Original article

Allometric scaling of marbofloxacin pharmacokinetics: a retrospective analysis

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Abstract

The association between physiologically dependent pharmacokinetic parameters (CL_B, $T_{1/2\beta}$, Vd_{ss}) of marbofloxacin and body weight was studied in eight animal species based on allometric equation $Y = aW^b$, where 'Y' is the pharmacokinetic parameter, 'W' is body weight, 'a' is allometric coefficient (intercept) and 'b' is the exponent that describes relation between pharmacokinetic parameter and body weight. The body clearance of marbofloxacin has shown significant (P<0.0001) relation with size (Bwt) in various animal species. However, half-life and volume of distribution were not in association with body weight. Although half-life and volume of distribution were not in a good correlation with body weight, statistically significant association between the body clearance and body weight suggests validity of allometric scaling for predicting pharmacokinetic parameters of marbofloxacin in animal species that have not been studied yet. However further study considering large sample size and other parameters influencing pharmacokinetics of marbofloxacin is recommended.

Key words: allometric scaling, clearance, half-life, marbofloxacin, volume of distribution

Introduction

Marbofloxacin is a fluoroquinolone developed for the treatment of animals (Schneider et al. 1996). It has some pharmacokinetic (PK) advantages such as a long elimination half-life, a large volume of distribution and a high bioavailability over other floroquinolones (Fitton 1992). Pharmacokinetics of a drug could be affected by a number of physiological,

pathological and pharmacological processes. For instance, the influence of weight or obesity has been described as one of the physiological factors that can contribute to variation of drug pharmacokinetics (Matthew et al. 2008). In addition, body size and related variation in pharmacokinetic parameters describing elimination rates have been observed for a range of drugs (Kirkwood and Merriam 1990).

The allometric technique helps to establish quan-

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titative relationships between drug disposition and body weight or organ perfusion rate (Lepiste and Jusco 2004). Thus, allometric scaling has been used for drug development, estimation of pharmacokinetic parameters of drugs in animal species with no previous pharmacokinetic data and comparison of pharmacokinetics difference of a drug between different species of animals (Mahmood and Balian 1999, Dinev 2008). The allometric scaling based on the principle that major physiologic processes are related to body weight raised to allometric exponent (Riviere 1999). Hence, the association of physiologically dependent pharmacokinetics parameters such as clearance, volume of distribution and half-life of drugs with body weight has been previous studied (Cox 2004, 2007).

Although the potential inaccuracy of allometric scaling is detailed in the previous studies (Riviere et al. 1997, Martinez et al. 2009), allometric scaling has been proven as useful for some drugs and species (KuKanich et al. 2004, Maxwell and Jacobson 2008). In this study, different animal species showing variations in pharmacokinetic parameters (CL_B, Vd_{ss} and $T_{1/2\beta}$) of marbofloxacin were included to assess an association between pharmacokinetic parameters and body weight.

Materials and Methods

Allometric scaling of marbofloxacin was performed based on the pharmacokinetic data published in the previous studies (Table 1). Only data analyzed by HPLC and obtained from plasma or serum samples after intravenous administration were included in the study. The data for elimination half-life ($t_{1/2\beta}$), volume of distribution at steady state (Vd_{ss}), total body clearance (CL_B) were used for allometric analysis. The body weight given in a range was averaged and the expected influences of age and sex were not considered.

The values of body weight, CL_B, $T_{1/2\beta}$ and Vd_{ss} were converted into logarithmic values and regression analysis for body weight and PK parameters was performed using SAS software (SAS Institute, Cary, NC, USA). Logarithmically transformed PK parameters (Y) and body weight (W) were fitted with the equation.

$$\text{Log } Y = c + b \log W$$

Where 'Y' is the parameter of interest, 'W' is the body weight and 'c' and 'b' are the slope and intercept respectively. The following allometric equation was then applied.

$$Y = aW^b$$

Where 'a' is the anti-logarithm of 'c'. Log-log plots of body weight V_s. CL_B, $T_{1/2\beta}$ and Vd_{ss} were constructed.

Correlation coefficient (r^2) and P values were obtained from the calculation of each correlation. Allometric equation was derived and used to predict the pharmacokinetic parameters for each animal and the accuracy of extrapolated values was expressed as mean error (M.E %) using the equation described elsewhere (Catells et al. 2001).

$$\text{M.E} = \frac{E-0}{E} \times 100$$

Where E is extrapolated value and O is observed value.

