Research Article

Parent-Metabolite Pharmacokinetic Models for Tramadol – Tests of Assumptions and Predictions

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Abstract

Allometric principles were used to discern cross-species differences in (±)-tramadol disposition and formation of its primary analgesic metabolite, (±)-O-desmethyl-tramadol (M1). Species differences in formation of M1 may help predict the analgesic effectiveness of tramadol. Tramadol was administered intravenously by a zero-order (constant infusion) process or rapid bolus dose and racemic concentrations of tramadol and M1 measured. Data were pooled to define differences between species (human, rat, cat, dog, goat, donkey and horse). A two-compartment linear disposition model with first-order elimination was used to describe tramadol and M1 disposition. Slow metabolizers were detected in 6% of the population and tramadol clearance to M1 was 16.2% that of extensive metabolizers. Tramadol clearance to M1 was slower and tramadol clearance by other pathways was faster in rats, dogs, and horses compared to humans. There are substantial differences between species in the pharmacokinetics of tramadol and its M1 metabolite, which are not explained by differences in body weight. The hypothesis that volumes of distribution are similar across species was shown not to be true. M1 exposure in the goat, donkey and cat was comparable to humans, which indicates it is likely to be an effective analgesic at typically used doses in these species but not in dogs or horses.

ABBREVIATIONS

Tramadol: (±)-Tramadol; **M1:** (±)-*O*-Desmethyl-Tramadol; **CLPM:** Clearance to M1; **CLPO:** Tramadol Clearance by Other Routes; **QP:** Inter-Compartmental Clearance; **CLMO:** Clearance of M1; **VP1:** Central Volume; **VP2:** Peripheral Volume; **QM:** M1 Inter-Compartmental Clearance; **VM1:** Central Volume; **VM2:** Peripheral Volume; **T$_{\frac{1}{2}}$:** Elimination Half-Life; **M5:** *O-N*-Didesmethyl-Tramadol; **M2:** *N*-Desmethyl-Tramadol; **Fm:**

Fraction of Tramadol Converted to M; **Fo:** Fraction of Tramadol Eliminated by Other Pathways; **HPLC:** High Performance Liquid Chromatography; **GCMS:** Gas Chromatography Mass Spectrometry; **LC/MS/MS:** HPLC-Coupled Tandem Mass Spectrometry; **PPV:** Population Parameter Variability; **RSE:** Relative Standard Error; **RUV:** Residual Unidentified Variability

INTRODUCTION

Pharmacokinetic models describing concentrations, e.g. in plasma, of parent and metabolite after administration of the parent compound must make assumptions because the system is a priori unidentifiable. Tramadol is a centrally acting racemic analgesic structurally related to morphine that mediates analgesia by multiple mechanisms [1]. The moiety (+)-tramadol and its metabolite (+)-*O*-desmethyl-tramadol (M1) are weak µ-opioid receptor agonists relative to morphine and the antinociceptive effects of tramadol are attributed to a combination of mechanisms. Along with µ-opioid receptor activity, (+)-tramadol and (+)-M1 stimulate neuronal serotonin efflux while reuptake is inhibited by (+)-tramadol [2,3]. Further analgesia is caused by (-)-tramadol competitively inhibiting noradrenaline reuptake in the spinal cord [4].

Ninety percent of ^{14}C label can be recovered in the urine after oral administration of ^{14}C tramadol to humans [5]. Twelve percent of tramadol and 15% of M1 (expressed as fraction of the tramadol dose) are excreted in the urine unchanged in humans [6]. The mean elimination half-life ($T_{1/2}$) is 6 hours and the total clearance following intravenous administration has been reported to be 29 L/h in adult humans [7,8]. In all species, the main tramadol metabolites are M1 and M1 glucuronide and sulfate conjugates, *O,N*-didesmethyl-tramadol (M5) and M5 conjugates, and *N*-desmethyl-tramadol (M2). In rats and dogs, only 1% of administered tramadol is excreted unchanged in the urine [5].

O-Demethylation of tramadol to M1, the main analgesic metabolite, is catalyzed by CYP2D6. CYP2D6 polymorphisms have been shown to influence M1 production and its subsequent analgesic effect in humans [9]. (+)-M1 alone has been shown to provide substantial antinociception in rats [10].

The pharmacokinetics of tramadol and M1 after intravenous administration of tramadol have been reported in several adult human studies [8,9,11-13] as well as in dogs [14-16], goats [17], horses [18-21], donkeys [22], cats [23] and rats [24]. Of particular importance to the current analysis, one of these studies observed M1 concentrations after direct intravenous administration of M1, allowing estimation of the volume of distribution of M1 [14]. Data have been pooled from these studies in order to construct a pharmacokinetic model for tramadol and M1. This model has been used to define quantitatively the elimination pathway of tramadol and M1 by comparison to adult humans. The use of allometric principles allows comparison of species differences by normalizing size, which ranges over three orders of magnitude. The assumption that volumes of distribution (such as for M1) are similar across species has been tested using direct estimates from studies in dogs.

MATERIALS AND METHODS

Tramadol was administered intravenously in all studies.

All non-human species were fasted for 8 to 12 hours prior to administration of tramadol except cats, which had free access to food during the study (Table 1). Human data were acquired from 57 healthy and 56 post-surgery adults. All non-human species were considered to be in the adult stage of their lifespan. Institutional informed consent and ethical approval was obtained for all studies. Specific details can be found in the original publications. All references to tramadol and its M1 metabolite are to the (±) racemic form.

Population parameter estimations

A two-compartment (central and peripheral) linear disposition model with zero-order input and first-order elimination fitted the tramadol concentrations from all species combined together more closely than a single compartment model. M1 disposition was also better described by a two-compartment model, with first-order input from the tramadol central compartment and first-order elimination (Figure 1). The model parameters were clearance of tramadol (parent) to M1 (CLPM), tramadol clearance by other routes (CLPO), tramadol inter-compartmental clearance (QP), tramadol central volume (VP1), tramadol peripheral volume (VP2), clearance of M1 (CLMO), inter-compartmental clearance of M1 (QM) and M1 central volume (VM1) and peripheral volume (VM2).

