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COMPARISON OF THE PHARMACOKINETICS OF SEVEN FLUOROQUINOLONES IN MAMMALIAN AND BIRD SPECIES USING ALLOMETRIC ANALYSIS

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Summary

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Allometric analysis is used to predict the pharmacokinetic behaviour of drugs in animal species where it has not been studied yet. This method was applied to calculate total body clearance, volume of distribution and elimination half-life of seven fluoroquinolone drugs. The results showed that provided information for quinolones' pharmacokinetics was very close to real data, with the highest accuracy for marbofloxacin. On the contrast, the prediction of pharmacokinetics of enrofloxacin and its active metabolite ciprofloxacin was the most unreliable. Birds should be separately subjected to allometric scaling in order to receive more accurate results. The comparison of data among species showed that in rabbits, pigs, sheep, donkeys and wild animals as gorals, alpakas and oryxes, allometric scaling of fluoroquinolones could not always provide a reasonable accuracy. Therefore, the specificity of metabolism and excretion of a given drug should be taken into account.

Key words: allometric scaling, birds, fluoroquinolones, mammals, pharmacokinetics

INTRODUCTION

Allometric analysis has been used to predict the pharmacokinetic behaviour of drugs and to estimate dosage regimens in animal species that have not been studied yet. It also has been used in drug development (Mahmood & Balian, 1999) and in comparison of pharmacokinetics of different substances between species (Dinev, 2008). The main assumption of this approach is that many physiological processes and organ sizes exhibit a power law relationship with the body weight of the species (Mahmood & Balian, 1999). The allometric scaling is regularly conducted using data for animal species, belonging to taxonomic groups with similar physiological characteristics as birds and mammals. Mammalian species could be further divided into carnivores, herbivores, or to ruminants and others (Kirkwood & Merriam, 1990; Riond & Riviere, 1990; Pashov *et al.*, 1997; Riviere *et al.*, 1997; Dinev, 2008). This division in groups is based on interspecies differences in the physiology and it is aimed to predict the specific pharmacokinetic properties of the drugs with a higher accuracy.

Interspecies pharmacokinetic scaling has been performed for a large variety of antibacterial agents (Duthu, 1985; Riond & Riviere, 1990; Pashov *et al.*, 1997;

Riviere *et al.*, 1997; Lashev, 1998). The most recent data concern fluoroquinolones as a class of antimicrobial drugs which is rapidly developing and widely used in veterinary medicine (Bregante *et al.*, 1999; Cox *et al.*, 2004; Cox, 2007). Pharmacokinetics of fluoroquinolones was extensively studied in a number of animal species and after different routes of administration. These drugs have similar distribution characteristics, however, elimination pathways and rates differ considerably among species and among quinolones. Less variations were found out in rates of absorption. Fluoroquinolones are rapidly absorbed to a high extent and well distributed in different tissues with volume of distribution greater than 1 L/kg in all investigated species (Haritova *et al.*, 2006a). Binding to plasma proteins varies among species and for different gyrase inhibitors, but in most cases it is low (Zlotos *et al.*, 1998). The major differences between animals with regard to elimination are connected with active transport, intestinal and hepatic metabolism, and renal excretion. Fluoroquinolones are metabolized by oxidation, demethylation and deethylation (Lefebvre *et al.*, 1998; Anadón *et al.*, 2002). They are excreted with urine by glomerular filtration and tubular secretion, with the exception of difloxacin which is found mainly in the faeces (Fernandez-Varon *et al.*, 2006b). These data were used in the allometric scaling of pharmacokinetic parameters of enrofloxacin and its major metabolite ciprofloxacin, marbofloxacin, danofloxacin and difloxacin (Lashev, 1998; Bregante *et al.*, 1999; Cox *et al.*, 2004; Cox, 2007). Data about allometric analysis in birds were not included in the published investigations. Fluoroquinolones such as pefloxacin and norfloxacin were not subjected to analysis. The findings indicated some differences between fluoroquinolones.

The objective of this study was to assess the relationship between elimination half-life, volume of distribution at steady-state, and total body clearance to body weight of seven fluoroquinolone drugs in different species by the method of allometric scaling. These data could serve for a better understanding of fluoroquinolone pharmacokinetics and could be further used for prediction of pharmacokinetic parameters in rare wild and exotic species or for first-in-animal dose selection.

MATERIALS AND METHODS

The allometric analysis of pharmacokinetic parameters of enrofloxacin and its metabolite ciprofloxacin, danofloxacin, marbofloxacin, difloxacin, pefloxacin and its metabolite norfloxacin, was performed using data from previously published studies (Tables 1–4). Only data for intravenously administered drugs, quantitated by microbiological assay or HPLC were used. The matrices of interest were serum or plasma. For analysis of each drug, data for elimination half-life ($t_{1/2\beta}$), volume of distribution at steady-state ($V_{d(ss)}$) and total body clearance (Cl_B) were used. Data for body weights were collected from the same studies and they referred to healthy adult animals. All values were calculated on the basis of any single published value of pharmacokinetic parameters versus body weights of the included animal species from each study. The analysis of data for enrofloxacin was performed for mammals and birds separately and together. Because of the lack of enough pharmacokinetic data for avian species, a separate analysis for other fluoroquinolones was not performed.

