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Allometric scaling of marbofloxacin, moxifloxacin, danofloxacin and difloxacin pharmacokinetics: a retrospective analysis

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The purpose of this study was to examine the allometric analyses of marbofloxacin, moxifloxacin, danofloxacin and difloxacin using pharmacokinetic data from the literature. The parameters of interest (half-life, clearance and volume of distribution) were correlated across species as a function of body weight using an allometric approach ($Y = aW^b$). Results of the allometric analysis indicated similarity between clearance and volume of distribution as they relate to body weight for all drugs. The elimination half-life was independent of body mass for all fluoroquinolones except moxifloxacin. Results of the analysis suggest that allometric scaling can be used as a tool for predicting pharmacokinetic parameters for fluoroquinolones.

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INTRODUCTION

Fluoroquinolones (FQs) have become a dominant class of antimicrobial agents over the last decade. No other class of antimicrobial agent has grown so rapidly. As a class they have demonstrated clinical efficacy against organisms that cause infections of the skin, soft tissue, oral cavity, urinary tract, prostate, external and internal middle ear, wounds, respiratory tract and bone in veterinary medicine (Papich & Riviere, 2001). There are numerous new FQs and the structural modifications have allowed this class to have a remarkably broad spectrum of activity. The newer FQs exhibit improved pharmacokinetic properties, such as longer half-lives, higher peak levels and increased volume of distribution, when compared with the older compounds.

Although there is considerable individual variation among the different compounds and in different species, generally FQs are rapidly absorbed following oral administration in monogastric species. Bioavailability for difloxacin was between 86% and 99% in calves, rabbits, pigs and chickens (Inui *et al.*, 1998; Ismail & El-Kattan, 2007; Marin *et al.*, 2007a). Danofloxacin had an oral bioavailability of 99% and 100% in chickens and goats (Knoll *et al.*, 1999; Aliabadi & Lees, 2001). The bioavailability of marbofloxacin is very good in cats (84.6%) and dogs (99.8%) but is lower in horses (62%) (Marbocyl, 2005). Moxifloxacin bioavailability is very similar to the other FQs (52–91%) (Siefert *et al.*, 1999a). The FQs possess the ability to diffuse from the blood into extravascular spaces in significant concentrations.

Drugs have low protein binding when binding is <50% (Bergogne-Berezin, 2002) and in most instances protein binding for FQs is low. Plasma protein binding for danofloxacin ranged from 13.5% in goats (Atef *et al.*, 2001), 44% in healthy pigs (Lindercrona *et al.*, 2000) to 49% in cows (Sarasola *et al.*, 2002). Protein binding for difloxacin is also considered to be low with values of 13.8% in goats, 21% in rabbits and between 32% and 37% in calves (Atef *et al.*, 2002; Fernandez-Varon *et al.*, 2007). Similar to the other FQs, marbofloxacin plasma protein binding is low (10–40%) (Lefebvre *et al.*, 1998; Aliabadi & Lees, 2002) as is moxifloxacin (29–45%) (Siefert *et al.*, 1999a).

Fluoroquinolones are metabolized by various phase I and phase II reactions in the liver. *N*-dealkylation is a very important phase I reaction of most FQs. Additionally, oxidation, hydroxylation, demethylation and de-ethylation of the parent molecule take place (Lode *et al.*, 1989; Kietzmann, 1999). Conjugative pathways are predominant for some drugs and some species (Sorgel, 1989); however, the degree of metabolism varies considerably across species.

Major elimination pathways are renal excretion and hepatic metabolism. Most FQs are excreted via urine, mainly by glomerular filtration and tubular secretion. Difloxacin is an exception, 80% of a dose was recovered in the feces and renal clearance accounted for <5% of the total clearance (Papich & Riviere, 2001). Marbofloxacin is primarily excreted in urine with minimal biotransformation. Small amounts of desmethyl- and *N*-oxide metabolites have been detected in dogs, pigs and cows (EMEA, 1996). Moxifloxacin in humans is metabolized by phase II reactions (conjugation) to two inactive metabolites, *N*-sulfate conjugate and an acylglucuronide (Moise *et al.*, 2000). Danofloxacin is eliminated by both renal and hepatic mechanisms. Its metabolism has been studied in rats, dogs, chickens, pigs and

cattle and the main residue in both urine and feces was unmetabolized danofloxacin (WHO, 1997).