When M1 is not administered directly, the fraction of tramadol converted to M1 (Fm), and the fraction of tramadol eliminated by other pathways (Fo) are unknown. Two different models with distinct assumptions were used to try to distinguish CLPO from CLPM and to identify CLMO and VM:

1. Complete conversion in all species (Fm = 1): Assumes all tramadol is converted to M1. Estimates of CLMO / Fm and VM1 / Fm are species specific. CLPO is assumed to be zero. While it is obvious that this assumption cannot be true (because unchanged tramadol is known to be excreted and other metabolites have been identified), it does permit local identifiability of some key parameters and provides a good description of the time course of concentration.

2. Metabolite volume is the same as in the dog (VM1 = VM1$_{dog}$): VM1 was estimated in 3 dogs after administration of M1. If the estimate of VM1 / Fm is greater than VM1 estimated in dogs then it may be assumed that VM1 is the same as the dog. If VM1 / Fm is less than VM1 for dogs, then VM1 must be less than the value in dogs but otherwise cannot be identified. The VM1 = VM1$_{dog}$ assumption allows Fm to be identified and CLPO can be distinguished from CLPM [25].

Parameter estimates were obtained using a nonlinear mixed effects approach, which can account for population parameter variability (between and within subjects), residual variability (random effects), and parameter differences predicted by covariates (fixed effects). Parameter estimation was performed using NONMEM version VII level 1.1 with the first-order conditional interaction method. Standard errors of the estimates were obtained by non-parametric bootstrapping [26]. Models were compiled with Intel Visual Fortran version 10.1.029 and executed on an Intel Xeon E5335 Processor with Microsoft Windows 2003 Server Service Pack 2. Model building was based

Table 1: Summary of studies used and analytical methods.

Publication	[8,11,12]	[13]	[9]	[14]	[14]	[15]	[17]	[20]	[21]	[23]	[24]	[22]
Study code	3	5	7	20	21	22	30	40	41	50	60	70
Species	Human	Human	Human	Dog	Dog	Dog	Goat	Horse	Horse	Cat	Rat	Donkey
Number subjects	41	16	56	6	3	6	5	6	6	6	4	12
Dose (mg/kg) of tramadol HCL except M1 (base) for study 21	100 mg bolus then, 50 mg over 30 min	100 mg bolus	3 over 18 min	4.4	1 (M1)	4	2	2	5	2	20	2.5 over 3 min
Duration of sampling (h)	24-30.5	48	3	6	4	24	15	24	8	8	5	24
Average observations/subject (tramadol)	15	13	3	8	-	9	7	16	9	12	8	9
Average observations/subject (M1)	0	13	3	8	8	6	7	14	7	12	8	6
Analytical method	GCMS		LC/MS	HPLC Fluorescence detection [36,37]		HPLC Fluorescence detection [21]	HPLC Ultraviolet detection [17]	LC/MS/MS	HPLC Fluorescence detection [21]	LC/MS/MS [23]	HPLC Fluorescence detection [38]	HPLC Fluorescence detection [22]
Enantiomer				Racemate		Racemate	Racemate	Racemate	Racemate	Racemate	+/- enantiomer	Racemate
LLOQ (tramadol and M1)				No details of assay performance		0.005 mg/L	0.025, 0.010 mg/L	0.001 mg/L	0.005 mg/L	0.001 mg/L	0.0025mg/L	0.005 mg/L
CV%					<4% inter- and intra-day	7% inter- and intra-day				7% intra day	<15%	7% inter-day
Mean weight kg (range)	71.1 (58-98)			9.4 (7.3-12.4)		20 (18-23)	47.8 (40.7-54.4)	402.7 (350-492)	513.5 (479-545)	4.1 (3.8-4.4)	0.251 (0.230-0.295)	343.5 (300-380)

Abbreviations: M1: (±)-*O*-desmethyl-tramadol; **HCL:** hydrochloride; **LLOQ:** lower limit of quantitation; **CV:** coefficient of variation; **HPLC:** high performance liquid chromatography; **GCMS:** gas chromatography mass spectrometry; **LC/MS/MS:** HPLC-coupled tandem mass spectrometry

on NONMEM's objective function and by a visual predictive check [27] with prediction correction [28]. Models were nested and an improvement in the objective function was referred to the chi-squared distribution to assess statistical significance, e.g. an objective function change of 3.84 is significant with Type I error of 0.05 with one additional parameter in the model.

Reported tramadol hydrochloride doses were converted to base tramadol, where 1 mg tramadol hydrochloride is equal to 0.8784 mg of tramadol.

M1 concentrations were converted to tramadol milligram equivalents for a simultaneous parent and metabolite fit using a molecular weight of 249.38 mg mmol^{-1} for M1 and 263.38 mg mmol^{-1} for tramadol (molar ratio 0.947). M1 measurements from dog study 20 were excluded from analysis because of contamination with other tramadol metabolites. All other assays are believed to have been selective for M1. Stereoselective concentration measurements were converted to racemic concentrations by summation of stereoisomer concentrations.

Covariate analysis

Fractional differences relative to adult humans were estimated for each population parameter.

Clearance and volume parameters for tramadol and M1 in all species were standardized to a body weight of 70 kg using an allometric model [29] (Equation 1)

$$Fsize = \left(\frac{Wi}{W_{STD}} \right)^{PWR} \tag{1}$$

where W_i is the weight in the ith individual. Allometric scaling with a PWR exponent of ¾ for clearance and 1 for volume of distribution was employed due to its strong theoretical and empirical basis [30]. Fsize is the allometrically scaled fraction of the standard weight, W_{STD}.

A mixture model was used to distinguish slow from extensive metabolizers of tramadol on the basis of their phenotype. This method estimates the fraction of all subjects (human and non-human) who appear to be in a slow metabolizer subgroup and the value of CLPM relative to CLPM in extensive metabolizers.