Table 1. Observed elimination half-life ($t_{1/2\beta}$), volume of distribution at steady state ($V_{d(ss)}$) and total body clearance (Cl_B) values of enrofloxacin and ciprofloxacin. Mean ± SD are given in italic; in brackets: ratio of predicted vs observed pharmacokinetic parameters

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B (L /kg/h)	Reference
Enrofloxacin – mammals					
Rabbit	4	2.5	0.93	0.61	Broome *et al.*, 1991
	3.25	2.19	3.4	1.37	Cabanes *et al.*, 1992
	4.75	1.86		1.43	Aramayona *et al.*, 1996
	3.5	2.22		1.41	Bregante *et al.*, 1999
	2.58	2.15	3.26	1.05	Haritova, 2001
	3.38	2.12	3.86	1.29	Tanchev *et al.*, 2005
	3.2	3.5	4.96	2.1	Elmas *et al.*, 2006
Mean		*2.36±0.54 (1.19)*	*3.28±1.47 (1.32)*	*1.32±0.4 5(0.84)*	
Rat	0.29	1.8 (1.28)	4.78 (1.11)	1.28 (1.41)	Bregante *et al.*, 1999
Mouse	0.03	1.48 (1.34)	10.5 (0.83)	4.09 (0.71)	Bregante *et al.*, 1999
Pig	81	9.64	1.26	0.1	Anad n *et al.*, 1999
	30	10.5		0.45	Post *et al.*, 2003
Mean		*10.07±0.61 (0.32)*	(1.24)	*0.28±0.25 (2.91)*	
Dog	13.4	2.4	7	1.62	K ng *et al.*, 1993
	8.6	4.4	3.7	0.65	Monlouis *et al.*, 1997
Mean		*3.40±1.41 (0.94)*	*5.35±2.33 (0.51)*	*1.14±0.69 (0.82)*	
Cat	3.2	6.7 (0.40)	4.0 (0.79)	0.57 (1.75)	Richez *et al.*, 1997a
Horse	536	5.33	2.46	0.37	Haines *et al.*, 2000
	500	6.68	1.66	0.22	Papich *et al.*, 2002
	491	7.42	1.6	0.28	Peyrou *et al.*, 2006
Mean		*6.48±1.06 (0.59)*	*1.91±0.48 (0.57)*	*0.29±0.08 (1.04)*	
Cow	159	2.2	1.4	0.56	Richez *et al.*, 1994
	415	2.3			Richez *et al.*, 1994
	544	1.68	0.47	0.58	Kaartinen *et al.*, 1995
	700	2.82		0.82	Bregante *et al.*, 1999
	400	1.5	1.9	0.49	Rantala *et al.*, 2002
	370	2.61	0.45	1.14	Varma *et al.*, 2003
Mean		*2.19±0.51 (1.78)*	*1.06±0.72 (1.57)*	*0.60±0.38 (0.47)*	
Buffalo	138.5	2.92 (1.18)	5.33 (0.26)	1.94 (0.20)	Kumar *et al.*, 2003
Goral	30	13.3 (0.23)	2.15 (0.90)	0.19 (3.24)	Gandolf *et al.*, 2006

Table 1. (continued)

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B (L /kg/h)	Reference
Llama	123.6	3.38	3.46	0.70	Cristensen *et al.*, 1996
	122.5	3.94	4.0	0.76	Kreil *et al.*, 2001
Mean		*3.66±0.40*	*3.73±0.38*	*0.73±0.04*	
		(0.94±0.10)	*(0.38±0.04)*	*(0.56±0.03)*	
Alpaca	70	13.04 (0.25)	0.44 (3.66)	0.09 (5.53)	Gandolf *et al.*, 2005
Goat	17.5	1.14	1.2	0.81	Rao *et al.*, 2000
	22.2	3.98	1.22	0.24	Elmas *et al.*, 2001
	14.5	2.73	1.94	0.7	Elsheikh *et al.*, 2002
Mean		*2.62±1.42 (1.50)*	*1.45±0.42 (1.56)*	*0.58±0.30 (1.46)*	
Sheep	50	1.46		1.3	Pugliese *et al.*, 1991
	40	3.73	3.02	0.55	Mengozzi *et al.*, 1996
	45	2.5		0.28	Bregante *et al.*, 1999
	18.5	3.26	2.27	0.53	Elsheikh *et al.*, 2002
	54.5	3.3	0.74	0.60	Haritova *et al.*, 2003
	27.5	2.60	2.7	0.55	Rahal *et al.*, 2006
Mean		*2.81±0.81 (1.24)*	*2.18±1.01 (1.14)*	*0.69±0.35 (1.0)*	
Camel	414.2	5.76			Harron *et al.*, 1997
	414.2	4.91	0.5	0.084	
	414.2	5.71	0.7	0.072	
	414.2	3.81	0.4	0.084	
Mean		*5.05±0.91 (0.76)*	*0.53±0.15 (2.16)*	*0.08±0.01 (3.82)*	
Oryx	200	0.69 (5.15)	0.80 (1.60)	0.20 (1.81)	
Enrofloxacin – birds					
Chicken	2.5	10.29	2.77	0.29	Anad n *et al.*, 1995a
	1.7	3.65	2.43	0.148	Abd El-Aziz *et al.*, 1997
	1.82	4.16	2.4	0.130	Abd El-Aziz *et al.*, 1997
	1.68	4.34	2.24	0.13	Abd El-Aziz *et al.*, 1997
	2.7	7.52	1.77	0.18	Garcia Ovando *et al.*, 1997
	2.98	10.96	2.92	0.25	Bugyei *et al.*, 1999
	2.7	6.99	1.98	0.20	Garcia Ovando *et al.*, 1999
	0.66	5.56	3.9	0.62	Knoll *et al.*, 1999
	2.95	5.54	4.55	0.67	Haritova *et al.*, 2004
	1.5	7.42	2.72	0.26	Seyhan & Kaya, 2006
Mean		*6.64±2.50 (0.88)*	*2.77±0.86 (1.09)*	*0.29±0.20 (1.26)*	

