Allometric analysis of ciprofloxacin and enrofloxacin pharmacokinetics across species

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The purpose of this study was to examine the allometric analysis of ciprofloxacin and enrofloxacin using pharmacokinetic data from the literature. The pharmacokinetic parameters used were half-life, clearance and volume of distribution. Relationships between body weight and the pharmacokinetic parameter were based on the empirical formula $Y = aW^b$, where Y is half-life, clearance or volume of distribution, W the body weight and a is an allometric coefficient (intercept) that is constant for a given drug. The exponential term b is a proportionality constant that describes the relationship between the pharmacokinetic parameter of interest and body weight. A total of 21 different species of animals were studied. Results of the allometric analyses indicated similarity between clearance and volume of distribution as they related to body weight for both drugs. Results of the current analyses indicate it is possible to use allometry to predict pharmacokinetic variables of enrofloxacin or ciprofloxacin based on body size of species. This could provide information on appropriate doses of ciprofloxacin and enrofloxacin for all species.

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INTRODUCTION

Drug dosage extrapolation among species assumes that pharmacodynamic similarities exist when pharmacokinetic equivalency is achieved. In other words, achieving equivalent peak serum and tissue concentrations and duration of drug exposure will achieve similar physiologic effects among species. Species-dependent differences at the site of drug action, such as the number of receptors or affinity of receptors for the drug, can preclude achieving equivalent effects for many classes of drugs. But achieving equivalent antimicrobial drug exposure in different species should achieve similar killing of microorganisms. The ability to achieve pharmacokinetic equivalency depends on the physiology and morphology of the tissues and organs responsible for drug absorption, distribution, biotransformation, and excretion of drugs.

The allometric approach is a basic mathematical tool for analyzing differences in anatomy, physiology, biochemistry, and pharmacokinetics in animals of different sizes. At least 750 allometric equations have been reported (Calder, 1984). The usual allometric approach relates one biologic function or structure (y) to another (x) through an empirical power function:

$$y = a(x)^b$$

Drug plasma concentrations are dependent on the pharmacokinetic parameters of the drug, including half-life, clearance, volume of distribution, or the area under the drug concentration vs. time curve (*AUC*) (Baggot, 1977; Rowland, 1986; Benet *et al.*, 1996). Because most pharmacokinetic parameters are dependent on physiologic functions, it is possible to compare these parameters among species on the basis of allometric relationships, i.e. where y is the value of the pharmacokinetic parameter and x the body weight (Boxenbaum, 1982; Riond & Riviere, 1990; Pashov *et al.*, 1997; Riviere *et al.*, 1997). Allometry may be performed on any pharmacokinetic parameter, however, the half-life profile is most often studied because of the abundance of this parameter in the published literature. Half-life is a composite of volume of distribution and clearance. Therefore, clearance can be studied and may provide less biased information.

Interspecies scaling assumes that biochemical and physiologic processes responsible for rate of drug elimination vary in accordance to basal metabolic rate. A number of physiologic factors other than basal metabolism can modify these biochemical/physiological relationships. These factors include change in protein binding, saturation of drug elimination processes, diet, genetic polymorphism, drug-induced alterations in physiologic processes, biotransformation, interspecies differences in enterohepatic circulation, and tubular reabsorption as influenced by urinary pH (Mellett, 1969; Williams, 1973; Sorgel, 1989; Pashov *et al.*, 1997; Riviere *et al.*, 1997). Differences in pharmacokinetic parameters and biologic activity of drugs among species may be

related to physicochemical interactions of drugs with food, or to biodegradation of compounds in the rumen, caecum, or colon (Baggot, 1977, 1980, 1990; Pashov *et al.*, 1997).