Studies indicate that FQs penetrate into the milk from blood. The penetration of danofloxacin from the blood of cows into milk was rapid and extensive with concentrations in the milk exceeding those in the serum (Shem-Tov *et al.*, 1998). Similar results also occurred when difloxacin and moxifloxacin were administered to lactating goats (Fernandez-Varon *et al.*, 2005a; Marin *et al.*, 2007a). Marbofloxacin penetration into milk was rapid and extensive with milk concentrations exceeding those in serum 2 h after administration to lactating cows and ewes (Shem-Tov *et al.*, 1997).

Because most pharmacokinetic parameters are dependent on physiologic functions, it is possible to compare these parameters among species on the basis of allometric relationships ($Y = aW^b$) where Y is the relevant pharmacokinetic parameter, W is body weight, and a and b are the coefficient and exponent of the allometric equation. Allometry may be performed on pharmacokinetic parameters, such as half-life, volume of distribution, area under concentration–time curve and clearance. Interspecies scaling assumes that biochemical and physiologic processes responsible for rate of drug elimination vary in accordance to basal metabolic rate. Physiologic factors other than basal metabolism that can modify these relationships include biotransformation, protein binding, saturation of drug elimination processes, genetic polymorphism, diet, drug-induced alterations in physiologic processes, tubular reabsorption as influenced by urinary pH and interspecies differences in enterohepatic circulation (Sorgel, 1989; Pashov *et al.*, 1997; Riviere *et al.*, 1997).

Currently there are six FQs (enrofloxacin, difloxacin, danofloxacin, marbofloxacin, oribifloxacin and sarafloxacin) that have been approved for animal use in the USA (Martinez *et al.*, 2006). The allometric relationships of enrofloxacin pharmacokinetics have been assessed across a variety of species as has ciprofloxacin

Table 1. Moxifloxacin, marbofloxacin and danofloxacin animal species database

Species	Wt (kg)	$t_{1/2}$ (h)	*Cl* (mL/min/kg)	$V_{d(ss)}$ (L/kg)	Source
Moxifoxacin					
Mus musculus, Mouse	0.03	0.9	70.2	3.7	Siefert *et al.* (1999a)
Rattus rattus, Rat	0.2	1.2	42.5	3.6	Siefert *et al.* (1999a)
	0.2	1.2	34.7	3.6	Siefert *et al.* (1999b)
Macaca mulatta, Monkey	4.4	6.9	11.5	4.9	Siefert *et al.* (1999a)
	4.4	7.0	8.8	5.3	Siefert *et al.* (1999b)
Canis famillaris, Dog	12.2	8.6	3.7	2.7	Siefert *et al.* (1999a)
Sus scrofa, Minipig	14.3	5.7	10.8	3.8	Siefert *et al.* (1999a)
Homo sapiens, Human	76	13.0	2.2	2.0	Siefert *et al.* (1999a)
	76	8.2	1.9	1.4	Wise *et al.* (1999)
	91.5	15.4	2.1	2.1	Stass & Kubitza (1999)
Orictolagus uniculus, Rabbit	3.5	1.8	13.3	2.0	Fernandez-Varon *et al.* (2005b, 2007)
	3.9	2.2	13.0	2.1	
Marbofloxacin					
Canis famillaris, Dog	9.7	10.8	1.6	1.2	Lefebvre *et al.* (1998)
Capra hircus, Goats	47	7.2	4.0	1.3	Waxman *et al.* (2001)
	45	7.2	3.8	1.3	Waxman *et al.* (2004)
Equus caballus, Horse	450	4.7	3.2	1.2	Carretero *et al.* (2002)
	568	7.6	4.0	1.5	Bousquet-Melou *et al.* (2002)
	509	7.4	4.6	1.6	Peyrou *et al.* (2005)
Bos domesticus, Cow	600	5.7	5.2	1.2	Marbocyl website
Felis domestica, Cat	3.2	10.3	2.2	1.5	Marbocyl website
Sus scrofa, Pig	227	8.2	2.8	1.8	Marbocyl website
Ovis aries, Sheep	33.5	2.0	9.2	1.5	Marbocyl website
Danofloxacin					
Camelus dromedarius, Camel	256	5.4	7.3	2.5	Aliabadi *et al.* (2003a)
Ovis aries, Sheep	52	3.4	11.8	2.8	Aliabadi *et al.* (2003b)
	27.5	3.4	10.5	2.8	McKellar *et al.* (1998)
Sus scrofa, Pig	32	6.7	9.5	5.2	Lindercrona *et al.* (2000)
Equus caballus, Horse	463	6.3	5.7	2.0	Fernandez-Varon *et al.* (2006)
Orictolagus uniculus,Rabbit	3.1	4.9	12.7	7.3	Fernandez-Varon *et al.* (2007)
Capra hircus, Goats	30	1.4	9.8	1.4	Atef *et al.* (2001)
	74.2	4.7	9.5	3.0	Aliabadi & Lees (2001)
Difloxacin					
Orictolagus uniculus, Rabbit	3.9	4.2	6.8	2.0	Fernandez-Varon *et al.* (2007)
Ovis aries, Sheep	52	11.4	3.5	1.7	Marin *et al.* (2007b)
Equus caballus, Horse	451	2.7	4.7	1.0	Fernandez-Varon *et al.* (2006)
Capra hircus, Goats	28	6.3	2.2	1.1	Atef *et al.* (2002)