Table 1. (continued)

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B (L /kg/h)	Reference
Turkey	6.95	6.05	4.06	0.47	Haritova *et al.*, 2004
	7	6.64	3.57	0.41	Dimitrova *et al.*, 2007
Mean		*6.35±0.42 (0.69)*	*3.82±0.35 (0.81)*	*0.44±0.04(0.72)*	
Houbara bustard	1.3	6.55			Bailey *et al.*, 1998
	1.25	5.63	2.98	0.34	
Mean		*6.06±0.65 (0.90)*	(0.91)	*(0.74)*	
Ciprofloxacin					
Rabbit	3	1.63	4.1	1.73	Abadia *et al.*, 1994
	4.5	1.6	3.8	1.63	Aramayona *et al.*, 1996
Mean		*1.62±0.02 (1.81)*	*3.95±0.21 (0.84)*	*1.68±0.08 (0.46)*	
Rat	0.23	2.2	4.6	1.60	Siefert *et al.*, 1986
	0.25	1.71	9.2	1.98	Nouaille-Degorce *et al.*, 1998
	0.25	1.54	11.3	2.16	
Mean		*1.81±0.34 (1.50)*	*8.37±3.43 (0.73)*	*1.91±0.28 (0.58)*	
Human	78.5	4.0	2.25	0.43	Wise *et al.*, 1984
	67.5	3.0			H ffken *et al.*, 1985
	77.4	4.27			Drusano *et al.*, 1987
	81.5	2.7	2.17	0.57	Dudley *et al.*, 1987
	81.5	2.9	2.40	0.57	Dudley *et al.*, 1987
	81.5	2.8	2.00	0.49	Dudley *et al.*, 1987
	69	4.17	1.81	0.38	Kees *et al.*, 1989
	73	4.3	2.4	0.50	Lettieri *et al.*, 1992
	87	4.6	2.19	0.45	Shab *et al.*, 1996
Mean		*3.71±0.76 (0.92)*	*2.20±0.21 (0.90)*	*0.49±0.07 (1.11)*	
Monkey	4.2	4.3 (0.66)	1.8 (1.81)	0.28 (2.73)	Siefert *et al.*, 1986
Pig	30.5	2.6 (1.22)	3.8 (0.61)	1.04 (0.58)	Nouws *et al.*, 1988
Dog	14.5	3.0		0.276	Abadia *et al.*, 1994
	14.5	2.09		0.257	Abadia *et al.*, 1994
	14.5	2.55		0.205	Abadia *et al.*, 1994
Mean		*2.55±0.45 (1.23)*		*1.02±0.15 (0.66)*	

Table 1. (continued)

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B (L /kg/h)	Reference
Cat	4.33	4.53	3.85	0.64	Landoni & Albarellos, 2003
	5.2	4.53	3.85	0.64	Albarellos *et al.*, 2004
Mean		*4.53±0.0 (0.65)*	*3.17±1.18 (1.15)*	*0.64±0.0 (1.18)*	
Horse	448	4.85	3.45	0.43	Yun *et al.*, 1994
	132.3	2.63	(0.52)	1.087	Dowling *et al.*, 1995
Mean		*3.74±1.57 (0.99)*		*0.76±0.46 (0.73)*	
Cow	72.5	2.4	2.5	0.73	Nouws *et al.*, 1988
	58	2.69	1.71	0.45	Mohan & Garg, 2003
Mean		*2.55±0.21 (1.28)*	*2.11±0.56 (1.0)*	*0.59±0.19 (0.98)*	
Buffalo	95	3.88 (0.82)	2.40 (0.79)	0.71 (0.73)	Saini & Srivastava, 2001
Sheep	42	1.2 (2.66)	1.89 (1.15)	1.08 (0.53)	Munoz *et al.*, 1996
Chicken	1.35	9.01	1.13	0.092	Atta & Sharif, 1997
	2.7	2.25	1.83	0.75	Garcia-Ovando *et al.*, 1997
	2.7	3.11	4.04	0.93	Garcia-Ovando *et al.*, 1999
	2.5	8.84	4.04	0.48	Anad n *et al.*, 2001
Mean		*5.8±3.62 (0.71)*	*2.79±1.5 (1.79)*	*0.56±0.36 (3.31)*	

