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ALLOMETRIC ANALYSIS OF ANTIBACTERIAL DRUGS IN AVIAN SPECIES

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Summary

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The purpose of this study was to examine the allometric relationships of fluoroquinolones, penicillins, aminoglycosides, sulfonamides, tetracyclines and florfenicol in bird species using pharmacokinetic data from the literature. The parameters of interest (half-life, volume of distribution, and total body clearance) were correlated as a function of body weight applying an allometric approach ($Y=aW^b$). Values of the coeficient *a* and the exponent *b* were close to the theorethical values for the clearance and volume of distribution of most drugs, except for sulfadimidine, tobramycin and apramycin. The elimination half-life was relatively independent of body mass for penicillins, pefloxacin, doxycycline and trimethoprim. Results of the analysis suggest that allometric scaling can be used as a tool for predicting pharmacokinetic parameters for most drugs in avian species. The predictive power is stronger, when only data for bird species are included, in comparison to simultaneous allometric scaling of the data for avian and mammalian species.

Key words: antibacterials, birds, pharmacokinetics, allometric scaling

INTRODUCTION

The increased number of non-domesticated animal species, subject to veterinary care, expands the area of drugs' application. That fact outlines the significance of the problem for determination of doses and dosage regimens in animal species for which no relevant prior studies are available. Although the knowledge of the pharmacokinetics of drug substances (important in terms of dosing) is expanded the data for minor species, as well as wild and exotic animals, are limited. As a result, dosing is often based on extrapolation of data from species for which sufficient data were generated (Hunter *et al.*, 2008).

Allometric scaling shares the assumptions that inter-species differences are clinically negligible and that the drug pharmacokinetics has a log-log (allometric) relationship to body weight (Hunter, 2010). Over the past twenty years allometric scaling is recommended and used as a method for determining the pharmacokinetic characteristics and the dose of a drug in cases of lack of scientific data or empirical experience for an animal species. The basis of the method of allometric scaling is the relationship between the metabolism and the body weight of animal species. Several authors aimed at determining the relationship of the main pharmacokinetic parameters of drugs ($t_{1/2}$,

Cl_B, V_d, V_{ss}) with body weight (Kirkwood & Widdowson, 1990; Riviere *et al.*, 1997; Cox, 2007; Hunter *et al.*, 2008). Extrapolation of dosing regimens by using allometric scaling from both mammals and domestic poultry to other species is complicated and the published literature is limited (Hunter *et al.*, 2008). Differences were found even within the same class of animals such as birds (Suarez, 1996; McKechnie & Wolf, 2004; Kabat *et al.*, 2008). Most studies, treating the pharmacokinetics of drugs in bird species, present data for the family Galliformes, ducks, pigeons and parrots (Hunter *et al.*, 2008). Published investigations concern mainly antibacterial drugs as oxytetracycline, florfenicol and enrofloxacin and are based on data for mammals and birds (Riviere *et al.*, 1997; Cox *et al.*, 2004; Lashev & Haritova, 2006; Cox, 2007; Haritova & Lashev, 2009).

The anatomic and physiological differences among bird species are considerably less pronounced compared to mammals allowing to assume a relatively lower imprecision in the extrapolation of data using the allometric approach (Anadon, 1999). These relationships could be used also to compare the systemic behaviour of antibacterials on the basis of equations depicting the respective pharmacokinetic parameters. The following three pharmacokinetic parameters are included: elimination half-life ($t_{1/2el}$), total body clearance (Cl_B) and steady-state volume of distribution: V_{ss} or Vd_{area}.

The current investigation aimed to analyse the published information about antibacterial drugs' pharmacokinetics in order to find allometric relationships for basic pharmacokinetic parameters in birds. The analysis was made using data from the pharmacokinetics of fluoroquinolones, aminoglycosides, penicillins, tetracyclines, florfenicol, sulfonamides and trimethoprim.

MATERIALS AND METHODS

The simple allometric approach has been based on the following power function: $Y=a.W^b$, where Y is the value of the respective pharmacokinetic parameter ($t_{1/2\beta}$; $V_{d(ss)}$ or Cl_B), a is the coefficient, W is the body weight and b is the exponent of allometric equation. The least squares linear regression method was used for estimation of correlation between pharmacokinetic parameters of interest and body weight. In order to increase the predictive power of the allometric analysis, data from a wide range of pharmacokinetic studies are required. The current review focused only on the allometric analysis of intravenously administered antibacterial drugs in bird species. The allometric coefficients were calculated on the basis of the mean values of the published pharmacokinetic parameters for each animal species versus respective body weight of healthy mature birds.

