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BRIDGING PHARMACOKINETICS BETWEEN HERBIVOROUS MAMMAL SPECIES BY ALLOMETRIC ANALYSIS: A CASE STUDY OF CEFTIOFUR

HARITOVA ANELIYA and LASHEV L

Trakia University, Faculty of Veterinary Medicine, Stara Zagora, Bulgaria

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The objective of the present study was to analyze the relationship between pharmacokinetic parameters of cephalosporine antibiotic ceftiofur in mammals and the respective body weight (W), using reported data from different authors. The parameters of interest: clearance (Cl_B), volume of distribution at steady state (V_{ss}) and elimination half-life were correlated across mammal species, as a function of W using the conventional allometric equation $Y=aW^b$, where Y is the pharmacokinetic parameter, W is the body weight, a is the allometric coefficient (intercept) and b is the exponent that describes the relationship between the pharmacokinetic parameter and W. Our estimates $Cl=0.155W^{0.82}$; $Vss=1.01W^{1.03}$, indicated that the increase in these parameters with W approximates a linear power relationship with slopes being specific for the investigated substance. Overall, the results of this study indicated that it is possible to use allometry to predict pharmacokinetic variables of ceftiofur based on W of species.

Key words: allometric scaling, ceftiofur, herbivorous mammals, pharmacokinetics

INTRODUCTION

Allometric scaling is a common technique for establishing the relationships between drug disposition and body weight, or organ perfusion rate (Hunter, 2010). It is based on the assumption that there are anatomical, physiological, and biochemical similarities among animals, which can be described mathematically (Boxenbaum, 1984). This kind of interspecies correlation is useful for extrapolation to animals whose access is difficult. The predictive value of allometry for interspecies scaling of drug pharmacokinetics depends on the selection of appropriate parameters. The allometric equations generated separately for parameters such as body clearance and volume of distribution at steady state for ceftiofur could be applied to generate equivalent values in new animal species hitherto not tested and/or enable an optimised dose design in new animal species. This is the reason why the most frequently used pharmacokinetic parameters are body clearance (Cl_B), volume of distribution (Vss) and elimination half life ($t_{1/2}$) (Cox, 2007).

In the past few years, the pharmacokinetics of ceftiofur has been investigated in various animal species including most popular domesticated herbivoroes (Brown *et al*., 1996; Drew *et al*., 2004 Errecalde *et al*., 2006; Dumokceaux *et al*., 2005). This prompted us to assess the relationship between the main pharmacokinetic parameters and body weight across mammal species for this valuable drug, and to determine the scaling coefficients in those cases where significant relationships are found.

MATERIALS AND METHODS

Data of published reports about the biological half-life ($t_{1/2}$), total body clearance (Cl_B) and volume of distribution (Vss) of ceftiofur after intravenous administration in different mammalian species were collected (Table 1).

Table 1. Pharmacokinetic parameters of ceftiofur after intravenous administration to seven mammal species

Specie	Body weight (kg)	$t_{1/2}$ (h)	Cl_B (l/kg/h)	Vss (l/kg)	Reference
Cow	200	15.30	0.013	0.298	Liu *et al.*, 1996
	246	5.95	0.039	0.258	Brown *et al.*, 1996
	186	5.05	0.029	0.206	El Gendy *et al*., 2007
	500	7.12	0.036	0.253	Whittem *et al*., 1995
	500	5.09	0.026	0.178	Tohamy, 2008
Mean	326.4	7.70	0.029	0.239	
Buffalo	247	1.61	0.065	0.134	El Gendy *et al*., 2007
Goat	35	1.63	0.198	0.380	Errecalde *et al*., 2006
	58	2.86	0.062	0.260	Courtin *et al.*, 1997
Mean	46.5	2.24	0.130	0.320	
Sheep	46.1	2.43			Craigmill *et al*., 1997
Alpaca	72.7	5.60	0.082	0.540	Drew *et al*., 2004
Llama	123.6	2.19	0.059	0.190	Christensen *et al*., 1996
Camel	400	3.18	0.030	0.130	Goudah, 2007
Elephant	3530	3.80	0.069	0.510	Dumokceaux *et al*., 2005

All available publications, where the body weight of experimental animals was indicated at an age that certified a complete maturation of liver and kidneys, and where antibiotic concentrations were measured by high-performance liquid chromatography, were used. All values were transformed in equal dimensions for each studied parameter (total body clearance in L/h, the volume of distribution – in

L, the biological half-life – in h). After a *log* transformation of the average values of these pharmacokinetic parameters by species, an analysis of the relationship between the parameters investigated and the animal's body weight was made. For this purpose, a regression analysis and the least square method was used. The equations were from the type: logPhP = c+b.logW, where: PhP – value of the respective pharmacokinetic parameter; W – body weight; c and b – coefficients indicating the Y-axis intercept and the slope of the regression curve, respectively. The equation could be transformed into PhP=a.Wb, where a is the antilogarithm of c. Coefficients of determination "r" and P-values were calculated for each correlation.

