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Pharmacokinetics of tramadol following intravenous and oral administration in male rhesus macaques (*Macaca mulatta*)

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Abstract

Recently, tramadol and its active metabolite, O-desmethyltramadol (M1), have been studied as analgesic agents in various traditional veterinary species (*e.g.* dogs, cats, etc.). This study explores the pharmacokinetics of tramadol and M1 after intravenous (IV) and oral (PO) administration in rhesus macaques (*Macaca mulatta*), a nontraditional veterinary species. Rhesus macaques are Old World monkeys that are commonly used in biomedical research. Effects of tramadol administration to monkeys are unknown, and research veterinarians may avoid inclusion of this drug into pain management programs due to this limited knowledge. Four healthy, socially-housed, adult male rhesus macaques (*Macaca mulatta*) were used in this study. Blood samples were collected prior to, and up to 10 h post tramadol administration. Serum tramadol and M1 were analyzed using liquid chromatography-mass spectrometry. Noncompartmental pharmacokinetic analysis was performed. Tramadol clearance was 24.5 (23.4-32.7) mL/min/kg. Terminal half-life of tramadol was 111 (106-127) min IV and 133 (84.9-198) min PO. Bioavailability of tramadol was poor [3.47% (2.14-5.96%)]. Maximum serum concentration of M1 was 2.28 (1.88-2.73) ng/mL IV and 11.2 (9.37-14.9) ng/mL PO. Sedation and pruritus were observed after IV administration (*180 words*).

Keywords

pharmacokinetics; tramadol; macaque; analgesia; opioid

Introduction

Tramadol is a synthetic, centrally-acting opioid agonist that also acts as a serotonin and norepinephrine reuptake inhibitor (Hennies et al., 1982; Hennies et al., 1988; Johnson et al., 1989; Grond & Sablotzki, 2004). The Drug Enforcement Administration recently classified

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tramadol as a schedule IV drug. Tramadol is available for injection or oral administration in many countries; however, tramadol is only available for oral administration in the United States. Tramadol has a low potential for addiction and abuse; and as such, is often used in the local veterinary clinic as the only on-shelf oral narcotic-like pain medication without significant concern for staff-based and/or client-based misuse (Raffa et al., 1993; Hummel et al., 1994; Scott & Perry, 2000; Grond & Sablotzki, 2004; Pypendop & Ilkiw, 2008).

Tramadol's complex mechanism of action has been partially attributed to its many different chiral isomers, and over 26 metabolites have been characterized to date. O-desmethyltramadol (M1) is the only metabolite that has been described to have analgesic effects in humans (Raffa et al., 1993; Poulsen et al., 1996; Wu et al., 2002; Grond & Sablotzki, 2004; Enggaard et al., 2006). Analgesic efficacy is dependent on a complex set of interactions between opioid, adrenergic, and serotonin receptor mechanisms (Hennies et al., 1988; Raffa et al., 1992; Poulsen et al., 1996; Grond & Sablotzki, 2004). Hepatic metabolism results in demethylation of tramadol to produce a multitude of metabolites including O-desmethyltramadol. This metabolite, M1, has over 200 times the affinity of tramadol for opioid receptors (Hennies et al., 1988; Poulsen et al., 1996); and as such, has been studied extensively in both humans and animals for its analgesic potential (Lehmann et al., 1990; Grond et al., 1999; Grond & Sablotzki, 2004). In humans, the biotransformation of tramadol to M1 is mediated by CYP2D6 (Wu et al., 2002). Multiple isoforms of the CYP2D6 enzyme exist in humans and M1 metabolism is impacted by individual phenotypic differences (*e.g.* CYP ultrametabolizers vs. CYP poor metabolizers) (Poulsen et al., 1996; Kirchheiner et al., 2008). Macaques are well documented to have marked similarities in CYP2D6 metabolism to humans (Uno et al., 2010; Uno et al., 2011), and we hypothesized that macaques should be able to metabolize tramadol similarly to humans. Poor metabolism of tramadol to M1 is presumed to result in reduced analgesic efficacy of tramadol both in humans and in other animal species (Wu et al., 2002; Cox et al., 2010).