Group parameters were based on fixed effects for clearance using species and size. Equation 2 illustrates how a group value of CLPM$_{GRP}$ is calculated from a standard value of CLPM$_{STD}$ (adult human 70 kg).
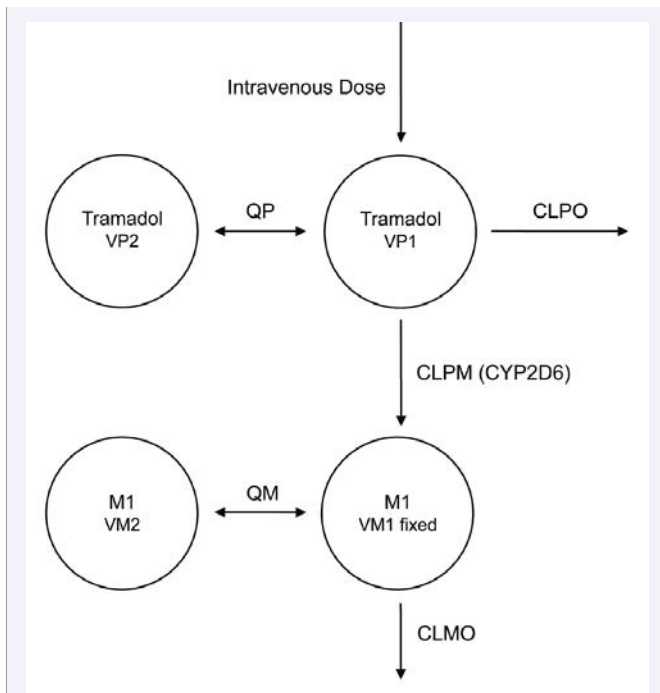
Figure 1 Schematic representation of the pharmacokinetic model for tramadol and its M1 metabolite. A two-compartment linear disposition model describes the parent drug with inter-compartmental clearance (QP). Total clearance of tramadol is the sum of CLPM (clearance to M1) and CLPO (clearance by other routes). An additional two compartments for the metabolite M1 are linked to the tramadol central compartment by M1 formation (CLPM). QM is the inter-compartmental clearance of M1. CLMO is the clearance of M1.

$$CLPM_{GRP} = CLPM_{STD} \bullet Fspecies \bullet Fsize \qquad (2)$$

Individual parameter estimates (e.g.. $CLPM_i$) were predicted from the group estimate and the variance of η_i, the random between subject differences in the parameter, using an exponential model (Equation 3):

$$CLPM_i = CLPM_{GRP} \bullet \exp(\eta_i) \qquad (3)$$

Residual unidentified variability was described using a combined proportional and additive residual error model for each observation prediction with random differences, ε_{PROP}, ε_{ADD}. Between-subject differences in residual error were separately identified for tramadol and M1. The variance of the residual unidentified variability, $\eta_{RUV,i}$, was estimated [31]. This is illustrated for a concentration observation prediction, C, in Equation 4.

$$Y = C \bullet (1 + \varepsilon_{PROP}) + \varepsilon_{ADD} \bullet \exp(\eta_{RUV,i}) \qquad (4)$$

RESULTS AND DISCUSSION

The first assumption that was tested (Fm = 1) assumed complete conversion of tramadol to M1. All estimates of VM1 / Fm were larger than the VM1 estimated in dogs except in cats (74%) and donkeys (72% of dog VM1). The estimate of VM1 / Fm is always an upper bound on the value for VM1 because Fm must be <=1. This means that the VM1 in cats and donkeys must

indeed be smaller than the dog, but in other species the finding of a larger VM1 / Fm could be explained by an additional pathway for tramadol elimination (CLPO) other than formation of M1. In cats either the true VM1 is less than that of dogs, or CLPO is zero.

A second assumption (VM1 = VM1$_{dog}$) was then tested by assuming VM1 in all species was equal to the dog (except the cat and donkey), which allowed estimation of CLPO. The Fm = 1 assumption was kept for the cat and donkey and VM1 / Fm was estimated separately with CLPO fixed to zero. The VM1 = VM1$_{dog}$ objective function (17343.5) was similar to the Fm = 1 model (17350.8), which confirms the inter-changeability of the Fm = 1 with VM1 = VM1$_{dog}$ assumptions. A major improvement in the objective function (17305.7) was obtained by allowing total tramadol clearance in dog Studies 20 and 21 to be different (4.74 times bigger; 14% bootstrap relative standard error (RSE)) compared to dog Study 22. Removing the mixture model to distinguish two distributions of CLPM from the final model worsened the objective function from 17305.7 to 17319.8. This is a significant (p=0.00085) change for the removal of 2 parameters and provides strong support for the existence of a subgroup of slow metabolizers relative to the rest of the population. The parameter estimates for this model including 2 distributions for clearance and different total tramadol clearance for 2 of the dog studies are shown in Tables 2 to 4.

The visual predictive check plots for tramadol (Figure 2) and M1 (Figure 3) show good agreement between the predicted and observed median and 90% intervals. Parameter estimates for the VM1 = VM1$_{dog}$ model are shown in Tables 2, 3 and 4. The mixture

Table 2: Human parameter estimates and population parameter variability across all species.

Parameter	Description	Value (RSE)	Units	PPV
CLPM$_{extensive}$	Clearance of tramadol to M1	10.5 (13%)	L/h/70 kg	0.525
CLPM$_{slow}$	CLPM in slow metabolizers	1.70 (27%)	L/h/70 kg	0.059
CLPO	Clearance of tramadol by other pathways	18.4 (9%)	L/h/70 kg	0.762
QP	Inter-compartmental clearance of tramadol	105 (29%)	L/h/70 kg	0.647
VP1	Central volume of tramadol	90 (16%)	L/70 kg	0.549
VP2	Peripheral volume of tramadol	79 (17%)	L/70 kg	0.633
CLMO	Clearance of M1	84.2 (10%)	L/h/70 kg	0.154
QM	Inter-compartmental clearance of M1	274 (112%)	L/h/70 kg	1.65
VM1	Central volume of M1[a]	78.9	L/70 kg	0.401
VM2	Peripheral volume of M1	131 (24%)	L/70 kg	0.412

Model assumed VM1 was the same as in dogs.

[a]Fixed to value estimated in dogs administered M1 intravenously.