Table 2. Observed elimination half-life ($t_{1/2\beta}$), volume of distribution at steady state ($V_{d(ss)}$) and total body clearance (Cl_B) values of danofloxacin and difloxacin. Mean ± SD are given in italic; in brackets: ratio of predicted vs observed pharmacokinetic parameters

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B(L/kg/h)	Reference
Danofloxacin					
Rabbit	3.1	4.88 (1.17)	3.16 (2.27)	0.76 (0.98)	Fernandez-Varon *et al.*, 2007
Pig	10	8			Mann & Frame, 1992
	28.2	5.49	3.26	0.45	Richez *et al.*, 1997b
	48	7.0	4	0.41	Friis & Nielsen, 1997
Mean		*6.83±1.26 (0.71)*	*3.63±0.52 (0.87)*	*0.43±0.03 (1.35)*	
Horse	500	6.61 (0.57)		0.34 (1.32)	Fernandez-Varon *et al.*, 2006a
Cow	112	2.9			Mann & Frame, 1992
	94	2.65	3.12	1.02	Aliabadi & Lees, 2002b
Mean		*2.78±0.18 (1.51)*	(0.72)	(0.52)	

Table 2.
(continued)

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B(L/kg/h)	Reference
Goat	77.2	4.67	3.02	0.57	Aliabadi & Lees, 2001
	29.1	4.54	2.64	0.58	Ismail, 2006
	39.7	5.46	2.44	0.99	Escudero *et al.*, 2007
Mean		*4.89±0.50 (0.93)*	*2.70±0.29 (1.10)*	*0.71±0.24 (0.85)*	
Sheep	50	3.35	2.76	0.63	McKellar *et al.*, 1998
	52.2	3.39	2.76	0.71	Aliabadi *et al.*, 2003b
	60.1	3.27	2.19	0.79	Escudero *et al.*, 2007
Mean		*3.34±0.06 (1.32)*	*2.57±0.33 (1.06)*	*0.71±0.08 (0.80)*	
Camel	256	5.37 (0.72)	2.53 (0.63)	0.44 (1.09)	Aliabadi *et al.*, 2003a
Chicken	0.66	6.73		1.41	Knoll *et al.*, 1999
	0.68	5.8		0.24	El-Sayed *et al.*, 2004
Mean		*6.27±0.66 (1.05)*		*0.83±0.83 (2.1)*	
Turkey	8.1	8.64 (0.61)	6.59 (0.78)	0.57 (1.18)	Haritova *et al.*, 2006b
Difloxacin					
Rabbit	2.25	3.25	1.51	0.59	Abd El-Aty *et al.*, 2005
	3.85	4.19	1.95	0.41	Fernandez-Varon *et al.*, 2008
Mean		*3.72±0.66 (1.11)*	*1.73±0.31 (1.53)*	*0.50±0.13 (1.14)*	
Pig	9.7	7.92	1.70	0.16	Inui *et al.*, 1998
	30	10.7	4.12	0.27	Van den Hoven, 2000
Mean		*9.31±1.97 (0.51)*	*2.91±1.71 (0.87)*	*0.21±0.08 (1.85)*	
Dog	15	8.2 (0.57)	2.6 (0.79)	0.3 (1.22)	Van den Hoven, 2000
Horse	450.5	2.6 (2.3)	1.02 (1.15)	0.28 (0.55)	Fernandez-Varon *et al.*, 2006b
Cow	150	6.5	1.8	0.19	Van den Hoven, 2000
	257.8	5.56	1.12	0.13	Ismail, 2007
Mean		*6.03±0.66 (0.96)*	*1.46±0.48 (1.02)*	*0.16±0.04 (1.20)*	
Goat	56.8	4.92 (1.05)	1.16 (1.46)	0.32 (0.81)	Marin *et al.*, 2007
Chicken	0.6	4.1	3.07	0.72	Inui *et al.*, 1998
	1	2.3	2.91	0.88	Van den Hoven, 2000
Mean		*3.20±1.27 (1.25)*	*2.99±0.11 (1.05)*	*0.80±0.12 (1.0)*	
Turkey	2	2.2 (1.79)	5.19 (0.53)	1.69 (0.36)	Van den Hoven, 2000

Table 3. Observed elimination half-life ($t_{1/2\beta}$), volume of distribution at steady state ($V_{d(ss)}$) and total body clearance (Cl_B) values of marbofloxacin. Mean ± SD are given in italic; in brackets: ratio of predicted vs observed pharmacokinetic parameters