Analgesic efficacy of tramadol in mild to moderate pain has been well described in humans (Grond et al., 1995). In humans, minimum effective plasma concentrations of tramadol have been found to range from 298 (127-469) ng/mL (Lehmann et al., 1990) to 590 (180-1000) ng/mL (Grond et al., 1999), and minimum effective plasma concentrations of M1 have been found to range from 39.6 (10.1-69.1) ng/mL (Lehmann et al., 1990) to 84 (50-134) ng/mL (Grond et al., 1999). Analgesic efficacy of tramadol in veterinary species continues to be explored; and the antinociceptive potential of tramadol has been reported in rats, mice, dogs, cats, and humans (Raffa et al., 1992; Hummel et al., 1994; Hummel et al., 1996; Affaitati et al., 2002; Guneli et al., 2007; Pypendop et al., 2009; Tsukahara-Ohsumi et al., 2010; Kukanich & Papich, 2011; Lopopolo et al., 2013).

Pharmacokinetic profiles of tramadol have been characterized in humans (Garcia Quetglas et al., 2007; Xia et al., 2012) as well as in multiple veterinary species including dogs (Kukanich & Papich, 2004; Kukanich & Papich, 2011), cats (Pypendop & Ilkiw, 2008), horses (Guedes et al., 2013; Knych et al., 2013; Knych et al., 2013), camelids (Cox et al., 2011; Edmondson et al., 2012), rabbits (Souza et al., 2008), and exotic fowl (Souza et al., 2009; Black et al., 2010; Souza et al., 2011; Sanchez-Migallon Guzman et al., 2012); however, to the authors' knowledge, the clinical use of tramadol has not been reported in any

species of nonhuman primate (*e.g.* Old World monkeys, New World Monkeys, or Greater Apes).

Rhesus macaques (*Macaca mulatta*) are an Old World species of nonhuman primate originating from India and Asia. These monkeys are one of the more common species of nonhuman primates that veterinarians provide supportive care to worldwide. They have very similar anatomy and physiology to humans and have become a common biomedical model to study various human diseases (*e.g.* human immunodeficiency virus) (Schmitz & Korioth-Schmitz, 2013). As such, tramadol, which is well tolerated and effective in humans, may be expected to be equally tolerated and effective in rhesus macaques. The purpose of this study was to explore the pharmacokinetics of oral tramadol administration as compared to intravenous tramadol administration in rhesus macaques in order to provide basic knowledge needed to potentially later explore analgesic efficacy of tramadol and its active metabolite M1 in this nontraditional veterinary species. Until efficacy trials can be performed in rhesus macaques, we elected to apply human minimum effective concentrations of tramadol (*i.e.* ≥ 298 ng/mL) and M1 (*i.e.* ≥ 39.6 ng/mL) as benchmark targets that could assist in analyzing the analgesic potential of tramadol in this monkey species (Lehmann et al., 1990).

Materials and Methods

Animals

Four, healthy, adult, intact male rhesus macaques (*Macaca mulatta*) of Indian origin were used in this study [10±2 y (mean±SD); 17±2 kg (mean±SD); 3.5/5.0 (2.5-4.0/5.0) body condition score (median (range))]. Macaques were captive-born, socially-reared, socially-housed, and free of any drug administration for over 30 days prior to enrollment in this study. Positive-reinforcement training was used to condition macaques to all restraint techniques used in this study (Bliss-Moreau et al., 2013). Macaques were fasted for 10 h prior to start of each study. Water was available *ad libitum* throughout the studies. The studies were approved by the Institutional Animal Care and Use Committee of the University of California, Davis. Monkeys were housed in species-specific indoor cages in an Association for Assessment and Accreditation of Laboratory Animal Care International-accredited facility.

Dose Selection

The veterinary literature was reviewed and a dosing range of 1-4 mg/kg was found to be a consistent recommendation, regardless of species (Plumb, 2011). We selected a mid-to-high-range dose of 3.00 (2.56-3.41) mg/kg as the test dose for our studies, taking into account the weights of our subjects (17±2 kg, mean±SD) so that the dose was administered as a commercially available 50 mg tablet. This allowed us to mimic a clinically-relevant dosing option easily available to the research and/or zoo medicine clinician(s). Since tramadol administration has never been documented in monkeys, we were asked by on-site research veterinarians to decrease our dose for the IV study due to heightened safety concerns for the monkeys. The final IV dose selected was 1.50 mg/kg.