though; it is not approved for animal use (Bregante *et al.*, 1999; Mahmood, 1999; Cox *et al.*, 2004). However, to our knowledge no one has looked at the other FQs. The objective of this study was to assess the relationship between half-life ($t_{1/2}$), total body clearance (Cl) or volume of distribution at steady-state [$V_{d(ss)}$] and body weight across different species for FQs that have been approved for use in veterinary medicine and to determine the scaling coefficients in those cases where significant relationships were found.

MATERIALS AND METHODS

The relationships between body mass and $t_{1/2}$, $V_{d(ss)}$, or Cl of marbofloxacin, moxifloxacin, difloxacin and danofloxacin were analyzed using data from previously published studies in 13 total species (Table 1): seven for moxifloxacin, seven for marbofloxacin, four for difloxacin and six for danofloxacin. There was not enough information available for orbifloxacin or sarafloxacin to perform allometric modeling. Values for $t_{1/2}$, Cl and $V_{d(ss)}$ were obtained after intravenous (i.v.) administration of the drug. The matrices of interest were serum or plasma. Data for body weights were obtained from these studies. When a range of body weights was given mean values were used. Average values for the species and breed were obtained from literature sources if body weights were not listed. Records were deleted if subjects were diseased or if other drugs were co-administered. Analyses did not consider the influence of age or sex. Missing values were calculated if appropriate information was available from the citation.

Regression analysis of logarithmic values for body weight, $t_{1/2}$, Cl or $V_{d(ss)}$ was performed using SAS software (SAS Institute, Cary, NC, USA). The analyses were performed using mean values from individual citations, even though 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 equation:

$$\log(\text{pharmacokinetic parameter of interest}) = \log c + b(\log W).$$

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 log c. Coefficients of determination and P-values were computed for each regression analysis under study. Double logarithmic plots of body mass 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 $V_{d(ss)}$, Cl, or $t_{1/2}$ vs. the logarithm of body weight for the FQs are listed in Table 2. There was a statistically significant relationship between marbofloxacin clearance ($P = 0.0001$; $1.96W^{1.1}$) and volume of distribution ($P = 0.0001$; $1.34W^{1.0}$) compared with body weight (Fig. 1a,b) in the study. Marbofloxacin half-life was not related to body mass.