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$ (L/kg)	Cl_B(L/kg/h)	Reference
Marbofloxacin					
Rabbit	3	5.59 (1.18)	2.13 (0.62)	0.40 (0.43)	Schneider *et al.*, 2000
Dog	14.5	12.4	1.36	0.1	Schneider *et al.*, 1996
	14.5	13.9	1.66	0.114	Schneider *et al.*, 1996
	9.6	10.8	1.33	0.1	Lefebvre *et al.*, 1998
Mean		*12.37±1.55 (0.54)*	*1.45±0.18 (0.92)*	*0.10±0.01 (1.81)*	
Cat	4.33	7.98 (0.83)	1.01 (1.30)	0.43 (0.41)	Albarellos *et al.*, 2005
Horse	568	7.56	1.48	0.25	Bousquet-Melou *et al.*, 2002
	500	4.74	1.17	0.19	Carretero *et al.*,2002
	491	7.42	1.60	0.28	Peyrou *et al.*, 2006
Mean		*6.57±1.59 (1.07)*	*1.39±0.30 (0.97)*	*0.24±0.06 (0.95)*	
Cow	500	5.72	1.16	0.31	Thomas *et al.*, 2001
	152	4.23	1.09	0.21	Aliabadi & Lees, 2002a
	150	4.6		0.18	Ismail, 2006
Mean		*4.98±1.05 (1.37)*	*1.13±0.05 (1.17)*	*0.26±0.07 (0.84)*	
Goat	47	7.17	1.31	0.23	Waxman *et al.*, 2001
	45	7.32	1.19	0.24	Waxman *et al.*, 2003
	47	7.18	1.31	0.23	Waxman *et al.*, 2004
Mean		*7.25±0.1 (0.92)*	*1.25±0.08 (1.05)*	*0.24±0.01 (0.83)*	
Chicken	2.5	5.26 (1.25)	0.77 (1.72)	0.17 (0.97)	Anad n *et al.*, 2002
Turkey	10	7.37 (0.9)	1.41 (0.93)	0.16 (1.15)	Haritova *et al.*, 2006c
Eurasian buzzard	0.89	4.11 (1.60)	1.66 (0.88)	0.20 (0.83)	Garcia-Montijano *et al.*, 2001
Gold macaw	1.04	4.3 (1.53)	1.3 (1.02)	0.29 (0.58)	Carpenter *et al.*, 2006

Table 4. Observed elimination half-life ($t_{1/2\beta}$), volume of distribution at steady state ($V_{d(ss)}$) and total body clearance (Cl_B) values of pefloxacin and norfloxacin. Mean ± SD are given in italic; in brackets: ratio of predicted vs observed pharmacokinetic parameters

Species	Body weight (kg)	$t_{1/2\beta}$ (h)	$V_{d(ss)}$(L/kg)	Cl_B (L/kg/h)	Reference
Pefloxacin					
Cow	96	2.21 (1.12)	1.22 (1.44)	0.45 (2.94)	Srivastava *et al.*, 2000
Goat	30	1.6	5.14	3.6	Abd El-Aty & Goudah, 2002
	17.5	1.12	1.08	0.821	Malik *et al.*, 2002
Mean		*1.36±0.34(2.16)*	*3.11±2.87(1.03)*	*2.21±1.97(0.63)*	
Sheep	59	6.88 (0.38)		0.176 (6.54)	Moutafchieva & Djouvinov, 1997
Chicken	2.5	8.54 (0.41)	1.57 (1.25)	0.475 (0.98)	Isea *et al.*, 2003
Pigeon	0.3	3.33 (1.29)	2.3 (0.91)	0.19 (1.33)	Moutafchieva & Djouvinov, 1997
Norfloxacin					
Rabbit	1.5	3.14 (0.98)	0.17 (12.6)		Park *et al.*, 1998
Rat	0.292	3.33	3.42	0.89	Chenel *et al.*, 2003
	0.292	2.92	3.42	0.92	Chenel *et al.*, 2003
Mean		*3.13±0.29(0.90)*	*3.42±0.0(0.67)*	*0.91±0.02(0.35)*	
Pig	81.5	3.65	2.21	0.66	Anad n *et al.*, 1995b
	60	7.42	4.66	0.8	Chang *et al.*, 2007
Mean		*5.54±2.67(0.80)*	*3.43±1.73(0.66)*	*0.73±0.1(0.5)*	
Dog	18	3.56 (1.01)			Brown *et al.*, 1990
Horse	450	6.45			Park *et al.*, 1994
	452.3	5.44	2.19	0.49	Park and Yun, 2003
Mean		*5.95±0.71(0.74)*	*(0.84)*	*(0.77)*	
Donkey	103	3.48 (1.15)	1.93 (1.0)	0.07 (5.23)	Lavy *et al.*, 1995
Cow	91.7	2.38	2.0	0.7	Soback *et al.*, 1994a
	91.7	1.65	2.1	0.97	Soback *et al.*, 1994a
	500	5.88	3.1	0.62	Gips & Soback, 1999
Mean		*3.3±2.26 (1.61)*	*2.40±0.61 (0.82)*	*0.76±0.18 (0.50)*	
Sheep	60	3.35	2.76	0.63	Soback *et al.*, 1994b
	65	6.2	1.40	0.19	Soback *et al.*, 1994b
Mean		*4.78±2.02 (0.89)*	*2.08±0.96 (1.05)*	*0.41±0.31 (1.26)*	
Chicken	2.5	8	3.14	0.36	Anad n *et al.*, 1992
	1.0	3.65	3.8		Chen *et al.*, 1994
Mean		*5.83±3.08 (0.61)*	*3.47±0.47 (0.63)*	(0.93)	
Turkey	5.5	1.65	6.89	0.03	Gulkarov & Ziv, 1994
	5.5	1.43	2.27	0.05	
Mean		*1.54±0.16 (2.18)*	*4.58±3.27 (0.61)*	*0.04±0.01 (8.27)*	

The simple allometric approach has been based on the following power function:

$$Y = a.W^b \quad (1)$$

where Y is the value of the respective pharmacokinetic parameter ($t_{1/2\beta}$; $V_{d(ss)}$ or Cl_B), a is the coefficient equal to antilog of c in equation 2, W is the body weight and b is the exponent of allometric equation.