The analysis of pharmacokinetic parameters of abovementioned antibacterial drugs was performed using data from previously published pharmacokinetic studies or our unpublished results. The unpublished data concern danofloxacin (10 mg/kg), marbofloxacin (5 mg/kg) and enrofloxacin (10 mg/kg) in Japanese quails and common pheasants. Pharmacokinetic parameters were calculated with WinNonLin 5.0.1 software (Pharsight Corporation, Mountain View, CA, USA).

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 presented in Table 1. Statistically significant dependence of $t_{½el}$ and body weight was found for the *fluoroquinolones* enrofloxacin and marbofloxacin. The highest value of *a* for the investigated pharmacokinetic parameters was determined for danofloxacin. They were similar for the rest of the fluoroquinolones.

The analysis showed statistically significant correlations between V_{dss}, Cl_B and body weight. The analysis of the data for *aminoglycosides* and *aminocyclitols* showed statistically significant correlation of V_{dss}, Cl_B, $t_{½el}$ to the body weight, except for the data for $t_{½el}$ for gentamicin. The values of *a* for tobramycin and gentamicin for the studied parameters were similar, but different from those of apramycin.

Allometric parameters for *aminopenicillins*, *sulfonamides* and *trimethoprim*, *tetracyclines* and *florfenicol* showed statistically significant dependence of V_{dss} and Cl_B from the body weight (Table 1). Such a dependence was not found for $t_{½\beta}$. The values of *b* and *a* for the clavulanic acid were similar to these of amoxicillin. Difference in the values of these parameters was observed for oxytetracycline and doxycycline.

DISCUSSION

Quinolones

The pharmacokinetics of fluoroquinolones has been extensively submitted to allometric analyses. Most of them however did not attempt to distinguish birds from mammals and therefore are a source of imprecision (Hunter *et al.*, 2008). We present allometric relationships on the basis of data for birds only (Tables 1 and 2).

Discussed from a comparative point of view, allometric coefficients and exponents show that the distribution of danofloxacin is the highest, and that of marbofloxacin is the lowest. The highest values of total body clearance are those of danofloxacin and low values are typical for marbofloxacin. The biological half-life values are comparable. Inclusion of additional data for danofloxacin and pefloxacin for different avian species should provide more precise results.

The biological half-life values of different substances for species belonging to order Struthioniformes are lower than the values for other investigated species i.e. Galliformes (Waxman 2000; De Lucas *et al.*, 2004a; 2004b; 2005). Probably, Struthioniformes species should be included in a separate group for calculation of more accurate pharmacokinetic parameters. Compared to other avian species they also show much higher values of the total body clearance. The possible reason could be their specific excretory system and activities of the drug metabolizing enzyme systems (Amsallem-Holtzman & Ben-Zvi, 1997).

Previous results of ours and other authors have shown that even when very high values for *r* are obtained, allometric scaling may not accurately extrapolate Cl_B or V_{ss} to an unknown animal species (Martinez *et al.*, 2006). They also support the opposite fact, i.e. that in many cases, low values of *r* provided highly accurate extrapolations especially for $t_{½el}$ (Mahmood, 2001). The predicted values, presented as percent of inaccuracy, were with low deviation from the observed results (Table 2). In most cases they can be used for dose calculation.

Table 1. Values of allometric parameters for antibacterial substances in bird species