Abbreviations: **PPV:** Population Parameter Variability (sqrt (NONMEM OMEGA estimate)); **RSE:** Relative standard error (bootstrap standard error / estimate x 100); **M1:** (±)-*O*-desmethyl-tr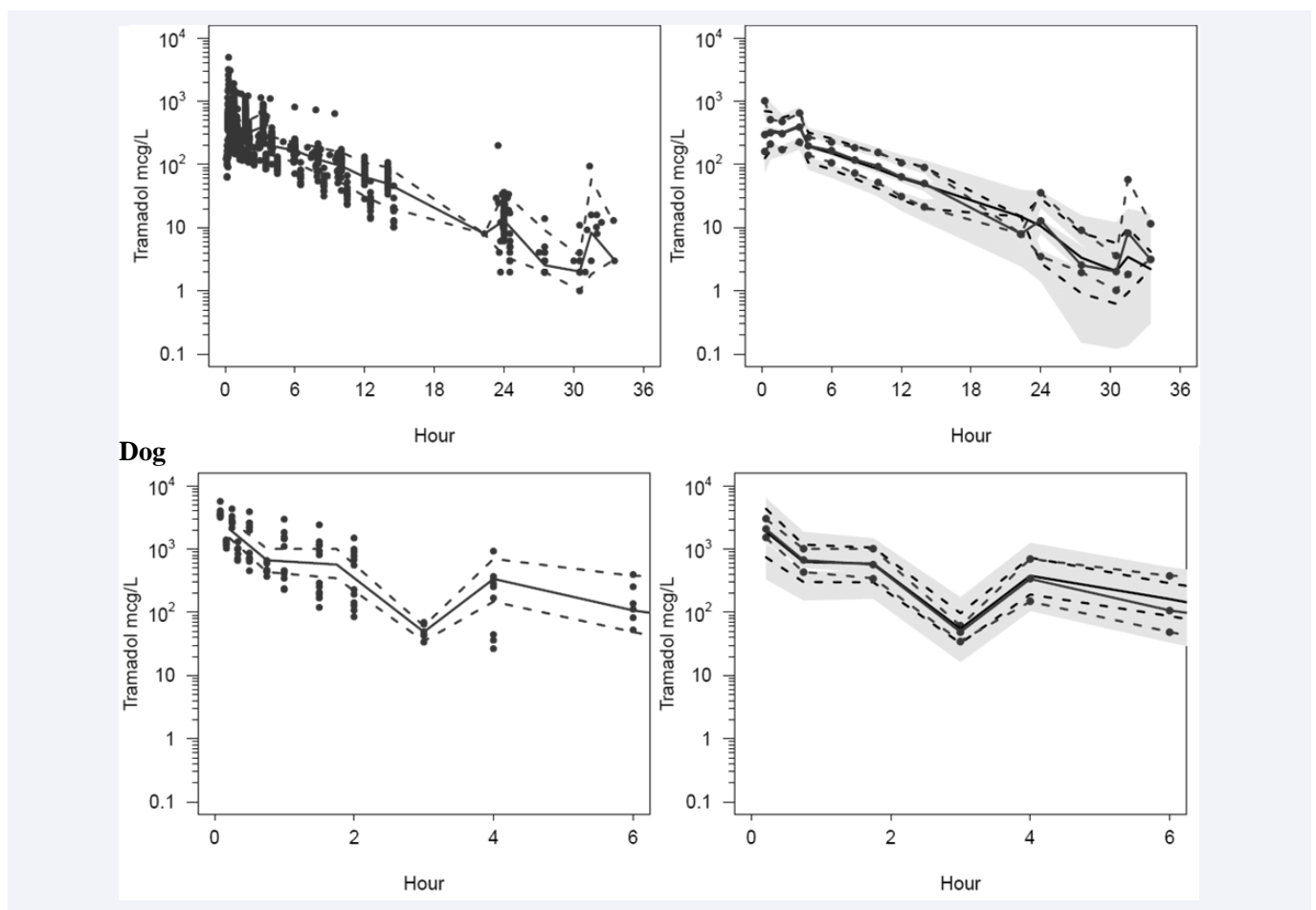amadol; **CLPM:** clearance to M1; **CLPO:** tramadol clearance by other routes; **QP:** inter-compartmental clearance; **CLMO:** clearance of M1; **VP1:** central volume; **VP2:** peripheral volume; **QM:** M1 inter-compartmental clearance; **VM1:** central volume; **VM2:** peripheral volume

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Table 3: Correlation of population parameter variability.

	CLPM$_{extensive}$	CLPO	VP1	QP	VP2
CLPM$_{extensive}$	1				
CLPO	-0.021	1			
VP1	-0.477	0.863	1		
QP	0.754	0.264	-0.04	1	
VP2	0.888	-0.094	-0.485	0.854	1
	CLMO	**VM1**		**QM**	**VM2**
CLMO	1		QM	1	
VM1	0.886	1	VM2	-0.609	1

Model assumed VM1 was the same as in dogs.