The log transformation of (1) gives:

$$log\ Y = logc + b.logW \quad (2)$$

where Y is $t_{1/2\beta}$, $V_{d(ss)}$ or Cl_B, log$c$ is the y-intercept and b is the slope.

The least squares linear regression method was used for estimation of correlation between pharmacokinetic parameters of interest and body weight. Statistical analysis was done by Statistica 6.1 software (Statistica for Windows, StatSoft. Inc., Tulsa, OK, USA).

RESULTS

Results of the regression analysis conducted are listed in Table 5. The values of the exponent b for $t_{½\beta}$ were very low for all fluoroquinolones. Its value for $V_{d(ss)}$ and Cl_B was between 0.74 and 1.29 for all studied drugs, the lowest (0.67) being that of $V_{d(ss)}$ of danofloxacin.

There was no association between $t_{1/2\beta}$ and body weight in all species and for all quinolone drugs of interest. Therefore, animals were divided into mammals and birds for allometric scaling of enrofloxacin, for which enough pharmacokinetic data are available. Although the correlation was improved, a statistically significant relationship between $t_{1/2\beta}$ and body weight was not observed. The highest value of y-intercept for $t_{1/2\beta}$ was calculated for marbofloxacin.

A statistically significant relationship was found between body weight and $V_{d(ss)}$ as well as between body weight and Cl_B when all species were analyzed (Table 5). The highest intercept for $V_{d(ss)}$ was found for danofloxacin and the lowest – for marbofloxacin. The values of y-intercept were similar for enrofloxacin and ciprofloxacin when data about mammals and birds were analyzed together. The same was valid for pefloxacin and norfloxacin. The lowest value of Cl_B was calculated for marbofloxacin.

Predicted values of $t_{1/2\beta}$, $V_{d(ss)}$ and Cl_B were compared to literature values (Tables 1–4). The allometric approach had the highest predictive power with the lowest error with regards to the pharmacokinetic parameters of marbofloxacin, danofloxacin and norfloxacin. Pigs, rabbits, sheep, chickens and turkeys are the animal species with higher deviation of the predicted vs reported values.

DISCUSSION

Simple allometric scaling is an attractive low-cost and time-efficient alternative to provide reliable predictions of $t_{1/2\beta}$, $V_{d(ss)}$ and Cl_B. Despite the risk for deviation of the estimated values from the observed pharmacokinetic parameters in some cases, interspecies scaling in veterinary medicine could be used to analyze the pharmacokinetic behaviour of the drugs and to focus the efforts on providing good explanations for the observed differences between animal species (Mahmood, 2007). The experience with allometric scaling shows that with higher number of the analyzed data, including number of animal species and number of individual studies for each species, the method would have the best predictive value (Mahmood & Balian, 1999; Mahmood,

Table 5. Values of elimination half-life ($t_{½\beta}$), volume of distribution at steady state ($V_{d(ss)}$) and total body clearance (Cl_B) for allometric equations

Substance	Species	n	Parameters	a	b	*r*	*P*
Enrofloxacin	Mammals, birds	50	$t_{½\beta}$	3.767	–0.006	0.020	>0.05
		42	Cl_B	0.924	0.818	0.918	<0.001
		46	$V_{d(ss)}$	3.848	0.794	0.951	<0.001
	Mammals	41	$t_{½\beta}$	2.490	0.066	0.241	>0.05
		39	Cl_B	1.330	0.755	0.911	<0.001
		33	$V_{d(ss)}$	4.050	0.783	0.941	<0.001
	Birds	14	$t_{½\beta}$	5.600	0.130	0.275	>0.05
		13	Cl_B	0.245	1.130	0.795	<0.01
		13	$V_{d(ss)}$	2.660	1.078	0.928	<0.001
Ciprofloxacin	Mammals, birds	22	$t_{½\beta}$	2.794	0.036	0.154	>0.05
		30	Cl_B	0.919	0.875	0.935	<0.001
		26	$V_{d(ss)}$	4.167	0.827	0.947	<0.001
Danofloxacin	Mammals, birds	17	$t_{½\beta}$	6.300	–0.089	0.045	>0.05
		15	Cl_B	0.828	0.902	0.933	<0.001
		13	$V_{d(ss)}$	10.520	0.665	0.807	<0.001
Marbofloxacin	Mammals, birds	18	$t_{½\beta}$	6.580	0.003	0.016	>0.05
		18	Cl_B	0.168	1.043	0.984	<0.001
		17	$V_{d(ss)}$	1.320	0.999	0.995	<0.001
Difloxacin	Mammals, birds	12	$t_{½\beta}$	3.730	0.081	0.348	>0.005
		12	Cl_B	0.734	0.743	0.960	<0.001
		12	$V_{d(ss)}$	3.018	0.857	0.978	<0.001
Norfloxacin	Mammals, birds	18	$t^{1}\!/_{2\beta}$	3.010	0.061	0.291	>0.05
		14	Cl_B	0.326	1.025	0.907	<0.001
		16	$V_{d(ss)}$	2.210	0.970	0.915	<0.001
Pefloxacin	Mammals, birds	6	$t_{½\beta}$	3.825	–0.096	0.259	>0.05
		5	Cl_B	0.357	1.287	0.959	<0.01
		5	$V_{d(ss)}$	2.022	0.969	0.962	<0.01