Substance	Parameter	r	n	Substance	Parameter	r	n
Marbofloxacin	$t_{1/2el}=4.61W^{0.27}$	0.700*	8	Doxycycline	$t_{1/2el}=6.81W^{0.04}$	0.388	5
	$Cl_B=0.23W^{0.73}$	0.982***	8		$Cl_B=0.13W^{1.0}$	0.994***	5
	$V_{ss}=1.22W^{0.97}$	0.973***	8		$V_{ss}=1.21W^{1.03}$	0.944**	5
Enrofloxacin	$t_{1/2el}=4.72W^{0.292}$	0.837**	6	Florfenicol	$t_{1/2el}=2.47W^{0.29}$	0.589	5
	$Cl_B=0.62W^{0.62}$	0.621*	6		$Cl_B=1.37W^{0.28}$	0.872*	5
	$V_{ss}=3.02W^{0.95}$	0.927**	6		$V_{ss}=2.83W^{0.41}$	0.938**	5
Danofloxacin	$t_{1/2el}=5.52W^{0.11}$	0.461	5	Sulfadiazine	$t_{1/2el}=2.97W^{0.34}$	0.986**	3
	$Cl_B=0.91W^{0.78}$	0.936*	5		$Cl_B=0.11W^{0.78}$	0.993**	3
	$V_{ss}=6.88W^{0.91}$	0.973***	5		$V_{ss}=0.49W^{1.10}$	0.998**	3
Pefloxacin	$t_{1/2el}=4.23W^{0.06}$	0.172	4	Sulfadimidine	$t_{1/2el}=4.99W^{0.58}$	0.979***	4
	$Cl_B=0.51W^{1.21}$	0.966*	4		$Cl_B=0.14W^{0.29}$	0.824*	4
	$V_{ss}=2.71W^{1.14}$	0.949**	4		$V_{ss}=1.02W^{0.89}$	0.985***	4
Ampicillin	$t_{1/2el}=0.7W^{0.10}$	0.300	5	Trimethoprim	$t_{1/2el}=2.39W^{-0.004}$	–0.733	3
	$Cl_B=1.38W^{0.72}$	0.979**	5		$Cl_B=0.93W^{0.99}$	0.998*	3
	$V_{ss}=1.21W^{0.81}$	0.987**	5		$V_{ss}=3.06W^{0.94}$	0.999*	3
Amoxicillin	$t_{1/2el}=0.85W^{0.09}$	0.634	6	Tobramycin	$t_{1/2el}=2.03W^{0.50}$	0.939*	3
	$Cl_B=1.43W^{0.76}$	0.933***	6		$Cl_B=0.20W^{0.76}$	0.924*	3
	$V_{ss}=1.11W^{1.01}$	0.967***	6		$V_{ss}=0.45W^{1.03}$	0.951*	3
Clavulanic acid	$t_{1/2el}=1.12W^{0.002}$	–0.068	3	Gentamicin	$t_{1/2el}=1.56W^{0.29}$	0.703	5
	$Cl_B=0.8W^{0.96}$	0.998*	3		$Cl_B=0.12W^{0.55}$	0.948**	5
	$V_{ss}=0.89W^{1.08}$	0.994*	3		$V_{ss}=0.25W^{0.84}$	0.999***	5
Oxytetracycline	$t_{1/2el}=3.38W^{0.24}$	0.534	7	Apramycin	$t_{1/2el}=0.92W^{0.52}$	0.883*	4
	$Cl_B=0.24W^{0.84}$	0.889**	7		$Cl_B=0.21W^{1.09}$	0.993***	4
	$V_{ss}=0.74W^{0.75}$	0.976***	6		$V_{ss}=0.11W^{0.88}$	0.961**	4

$t_{1/2el}$ – elimination half-life; Cl_B – total body clearance; V_{ss} – steady state distribution volume; W – body weight; r – correlation coefficient; * P<0.05; ** P<0.01; *** P<0.001; n – number of the included avian species.

Table 2. Values of selected pharmacokinetics parameters (ratio of predicted vs observed pharmacokinetic parameters) for enrofloxacin (EFC), marbofloxacin (MFC), danofloxacin (DFC) and pefloxacin (PFC) in avian species