RESULTS

The allometric relationship between the pharmacokinetic parameters investigated and W is shown in Table 2. The equation describing the regression of Cl_B versus W is $Cl_B=0.155W^{0.82}$. A good correlation was registered – r=0.9285, ($p<0.001$). A good correlation with W was also observed for Vss. The respective equation is $Vss=0.21W^{1.03}$, and the value of "r" was 0.9299 ($p<0.001$). However, ceftiofur elimination half-life as not related to W ($t_{1/2}=1.96W^{0.09}$; r=0.248; $p>0.05$).

Table 2. Allometric relationship between body clearance, volume of distribution and elimination half life of ceftiofur and the body mass

Parameters	$t_{1/2}$ (h)	Cl_B (L/h)	Vss (L)
a	1.96	0.155	0.21
b	0.09	0.82	1.033
r	0.248	0.9285	0.9299
p	>0.05	<0.001	<0.001

a – allometric coefficient, b – allometric exponent, r – correlation coefficient

Table 3. Values of selected pharmacokinetic parameters (observed, predicted and inaccuracy % for ceftiofur in herbivorous mammal species

Species	W (kg)	Cl_B (L/h)		Vss (L)	
		Calculated	Predicted	Calculated	Predicted
Cattle	326.4	9.47	17.80 (88.5)	78.0	81.5 (4.5)
Buffalo	247	16.10	14.20 (11.8)	33.1	61.2 (84.5)
Goat	46.5	6.05	3.61 (40.4)	14.9	11.0 (26.2)
Alpaca	72.7	5.96	5.21 (13.6)	39.3	17.4 (55.7)
Llama	123.6	7.26	8.05 (10.9)	23.5	29.9 (27.2)
Camel	400	12	21.10 (75.7)	52.0	100.5 (93.3)
Elephant	3530	243.6	125.70 (49.4)	1800	947.2 (47.4)

Our estimates for body clearance and volume of distribution indicate that the increase of their values with W approximates a linear power relationship which slopes are specific for this substance. Values of selected pharmacokinetic parameters: observed, predicted and inaccuracy (%) are presented in Table 3.

DISCUSSION

Ceftiofur obeys first order kinetics, low and linear percentage of protein binding, and mainly renal elimination process (Craigmill *et al*., 1997; Drew *et al.,* 2004; Dumokceaux *et al.,* 2005). These pharmacokinetic characteristics are optimal for adequate allometric analysis for any substance (Mahmood, 2007). Accordingly we found good correlation between Cl_B and Vss values of ceftiofur and body weight. Both values are similar to the ones reported by other authors for other beta-lactame antibiotics using the same analysis (Matsui *et al*., 1982; Mordenti, 1985). The low value of the allometric exponent (0.09) is not consistent with the reported low degree of correlation of $t_{1/2}$ with W for other beta-lactame antibiotics (Mordenti, 1985, Gardner and Papich, 2001).

The present study demonstrated that interspecies scaling of ceftiofur pharmacokinetics is valuable across mammal species. Elimination half-life is independent of W, whereas Cl_B and Vss can be extrapolated using allometric equations. This would be of help to predict ceftiofur disposition and doses for species that have not been studied. The differences between calculated and observed values could be defined as acceptable.

Address for correspodence:
Lashev Lubomir
Faculty of Veterinary Medicine, Trakia Universiry
Department of Pharmacology, Physiology and Physiological Chemistry
6000 Stara Zagora, Bulgaria
E-mail: lashev@uni-sz.bg

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ALOMETRIJSKA ANALIZA FARMAKOKINETIKE KOD SISARA BILJOJEDA: STUDIJA CEFTIOFURA

HARITOVA ANELIYA i LASHEV L

SADRŽAJ

Cilj ovog istraživanja je bila analiza odnosa između farmakokinetičkih parametara cefalosporinskog antibiotika ceftiofura kod sisara različite telesne mase (W). Ispitivani su sledeći parametri: klirens (Cl_B), volumen distribucije u stanju mirovanja (V_{ss}) i poluživot eliminacije. Parametri su upoređivani kod različitih vrsta sisara, kao funkcija telesne mase primenom konvencionalne alometrijske jednačine $Y=aW^b$, gde je Y - farmakokinetički parametar, W - telesna masa, a - alometrijski koeficijent i b - eksponent koji opisuje odnos između farmakokinetičkog parametra i telesne mase. Vrednosti koje smo mi dobili ($Cl=0.155W^{0.82}$; $Vss=1.01W^{1.03}$) ukazuju da povećanje ovih parametara sa povećanjem telesne mase dostiže približno linearan odnos sa odstupanjima specifičnim za ispitivanu supstancu. Rezultati ovih ispitivanja ukazuju da je moguća primena alometrijskog metoda u predviđanju farmakokinetičkih varijabli ceftiofura u odnosu na telesnu masu pojedinih vrsta.