Fluoroquinolones, such as enrofloxacin and ciprofloxacin, have similar distribution characteristics; however, elimination pathways and rates differ considerably among species. Oral absorption of fluoroquinolones is generally fast and substantial in humans, monogastric species, and preruminant age calves, with up to 80% of the ingested dose absorbed into the systemic circulation (Vancutsem *et al.*, 1990). These drugs have volumes of distribution greater than 1 L/kg. Binding to plasma proteins is variable among species (Bregante *et al.*, 1999) and for different quinolones (Zlotos *et al.*, 1998a, b). Major elimination pathways are renal excretion and hepatic metabolism. Fluoroquinolones are affected by all potential renal excretion mechanisms (glomerular filtration, tubular secretion, and tubular reabsorption). In the liver, they are metabolized primarily by oxidation but also demethylation and deethylation of the parent molecule (Lode *et al.*, 1989). Conjugative pathways are predominant for some drugs and some species (Sorgel, 1989); however, the degree of metabolism varies considerably across species.

Pharmacokinetic characteristics of ciprofloxacin and enrofloxacin have been determined in several different species. Bregante *et al.* (1999) conducted a study to compare the pharmacokinetics of enrofloxacin in five species and then subsequently looked at correlations of pharmacokinetic variables with body weight. Mahmood (1999) examined correlations of ciprofloxacin pharmacokinetic variables with body weight in three species. Both of theses studies examined mammalian species and in Mahmood's (1999) study only three different species were used. According to Riviere *et al.* (1997) a minimum of four species is deemed necessary for a proper analysis. Because of the growing number of exotic species that are being treated we wanted to include as many species as we could obtain data for in the study. The objectives of this study were to determine whether allometric scaling based on body weight could be used to predict half-life ($t_{1/2}$), total body clearance (Cl) and volume of distribution at steady state [$V_{d(ss)}$] for these two fluoroquinolones. These relationships may impact interspecies scaling of drug dose.

MATERIALS AND METHODS

The relationships between body mass and $t_{1/2}$, $V_{d(ss)}$, or Cl of ciprofloxacin and enrofloxacin were analyzed using data from previously published studies in 21 total species: 13 for ciprofloxacin (Table 1) and 15 for enrofloxacin (Table 2). Reported values for $t_{1/2}$, Cl and $V_{d(ss)}$ were determined after intravenous (i.v.) administration of the drug. The matrices of interest were serum, plasma, or blood. Data for body weights were collected from these same studies. Mean values were used when a range of body weights was given. When body weights were not indicated, average values for the species and breed were collected from the literature sources. Records were deleted if subjects were diseased

Table 1. Ciprofloxacin animal species database

Species	$t_{1/2}$ (h)	Cl (mL/min/kg)	$V_{d(ss)}$ (L/kg)	Source
Bos domesticus, Cow	2.4	12.1	2.5	Nouws *et al.* (1988a)
Sus scrofa, Pig	2.6	17.3	3.8	Nouws *et al.* (1988a)
Ovis ovis, Sheep	1.2	18	1.9	Munoz *et al.* (1996)
Orictolagus uniculus, Rabbit	1.6	27.2	3.8	Aramayona *et al.* (1996)
Canis famillaris, Dog	3, 2.2, 2.6	19, 18, 14	4.9, 3.3, 3.1	Abadia *et al.* (1994)
	2.8	7.8	1.9	Cester and Toutain (1997)
Rattus rattus, Rat	2.2	26.7	4.6	Siefert *et al.* (1986)
Macaca mulatta, Monkey	4.3	4.7	1.8	Siefert *et al.* (1986)
Homo sapiens, Human	4.3, 4.4	8.3, 8.2	2.4, 2.4	Lettieri *et al.* (1992)
	2.7, 2.9, 2.8	9.6, 9.6, 8.2	9.6, 9.6, 8.2	Dudley *et al.* (1987a)
	2.9	9.3	2.6	Bergan *et al.* (1987)
	4.2	8.2	2	Dudley *et al.* (1987b)
	2.3	9.8	2.0	Deppermann *et al.* (1989)
	3.6, 3.7, 3.5	8.8, 7.6, 7.8	2.1, 1.9, 1.8	Nix *et al.* (1992)
	3.7	9.6	2.0	Wingender *et al.* (1984)
	3.5, 3.9, 3.6	9.0, 8.2, 8.0	2.7, 2.7, 2.5	Bergan *et al.* (1988)
	4.2	8.7	2.3	Catchpole *et al.* (1994)
	3.3, 3.7, 3.5	8.1, 7.9, 7	2.2, 2.3, 1.9	Ljungberg and Nilsson-Ehle (1988)
	4.8, 3.3	10.6, 10.2	4.4, 2.9	Lode *et al.* (1988)
Capra hircus, Goat	2.7	19.6	3.4	Garcia Ovando *et al.* (2000)
Gallus gallus domesticus, Chicken	2.3	12.5	1.8	Garcia Ovando *et al.* (1997)
	3.1	15.5	4.0	Garcia Ovando *et al.* (1999)
	8.8	8	4	Anadon *et al.* (2001)
Cyprinus carpio, Carp	14.5	2.5	2.7	Nouws *et al.* (1988b)
Salmo gairdneri, Trout	11.2	4.8	2.7	Nouws *et al.* (1988b)
Clarias gariepinus, African catfish	14.2	4.5	5.6	Nouws *et al.* (1988b)