Species (body weight, kg)	$t_{1/2el}$ (h)		V_{ss} (L)		Cl_B (L/h)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Enrofloxacin						
Chicken (2.12)	6.64	5.84 (1.14)	5.87	6.16 (0.95)	0.615	0.99 (0.62)
Turkey (6.98)	6.35	8.25 (0.77)	26.66	19.12 (1.39)	3.07	2.07 (1.48)
Duck (1.09)	6.47	4.82 (1.34)	1.42	3.28 (0.43)	0.97	0.65 (1.49)
Bustard (1.25)	5.63	5.02 (1.12)	3.73	3.73 (1.00)	0.42	0.71 (0.59)
Pheasant (1.05)*	4.62	4.70 (0.98)	3.85	3.16 (1.22)	0.62	0.64 (0.97)
Quail (0.2)*	2.33	2.94 (0.79)	0.93	0.65 (1.43)	0.29	0.23 (1.26)
Marbofloxacin						
Buzzard (0.9)	4.11	4.48 (0.92)	1.00	1.10 (0.91)	0.18	0.21 (0.86)
Duck (2.5)	6.35	5.90 (0.92)	2.00	2.97 (0.69)	0.57	0.45 (1.27)
Vulture (7.25)	3.28	7.87 (0.42)	10.95	8.33 (1.31)	0.80	0.98 (0.82)
Chicken (2.5)	6.47	5.90 (1.10)	1.90	2.97 (0.64)	0.43	0.45 (0.96)
Parrot (1.04)	12.51	4.65(2.69)	1.37	1.27 (1.08)	0.30	0.24 (1.25)
Quail (0.2)*	3.21	2.98 (1.08)	0.30	0.26 (1.15)	0.07	0.07 (1.00)
Turkey (8.5)	7.38	8.22 (0.90)	11.99	9.73 (1.23)	1.18	1.10 (1.07)
Pheasant (1.0)*	7.36	4.61 (1.60)	1.51	1.22 (1.24)	0.20	0.23 (0.87)
Danofloxacin						
Duck (3.75)	3.91	6.40 (0.61)	20.25	22.91 (0.88)	3.80	2.70 (1.41)
Turkey (8.2)	8.64	6.99 (1.24)	57.00	46.7 (1.22)	4.84	4.99 (0.97)
Pheasant (1.04)*	6.82	5.54 (1.23)	4.40	7.13 (0.62)	0.47	0.99 (0.47)
Quail (0.174)*	3.84	4.54 (0.85)	1.48	1.40 (1.06)	0.28	0.24 (1.17)
Chicken (0.67)	6.73	5.28 (1.27)	6.80	4.78 (1.42)	0.95	0.70 (1.36)
Pefloxacin						
Chicken (2.2)	6.60	4.41 (1.50)	0.84	1.31 (0.64)	3.65	6.66 (0.55)
Duck (4)	3.10	4.56 (0.68)	4.00	2.69 (1.49)	18.40	13.18 (1.4)
Pigeon (0.3)	3.30	3.96 (0.83)	0.14	0.12 (1.17)	0.68	0.68 (1.00)
Pheasant (1)	5.00	4.23 (1.18)	0.45	0.51 (0.88)	3.54	2.71 (1.31)

$t_{1/2el}$ – elimination half-life; Cl_B – total body clearance; V_{ss} – steady state distribution volume. The cited data are taken from the following authors: Anadon *et al.,* 1995 (EFC, chicken), Abd El-Aziz *et al,.* 1997 (EFC, chicken), Bailey *et al.,* 1998 (EFC, bustard), Bugyei *et al.,* 1999 (EFC, chicken), Garcia-Ovando *et al.,* 1999 (EFC, chicken), Knoll *et al.,* 1999 (EFC & DFC, chicken), Harrenstein *et al.,* 2000 (MFC, buzzard), Garcia-Montijano *et al.,* 2001 (MFC, vulture), El-Gendi *et al.,* 2001 (DFC, chicken), Anadon *et al.*, 2002 (MFC, chicken), Isea *et al.,* 2003 (PFC, chicken), Haritova *et al.* ,2004a (EFC, hen & turkey), Tansacul *et al.,* 2008 (FC, hen), Babu *et al.,* 2006 (PFC, chicken), Carpenter *et al.,* 2006 (MFC, parrot), Haritova *et al.,* 2006a (DFC, turkey), Haritova *et al,.* 2006b (MFC, turkey), Dimitrova *et al.,* 2007 (EFC, turkey), Moutafchieva *et al,* 2009 (PFC pheasant & pigeon), Dimitrova *et al.,* 2008 (PFC, duck), Garcia-Montijano *et al.,* 2011 (MFC, buzzard), Goudah & Mouneir, 2009 (DFC, duck), Yuan *et al.,* 2011 (PFC, duck), Dimitrova *et al.*(unpublished data); Lashev *et al.*, 2012 (EFC, DFC, MFC - pheasant & quail).

Compared to data for mammals (Cox *et al.*, 2004; Cox, 2007; Haritova & Lashev, 2009) the present calculations of values of the investigated parameters per kg body weight show the following trends: for marbofloxacin – shorter elimination half-life, higher clearance, the same volume of distribution; for enrofloxacin – shorter elimination half-life, lower clearance, lower volume of distribution; for danofloxacin – shorter elimination half-life, equal clearance and higher volume of distribution.

Aminoglycosides and aminocyclitols

The pharmacokinetics of aminoglycosides is characterised by low concentration in tissues compared to the serum and accordingly low volumes of distribution. They are eliminated by glomerular filtration. Despite of the twice lower glomerular filtration rate in birds than in mammals, the pharmacokinetics of gentamicin following intravenous administration is comparable in both. Therefore, it could be presumed that the tubular reabsorption of these drugs in birds is of little significance. Additionally, the glomerular filtration in birds is intermittent, which could be of significance for the aminoglycoside elimination (Pedersoli *et al.*, 1989a,b).

