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Bridging Pharmacokinetics between Laboratory/Veterinary animal Species and Man by Allometry : A Case Study of intravenous Tramadol

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Abstract
Tramadol, an important non-narcotic analgesic agent, has found clinical utility in several veterinary species in addition to its well accepted human use. The availability of published data on clearance and volume of distribution of Tramadol in veterinary/laboratory animal species rendered the applicability of allometry. The results of the interspecies scaling for both clearance ($2.036353W^{0.894801}$;R^2 = 0.781829) and volume of distribution ($2.526827W^{1.009582}$;R^2 =0.943264) suggested that simple allometry could help in formulating an effective dosing strategy of Tramadol in a new veterinary species. For instance, the predicted clearance for Tramadol was within 2-fold of the observed value in camels (predicted: 1.08 L/h; observed: 1.94 L/h); while, the predicted steady state volume of distribution value was in close proximity to the observed value in camels (predicted: 2.67 L; observed: 2.58 L). Also, simple allometry performed by the use of laboratory animal (rat, rabbit, dog) and human data predicted clearance and volume parameters in cat, goat, horse and camel within 4-fold and 2-fold, respectively. In summary, interspecies allometry scaling inclusive human data can be potentially used as a tool for dosing strategy when a new veterinary species is chosen.

Tramadol, known for its analgesic activity, has purported mechanism of action through variety of centrally acting receptors such as adrenergic and serotonin with relatively low affinity towards opioid receptors [1, 2, 3]. Tramadol is well absorbed after oral doses and undergoes extensive metabolism in both preclinical species and human subjects [4, 5]. One of the metabolites of Tramadol, namely O-desmethylTramadol formed via an oxidative deaklyation process has been shown to be active [6]. However, it should be noted that studies involving ^{14}[C]-Tramadol are limited in many veterinary species for an unambiguous determination of routes of elimination of Tramadol. On the basis of the information gathered in human subjects, Tramadol undergoes extensive metabolism (both Phase I and Phase II reactions are implicated) and many of the metabolites are excreted in the urine either intact and/or sulphate/glucuronide conjugates [4]. Both hepatic impairment and renal insufficiency can alter the pharmacokinetics of Tramadol suggesting the important roles of metabolism and urinary elimination pathways in the disposition of Tramadol [7].

The work of Mastocinque and Fantoni (2003) suggested that Tramadol produced beneficial effects comparable to morphine in reducing post-operative pain following ovariohysterectomy after pyometra in dogs [8]. On a similar note, Tramadol was shown to exhibit good analgesic activity following intravenous and epidural administration to horses [9, 10]. The pharmacokinetic disposition of Tramadol and its active metabolite, O-desmethyltranadol, has been well documented in a number of animal species and human subjects [11, 12, 13, 14, 15, 16, 17, 18, 19].

Since the use of Tramadol is gaining popularity across various animal species and human subjects, the aim of this work was to apply simple allometric principles to scale the derived pharmacokinetic parameters of Tramadol. The allometric equations generated separately for parameters such as clearance and volume of distribution at steady state for Tramadol could be applied to generate equivalent values in new animal species hitherto not tested and/or enable an optimised dose design in the new animal species. In the allometric scaling work attempted in this exercise, the active metabolite of O-desmethylTramadol was not considered for the following reasons: 1) the formation of O-desmethylTramadol is highly variable across species owing to a number of factors including presence of gentic polymorphism; 2) it was felt that incorporation of O-desmethylTramadol may not help guide the dosing strategy of Tramadol since “f” would be confounding across species; 3) O-desmethylTramadol formation is likely to happen in the various species contributing for the purported activity and lack of consideration of the active metabolite may not pose a big risk in the dosing strategy of Tramadol.