Abbreviations: **CLPM:** clearance to M1; **CLPO:** tramadol clearance by other routes; **QP:** inter-compartmental clearance; **CLMO:** clearance of M1; **VP1:** central volume; **VP2:** peripheral volume; **QM:** M1 inter-compartmental clearance; **VM1:** central volume; **VM2:** peripheral volume
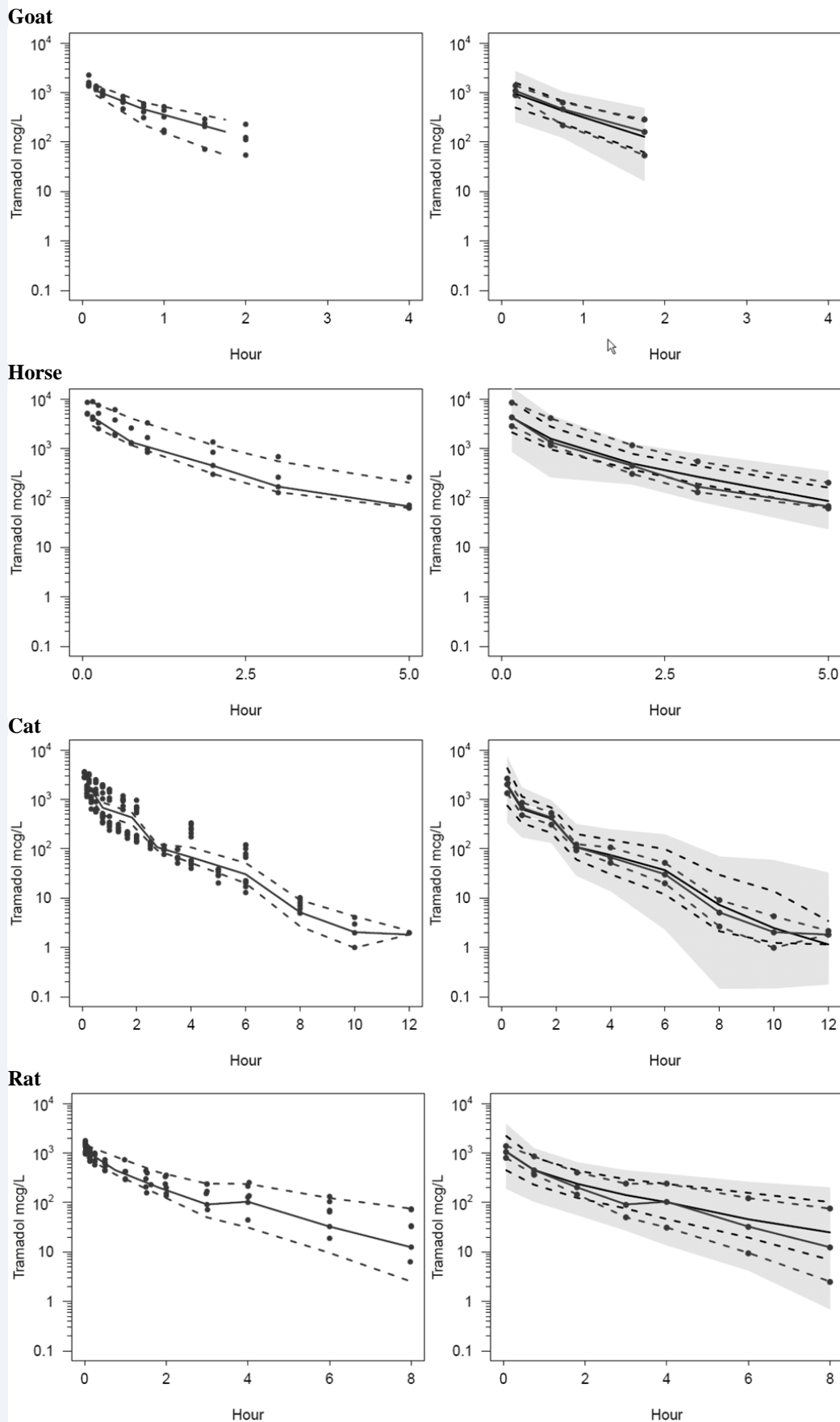
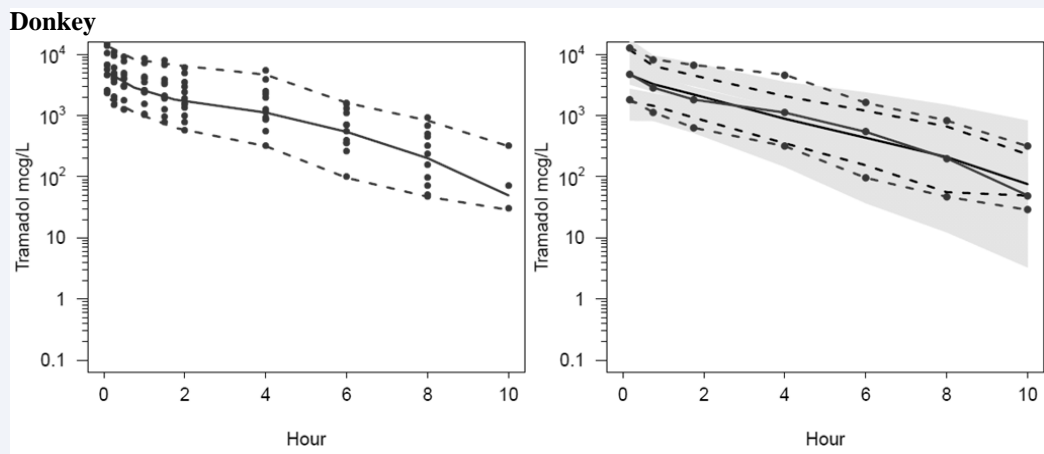**Table 4:** Residual unidentified variability (RUV) and population parameter variability.

Parameter	Description	Value	Units	PPV
CVCP	Proportional error tramadol	0.123	-	0.391
SDCP	Additive error tramadol	0.901	mcg/L	
CVCM	Proportional error M1	0.223	-	0.370
SDCM	Additive error M1	0.580	mcg/L	

Model assumed VM1 was the same as in dogs. CVCP and CVCM are fractional coefficients of variation. Correlation of PPV RUV tramadol with PPV RUV M1 = -0.221.
Abbreviations: **PPV:** Population Parameter Variability; **M1:** (±)-*O*-desmethyl-tramadol