The pharmacokinetics of all three reviewed antibiotics was previously analysed by the allometric approach, especially

Table 3. Values of selected pharmacokinetic parameters (ratio of predicted vs observed pharmacokinetic parameters) for apramycin (APR), gentamicin (GMC) and tobramycin (TMC) in avian species

Species (body weight, kg)	$t_{1/2el}$ (h)		V_{ss} (L)		Cl_B (L/h)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Apramycin						
Quail (0.13)	0.50	0.32 (1.56)	0.017	0.017 (1.0)	0.024	0.022 (1.09)
Pigeon (0.3)	0.25	0.49 (0.51)	0.024	0.036 (0.67)	0.06	0.06 (1.00)
Chicken (1.22)	1.24	1.02 (1.22)	0.21	0.125 (1.68)	0.183	0.26 (0.70)
Turkey (6.95)	2.62	2.53 (1.04)	0.716	0.578 (1.24)	2.01	1.70 (1.18)
Gentamycin						
Turkey (8.9)	2.35	2.99 (0.79)	0.42	0.37 (1.14)	1.51	1.56 (0.97)
Chicken (4.7)	3.38	2.47 (1.37)	0.22	0.26 (0.85)	0.94	0.91 (1.03)
Hawk (1.38)	1.35	1.72 (0.78)	0.16	0.13 (1.23)	0.33	0.33 (1.00)
Owl (1.38)	1.93	1.72 (1.12)	0.12	0.13 (0.92)	0.32	0.33 (0.97)
Eagle (3.75)	2.46	2.31(1.06)	0.23	0.23 (1.00)	0.79	0.76 (1.04)
Tobramycin						
Pigeon (0.26)	0.82	1.03 (0.80)	0.076	0.11 (0.69)	0.05	0.07(0.71)
Chicken (0.462)	1.84	1.37 (1.34)	0.35	0.20 (1.75)	0.18	0.11 (1.64)
Duck (4.0)	3.84	4.08 (0.94)	1.70	1.86 (0.91)	0.51	0.57 (0.89)

$t_{1/2el}$ – elimination half-life; Cl_B – total body clearance; V_{ss} – steady state distribution volume. The data cited are taken from the following authors: Bird *et al.*, 1983 (GMC, hawk, owl, eagle); Pedersoli *et al.*, 1989a (GMC, turkey); Pedersoli *et al.*, 1989b (GMC, roosters); Lashev & Mihailov, 1994a (APR, quail); Lashev, 1998 (GMC, APR, turkey & chicken); Dimitrova *et al.*, 1998 (TMC, pigeon); Haritova *et al.*, 2004b (APR, turkey & hen); Lashev *et al.*, 2005 (TMC, chicken); Dimitrova *et al.*, 2009 (TMC, duck).

those of gentamicin (Kirkwood & Marriam, 1990; Martin-Jimenez & Riviere, 2001) and apramycin (Lashev, 1998; Dinev, 2008). All cited reports are based on data for mammals only or mixed data for mammals and birds. The relationship of the three selected pharmacokinetic parameters to the body weight of birds for gentamicin, tobramycin and apramycin are presented in Tables 1 and 3. The values of the predicted total body clearance and the volume of distribution are close to the observed (Table 3).

It can be summarized that the pharmacokinetics of the aminoglycoside antibiotics, except for $t_{½el}$ of gentamicin, strongly depended on the body weight of birds. Compared to mammals, birds have longer half-life, similar volume of distribution and lower clearance per kg body weight (Kirkwood & Merriam, 1991; Dinev, 2008).

Penicillins

In birds, aminopenicillins (ampicillin and amoxicillin) are recommended because of the sufficient degree of absorption following oral administration and the broad antibacterial spectrum. They demonstrate moderate distribution and tubular secretion as the main pathway for elimination. The pharmacokinetics of both aminopenicillins after i.v. administration is very similar. This similarity reflects on the respective allometric equations. In bird species both antibiotics show very close values of the allometric parameters. The allometric exponent for $t_{1/2el}$ is lower than the theoretical value, but the respective values for other two parameters are very close to the theoretical ones (Tables 1 and 4). Allometric coefficients reflect short elimination half-life values in all bird species. They are not different from those calculated for the same substances using data for mammals and birds (Lashev, 1998).