As tabulated in Table 1, the intravenous pharmacokinetics of Tramadol have been generated in number of species over the last decade. A quick examination of the numerical values of both clearance and volume terms in relation to the body

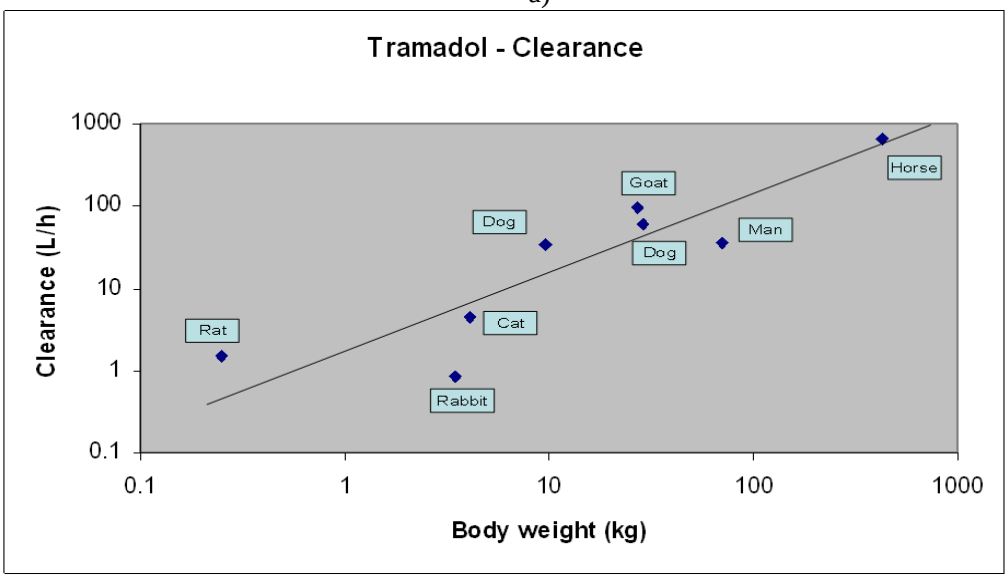
Table 1: Demography and tabulation of pharmacokinetic parameters of Tramadol following intravenous administration to various animal species and human subjects

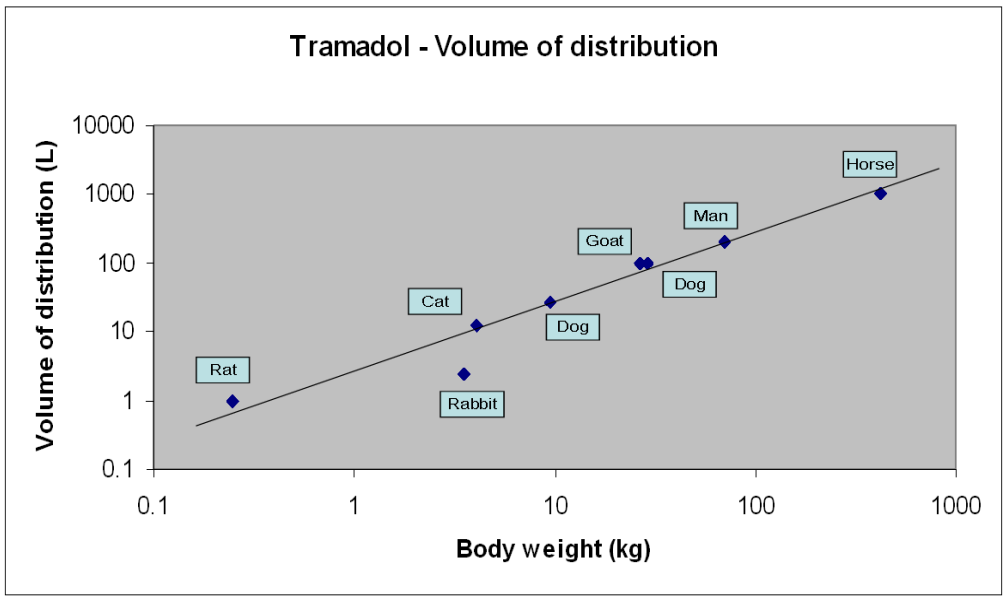
Species (n size)	*Mean Body Weight (kg)*	*Mean Clearance (L/h)*	*Mean Steady state volume of distribution (L)*	*Reference*
Rat*	0.25	1.475	0.965	Parasrampuria *et al*., 2007
Rabbit (n=2)	3.5	0.824	2.43	Kucuk *et al*., 2005
Cat (n=6)	4.1	4.56	12.30	Pypendop & Ilkiw, 2007
Dog (n=6)**	9.5	34.73	27.52	Kuanich & Papich, 2004
Dog*(n=6)**	28.8	61.48	98.50	McMillan *et al*., 2008
Goat (n=6)	26.9	95.34	99.15	Souza *et al*., 2007
Human#	70	36	200.5	Klotz 2003
Horse (n=7)	425	663	1022	Shilo *et al*., 2007