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Goat

Horse
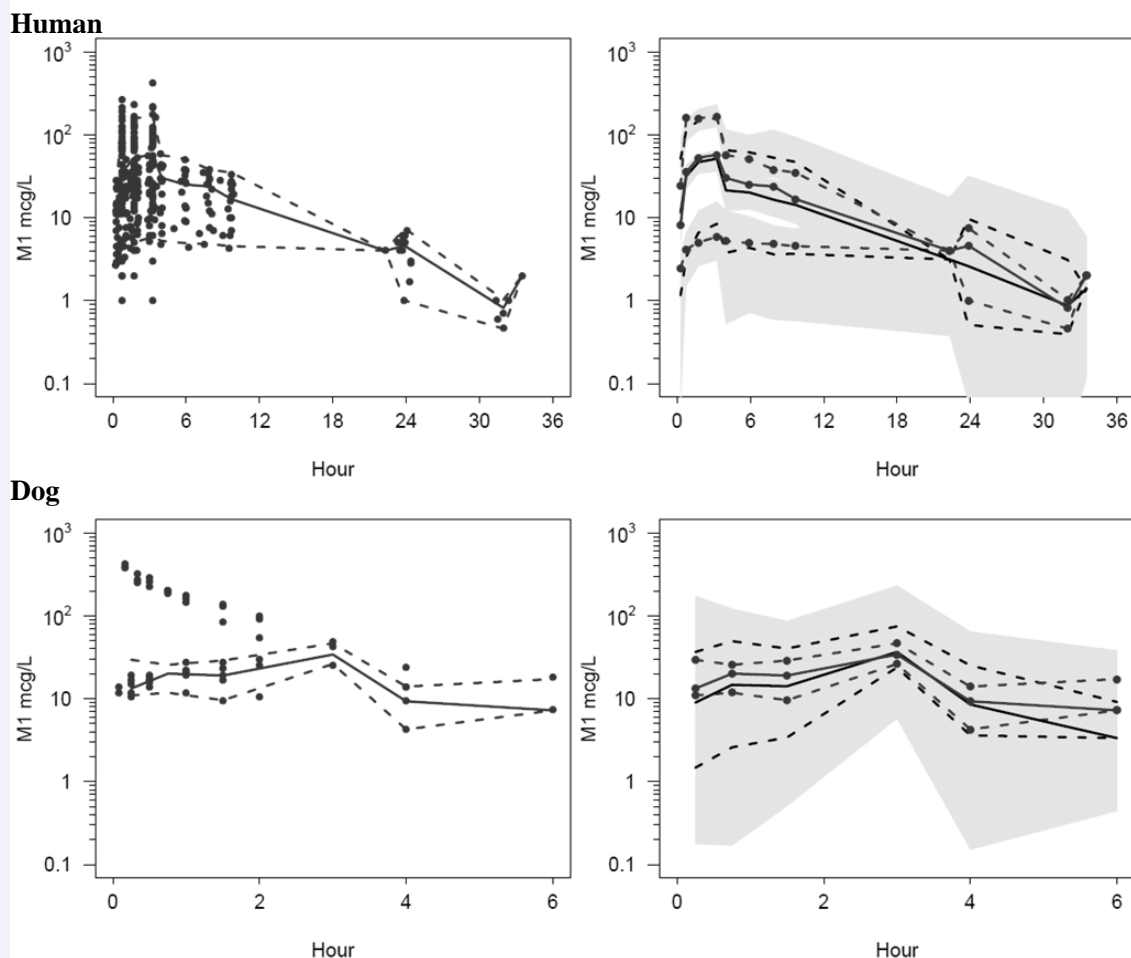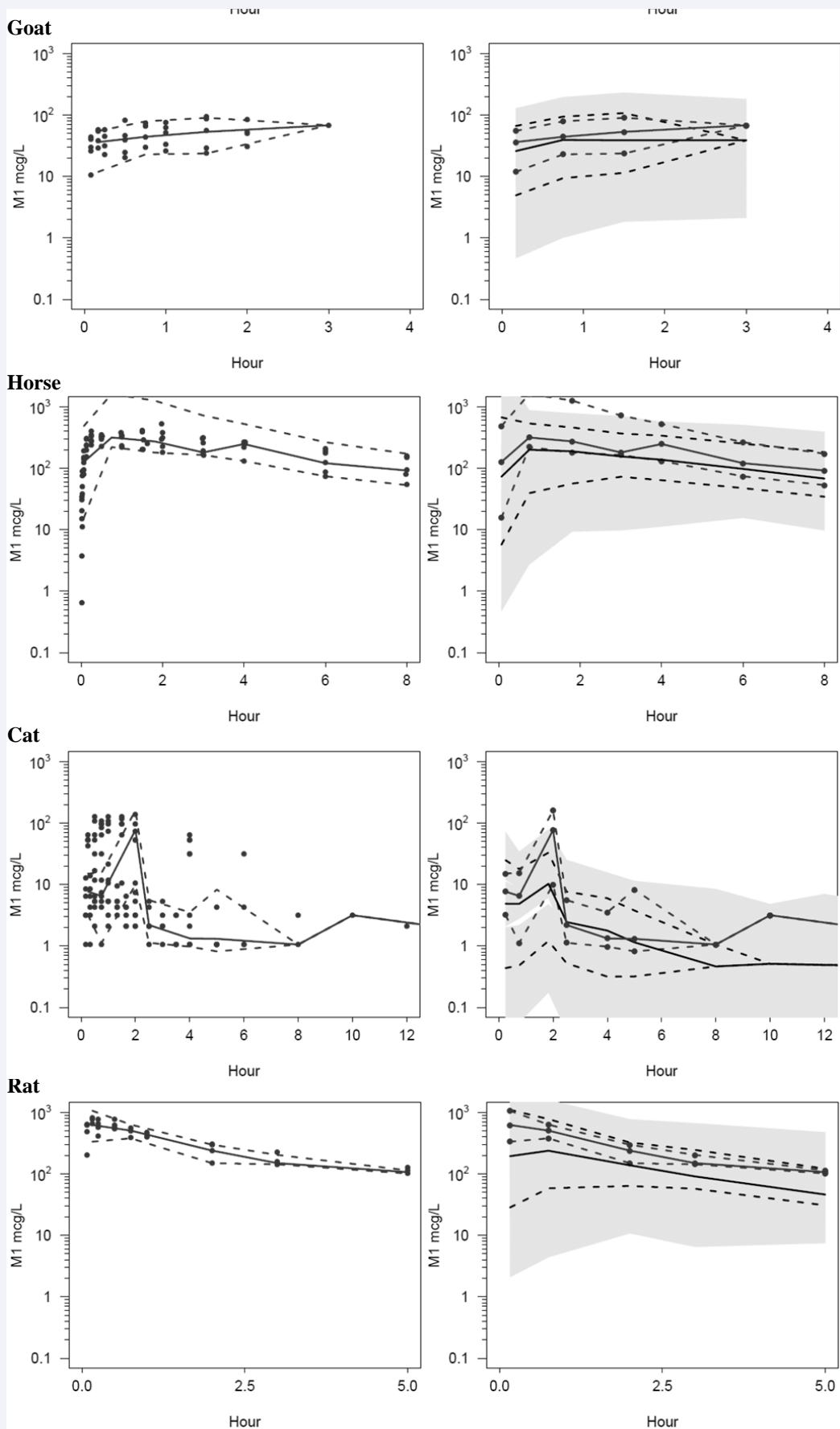

Cat

Rat

Donkey

Figure 2 Visual predictive check for tramadol. Vm1 = VM1$_{dog}$ model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all observed concentrations. Right hand plot shows prediction corrected percentiles (10, 50, 90) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas).