Table 2. Half-life, clearance and volume of distribution values for allometric equations

Group	*n*	*a*	*b*	r^2	*P*-value
Half-life					
Marbofloxacin	14	9.36	−0.063	0.070	0.3610 NS
Moxifloxacin	12	2.4	0.36	0.830	0.0001
Danofloxacin	8	2.93	0.086	0.0647	0.5433 NS
Difloxacin	4	7.29	−0.0860	0.0721	0.7315 NS
Clearance					
Marbofloxacin	14	1.96	1.13	0.963	0.0001
Moxifloxacin	12	18.77	0.54	0.951	0.0001
Danofloxacin	8	17.65	0.84	0.989	0.0001
Difloxacin	4	4.87	0.94	0.940	0.0303
Volume of distribution					
Marbofloxacin	14	1.34	1.01	0.996	0.0001
Moxifloxacin	12	3.25	0.91	0.977	0.0001
Danofloxacin	8	3.56	0.93	0.937	0.0001
Difloxacin	4	2.16	0.88	0.986	0.0071

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

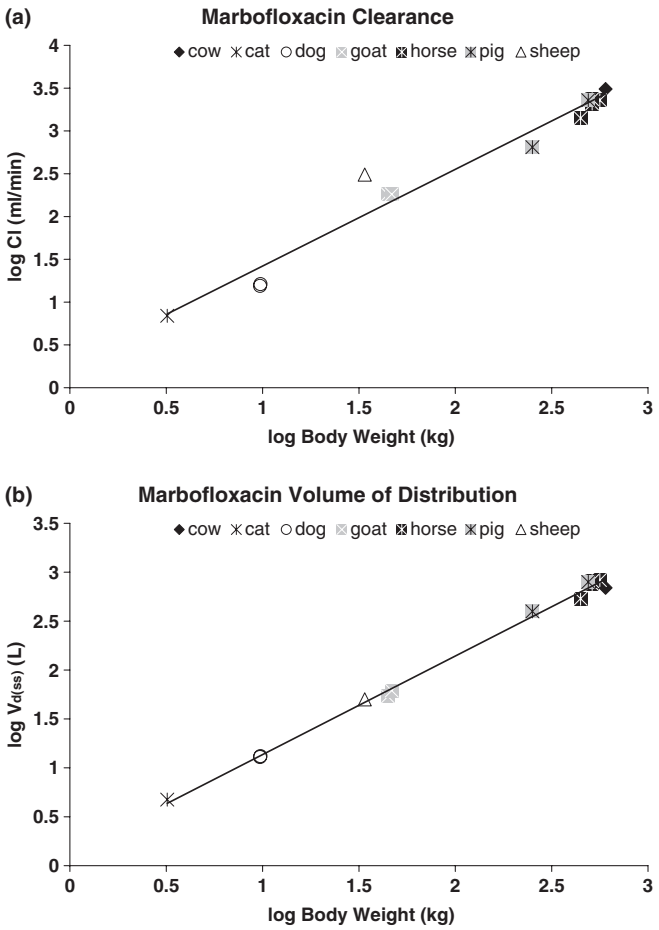

Fig. 1. Allometric association for marbofloxacin between (a) clearance and (b) volume of distribution and body weight.

Results of the regression analysis conducted for danofloxacin and difloxacin were similar to that of marbofloxacin. There was not an association between half-life and body weights among the

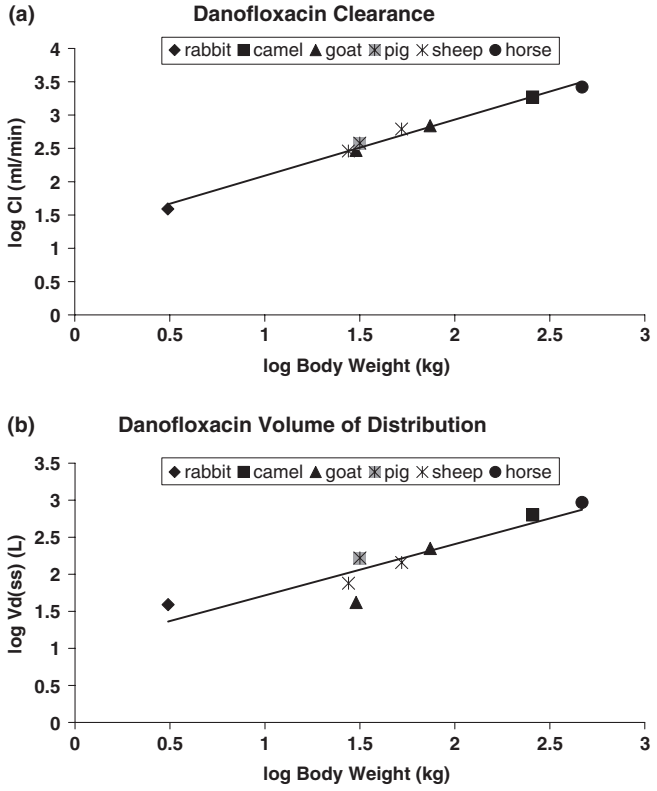

Fig. 2. Allometric association for danofloxacin and body mass for (a) clearance and (b) volume of distribution.