The allometric values for *clavulanic acid* are similar to those of amoxicillin (Table 1). Therefore, the allometric relationship for the dose extrapolation of the combination clavulanic acid-amoxicillin should be adequate for both compounds. The values of the predicted pharmacokinetic parameters are close to the observed but allometric scaling resulted in higher inaccuracy for the data of ampicillin, especially in quails and ducks.

Sulfonamides and trimethoprim

At present, the application of sulfonamides and potentiated sulfonamides in the veterinary practice is limited. In countries, where this group is applied, the most often administered representative is sulfachloropyrazine as anticoccidial drug. Sulfadiazine and sulfadimidine are also used separately or as combinations with trimethoprim in the treatment of bacterial infections. Sulfonamides are eliminated via metabolism and renal excretion. The involvement of both processes depends on species, gender and age-related anatomic and physiological characteristics such as enzyme activity, renal structure and function. Acetylation and hydroxylation rates are not uniform in the various species and substances. Data about their disposition in the body and comparisons of observed and predicted pharmacokinetic parameters are summarized in Table 5. They indicate that the difference between predicted and calculated values in most cases is very small.

Table 4. Values of selected pharmacokinetic parameters (ratio of predicted vs observed pharmacokinetic parameters) for amoxicillin (AMO) and ampicillin (AMP) in avian species.

Species (body weight, kg)	$t_{1/2el}$ (h)		V_{ss} (L)		Cl_B (L/h)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Amoxicillin						
Pigeon (0.41)	0.87	0.79 (1.10)	0.47	0.45 (1.04)	0.35	0.72 (0.49)
Turkey (7.8)	1.00	1.04 (0.96)	11.54	8.81 (1.31)	7.60	6.87 (1.10)
Chicken (2.5)	1.13	0.93 (1.22)	3.83	2.80 (1.37)	2.38	2.88 (0.83)
Duck (1.82)	0.70	0.90 (0.78)	1.37	2.03 (0.67)	2.89	2.26 (1.28)
Pheasant (1.05)	0.92	0.86 (1.07)	0.70	1.17 (0.60)	1.73	1.48 (1.17)
Quail (0.15)	0.67	0.71 (0.94)	0.22	0.16 (1.38)	0.52	0.34 (1.53)
Ampicillin						
Chicken (2.27)	0.61	0.76 (0.80)	2.26	2.35 (0.96)	2.56	2.49 (1.03)
Turkey (13.6)	0.77	0.91 (0.85)	10.2	10.02 (1.02)	9.11	9.04 (1.01)
Duck (1.33)	1.62	0.72 (2.25)	2.38	1.52 (1.57)	1.61	1.69 (0.95)
Pigeon (0.33)	0.40	0.63 (0.63)	0.37	0.55 (0.67)	0.37	0.69 (0.54)
Quail (0.13)	0.55	0.57 (0.96)	0.80	0.23 (3.48)	0.99	0.32 (3.09)

$t_{1/2el}$ – elimination half-life; Cl_B – total body clearance; V_{ss} – steady state distribution volume. The data cited are taken from the following authors: Dorrestein *et al.*, 1987 (AMO & AMP, chicken); Careles *et al.*, 1995 (AMO & clavulanic acid, chicken and turkey); Escudero *et al.*, 1998 (AMO & AMP, chicken, pigeon and turkey); Lashev, 1998 (AMO & AMP, pigeon, quail, chicken and turkey); Soenens *et al.*, 1998 (AMO, pigeon); Poapolathep *et al.*, 2001 (AMO, duck); El-Soud *et al.*, 2004 (AMO, chicken); Poapolathep *et al.*, 2005 (AMP, duck); Fernandez-Varon *et al.*, 2006a (AMP, turkey); Fernandez-Varon *et al.*, 2006b (AMP, chicken); Jersele *et al.*, 2009a (AMO & clavulanic acid, chicken and turkey); Jersele *et al.*, 2009b (AMO & clavulanic acid, chicken).

Both the allometric coefficients and exponents calculated for bird species are different from these in mammals (Lashev, 1998). Therefore, a more precise prediction of primary pharmacokinetic parameters can be obtained if only data for bird species are used.

Trimethoprim shows a first order pharmacokinetics. Its distribution in tissues is uniform. The excretion is via the kidneys, partially unchanged and partially metabolised. It could be stated that unlike mammals its pharmacokinetics in birds does not vary significantly (Lashev & Tanchev, 2002). The presented data for trimethoprim half-life are close to the found for non ruminant mammals (Lashev, 1998).