model for identification of M1 metabolizer type estimated that 6.0% (49% bootstrap RSE) of the overall population (human and non-human) were slow metabolizers and that these individuals have 16.2% (24% bootstrap RSE) of the CLPM of extensive
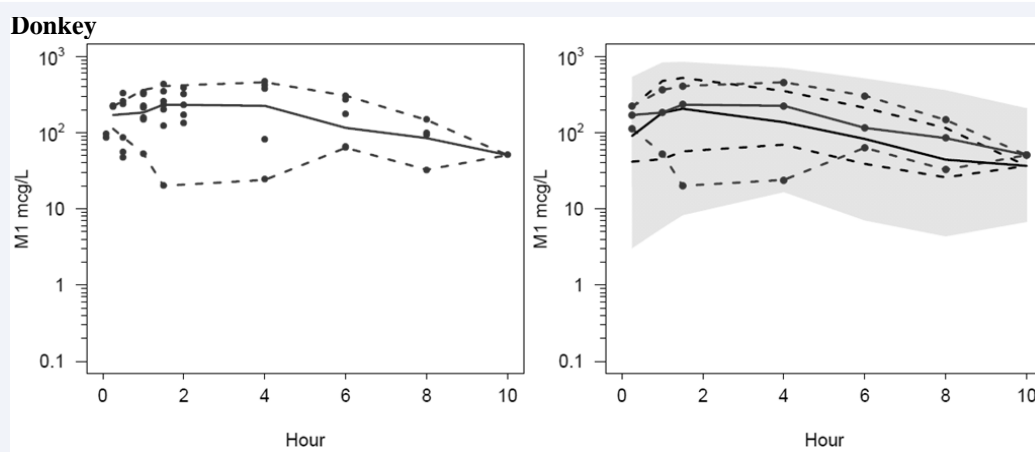
metabolizers. All slow metabolizers were human except for 1 horse in study 41.

A fundamental assumption of the modelling of inter-species differences was the appropriateness of the theoretical allometric

Human

Dog

Goat

Horse

Cat

Rat

Figure 3 Visual predictive check for the M1 metabolite of tramadol. Vm1=VM1dog model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all observed concentrations. Right hand plot shows prediction corrected percentiles (10, 50, 90) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas). All horse M1 concentrations after 8 hours are from the same subject ID = 40002 [20].

coefficients of ¾ for clearance and 1 for volume parameters. Although a very wide range of weights were included when considering all species, the use of species-specific parameters means that weight differences are only reflected within each species. The within-species range of weights was relatively small and thus testing if the allometric exponents were different from theoretical values could not be performed with any confidence [29].

After using allometry to account for differences in size, there remain large between-species differences in tramadol and M1 pharmacokinetic parameters. These must be attributed to other factors such as genotype, diet and environment, which are not related to size. Although protein binding changes with pH and carnivorous species tend to have a blood pH lower than that of herbivorous species, tramadol is only 20% protein bound in humans [7] and 15% in dogs [32] so plasma protein binding is

not expected to explain the large differences observed.

By assuming the volume of distribution of M1 in the dog is the same as that in other species (except the cat and donkey) it was possible to identify and quantify the clearance of tramadol by other pathways. The mixture model estimate of 6.0% slow metabolizers based on the distribution of CLPM agrees with the fraction of slow CYP2D6 genotypes reported in the literature for humans [33]. Our estimate of the relative clearance of tramadol to its M1 metabolite of 16.2% in slow metabolizers is the only estimate we are aware of because of the impracticality of directly determining this fraction in humans.

The total clearance of tramadol and its elimination by conversion to M1 show marked differences between species (Table 5, Figure 4, Figure 5). The dog is outstanding in having much lower clearance to M1 in Study 22 (CLPM). We have shown that the assumption that the volume of distribution of M1 is

**Table 5:** Comparison of pharmacokinetic parameters across species.

Parameter	Rat	Cat	Dog study 20, 21	Dog study 22	Goat	Donkey	Horse study 40	Horse study 41
$CLPM_{extensive}$	0.658 (35%)	3.5 (19%)	0.517^a	0.109 (37%)	1.13 (33%)	1.71 (31%)	0.39 (33%)	0.718 (31%)
CLPO	2.79 (27%)	0	7.39^a	1.56 (24%)	4.72 (25%)	0	7.89 (12%)	5.99 (13%)
QP	0.193 (66%)	0.62 (19%)	0.306 (55%)	0.156 (224%)	2.94 (70%)	1.73 (61%)	1.33 (34%)	0.605 (35%)
VP1	2.12 (35%)	1.03 (24%)	2.02 (26%)	0.771 (79%)	0.243 (59%)	0.0405 (111%)	0.669 (25%)	0.983 (27%)
VP2	1.37 (35%)	1.12 (12%)	0.696 (153%)	0.146 (83%)	0.579 (28%)	0.344 (26%)	0.937 (15%)	0.397 (20%)
CLMO	0.394 (45%)	0.389 (29%)	1.13^b	0.827 (40%)	0.448 (86%)	1.86 (35%)	3.95 (31%)	0.691 (41%)
QM	0.104 (38%)	0.157 (29%)	2.27^b	0.287 (86%)	2.23 (189%)	12.1 (31%)	2.04 (67%)	0.216 (31%)
VM1	1	0.742 (27%)	1^b	1	1	0.719 (31%)	1	1
VM2	1	0.742	1	1	1	0.719	1	1

Values are fractional differences relative to human. Relative standard error (bootstrap standard error/estimate x 100) is shown in parentheses. VM1 and VM2 were assumed to be the same in all species except the donkey which had an estimate of VM1 / Fm and VM2 / Fm that was 0.719 × and the cat 0.742 × the value of VM1 in the dog (Study 21).

[a]$CLPM_{extensive}$ and CLPO for dog study 20, 21 calculated from dog study 22 times 4.74 (ratio of total parent metabolite clearance in dog study 20, 21 to dog study 22).