Results

The allometric relationship between clearance, volume of distribution, half-life and body weight are shown in Figs. 1, 2 and 3. The relationship observed

Table 1. Mean ± SD experimental values of marbofloxacin pharmacokinetic parameters in eight mammalian species after intravenous (i.v.) administration.

| Species	Weight (kg)	$T_{1/2\beta}$ (h)	CL_B (L/Kg/h)	Vd_{ss} (L/Kg)	Sources
Goat	47	7.18 ± 1.09	0.23 ± 0.03	1.31 ± 0.15	Waxman et al. 2001
Donkey	387.5	8.88 ± 2.2	0.10 ± 0.02	1.15 ± 0.09	González et al. 2007
Cat	3.95	7.98 ± 0.57	0.09 ± 0.02	1.01 ± 0.15	Albarellos et al. 2005
Sheep	75	3.96 ± 1.54	0.48 ± 0.04	1.96 ± 0.09	Sidhu et al. 2010
Calves	170	4.60 ± 0.60	0.003 ± 0.0	1.10 ± 0.14	Ismail and El-Kattan, 2007
Rabbits	2.65	5.78 ± 0.25	0.20 ± 0.01	1.65 ± 0.21	Abo-El-Sooud and Goudah, 2010
Dogs	9.7	8.08 ± 6.25	0.23 ± 0.06	2.32 ± 1.00	Our study (not published)
Pigs	99	7.94 ± 1.21	0.12 ± 0.02	1.3 ± 0.14	Ding et al. 2010
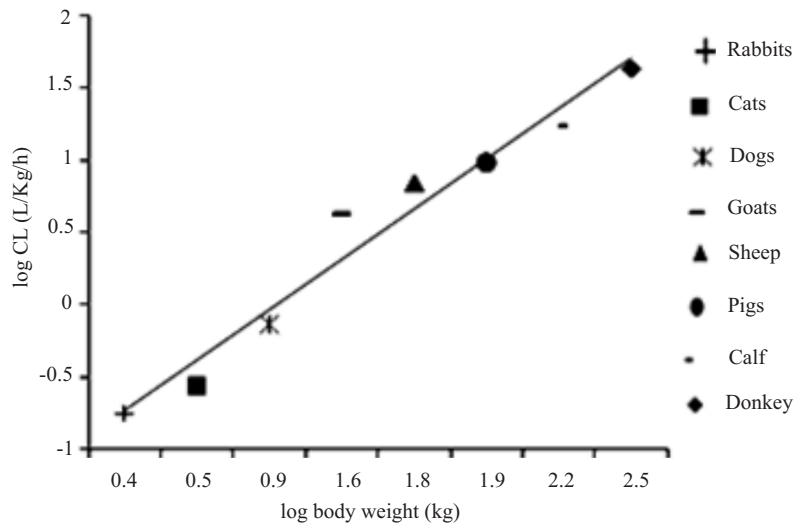
Fig. 1. Allometric association for marbofloxacin between clearance and body weight in different animal species.
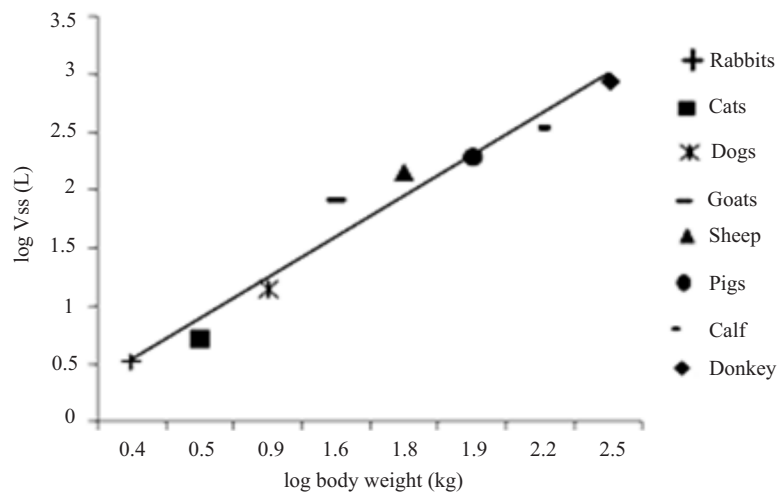

Fig. 2. Allometric association for marbofloxacin between volume of distribution and body weight in different animal species.
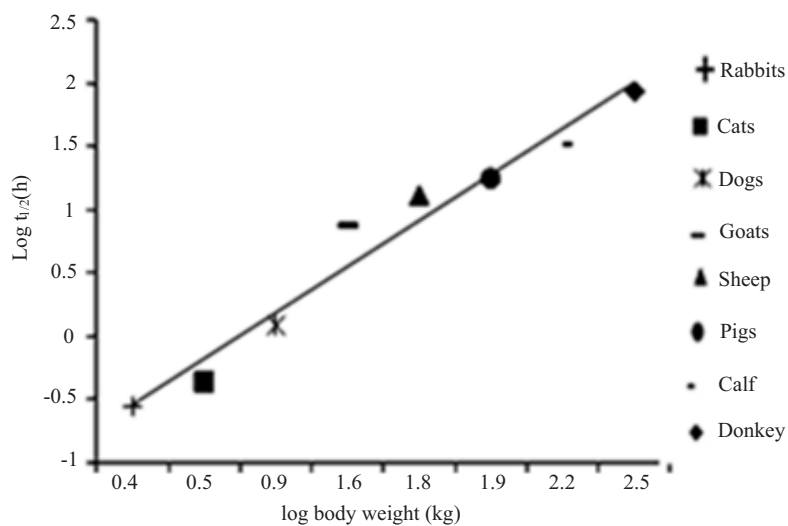

Fig. 3. Allometric association for marbofloxacin between half-life and body weight in different animal species.

