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Short communication

COMPARATIVE ALLOMETRIC ANALYSIS OF THREE ISOXAZOLYLPENICILLINS IN FOUR MAMMALIAN SPECIES

L. LASHEV & D. J. DIMITROVA

Department of Pharmacology, Physiology of Animals and Chemistry, Faculty of Veterinary Medicine, Trakia University, Stara Zagora, Bulgaria

Summary

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Comparative allometric analysis of selected pharmacokinetic parameters of cloxacillin, dicloxacillin and flucloxacillin in four animal species (cats, dogs, pigs and sheep) was performed. The correlations between the total body clearance (CL_B) and the volume of distribution (Vd_{area}) to the body weight of animals were established. They can be expressed by the equations: cloxacillin – $CL_B = 5.68W^{1.18}$, $Vd_{area} = 0.24W^{1.56}$; dicloxacillin – $CL_B = 17.95W^{0.92}$, $Vd_{area} = 2.93W^{0.62}$; and flucloxacillin – $CL_B = 10.59W^{0.97}$, $Vd_{area} = 1.52W^{1.43}$. No statistically significant correlation was found for the half-life values.

Key words: allometry, cloxacillin; dicloxacillin; flucloxacillin, pharmacokinetics

The three isoxazolylpenicillin antibiotics (cloxacillin, dicloxacillin, flucloxacillin), examined in the present study, have similar antibacterial spectrum and are active mainly against beta-lactamase producing staphylococci. Their use in the veterinary medicine is rare and data of their pharmacokinetics in animals are scarce. During the last years, these antibiotics were extensively investigated in different mammalian species (Dimitrova, 2007). The results of these investigations allow to perform an allometric analysis, which provides additional information about their pharmacokinetics taking into account interspecies relationships. The aim of the present study was to compare the interspecies correlations between the values of total body clearance, volume of distribution and biological half-life of cloxacillin, dicloxacillin, flucloxacillin and the body weight in four mammalian species.

Data from published papers for the half-life, total body clearance and volume of distribution (Vd_{area}) of cloxacillin, dicloxacillin and flucloxacillin in cats, dogs, pigs and sheep after their intravenous (*i.v.*) application were analyzed (Table 1). All results are obtained in the Department of Pharmacology, Faculty of Veterinary Medicine, Trakia University, Bulgaria and published by Dimitrova (2007).

The data included are taken from experiments with animals at an age certify-

ing complete maturation of liver and kidney functions. In all cases, serum antibiotic concentrations were measured using a microbiological method with test-microorganism *Bacillus mycoides HB*$_2$. All values were expressed in uniform dimensions for each studied parameter (the total body clearance in mL/min, 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 these parameters and the body weight was made. For this purpose, a regression analysis and the least square method were used. The equations were of the type:

$$log\ PhP = log\ c + b.\ log\ W$$

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 equations could be transformed into $PhP = aW^b$, where *a* is the antilogarithm of *c*.

The values of the parameters for the three antibiotics and four animal species, included in the calculations, are presented in Table 1. The calculated allometric coefficients showed some differences between the antibiotics as start levels and dependence on the body mass (Table 2). These relationships could be expressed by the following equations:

- cloxacillin - $CL_B = 5.68W^{1.18}$, $Vd_{area} = 0.24W^{1.56}$

Table 1. Pharmacokinetic parameters of isoxazolilpenicillins (calculated and predicted) in mammalian species after *i.v.* administration

Antibiotic	Species	BW (kg)	$t_{1/2\beta}$ (h)	CL_B (mL/h)		$Vd_{(area)}$ (L)	
				Calculated*	Predicted**	Calculated	Predicted
Cloxacillin	cats	2.77	0.42	21.77	18.9	1	1.17
	dogs	17.7	1.15	413.3	168.6	41.7	21.23
	pigs	17	0.49	198	161	7.7	20
	sheep	45.8	0.68	663	518	66.4	93.6
	humans	65	–	–	782	–	162
Dicloxacillin	cats	2.42	1.21	39	40.5	5.6	5.07
	dogs	17.1	0.98	227	244	23.8	17
	pigs	20.5	0.83	354	289	9.1	19
	sheep	49.4	0.97	582.3	649	45.0	33
	humans	65	–	–	836	–	39
Flucloxacillin	cats	2.01	0.55	23.7	217	3.11	3.34
	dogs	17.6	1.22	99.4	171	49.8	39
	pigs	21.33	0.56	252	205	47.3	48.3
	sheep	47.6	0.94	578	449	103.3	119.5
	humans	65	–	–	607	–	170

* The values of the pharmacokinetics parameters are after Dimitrova (2007). ** Predicted values are calculated on the basis of the equations in the present paper; BW – body weght; $t_{1/2\beta}$ – the half-life of the elimination phase; CL_B – total body clearance; $Vd_{(area)}$ – volume of distribution.