When more than one value is listed, they represent multiple doses in the citation.

Table 2. Enrofloxacin animal species database

Species	$t_{1/2}$ (h)	*Cl* (mL/min/kg)	$V_{d(ss)}$ (L/kg)	Source
Bos domesticus, Cow	6.6, 4.9	3.2, 6.5	1.8, 2.3	Kaartinen *et al.* (1997a)
	16.3	7.5	0.18	Martinez-Larranaga *et al.* (1997)
	2.6	19.1	0.45	Varma *et al.* (2003)
Sus scrofa, Pig	7.3	6.2	3.9	Nielson and Gyrd-Hansen (1997)
	7.7	4.5	2.7	Richez *et al.* (1997b)
	3.5	7	2.9	Zeng and Fung (1997)
	9.6	1.7	1.3	Anadon *et al.* (1999)
	21,10.5	2.7, 7.5	5.5, 6.8	Post *et al.* (2002, 2003)
Ovis ovis, Sheep	3.7	9.2	3.0	Mengozzi *et al.* (1996)
	3.8	4	2.2	Pozzin *et al.* (1997)
	4.8	3.4	1.0	Bermingham *et al.* (2000, 2002)
Orictolagus uniculus, Rabbit	2.2	22.8	3.4	Cabanes *et al.* (1992)
	1.9	23.9	3.9	Aramayona *et al.* (1996)
Canis famillaris, Dog	2.4	27.1	7	Kung *et al.* (1993)
	4.4	10.9	3.7	Monlouis *et al.* (1997)
	2.3	12.2	2.5	Cester and Toutain (1997)
Lama glama, Llama	3.4	11.7	3.5	Christensen *et al.* (1996)
Felis domestica, Cat	6.7	9.5	4	Richez *et al.* (1997a)
Camelus dromedarius, Camel	11.9, 5.8, 4.9, 3.8	1.0, 1.4, 1.2, 1.4	1.0, 0.5, 0.7, 0.4	Harron *et al.* (1997)
Equus caballus, Horse	17.1	1.7	2.5	Bermingham *et al.* (2000)
	4.4	8.5	2.3	Kaartinen *et al.* (1997b)
	6.7	3.7	1.7	Papich *et al.* (2002)
	5.9	9.4	2.1	Boeckh *et al.* (2001)
Capra hircus, Goat	1.1	13.5	1.2	Rao *et al.* (2000)
	4.0	4	1.2	Elmas *et al.* (2001)
Gallus gallus domesticus, Chicken	10.3	4.8	2.8	Anadon *et al.* (1995)
	7.5	3	1.8	Garcia Ovando *et al.* (1997)
	7.0	3.3	2.0	Garcia Ovando *et al.* (1999)
	5.6	10.3	3.9	Knoll *et al.* (1999)
Dormaius novaehollandiae, Emu	3.3	6	1.6	Helmick *et al.* (1997)
Chlamydotis undulata macqueenii, Houbara bustard	5.6	5.7	3.0	Bailey *et al.* (1998)
Salmo salar, Atlantic salmon	34.2	2.3	6.1	Martinsen and Horsberg (1995)
Bison bison, Buffalo	2.9	32.4	5.3	Kumar *et al.* (2003)
	2.9	27.8	6.9	Sharma *et al.* (2003)