***n size not reported; **beagle dogs; ** mixed breed dogs; #population data (assumption of 100% bioavailability)**

Figure 1: Simple allometric scaling of the clearance (a) and steady state volume of distribution (b) of Tramadol after intravenous route of administration

a)





b)

Table 2: Prediction of veterinary animal pharmacokinetic parameters using laboratory animals (rat, rabbit, and dog) and human data

Species	*Clearance(L/h)*			*Steady state volume of distribution (L)*		
	Predicted	*Reported*	*Fold-change**	*Predicted*	*Reported*	*Fold-Change**
Cat	6.65	4.56	0.69	9.68	12.13	1.25
Goat	26.65	95.34	3.58	65.08	99.15	1.52
Horse	204.3	663	3.25	1065	1022	0.96
Camel	195.4	776	3.97	1002	1032	1.03

*** fold change calculated as a quotient of reported and predicted value**

weight provided hints that Tramadol pharmacokinetics may be amenable to allometry scaling.

Allometry scaling was performed by log-log regression of body weight versus the pharmacokinetic parameter as per the equation: $Y = aW^b$ (where 'W' and 'Y' denotes the body weight and pharmacokinetic parameter, respectively; 'a' and 'b' represent the intercept and exponent values, respectively, of the log-log regression line).

In spite of the use of data gathered from different laboratories, using different pharmacokinetic sampling schemes/protocols and with different bioanalytical platforms employed for the analysis of Tramadol, simple allometry appeared to satisfactorily scale the derived pharmacokinetic parameters for both clearance and volume of distribution terms (Figure 1).

The allometric equations derived for the clearance and steady state volume of distribution parameters of Tramadol were $2.036353W^{0.894801}$ (R^2 = 0.781829) and $2.526827W^{1.009582}$ (R^2 =0.943264), respectively. As suggested by the R^2 values the correlations for both parameters were satisfactory. While, it was noted that the value of the exponent for clearance parameter was within 20% of the desired value of 3/4ths deemed for a good fit, the value of the exponent for the volume term was coinciding with the desired value of 1.0 deemed for a good fit. The applicability of allometry principles in veterinary medicine has been recently reviewed and some important considerations have been proposed to improve the confidence in the scaling approaches (Mahmood *et al.*, 2006; Martinez *et al*, 2006). Accordingly, while commenting on the lack of institution of correction factors to scale the clearance term in veterinary species, it was suggested that an exponent value of >1.3 would be indicative of over prediction of the clearance parameter [20]. The obtained exponent value of 0.88 for the clearance parameter falls within the value suggested by Mahmood *et al* (2006) [20].

The applicability of the generated allometric equation for Tramadol to predict the clearance and volume of distribution at steady state of a new species was tested using camel as an example with a body weight of approximately 400 kg. Accordingly, the clearance value was predicted to be 434 L/h (i.e., 1.08 L/h/kg) and the steady state volume of distribution was predicted to be 1070 L (i.e., 2.67 L/h). A cursory examination of the two allometric relationships (Figure 1) suggested that in both instances rabbits tended to be somewhat of an outlier (more so for the clearance as opposed to volume of distribution) and such a phenomenon is bound to occur when a number of species are being subjected to allometric scaling.