2007). Results in our study confirm this observation, therefore, we tried to use as much data as possible from the published literature. Dividing animal species in groups according to physiological characteristics could improve the predictive power (Mahmood, 2007). Fluoroquinolones undergo a more complete conversion in mammals than in birds (Lefebvre *et al.*, 1998; Dimitrova *et al.*, 2007). Analysis of data for mammals and birds separately resulted in more accurate prediction of pharmacokinetic parameters in our study.

In addition, scaling can be species-dependent. In general, it is acknowledged that the inclusion of dogs and rabbits in allometry decreases the predictive value of the results for humans. At the same time, inclusion of monkeys and rats improves significantly the results (Tang & Mayersohn, 2005). In all cases data for at least one large species can improve allometric analysis results (Mahmood, 2007). Considering all this experience, data about enrofloxacin and marbofloxacin in ostriches, nandu and red tailed hawks were excluded from analysis. In these species, extremely short elimination half-lives and high total body clearance

values were observed because of quantitatively different activity, multiplicity and tissue specific expression of drug-metabolizing enzyme systems (Amsallem-Holtzman & Ben-Zvi, 1997; Bailey *et al*., 1998). Such phenomena are commonly observed in interspecies scaling (Pashov *et al.*, 1997; Lashev, 1998; Mahmood, 2007; White *et al.*, 2007). They could be explained with different inter-species metabolic and excretion rates, breed-, sex- and age-related differences, or variability in the results from different laboratories.

When the parameters are modeled as an inverse function of a physiological process, the exponent will equal (1–*b*). Half-life is a secondary parameter, derived of scaling to $V_{d(ss)}/Cl_B$. In that case a slope of zero would be expected if there is a perfect correlation between weight/Cl_B and weight/$V_{d(ss)}$. Therefore, it is not surprising that *b* tends to equal zero and is far from the theoretical value of 0.25. Our results are consistent with the values published by Cox *et al.* (2004) and Cox (2007) for quinolones (Table 6). In contrast, Breagante *et al.* (1999) found statistically significant correlation when results for enrofloxacin, obtained from the same laboratory and method of analysis, for five animal species were subjected to scaling. This observation could explain the significance of accuracy of data obtained with different methods of analysis. In our study the results were not improved even when scaling was performed after grouping of animals according to their physiological characteristics. Al-

Table 6. Previously published values for elimination half-life, volume of distribution and clearance from allometric equations

Substance	Species	n	Parameters	a	b	Reference
Enrofloxacin	Mammals, birds	22	Cl_B	3.63	0.90	Lashev, 1998
		25	$V_{d(area)}$	0.55	1.01	
	Mammals, birds	39	$t_{½\beta}$	6.8	0.062	Cox *et al.,* 2004
		39	Cl_B	0.432	0.939	
		39	$V_{d(ss)}$	4.11	0.803	
	Mammals	32	$t^1/_{2\beta}$	4.0	0.062	
		32	Cl_B	0.954	0.764	
		32	$V_{d(ss)}$	6.00	0.723	
	Mammals	5	$t^1/_{2\beta}$	1.926	0.06	Bregante *et al.,* 1999
		5	Cl_B	2.87	0.82	
		5	$V_{d(area)}$	10.90	0.90	
Ciprofloxacin	Mammals	10	Cl_B	1.04	0.93±0.01	Lashev, 1998
		10	$V_{d(area)}$	2.82	1.07±0.09	
	Mammals, birds, fish, reptiles	38	$t^1/_{2\beta}$	5.1	–0.123	Cox *et al.*, 2004
		38	Cl_B	0.35	1.13	
		38	$V_{d(ss)}$	2.2	1.07	
	Mammals	32	$t^1/_{2\beta}$	2.2	0.091	
		32	Cl_B	1.24	0.815	
		32	$V_{d(ss)}$	3.5	0.947	
	Mammals		$t^1/_{2\beta}$	–	0.041	Mahmood & Balian, 1999
			Cl_B	–	0.927	
			$V_{d(ss)}$	–	0.966	

n – number of observations.

though a correlation between body weight and $t_{½\beta}$ was not found, the predicted values for the elimination half-life were very close to observed ones. This fact could be attributed to a significant correlations between weight and Cl_B and weight and $V_{d(ss)}$. Values of *a*, representing the relationship of elimination half-life to body weight, indicate that the longest $t_{½\beta}$ for marbofloxacin and the shortest $t_{½\beta}$ for enrofloxacin in mammals and for ciprofloxacin in all animal species could be expected. These results are consistent with the published pharmacokinetic parameters for the studied quinolones (Tables 1–4).