When more than one value is listed, they represent multiple doses in the citation.

or if other drugs were co-administered. Analyses did not consider the influence of age or sex. If values for *Cl* or $V_{d(ss)}$ were missing they were calculated if appropriate information was available from the citation. Regression analyses were only performed on data from studies where HPLC analyses were done for both enrofloxacin and ciprofloxacin. Biological methods (microbiologic assay) do not differentiate between enrofloxacin and ciprofloxacin and other active metabolites.

Data were separated into two groups for both drugs. The groups were: (1) all species (including mammals, fish, reptiles, and birds), and (2) mammals only.

Regression analysis of logarithmic values for body weight, $t_{1/2}$, *Cl* or $V_{d(ss)}$ was preformed using SAS software (SAS Institute, Cary, NC, USA). The analyses were performed using mean values from individual citations, although there was no verification that the data was normally distributed. The linear regression of log $t_{1/2}$ (h), log $V_{d(ss)}$ (L) or log *Cl* (mL/min) vs. log body weight (*W*, kg) was analyzed so that estimates of the intercept *c* and slope *b* could be computed by the following equations:

$$\log t_{1/2} = c + b(\log W), \log V_{d(ss)} = c + b(\log W) \quad \text{or}$$
$$\log C- = c + b(\log W)$$

The allometric equation was then applied [$t_{1/2} = a(W)^b$, $V_{d(ss)} = a(W)^b$ or $Cl = a(W)^b$], where *a* is the antilogarithm of *c*. Coefficients of determination and *P*-values were computed for each regression analysis under study. Double logarithmic plots of body weight vs. $t_{1/2}$, *Cl* or $V_{d(ss)}$ were constructed to demonstrate significance found in the regression analysis.

RESULTS

Results of the regression analyses conducted on the logarithm of $t_{1/2}$, $V_{d(ss)}$, or *Cl* vs. the logarithm of body weight for ciprofloxacin are listed in Table 3. There was a statistically significant relationship between *Cl* ($P = 0.0001$), volume of distribution ($P = 0.0001$) and $t_{1/2}$ ($P = 0.004$) compared with body weight when all species were analyzed. Ciprofloxacin

Table 3. Ciprofloxacin half-life, clearance and volume of distribution values for allometric equations

Group	*n*	*a*	*b*	r^2	*P*-value
Half-life					
All species	38	5.1	−0.123	0.210	0.0038
Mammals	32	2.2	0.091	0.149	0.029
Clearance					
All species	38	5.8	1.13	0.915	0.0001
Mammals	32	20.6	0.815	0.906	0.0001
Volume of distribution					
All species	38	2.2	1.07	0.943	0.0001
Mammals	32	3.5	0.947	0.871	0.0001

n, sample size; *a*, intercept; *b*, slope; r^2, coefficient of determination.

half-life (Fig. 1a), clearance (Fig. 1b) and volume of distribution (Fig. 1c) were related to body weight in mammals with *P*-values of 0.029, 0.0001 and 0.0001, respectively.