In camels, the predicted value for clearance parameter was 2-fold lower as compared to the recently reported value for clearance (1.94 L/h/kg) in camels; however, the prediction of volume of distribution at steady state appeared to be in close proximity of the observed value for the volume term (2.58 L/h) [21]. Since unbound clearance values for Tramadol have not been reported in the various veterinary species, the allometric relationship between body weight and the unbound clearance of Tramadol could not be tested. In addition, the protein binding data of Tramadol in various animal species was not readily available to enable indirect calculation of the unbound clearance values of Tramadol. However, it should be noted that clearance parameter used in allometry has been obtained at pharmacologically relevant doses. Therefore, the predicted clearance parameter in a new animal species should enable a dosing strategy. In simple terms, the predicted clearance value may be compared to the hepatic blood flow in the new species to figure out if the dose needs to be re-adjusted factoring in the hepatic extraction of the drug. Needless to say, in addition to allometry dose predictions, safety considerations may also influence dose selection in the new veterinary species.

Therefore, simple allometry can be used to prospectively guide the dose selection of Tramadol for potential application in a new species as indicated by the results. This is important because Tramadol being atypical 'analgesic' is extensively

used not only in human subjects but also in several veterinary species. While the use of Tramadol in cats and dogs has been practised, Shilo et al (2007) have rationalized the utility of Tramadol in horses when compared to other alternatives to produce analgesia [15]. Accordingly, non-stereoidal anti-inflammatory agents (NSAIDs) have the risk of potential adverse effects and opioid analgesics have a greater risk of excessive CNS stimulation and therefore, the use of Tramadol may provide an important alternative to mitigate some of the therapeutic pitfalls from the use of NSAIDs or opioid analgesics [15]. Since the formation of active metabolite of Tramadol is under the influence of CYP2D6, a polymorphic enzyme, caution needs to be exercised in the dose selection of a new species if a possibility exists for an altered metabolism of Tramadol. In this context, the rate and extent of formation the active O-desmethylTramadol in cats appeared to be comparable to those values reported for poor metabolizer phenotypes of CYP2D6 [22, 23]. The work of Shilo *et al* (2007) also suggested that formation of low levels of the O-desmethyl metabolite in horses [15], which corroborated with earlier data of lack of formation of O-desmethylTramadol in a *in vitro* metabolism study in horses [24]. However, in camels, the formation O-desmethylTramadol was not affected [21]. The urinary excretion of O-desemthylTramadol was also confirmed along with other metabolites like N-hydroxyTramadol and N-bis-desmethylTramadol in camels [21]. Because it appeared that O-desmethylTramadol was long lived in the system as compared to Tramadol, Elghazali *et al* (2008) have suggested the measurement of O-desmethylTramadol as a tool for abuse testing [21]. Hence, overall there were some animal species that may present a lower enzymatic expression of CYP2D isozyme, which is responsible for the oxidative demethylation reaction of Tramadol. Therefore, the utility of O-desmethylTramadol in allometric scaling model may not overwhelmingly attractive supporting the lack of inclusion of the active metabolite in the allometric scaling approach attempted in this work.

In order to further validate the utility of laboratory animal PK in combination with human PK parameters to prospectively predict the PK parameter values of various veterinary animals, allometry was performed using rat, dog, rabbit and human PK parameters for both clearance ($2.347666W^{0.737953}$ (R^2 = 0.630926)) and volume of distribution ($2.31981W^{1.012747}$ (R^2 = 0.908827)). The respective allometry equations were used to predict the corresponding PK parameter values in cat, goat, horse and camel. As indicated in Table 2, the volume of distribution values were predicted within 2-fold of the reported values, whereas the clearance values were predicted within 4-fold of the reported values. Overall, the data suggests that it is possible to bridge PK data across laboratory/veterinary animal species and human subjects. In addition, the accuracy of the prediction may be improved by the incorporation of suitable correction factors which is practised for the prediction of human relevant PK parameters from laboratory animal data.

Conflict of interest statement:

The author of this paper has no conflict of interest to report.

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