Tetracyclines

Tetracyclines are the antibiotics which persist for the longest time in the birds' organism after intravenous administration. The penetration in tissues is significant. Some of them (oxytetracycline and tetracycline) are metabolized in various species without significant influence on their elimination. After parenteral administration almost 50% or more are excreted with the urine. The principal mechanism is glomerular filtration. The biliary excretion is also important. This characteristics makes the group of tetracyclines less suitable for applying the allometric scaling.

Our calculations show clear differences in the pharmacokinetics between oxytetracycline and doxycycline: longer elimination, lower level of the clearance and higher level of distribution for doxycycline. The allometric relationship of the pharmacokinetic parameter $t_{1/2el}$ for oxytetracycline could be defined as comparable to that in mammals (Kirkwood & Widdowson, 1990). Doxycycline half-life however, showed higher values of the coefficient *a* and lower dependence from the body mass if compared to mammals.

Florfenicol

The pharmacokinetics of florfenicol is characterized mainly with a two compartment model, wide distribution in most body tissues and elimination via urine, mainly as parent substance and metabolites. Although that the available pharmacokinetic data for florfenicol are adequate as a sufficient number of species are included in allometric analyses, the relationships between pharmacokinetic parameters (Cl_B and V_{ss}) and body weight in birds should be characterised as unusual, differing from those of mammalian species. The value of the exponent *b* was far from the theoretical one. Nevertheless, these values, and the comparison of predicted and observed pharmacokinetic parameters show small deviation of the values from the allometric analysis (Table 6). Compared to data in mammals, the present results show longer half-life, lower clearance and volume of distribution (Lashev & Haritova, 2006).

Table 5. Values of selected pharmacokinetic parameters (ratio of predicted vs observed pharmacokinetic parameters) for sulfadiazine (SDZ), sulfadimidine (SDD) and trimethoprim (TMP) in avian species.

Species (body weight, kg)	$t_{1/2el}$ (h)		V_{ss} (L)		Cl_B (L/h)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Sulfadiazine						
Chicken (1.9)	3.19	3.68 (0.87)	0.82	0.99 (0.83)	0.171	0.184 (0.93)
Ostrich (80)	13.23	13.0 (1.02)	63.20	61.6 (1.03)	3.360	3.340 (1.01)
Duck (1.08)	3.45	2.97 (1.16)	0.63	0.53 (1.19)	0.126	0.119 (1.06)
Sulfadimidine						
Chicken (1.54)	6.20	6.4 (0.97)	1.86	1.49 (1.25)	0.171	0.163 (1.05)
Pheasant (1.19)	5.68	5.52 (1.03)	0.92	1.18 (0.78)	0.110	0.151 (0.73)
Quail (0.127)	1.56	1.52 (1.03)	1.16	0.16 (7.25)	0.079	0.079 (1.00)
Duck (1.08)	4.30	4.99 (0.86)	1.14	1.09 (1.05)	0.183	0.147 (1.24)
Trimethoprim						
Quail (0.125)	2.38	2.37 (1.00)	0.14	0.12 (1.17)	0.49	0.44 (1.11)
Chicken (1.27)	2.69	2.39 (1.13)	0.91	1.18 (0.77)	3.19	3.830 (0.83)
Ostrich (80)	1.95	2.42 (0.81)	77.60	70.8 (1.10)	199.20	186.6 (1.07)

$t_{1/2el}$ – elimination half-life; Cl_B – total body clearance; V_{ss} – steady state distribution volume. The data cited are taken from the following authors: Löscher *et al.*,1990 (TMP, duck); Lashev & Mihailov, 1994b (TMP, quail); Poapolathep *et al.*, 2000 (SDZ, duck); Lashev & Mihailov 1995 (SDD, all included species); Baert *et al.*, 2003 (SDZ & TMP, chicken); Abu-Basha *et al.*, 2008 (SDZ & TMP, ostrich); Tansacul, 2008 (hen); Prakash *et al.*, 2009 (SDZ, roosters).