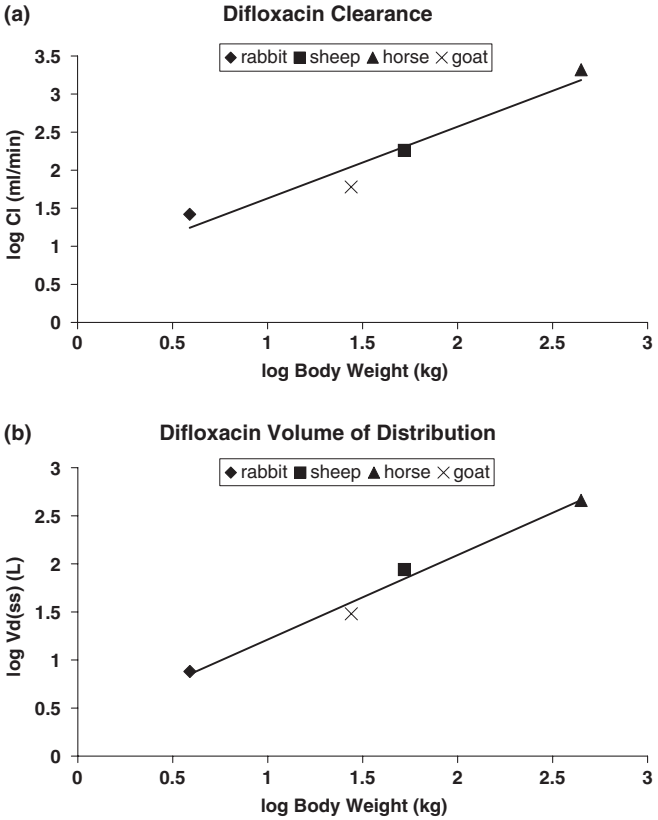

Fig. 3. Allometric association for difloxacin and body weight for (a) clearance and (b) volume of distribution.

species studied for either drug. Danofloxacin clearance and volume of distribution were significantly related to body weight in the analysis (Fig. 2a,b). The allometric equations were $17.65W^{0.84}$ (*Cl*) and $3.56W^{0.93}$ [$V_{d(ss)}$]. Difloxacin clearance ($4.87W^{0.94}$) and volume of distribution ($2.16W^{0.88}$) were also related to body weight (Fig. 3a,b).

Moxifloxacin half-life, clearance and volume of distribution were related to body weight (Fig. 4a,b). The allometric equations were $2.4W^{0.36}$, $18.77W^{0.54}$, and $3.25W^{0.91}$ for half-life, clearance and volume of distribution, respectively.

DISCUSSION

The volume of distribution parameters represent good correlation (r^2 ranged between 0.937 and 0.996; $P = 0.0001$ or 0.0071). Volume of distribution was allometrically related to body weight for all four drugs. The estimates for the FQs in this study are consistent with previously reported values for ciprofloxacin and enrofloxacin (Bregante *et al.*, 1999; Mahmood, 1999; Cox *et al.*, 2004).

In this study, clearance was allometrically related to body weight for all four drugs with allometric exponents ranging from 0.54 to 1.1. The r^2 (0.940 – 0.989) and *P*-values ($P = 0.0001$ & $P = 0.0303$) represent good correlation. The estimates for difloxacin and danofloxacin clearance are similar to previously published values (Bregante *et al.*, 1999; Mahmood, 1999; Cox *et al.*, 2004). While the estimate for moxifloxacin is slightly lower than the other estimates it is similar to the value that Siefert *et al.* (1999a) found. Marbofloxacin has a slightly higher exponent than the other FQs in this study and those found in the literature. Fluoroquinolones undergo both renal elimination and hepatic metabolism. The differences between exponents could suggest that when the total clearance value is used as the sum of hepatic and renal clearances, prediction may be difficult because the rate of the two elimination processes could be different in different species.