IV Study

On day of experimentation, conscious macaques willingly entered restraint chairs. An IV bolus of 1.50 mg/kg tramadol API (tramadol hydrochloride, Grünenthal Pharmaceuticals, ProtoChemicals, Mitlodi, Switzerland) was administered into the right cephalic vein of each monkey with a 23 gauge needle attached to a 3 mL syringe. *Oral Oral Study*

After 26 days of rest, conscious macaques again willingly entered restraint chairs. A 2-in piece of banana hiding a 50 mg tablet of tramadol HCl (tramadol hydrochloride, Amneal Pharmaceuticals of NY, Hauppage, NY) was offered to each monkey in attempts to voluntarily administer the 3.00 mg/kg median dose of tramadol (oral dosing range: 2.56-3.41 mg/kg). Two animals refused to completely swallow the test compound. Further testing was temporarily aborted in these 2 monkeys. Fourteen days later, the test compound was administered to these 2 monkeys *per os*.

In both studies, serial blood samples (1 mL/sample) were collected with 3 mL syringes and 23 gauge needles by venipuncture of the left cephalic vein. Blood samples were collected prior to tramadol administration and 2, 5, 10, 15, 23, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10 h after drug administration. Monkeys were returned to their home cages after 30 min, and all subsequent blood samples were collected after voluntary cage-side arm presentation by each monkey.

Adverse Effect Observations

Macaques were continuously observed for adverse effects for 2 h following initial drug administration. Macaques were then observed for adverse effects during 5-10 min at 3, 4, 6, 8, 10, 24, 48, 72 h after initial drug administration. Experienced monkey caretakers watched for nonspecific signs of sedation, injection-site pruritus, whole-body pruritus, depression, vomiting, diarrhea, constipation, anorexia/poor appetite, and iatrogenic phlebotomy trauma (*e.g.* bruising or hematoma).

Drug Analysis

Following collection, blood was held at room temperature for greater than 20 min to ensure complete clot formation. Serum was separated by centrifugation at 10°C and 1462×g (Allegra 6R Centrifuge, Beckman Coulter, Brea, CA) and was stored at -70°C until analysis for tramadol and M1 concentrations. Tramadol and M1 concentrations were determined by liquid-chromatography-mass spectrometry, using a previously described method (Knych et al., 2013). A partial validation was performed using a rhesus macaque serum matrix. The response for tramadol and M1 was linear and gave correlation coefficients (R^2) of 0.99 or better. The accuracy and precision of the assay were determined by assaying quality control samples in replicates (n=6) for tramadol and M1. The accuracy for tramadol (% nominal concentration) was 112, 110, and 105% at 0.30, 35.0, and 160.0 ng/mL, respectively. The precision for tramadol (% relative standard deviation) was 20.0, 6.0, and 3.0% at 0.30, 35.0, and 160.0 ng/mL, respectively. The accuracy for M1 was 106.0, 98.0, and 100.0% at 0.30, 35.0, and 160.0 ng/mL, respectively. The precision for M1 was 11.0, 12.0, and 5.0% at 0.30, 35.0, and 160.0 ng/mL, respectively. The assay was optimized to provide a limit of quantitation (LOQ) of 0.10 ng/mL for both tramadol and M1.

Pharmacokinetic Analysis

Nonlinear least square regression was performed on the time vs. serum tramadol concentration data using commercially-available software (WinNonlin 6.1, Pharsight, Cary, NC, USA). Changes in serum concentrations of tramadol and M1 over time were evaluated with noncompartmental analyses. Standard pharmacokinetic equations were used to calculate pharmacokinetic parameters (Gibaldi & Perrier, 1982; Gabrielsson & Weiner, 1997). Only those values above the LOQ were considered in the analyses. All parameters are reported as median (range).

Results

Pharmacokinetics of Tramadol after IV Administration of Tramadol

Tramadol concentrations were higher than the LOQ for the duration of the IV study. Changes in serum tramadol concentration over time are presented in Figure 1. Pharmacokinetic parameters for tramadol after 1.50 mg/kg IV administration are summarized in Table 1.

Pharmacokinetics of Tramadol after Oral Administration of Tramadol

The median dose of tramadol administered orally to rhesus macaques was 3.00 mg/kg with a range of 2.56-3.41 mg/kg. Tramadol concentrations were higher than the LOQ from 12.5 (2-45) min to 10 h. Changes in serum tramadol concentration over time are presented in Figure 1. Pharmacokinetic parameters for tramadol after 3.00 mg/kg PO administration are summarized in Table 2.