Table 2. Marbofloxacin clearance, half life and volume of distribution values for allometric equations.

Parameters	N	A	b	r^2	P-value
Clearance	8	0.06	1.10	0.93	0.0001
Half life	8	0.93	1.15	0.05	0.88
Volume of distribution	8	1.10	1.12	0.18	0.86

N – sample size, a – intercept, b – slope, r^2 – coefficient of determination

Table 3. Parameters of marbofloxacin (values and mean error) extrapolated from allometric equations.

Species	CL (L/h)		V_{ss}(L)		$T_{1/2}$ (h)	
	value	M.E (%)	value	M.E (%)	value	M.E (%)
Goat	4.22	94.55	83.18	98.42	90.53	5.47
Donkey	43.29	99.76	887.65	99.87	1028.78	89.71
Cat	0.27	67.3	5.16	80.44	5.22	−1721.56
Sheep	7.076	93.21	140.54	98.6	155.11	69.57
Calf	17.44	99.98	352.1	99.68	398.18	86.23
Rabbit	0.177	−12.84	3.29	49.99	3.29	−1989.68
Dog	0.741	−115.78	14.15	90.6	14.69	−775.71
Pig	9.611	98.75	191.92	99.32	213.58	55.69

between marbofloxacin clearance and body weight was statistically significant (P <0.0001). Whereas, half-life and, volume of distribution did not show statistically significant relationship with body weight of different animal species.

Regression analysis results for logarithmic values of clearance, volume of distribution, half-life versus logarithmic values of body weight for marbofloxacin are shown in Table 2. The allometric equations best fit to clearance, volume of distribution and half-life were $0.06 \, W^{1.10}$, $1.10 W^{1.12}$ and $1.07 \, W^{1.15}$ respectively. The correlation coefficient (r^2) for clearance, volume of distribution and half-life were 0.93, 0.18 and 0.05, respectively. P-values for clearance, volume of distribution and half-life were 0.0001, 0.88 and 0.86 respectively.

Discussion

Allometric estimates for marbofloxacin clearance and volume of distribution observed in the present study are in line with previously reported values (Cox 2007). However, estimates for marbofoxacin half-life across species ($t_{1/2\beta}$, b = 1.15) (Table 2) in this study is contrary to values presented in other study (Cox 2007). Theoretically expected allometric exponent values for clearance, half-life and volume of distribution of a drug that primarily cleared through kidney are 0.75, 0.25 (1 – 0.75) and 0.67-1 respectively. However, the corresponding values (b > 1) observed in this study (Table 2)

for clearance, volume of distribution and half life of marbofloxacin which primarily cleared through the kidney (Fernandez-Varon et al. 2006b) were above the theoretical allometric exponent values.

The correlation (r^2 = 0.93, P<0.0001) between clearance and body weight observed across different species in this study (Table 2 and Fig. 1) supports previous results that indicated the correlation between body size and pharmacokinetic parameters describing elimination rates of drugs (Kirkwood and Merriam 1990). In addition the correlation between clearance and body weight was in line with previously reported interspecies difference in drug clearance (Boxenbaum 1980, Lin et al. 1982). The scales for clearance, volume of distribution and half life of marbofloxacin observed in this study are in contrary to the scales for other floroquinolones (Cox 2004, 2007). Although scales for volume of distribution of marbofloxacin was frequently associated with body weight of different animal species (Haritova and Lashev 2009), the results obtained in this study (Table 2) suggest poor association between volume of distribution and body weight among species. This indicates that values obtained from allometric scaling might not always be extrapolated to predict the pharmacokinetics of marbofloxacin for animal species that have never been investigated.

Allometric exponent (1.15) (Table 2) observed in this study for the correlation between half-life of marbofloxacin and body weight of different animal spe-

cies was above values (0.25) reported in previous investigations (Riviere et al. 1997, Bregante et al. 1999, Riviere 1999). Since half-life is a hybrid pharmacokinetic parameter scaling to Vd/Cl, the variation in either of these variables between species could be the cause for the observed results for correlation of marbofloxacin half life and body weight. Based on the present results, it can be concluded that the significant relation of marbofloxacin clearance with body weight implies the direct association of marbofloxacin clearance with body weight among different animal species.

Acknowledgements

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