The allometric exponent *b* for most pharmacokinetic parameters related to physiological processes ranges from 0.67 to 1 (Riviere *et al.*, 1997). Its theoretical value for the volume of distribution is equal to 1 assuming that total body water directly correlates to body weight and that V_d is a function of total body water (Mahmood, 2007). Our results for marbofloxacin, difloxacin, pefloxacin and its metabolite norfloxacin are close to this theoretical value. Similar data were reported for ciprofloxacin and enrofloxacin by Lashev (1998), Bregante *et al.* (1999) and Cox *et al.* (2004) (Table 6). In our investigation and in other studies (Mahmood & Balian, 1999; Cox, 2007) the exponent *b* tends to be close to 0.8 for enrofloxacin, ciprofloxacin and danofloxacin. A value close to 1 was obtained when data for enrofloxacin in birds were analysed separately by allometry. These data, the high correlation coefficient and the very low *P*-value allow us to conclude that $V_{d(ss)}$ is proportional to body weight for all seven studied fluoroquinolones. Some controversial results were obtained for $V_{d(ss)}$ of enrofloxacin in alpacas and camels and of danofloxacin and norfloxacin in rabbits. A very high error in prediction of this pharmacokinetic parameter was observed, that could be partially explained by the physiological condition in camels (water-deprived). A reasonable explanation for the observed error in alpacas could not be given because data about physiological condition were not available. According to our data for all investigated drugs, it could be assumed that scaling of $V_{d(ss)}$ has a low prediction power in rabbits, which is difficult to be explained.

It is widely accepted that the metabolic rate is proportional to body mass raised to the three-quarter power ($W^{0.75}$). Moreover, overall renal and hepatic functions are determined by blood flow which on its turn is dependent on cardiac output and therefore, the cardiac output is scaled to *b* equal to 0.75 (Mahmood & Balian, 1999; Atanasov & Dimitrov, 2002; Mahmood, 2007). This is not always true, especially for drugs that undergo significant conversion. However, our values of *b* for Cl_B in mammals differ from 0.75 with exception of results for difloxacin (0.743) and enrofloxacin (0.755). One of the explanations for these results could be that most fluoroquinolones are excreted not only through kidneys and are metabolized in the liver. The exponent *b* is close to 1 for all other quinolones thus corresponding to the assumption that the exponent of simple allometric equation should be between 0.7 and 1 in order to predict clearance of the drugs (Mahmood & Balian, 1999). Similar values were found for enrofloxacin and ciprofloxacin in several studies (Lashev, 1998; Bregante *et al.*, 1999; Cox *et al.*, 2004; Cox, 2007). These data and the low *P*-value allow us to conclude that there was a clear relationship between Cl_B and body weight in our investigation. The small number of observations, included in pefloxacin scaling could explain the highest value of *b* for Cl_B

(>1.2). Allometric scaling could have some limitations if the clearance of a drug, that is partly metabolized and partly excreted renally, has to be predicted (Mahmood, 2007). Therefore, interpretation of data requires cautious and sound scientific judgement.

Altogether, allometric scaling could provide information for pharmacokinetics of quinolones very close to the realistic data. Prediction of pharmacokinetics of enrofloxacin and its active metabolite ciprofloxacin is the most unreliable. Explanation could be found in species-related differences in the rate of metabolism of these compounds. Relatively numerous predicted results differing significantly from the observed values were determined for pefloxacin and difloxacin, mainly due to limited data used for interspecies scaling. Our data suggest that pharmacokinetic parameters of marbofloxacin could be predicted with high accuracy. Comparing data of this analysis among species, it could be concluded that in pigs, rabbits and donkeys allometric scaling could not always result in reasonable accuracy. Values of $t_{1/2\beta}$, $V_{d(ss)}$ and Cl_B are also difficult to be predicted in animal species as gorals, alpacas and oryxes. Turkeys and chickens are among species in which prediction could not be always enough accurate.

Allometric extrapolation could be affected by the experimental design, species, analytical errors and variations from one laboratory to another (Kirkwood, 2004). There are several methods that can be used for improvement of the prediction of clearance. Some of them are based on correction with maximum life-span potential, brain weight, unbound fraction of drugs, incorporation of molecular structure parameters and liver blood flow for biliary excreted drugs (Mahmood & Sahajwalla, 2002; Mahmood, 2007). Different volume of distribution types can be used for accurate prediction of this parameter. In some cases volume of distribution in the central compartment (V_c) could be more useful than $V_{d(ss)}$ because steady-state is usually not achieved with the first dose (Mahmood, 2007). Elimination half-life could be estimated by simple allometry, from predicted clearance and volume of distribution and from predicted MRT. Grouping animals according to their anatomical and physiological characteristics could solve the problem with high deviation of estimated versus observed pharmacokinetic parameters. This is especially true for birds. Before allometric scaling and dose calculation, specificity of metabolism and excretion of a given drug in a particular species should be taken into consideration. Efforts to improve allometric scaling should continue in order to minimize shortcomings associated with its use.

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