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PREDICTED PHARMACOKINETIC PARAMETERS IN CAMELS OBTAINED BY ALLOMETRIC SCALING FROM OTHER SPECIES IS ACCURATE

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ABSTRACT

The objective of the present study was to evaluate how accurate the predicted pharmacokinetic (PK) parameters of some drugs are in camels, obtained by allometric scaling from animal species when compared to observed values established by us previously. The PK parameters tested were plasma clearance (Cl) and volume of distribution at steady state (Vss). The drugs evaluated were amikacin, gentamicin, kanamycin, tobramycin, antipyrine, flunixin, ketoprofen (R), ketoprofen (S), meloxicam, phenylbutazone, theophylline, and tramadol. The PK parameters scaled well for all drugs tested except meloxicam, where the predicted Cl was 12.5 fold greater than the observed value.

Key words: Allometry, camels, clearance, volume of distribution

Camels have not received much research attention in the field of pharmacokinetic (PK) compared to other animals. In most cases, the doses used in horses and cows were extrapolated to camels without clear scientific basis. In most veterinary preparations, manufacturers do not site dose regimens for camels; if they do, however, one does not find supportive experimental data. We have faced this issue several times when performing PK, pharmacodynamics (PD) and metabolism studies in camels. We had to rely on dose regimens used in bovine and horses. Our experiments covered different classes of drugs, including antipyrine (Wasfi *et al,* 1998a), non-steroidal anti-inflammatory drugs (Al Katheeri *et al,* 2000; Wasfi *et al,* 1997; 1998b; 2012), aminoglycosides (Hadi *et al,* 1994; Wasfi *et al,* 1992; 1993; 1999a), theophylline (Wasfi *et al,* 1999), tramadol (Elghazali *et al,* 2008) and others. While some pharmacokinetic studies in camels were carried out by other researchers, the total number of medicines investigated in camels is incredibly modest when compared to the list of drugs commonly used in veterinary medicine. As a result, it seems appropriate to use interspecies allometric scaling principles to predict pharmacokinetic parameters in camels when camel-specific PK data is lacking (Mahmood, 2006). Predicting PK parameters between species with differences in body weight of several orders of magnitude has been done effectively using allometric scaling (Martinez *et al,* 2006; Boxenbaum and Dilea, 1995; Lave *et al,* 1999; Obach *et al,* 1997; Mahmood, 2005). Tang and Mayersohn (2005), however, stressed the significance of species selection for the accuracy of allometrically predicted pharmacokinetic parameters in humans. Interspecies allometric scaling was extensively used for clearance (Cl) and volume of distribution (Vss). It is important, however, to acknowledge the factors that can influence the accuracy of the predictions of the PK parameters or else extrapolations can lead to sub-therapeutic or toxic doses (Mahmood *et al,* 2006). For this reason, correction factors or the use of other allometric equations have been suggested to improve the accuracy of drug clearance predictions (Mahmood *et al,* 2006). In its simplest form the pharmacokinetic parameter (Y) and body weight (W) are transformed logarithmically and fitted by linear regression to the equation:

$$\log Y = c + b \log W$$

Where Y is the PK parameter of interest, W is the body weight, while b and c are the slope and the intercept, respectively. Coefficients of determination (r^2) and P-values could be calculated for each correlation to evaluate the goodness of fit. The following allometric equation can then be applied:

$$Y = a W^b$$

Where (a) is the antilogarithm of the intercept (c).

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The objective of this study was to evaluate the accuracy of predicted pharmacokinetic parameters of some drugs in camels, obtained by allometric scaling from other mammalian species, when compared to observed values previously reported in camels.

Materials and Methods

Allometric functions for the drugs of interest were obtained from the report of Huang *et al* (2015). In this report, the authors obtained their initial PK data from the FARAD database from which they calculated the allometric functions. From these functions, we scaled the PK parameters (Vss and Cl) to camels for all the drugs reported in this study (12 drugs for Cl and 11 drugs for Vss). In addition, the allometric functions for aminoglycosides reported by Dinev (2008) was also used for scaling Vss and Cl parameters of the four aminoglycosides reported in this study. Based on both studies as well as data obtained from our previous studies, only data obtained by the intravenous route were used. Vss was expressed in litres and Cl was expressed in mL/minutes. The per cent error (PE) of predicted to observe value was calculated as:

$$PE\% = \frac{\text{Predicted value} - \text{Observed value} \times 100}{\text{Observed value}}$$

