ratio for fentanyl was 1.5, which may indicate a relative lack of representative data (insufficient spread of weights). Lidocaine was studied in the rat, rabbit, non-human primates, dog, pig, sheep, human and horse. Ketamine data were obtained from cats, sheep, pigs, horses and cows. In the case of morphine, the species involved were rat, rabbit, dog, goat, human and horse. Rats exhibited the largest half-life for this drug, which contradicts an allometric relationship with weight. There is no clear indication of whether there is a true lack of correlation for these drugs or the results presented here are flawed by factors related to the variability of the data across studies. A possibility would be that the hepatic elimination for fentanyl, lidocaine, ketamine and morphine were 'flow dependent' in some species and 'capacity dependent' in others, or that some clinically significant drug-induced changes affecting flow to the elimination organ would take place only in some species.

Another case is digoxin. This drug is not extensively bound to plasma proteins and is eliminated mostly by renal filtration, which should make this drug a good candidate for interspecies interpolation. Moreover, previous studies have indicated that the half-life of this drug allometrically correlates with body weight

across species (Okita, 1967; Mellet, 1969). Consequently, the results for this drug should also be considered inconclusive.

It is interesting that for some older drugs like penicillin, there is a poor correlation. In scanning the original sources of data, this is likely due to 'less than optimal' analytical and pharmacokinetic methodology, a scenario that may also be operative with many older drugs. At this point, there is no objective way to improve upon this when dealing with a composite databank source such as FARAD.

This compilation clearly shows that a number of veterinary drugs can be scaled between species with confidence. Using the allometric scaling approach for interspecies dose extrapolation, it may be possible to define an effective *AUC* in a species, and calculate a dose per unit W^b which could be used for all species (this assumes that drug action is correlated to *AUC*). There is no information on whether this predicted dose would produce an equivalent withdrawal time and thus tissue depletion studies would have to be conducted, as tissue residues may have additional limitations ('deep' tissue compartments, covalent tissue binding). Half-life has shown to be the most robust pharmacokinetic parameter for allometric predictions as it is a composite of *V*d and *Cl*, and even if there were a high intraspecific variability in these two parameters, the $t_{1/2}$ might remain stable.

Correlations of *V*d and *Cl* between species according to body size need to be investigated further. At least one of these parameters (besides $t_{1/2}$) would be needed to extrapolate an effective dose to a new species. By knowing the exponent for $t_{1/2}$ the component for clearance could be estimated assuming that *V*d scales to $b = 1$ (as is the case in some instances).

In summary, allometry can be an important tool for dose extrapolation with certain classes of drugs (mostly antimicrobials) that can be scaled across species. If parameter scaling is available for a drug, the first step for using a drug in a different species would be the estimation of pharmacokinetic parameters and *AUC* in that species. These parameters could be used to calculate the efficacious dose in one species from data in another species for which the drug dose-titration studies have already been conducted, or in which the drug has been approved.

The results of a study such as the present one should only be employed when strong correlations are obtained (e.g. group A drugs). When an allometric correlation is not detected, more controlled trials should be conducted to rule out data quality problems that might have biased the results.

This study emphasizes that the integration of allometric principles would be very efficient, economical and scientifically sound for the purposes of dose extrapolation in new species. This would be especially true if detailed pharmacokinetic studies conducted in the base-line reference species indicated that the pharmacokinetic parameters of the drug are amenable to extrapolation.

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