The analysis revealed that $t_{1/2}$ was allometrically related to body weight with an exponent of 0.086 or less for all the FQs except moxifloxacin which had an exponent of 0.36. The estimates for marbofloxacin, danofloxacin and difloxacin are similar to values reported for enrofloxacin (Bregante *et al.*, 1999; Cox *et al.*, 2004). Many studies do indicate that an exponent of 0.25 is common when the half-life of elimination is correlated with body weight (Riviere *et al.*, 1997; Bregante *et al.*, 1999; Riviere, 1999). Half-life is a hybrid pharmacokinetic parameter scaling to V_d/Cl therefore either of these variables could be the cause of the allometric exponents of $t_{1/2}$ that were found. Differences in metabolism among the mammalian species could also explain the values for the allometric exponents of half-life in the study.

There were some variations reported within species for some of the pharmacokinetic parameters. These could be due to the various conditions (sex, breed, age, fasted or fed) of the animals

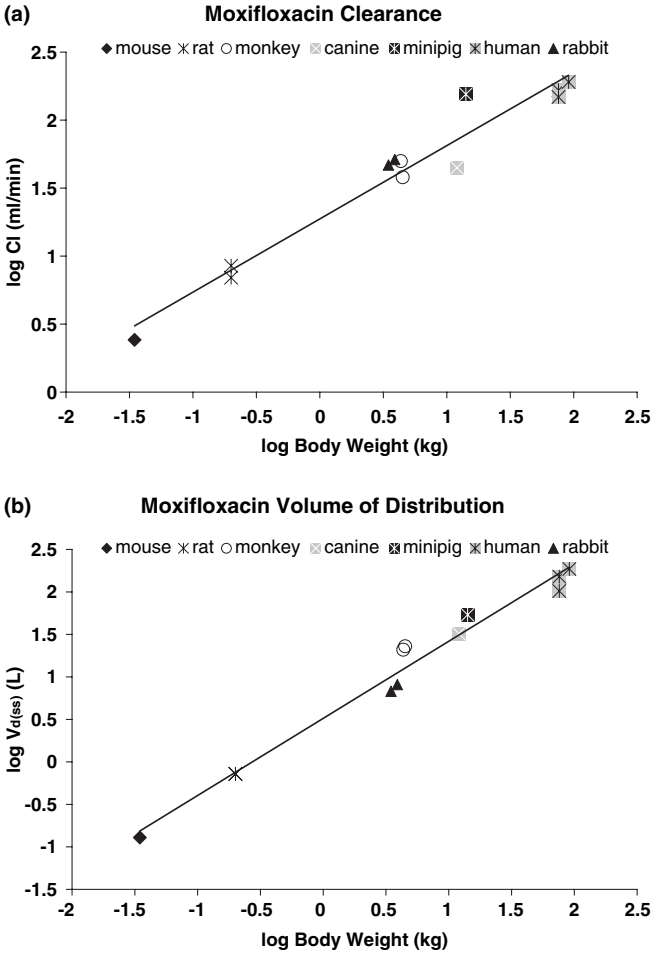

Fig. 4. Allometric association for clearance (a) or volume of distribution (b) and body weight for moxifloxacin.

used in the various studies. It has been suggested that the age of the animal (renal function maturity and metabolic capacity of liver) as well as breed difference may affect fluoroquinolone plasma concentrations and thus their pharmacokinetic parameters (Nouws *et al.*, 1988). 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 for other FQs.

The values in the analysis were not corrected for plasma protein binding as data was not available for all species that were studied. Protein binding is considered to be low for FQs. However, Bregante *et al.* (1999) found that correlations between body weight and pharmacokinetic parameters were significantly better when plasma free fractions were used in their allometric analyses. The results of this study support an allometric relationship for clearance and volume of distribution for all of the FQs, even though there was no correction for protein binding.

It was concluded that volume of distribution is proportional to body weight and clearance is allometrically related to body mass for all the FQs studied, while the elimination half-life is independent of body weight for all FQs except moxifloxacin. The data indicate that allometric scaling of the species studied is feasible and that the use of clearance and volume of distribution is preferable to half-life. The results from this study suggest that it could be possible to extrapolate the kinetic parameters 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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