Results and Discussion

Tables 1 and 2 summarises the predicted PK parameters when the coefficients and the exponents of the allometric scaling were obtained from Huang *et al* (2015). The PE% for the aminoglycosides for both Vss and Cl was reasonably accurate and ranged from -10.16% to 41.60% and from -30.10% to 39.14% for Cl and Vss, respectively. The PE% of the predicted Vss and Cl of these aminoglycosides was also accurate when the coefficients and the exponents of the allometric scaling were obtained from Dinev (2008) (Table 3). Aminoglycosides were known to be almost completely eliminated by renal excretion without metabolism. They also had small Vss due to limited tissue distribution as they are highly polar compounds. These properties were therefore expected to make them scale well among species based on body weight. It was stated that simple allometric approach was not applicable for drugs in certain situations one of which if a drug was significantly metabolised (Huang *et al,* 2015). Such an example is antipyrine, which was used as a test drug to investigate hepatic drug metabolism. Antipyrine offered the advantage of negligible plasma protein binding, low hepatic extraction ratio, and was metabolised almost entirely by the liver (Brodie and Axelrod, 1950). Huang *et al* (2015) found that the predicted Cl of antipyrine in humans was 6.6-fold higher than the observed Cl. It was reported that in humans more than 90% of the antipyrine dose administered was excreted into the urine in the form of metabolites, namely, norantipyrine, 4-hydroxyantipyrine and 3-hydroxymethylantipyrine (Schmid *et al,* 1995). At least six CYP isoforms were involved in the metabolism of antipyrine (Engel *et al,* 1996). The multiplicity of the CYP isoforms involved in the formation of antipyrine metabolites in humans, was probably the cause of the poor prediction of its Cl when scaled from animals. However, in the present study we found that antipyrine predicted Cl in camels

Table 1. Observed vs predicted Cl (ml/min) scaled from mammalian data to camels. The coefficients and the exponents of the allometric scaling were obtained from Huang *et al* (2015).

Compound	a	b	W (Kg)	Predicted	Observed	% PE	Reference
Amikacin	2.1	0.843	270	235.30	261.90	-10.16	Wasfi *et al* (1999a)
Gentamicin	3.809	0.78	270	300.00	243.00	23.46	Wasfi *et al* (1992)
Kanamycin	3.16	0.891	270	463.23	327.15	41.60	Wasfi *et al* (1993)
Tobramycin	3.725	0.786	270	304.01	243.00	25.11	Hadi *et al* (1994)
Antipyrine	7.7535	0.8496	400	1259.52	986.66	27.65	Wasfi *et al* (1998a)
Flunixin	1.4818	0.9607	475	552.45	680.83	-18.86	Wasfi *et al* (1998b)
Ketoprofen (R)	3.3113	0.8881	400	677.40	413.30	63.90	Wasfi *et al* (2000)
Ketoprofen (S)	1.7713	1.0056	400	732.70	464.00	57.91	Al Katheeri *et al* (2000)
Meloxicam	0.5037	0.9643	450	182.25	14.55	1152.57	Wasfi *et al* (2012)
Phenylbutazone	0.8474	0.7146	400	61.31	32.66	87.72	Wasfi *et al* (1997)
Theophylline	1.57	0.9249	385	386.54	437.60	-11.67	Wasfi *et al* (1999b)
Tramadol	10.351	1.1474	300	7198.60	9700.00	-25.79	Elghazali *et al* (2008)

W : body weight in Kg; a: coefficient; b: exponent; PE: per cent error of predicted value compared to observed value

Table 2. Observed vs predicted Vss (l) scaled from mammalian data to camels. The coefficients and the exponents of the allometric scaling were obtained from Huang *et al* (2015).

Compound	a	b	W(Kg)	Predicted	Observed	PE	Reference
Amikacin	0.1727	0.9826	270	42.30	60.52	-30.10	Wasfi *et al* (1999a)
Gentamicin	0.2724	0.9782	270	65.10	57.11	13.99	Wasfi *et al* (1992)
Kanamycin	0.0551	1.3509	270	106.09	83.54	27.00	Wasfi *et al* (1993)
Tobramycin	0.1947	1.071	270	78.23	56.22	39.14	Hadi *et al* (1994)
Antipyrine	0.5242	1.0911	400	361.91	263.60	37.30	Wasfi *et al* (1998)
Flunixin	0.3954	0.9053	475	104.77	158.65	-33.96	Wasfi *et al* (1998)
Ketoprofen (R)	0.2392	0.9452	400	68.90	60.40	14.08	Al Katheeri *et al* (2000)
Ketoprofen (S)	0.2759	0.915	400	66.32	61.60	7.66	Al Katheeri *et al* (2000)
Meloxicam	0.294	0.9006	450	72.08	41.76	72.61	Wasfi *et al* (2012)
Phenylbutazone	0.0371	1.2961	400	87.48	228.00	-61.63	Wasfi *et al* (1997)
Theophylline	0.6023	1.0249	385	268.94	415.80	-35.32	Wasfi *et al* (1999b)

W : body weight; a: coefficient; b: exponent; PE: per cent error of predicted value compared to observed value

Table 3. Observed vs predicted Cl and Vss scaled from mammalian data to camels. The coefficients and the exponents of the allometric scaling were obtained from Dinev (2008).