The results of the regression analysis conducted for enrofloxacin $t_{1/2}$, $V_{d(ss)}$ and *Cl* are listed in Table 4. The enrofloxacin allometric analysis was similar to that of ciprofloxacin. There was not an association between $t_{1/2}$ and body weights among all species for enrofloxacin. Clearance ($P = 0.0001$) and $V_{d(ss)}$ ($P = 0.0001$) were significantly related to body weight in the analysis. Enrofloxacin $t_{1/2}$ (Fig. 2a) was not significantly associated with body weight when mammals were analyzed. However, the analysis of $V_{d(ss)}$ (Fig. 2b) or *Cl* (Fig. 2c) and body weight in mammals produced a significant relationship ($P = 0.0001$).

DISCUSSION AND CONCLUSIONS

There is uniform agreement that for most parameters related to physiological processes the allometric exponent *b* ranges from 0.67 to 1.0; however when the parameter being modeled is an inverse function of a physiological process ($t_{1/2}$) then the exponent will be 1–*b* (Riviere *et al.*, 1997). If $b = 1$ there is a direct correlation between body weight and the parameter of interest.

Most drugs are primarily cleared by either the kidney or liver. Overall renal and hepatic function will be determined by blood flow which is dependent on cardiac output and observations suggest that cardiac output scales to $b = 0.75$ (Boxenbaum, 1982). Thus for drugs cleared primarily by the kidneys, *Cl* scales to $b = 0.75$ and $t_{1/2}$ (an inverse function of *Cl*) should scale to 0.25 (1–0.75). This is even true of drugs excreted by active tubular transport, unless transport is saturated.

If one is looking at V_d, which is a function of vascular, extracellular and total body fluid, *b* should be between 0.67 and 1.0 and if we assume that total body water directly correlates to body weight, $b = 1.0$. The $V_{d(ss)}$ is the preferred volume of distribution estimate for studies about disposition across species because it is considered the most robust estimate of V_d as it is mathematically and physiologically independent of the elimination process (Riviere, 1999). Our estimates for *Cl* and