Table 6. Values of selected pharmacokinetic parameters (ratio of predicted vs observed pharmacokinetic parameters) for doxycycline (Doxy) oxytetracycline (Oxy) and florfenicol (FLF) in avian species

Species (body weight, kg)	$t_{1/2el}$ (h)		V_{ss} (L)		Cl_B (L/h)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Doxycycline						
Ostrich (80)	7.67	7.99 (0.96)	133.60	108.1 (1.24)	12.00	10.4 (1.15)
Turkey (2.97)	8.50	7.09 (1.20)	3.15	3.68 (0.86)	0.45	0.39 (1.15)
Chicken (1.99)	5.63	6.98 (0.81)	1.61	2.44 (0.66)	0.18	0.26 (0.69)
Pigeon (0.49)	8.45	6.64 (1.27)	0.66	0.59 (1.12)	0.055	0.069 (0.80)
Dove (0.158)	5.41	6.37 (1.18)	0.23	0.18 (0.78)	0.027	0.021 (0.78)
Oxycycline						
Chicken (1.72)	3.16	3.84 (0.82)	2.39	1.10 (2.17)	1.12	0.38 (2.95)
Pigeon (0.26)	0.66	2.44 (0.27)	0.08	0.27 (0.30)	0.02	0.078 (0.26)
Pheasant (1.01)	2.53	3.37 (0.75)	–	0.74 (-)	0.26	0.25 (1.04)
Quail (0.12)	2.40	2.02 (1.19)	0.18	0.15 (1.20)	0.06	0.041 (1.46)
Cockatiel (0.099)	3.87	1.94 (1.99)	0.18	0.13 (1.38)	0.04	0.034 (1.18)
Parrot (0.13)	3.12	2.07 (1.51)	0.20	0.16 (1.25)	0.05	0.44 (0.11)
Turkey (10.1)	9.76	5.87 (1.66)	3.23	4.13 (0.78)	1.11	1.71 (0.65)
Florfenicol						
Chicken (1.78)	3.40	2.91 (1.17)	5.19	3.58 (1.45)	1.59	1.61 (0.99)
Pigeon (0.49)	1.78	2.01 (0.89)	1.91	2.11 (0.91)	1.30	1.12 (1.16)
Quail (0.22)	1.24	1.60 (0.78)	1.47	1.52 (0.97)	0.73	0.90 (0.81)
Duck (2.2)	7.17	3.10 (2.31)	3.48	3.91 (0.89)	2.24	1.70 (1.32)
Turkey (7.47)	2.40	4.40 (0.55)	5.75	6.45 (0.89)	1.94	2.39 (0.81)

$t_{1/2el}$ – elimination half-life; Cl_B – total body clearance; V_{ss} – steady state distribution volume. The data cited are taken from the following authors: Teare *et al.*, 1985 (Oxy, pheasant, parrot); Atef *et al.*, 1986 (Oxy, chicken); Florent & Florent, 1986 (Oxy, turkey); Serrano *et al.*, 1988 (Oxy, pigeon); Dyer 1989 (Oxy, turkey); Dorrestein *et al.*, 1990 (Doxy, pigeon); Dorrestein *et al.*, 1991 (Doxy, pigeon); Guimera *et al.*, 1992 (Oxy, hens); Anadon *et al.*, 1994 (Doxy, chicken); Küng and Wanner, 1994 (Doxy, chicken); Moreno *et al.*, 1996 (Oxy, hens); Santos *et al.*, 1996 (Doxy, turkey); Santos *et al.*, 1997 (Doxy, turkey); El-Banna, 1998 (FLF, duck); Shen *et al.*, 2002 (FLF, chicken); Tell *et al.*, 2003 (Oxy, quail); Shen *et al.*, 2003 (FLF, chicken); Insua, 2004 (FLF, chicken); Osofski *et al.*, 2005 (Oxy, quail, parrot); Abu-Basha *et al.*, 2006 (Doxy, ostrich); Baert and De Backer, 2006 (FLF, chicken); Park *et al.*, 2006 (FLF, chicken); Switala *et al.*, 2007 (FLF, turkey); Anadon *et al.*, 2008 (FLF, chicken); Pasmans *et al.*, 2008 (FLF, pigeon); Ismail *et al.*, 2009 (FLF, chicken, quail, pigeon); Koc *et al.*, 2009 (FLF, quail); El-Gendi *et al.*, 2010 (Doxy, chicken).

Our data show relatively small differences between observed and calculated values for pharmacokinetic parameters of interest in birds. These results show that the allometric approach can be applied by using data for bird species only and that the results are appropriate for dose extrapolation in birds. The equations presented could be used for calculation of the pharmacokinetic parameters, respectively,

doses in case of lack of information for certain bird species.

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