Vss (l)	a	b	W	Predicted	Observed	PE
Amikacin	0.44	0.86	270	54.25	60.52	-10.35
Gentamicin	0.37	0.91	270	60.36	57.11	5.69
Kanamycin	0.46	0.87	270	59.99	83.54	-28.19
Tobramycin	0.13	1.1	270	61.44	56.22	9.28
Cl (ml/min)	**a**	**b**	**W**	**Predicted**	**Observed**	**PE**
Amikacin	2.99	0.84	270	329.62	261.90	25.86
Gentamicin	1.21	1.01	270	345.51	275.00	25.64
Kanamycin	2.41	0.92	270	415.79	327.15	27.09
Tobramycin	6.41	0.63	270	218.08	243.00	-10.25

W: body weight; a: coefficient; b: exponent; PE: per cent error of predicted value compared to observed value. References of the observed values as in table 1.

scaled well from other species. We have previously found that the activity of mixed function oxidases estimated by *In vivo* antipyrine clearance, was similar in horses and camels (Wasfi *et al,* 1998a).

We observed a 12.5 fold increase of predicted meloxicam Cl in camels than the observed value (Wasfi *et al,* 2012). Meloxicam, however, was known to be extensively metabolised to four inactive metabolites in humans (Türck *et al,* 1996). In most species, however, meloxicam was cleared almost exclusively by metabolic mechanisms (Schmid *et al,* 1995). The prominent P450 enzyme involved in the phase 1 biotransformation of meloxicam in humans are CYP 2C9, with a minor contribution of CYP 3A4 (Chesne *et al,* 1998). We have previously shown that camel CYP2C and CYP3A subfamilies were both well expressed *in vitro* together with a high glucuronidating capacity (Al Katheeri *et al,* 2006). We recently reported the presence of methylhydroxy meloxicam in urine following intravenous administration of meloxicam (Wasfi *et al,* 2012). However, we have not investigated the presence and extent of other meloxicam metabolites in camels. Extensive metabolism of meloxicam in camels might be the cause of its poor Cl allometric prediction.

It is generally recognised that allometric scaling does not always work well and occasionally fails to predict PK values (Huang and Riviere, 2014). These "failures" frequently point to species-specific drug bio-disposition processes that inhibit proper scaling. For example, after administration of racemic ketoprofen to camels, we have observed a predominance of R-KP, a phenomena that was shared with sheep (Alkatheeri *et al,* 2000; Delatour *et al,* 1993). This, however, contrasts with the findings reported in other species like humans, rats, rabbits, calves, dogs,

cats, monkeys, horses and elephants (Hunter *et al,* 2003) where S-KP was predominant and had been attributed to unidirectional inversion of R-KP to S-KP. Interestingly, Hunter *et al* (2003) generated allometric equations for Vd, Clp, and t½ of each enantiomer versus body weight for 8 or 9 mammalian species and found that none of the pharmacokinetic parameters was scalable allometrically across the range of mammalian species evaluated. Interconversion of ketoprofen enantiomers was different between species and this was possibly the cause of the large PE% observed in predicted Cl in camels.

They argued that when the log-log transformation was used to plot Cl vs. body weight, a constant variance was surrounding camel metabolism, serum albumin, and adaptability when compared to other species, yet the limited data present in this study demonstrated that the allometric equations were in general suitable for predicting pharmacokinetic parameters for certain drugs in camels and are useful for estimating a first time in camel dose. However, for drugs which were extensively metabolised, one should take scaled parameters with caution. Hunter and Isaza (2008) evaluated three methods of drug scaling, the third method of which, allometric scaling, was pertinent to this study, where the authors pointed to practical considerations when scaling between species. For example, the authors pointed to the question about the use of the correlation coefficient (R^2) as an indicator of accuracy. They argued that when the log-log transformation was used to plot Cl vs body weight, a constant variance was assumed to be present around the Cl parameter; if this assumption was false, allometry should not be used. Since it was common practice to predict PK values between species with body weight variations of several orders of magnitude, a constant variance around the Cl parameter might not be anticipated. The calculation of the linear regression tends to be heavily influenced by the data at the high end of the calibration curve. The reason for this was that for heavier body weights, the absolute variation was greater. At the bottom of the curve, this frequently results in excessive error. However, It was possible to correct for this error and improve the experimental data's fit to the calibration curve by weighing the data inversely to body weight. According to the authors, the chosen species for allometic scaling, should preferably be closely related, share the bulk of physiological functions, and only vary in size. They further acknowledged that, medications with limited hepatic metabolism and blood-flow dependent clearance were the best candidates for allometric scaling. Our findings corroborated this idea, showing that the aminoglycosides, which had blood-flow dependent clearance, scaled better than the extensively metabolised meloxicam.

Data availability statement

All data necessary for calculations are presented in tables.

Author contributions

Both authors contributed in drafting and interpretations of the manuscript.

Animal welfare and ethics statement

Not applicable

Declaration of Competing Interest

The authors have no competing interests to declare.

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