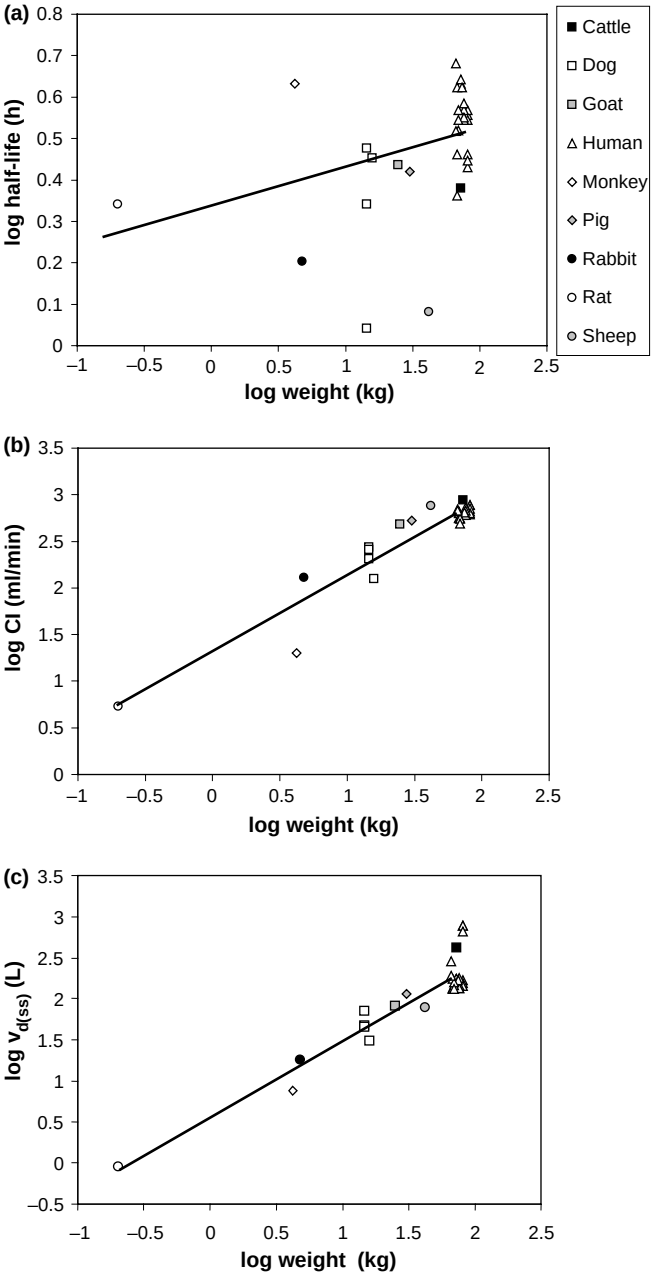

Fig. 1. Allometric association (double logarithmic) for ciprofloxacin between half-life (a), clearance (b) and volume of distribution (c) and body weight of mammals.

$V_{d(ss)}$ for both drugs are consistent with this theory. Clearance scales between $b = 0.76$ and 1.1 and $V_{d(ss)}$ $b = 0.65$ and 0.94 for both drugs. Our estimates for enrofloxacin in mammals [*Cl*, $b = 0.74$; $V_{d(ss)}$, $b = 0.81$] are consistent with previously reported values (Bregante *et al.*, 1999). The estimate for ciprofloxacin clearance in mammals ($b = 0.81$) is consistent with previously reported values (Mahmood, 1999). Mahmood (1999) also analyzed volume of distribution in the central compartment and found and exponent of 0.5 with a correlation of 0.931. Since volume of distribution determines dose for

Table 4. Enrofloxacin half-life, clearance and volume of distribution values for allometric equations

Group	*n*	*a*	*b*	r^2	*P*-value
Half-life					
All species	39	6.8	−0.062	0.036	0.241 NS
Mammals	32	4.0	0.062	0.022	0.415 NS
Clearance					
All species	39	7.2	0.939	0.797	0.0001
Mammals	32	15.9	0.764	0.594	0.0001
Volume of distribution					
All species	39	4.11	0.803	0.818	0.0001
Mammals	32	6.0	0.724	0.650	0.0001

n, sample size; *a*, intercept; *b*, slope; r^2, coefficient of determination; NS, not significant.

concentration dependent drugs, this is clinically relevant. As reported previously (Papich & Riviere, 2001) excluding interspecies differences in oral bioavailability doses of enrofloxacin are similar.

We found that body weight is proportional to $t_{1/2}$ by and exponent of 0.1 or less for both ciprofloxacin and enrofloxacin. A slope of zero for $t_{1/2}$ would be expected if there were a perfect correlation between weight and *Cl* and weight and $V_{d(ss)}$. Therefore given the high level of correlation observed in the study, it is not surprising that *b* tends toward zero. Half-life is a hybrid scaling to V_d/Cl therefore either of these variables could cause the small allometric exponent of $t_{1/2}$ we found. Looking at the range of values used in the regression analysis for ciprofloxacin clearance (5–800 mL/min; 125-fold range), $V_{d(ss)}$ (0.92–800 L; 870-fold range) vs. $t_{1/2}$ (1–4; fourfold range) it is easy to see how deviations from linearity that would appear relatively small within the primary parameters could have a substantial impact on $t_{1/2}$. This could explain the observation of a poor correlation for $t_{1/2}$ while correlations for *Cl* and $V_{d(ss)}$ were good.

There were some large discrepancies reported within species for some of the parameters. These could be due to the various conditions (lactating, pregnant, sex, breed, age, fasted or fed) of the animals used in the various studies. Nouws *et al.* (1988a) suggested that the age of the animal (maturity of renal function and metabolic capacity of liver) as well as breed difference may have affected the ciprofloxacin plasma concentrations and thus its pharmacokinetic parameters. The enrofloxacin $t_{1/2}$ values for the foal and the young camel were much higher than the horse or mature camel in our study. Aramayona *et al.* (1996) indicated that lactation and associated factors in rabbits could affect the binding of ciprofloxacin to plasma proteins. Lactation may be associated with different hormone levels that affect plasma protein binding. Siefert *et al.* (1986) noted that possible differences in ciprofloxacin metabolism exist between male and female rats. This could also be true in other species and could influence pharmacokinetic parameters of interest.