[b]Estimated from dog study 21 only

Abbreviations: **CLPM:** clearance to M1; **CLPO:** tramadol clearance by other routes; **QP:** inter-compartmental clearance; **CLMO:** clearance of M1; **VP1:** central volume; **VP2:** peripheral volume; **QM:** M1 inter-compartmental clearance; **VM1:** central volume; **VM2:** peripheral volume

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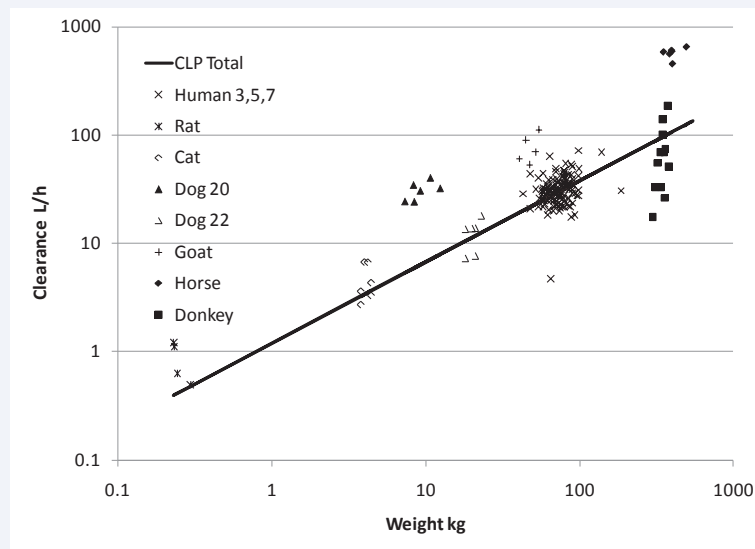
Figure 4 Weight-predicted (VM1 = VM1$_{dog}$ model) tramadol total clearance (CLPM + CLPO) compared to human allometric prediction (solid line). Numbers for each symbol refer to studies listed in Table 1.
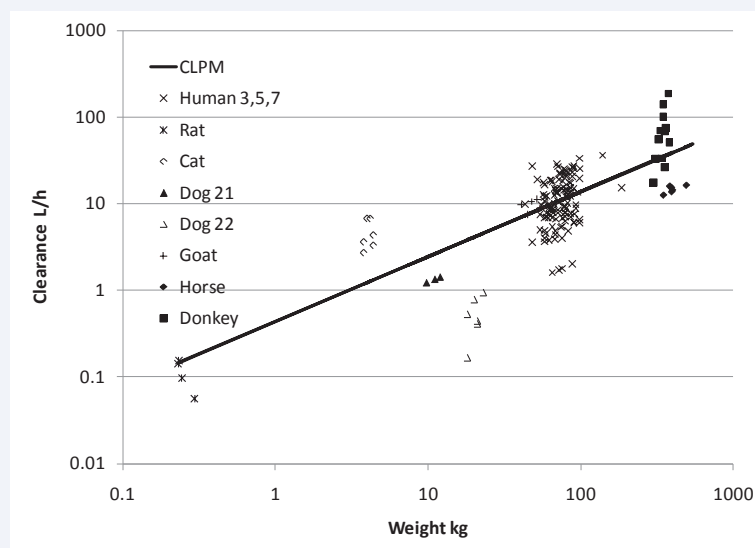
Figure 5 Individual predicted (VM1 = VM1$_{dog}$ model) tramadol clearance to M1 (CLPM) compared to human allometric prediction (solid line). Numbers for each symbol refer to studies listed in Table 1.

similar in all species cannot be true for the cat and the donkey. There are also large within-species differences in volumes of distribution of tramadol that raise further doubts about the assumption that the volume of distribution of M1 is the same in all species.

Two major limitations are recognized in this attempt to describe the pharmacokinetics of tramadol and M1. The first is the necessary assumption that the volume of distribution of M1 is the same in dogs and other species (except the cat and donkey). Unless M1 is administered directly, it is not possible to determine the volume of distribution of M1, though an estimate may be obtained under special conditions [34]. Without knowing (or assuming) this volume, it is impossible to determine the fraction of tramadol that is converted to M1 by a first-order process by

only measuring M1 concentrations. The second limitation is the use of racemic concentrations of tramadol and M1, which obscures the different pharmacokinetics of the stereoisomers. This remains a challenge for future studies in those species where only the racemate has been studied.

It is difficult to determine if tramadol has pain-relieving activity in non-human species. Human subjects with the CYP2D6 genotype associated with reduced formation of M1, have worse analgesia [9]. Furthermore, the M1 metabolite is 6 times more potent than tramadol in non-human models of analgesia [35]. If M1 is the main determinant of pain relief, then typical dose rates can be used with species-specific values for CLPM, CLPO and CLMO to predict the M1 average concentration. Comparison of the M1 concentration with those known to be effective in humans

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Table 6: Prediction of M1 average steady state concentration relative to human at typical dose rates of tramadol hydrochloride.

Species	Reference for Analgesic Dose	Dose (mg/kg)	Dose Interval (h)	Weight (kg)	Relative to Human M1 (84 mcg/L)
Human	[39]*	2	6	70	100%
Rat	[40]	5	6	0.5	60%
Cat	[41]	4	6	4	692%
Dog	[42]	10	6	15	43.4%
Goat	None	2	6	50	68%
Donkey	None	2	6	350	221%
Horse study 40	[43]**	2	6	450	0.8%
Horse study 41		2	6	500	10%

Tramadol average concentration = Dose Rate / (CLPM + CLPO)

Rate of conversion to M1 = Tramadol average concentration × CLPM

M1 average concentration = (Rate of conversion to M1) / CLMO

CLPO and CLMO in cats and donkeys are CLPO / Fm and CLMO / Fm.

*=1 mg/kg/6h produced minimum effective M1 analgesic concentrations in patients with post-operative pain around 50% of those predicted from 2 mg/kg/6h (84 mcg/L)

**=2mg/kg intravenous single dose to horses did not produce analgesia

can be used to see if dosing rates used in non-human species are likely to be effective. Table 6 shows the predicted M1 average steady state concentrations relative to humans. It seems unlikely that effective pain relief would be achieved in dogs or horses with typically used doses.

CONCLUSION

There are substantial differences between species in the pharmacokinetics of tramadol and its primary metabolite, which are not explained by differences in body weight. The hypothesis that volumes of distribution are similar across species was shown not to be true. M1 exposure in the goat, donkey and cat was comparable to humans, which indicates it is likely to be an effective analgesic at typically used doses in these species but not in dogs or horses.

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