Table 2. Coefficients of allometric equations presenting the relationship of pharmacokinetic parameters of isoxazolylpenicillins to body mass in four mammalian species

Antibiotic	Coefficient	Parameters		
		$t_{1/2\beta}$	CL_B	$Vd_{(area)}$
Cloxacillin	*r*	0.5360	0.9685	0.9707
	b	0.20	1.18	1.56
	a	0.37	5.68	0.24
	P	> 0.05	< 0.05	< 0.05
Dicloxacillin	*r*	0.7570	0.9928	0.8430
	b	0.09	0.92	0.62
	a	1.26	14.95	2.93
	P	> 0.05	< 0.05	< 0.05
Flucloxacillin	*r*	0.5427	0.9624	0.9937
	b	0.16	0.97	1.13
	a	0.51	10.59	1.52
	P	> 0.05	< 0.05	< 0.05

$t_{1/2\beta}$ – terminal elimination half-life; CL_B – total body clearance; $Vd_{(area)}$ – volume of distribution; a – coefficient; b – exponent; r – correlation coefficient; P – statistical significance of the relationship

- dicloxacillin - $CL_B=17.95W^{0.92}$, $Vd_{area}=2.93W^{0.62}$
- flucloxacillin - $CL_B=10.59W^{0.97}$, $Vd_{area}=1.52W^{1.13}$

No statistically significant correlation was found between the half-life values and the body weight. Data concerning the allometric relationship between different pharmacokinetic parameters and the animal's body weight were published for a number of antibacterial drugs: penicillins, quinolones, sulphonamides, tetracyclines, phenicoles (Duthu, 1985; Lashev & Pashov, 1992; Lashev *et al.*, 1992; 1995; Bregante *et al.,* 1999; Martin-Jimenez *et al.*, 2001; Cox *et al.*, 2004). They show variations of the coefficients, depending on the specificity of the disposition of the drugs in the body, but within the limit of calculated basic values. Compared to other antibacterials, isoxasolylpenicillins showed higher values of clearance and distribution volume coefficients (Duthu, 1985; Lashev & Pashov, 1992; Lashev *et al.*, 1995; Bregante *et al.*, 1999; Cox *et al.*, 2004; Lashev & Haritova, 2006). We assume that the relatively small number of the species included could also be a possible reason for these differences. The available data show no difference between the pharmacokinetics of the antibiotics examined. They exhibited similar coefficients showing an allometric relationship between the body weight and pharmacokinetic parameters. Comparable results were also found out for other drugs with similar chemical structure and behaviour in the organism: ampicillin and amoxicillin; thiamphenicol and florfenicol; enrofloxacin and ciprofloxacin, aminoglycosides (Duthu, 1985; Lashev & Pashov, 1992; Lashev *et al.*, 1995; Cox *et al.*, 2004; Lashev & Haritova, 2006). On the other hand, quite obvious differences were registered for tetracyclines and sulphonamides (Lashev & Pashov, 1992; Lashev *et*

al., 1995; Riviere *et al.*, 1997). In the present study we found relationships between the clearance and volume of distribution and body weight as well as lack of correlation for elimination half-life. The high level of correlation for the first two parameters is anticipated, as well as the very low correlation of half-life to body weight. Similar results are published for other antibacterials (Cox *et al.*, 2004; Lashev & Haritova, 2006). They can be modified by different factors as lactation, gender, age (Cox *et al.*, 2004). In our case the binding to proteins could also be of importance. All these factors, as well as specificity of the structure of investigated drugs and the respective pharmacokinetic relations are explanations for the differences found. Similar differences exist between other drugs having comparable structures (Duthu, 1985; Lashev *et al.*, 1995; Riviere *et al.*, 1997; Cox *et al.*, 2004; Lashev & Haritova, 2006).

Our conclusion is that the clearance and the volume of distribution are proportional to the body weight, but the same could not be said for the half-life. Some differences between the antibiotics have also been found. Despite the relatively small number of the species included in the work, our results could be used for prediction of their pharmacokinetics in uninvestigated species, for example exotic animal species.

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Correspondence:

Prof. L. Lashev
Department of Pharmacology, Physiology of Animals and Chemistry,
Faculty of Veterinary Medicine,
Trakia University,
6000 Stara Zagora, Bulgaria
e-mail: lashev@uni-sz.bg