We did not try to correct for plasma protein binding in our analysis since data was not available for all species that were studied. Protein binding can be significant for fluoroquinolones but it is also difficult to compare results of studies in which protein binding was measured because of differences among

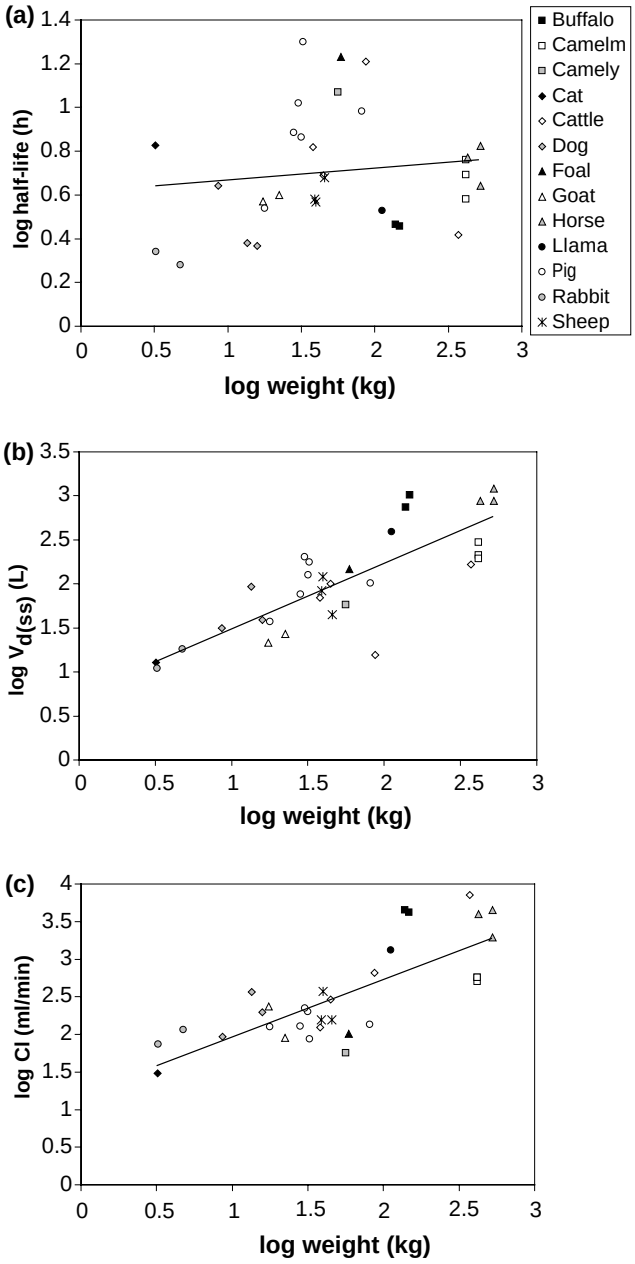

Fig. 2. Allometric association (double logarithmic) for enrofloxacin between half-life (a), volume of distribution (b) and clearance (c) and body weight of mammals.

laboratories and variations in methods used (Zlotos *et al.*, 1998b). Bregante *et al.* (1999) corrected for plasma protein binding in their study by using the plasma free fraction after finding significant differences in protein binding of the species they studied. Never the less, our results support an allometric relationship for clearance and volume of distribution without such a correction.

We concluded that clearance and volume of distribution are proportional to body weight for both drugs, while the elimination half-life for ciprofloxacin and enrofloxacin is independent of body weight. The results from this study suggest that it could be possible to extrapolate the kinetic parameters of enrofloxacin and

ciprofloxacin across species using allometric equations which could be a useful tool to predict their disposition in species that have not been studied yet.

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