Pharmacokinetics of M1 after IV Administration of Tramadol

M1 concentrations were greater than the LOQ from 2 min to 10 h. Changes in serum M1 concentration over time are presented in Figure 2. Pharmacokinetic parameters for O-desmethyltramadol, the active metabolite of tramadol, after IV administration of 1.50 mg/kg tramadol are summarized in Table 3.

Pharmacokinetics of M1 after PO Administration of Tramadol

M1 concentrations were greater than the LOQ from 19 (10-90) to 10h. Changes in serum M1 concentration over time are presented in Figure 2. Pharmacokinetic parameters for M1 after 3.00 mg/kg tramadol administration are summarized in Table 4.

Adverse Effects of IV Administration

No significant adverse effects (*e.g.* vomiting, constipation, decrease in respiratory rate, etc.) were noted after administration of tramadol through the IV route. For 30-60 min after IV administration, macaques appeared slightly sedated; however, all monkeys were quick to respond to visual and auditory stimuli during this time. No injection site pruritus was noted after IV administration of tramadol; however, whole body pruritis (*e.g.* scratch and/or nose wipe) was observed in one monkey for 30 min-2 h after injection.

Adverse Effects of Oral Administration

No significant adverse effects (*e.g.* vomiting, constipation, decrease in respiratory rate, etc.) were noted after administration of tramadol through the PO route. Voluntary compliance of oral tramadol was poor (2 out of 4 refused to swallow the tramadol tablet concealed in a small piece of banana). No sedation, pruritis, or other additional side-effect was noted after oral administration of tramadol.

Discussion

This study reports the pharmacokinetic profiles of tramadol, and its active metabolite O-desmethyltramadol, or M1, in adult male rhesus macaques (*Macaca mulatta*) after IV bolus and oral administration of tramadol. To date, the disposition of tramadol and M1 has not been characterized nonhuman primates. The pharmacokinetic parameters reported here provide basic information necessary for design of further studies of analgesic efficacy in this nontraditional veterinary species.

The volume of distribution of approximately 4 L/kg is consistent with lipid solubility of the test compound. Alternatively, low tissue affinity to tramadol could also impact the overall distribution. Clearance was similar to what has been reported in cats (24.5 mL/min/kg monkeys vs. 20.7 mL/min/kg cats) (Pypendop & Ilkiw, 2008); however, it was much faster than what has been reported for humans (6-9 mL/min/kg) (Lintz et al., 1986; Garcia Quetglas et al., 2007). This suggests that macaques may metabolize tramadol more similarly to cats than humans, and that the liver of the macaque may be able to biotransform tramadol better than had been initially expected. To the authors' knowledge, the metabolism of tramadol in the rhesus macaque has yet to be described. As such, it is more than possible that an alternate P450 enzyme is responsible for facilitating metabolism in rhesus macaque as compared to humans.

Oral bioavailability was found to be very low, and this suggests either limited absorption, large first-pass effect, or both. Limited absorption could be related in the formulation of tramadol and differences in gastrointestinal anatomy and physiology between humans and rhesus macaques. In addition, while efforts were made to ensure that the tablet was properly administered orally, it is possible that the entire dose was not delivered. First-pass effect is suggested by the higher M1 concentrations following oral tramadol administration, compared to IV administration. The extent of the effect is, however, difficult to determine, particularly since it is expected that many other, unmeasured metabolites were produced.

Terminal half-life of tramadol was similar for oral and IV administration, suggesting that absorption of tramadol did not impact the terminal phase significantly (133 min PO vs. 111 min IV).

In one monkey, a rise in serum concentrations took place over the first 15 min on the IV study. The reasons for this finding are unclear, as there are few physiological factors explaining a rise in serum drug concentration following intravenous bolus administration. Slow circulation and poor initial mixing of the drug within the central compartment might have contributed; however it is unclear why this would have occurred in this subject only.

No observation during the study suggested that this subject likely had a lower cardiac output than the 3 others. Erroneous labeling of the samples, resulting in incorrect time assignment for the serum concentrations cannot be entirely ruled out, but is considered unlikely as care was taken to correctly identify each sample during the study and drug analysis.

Overall, M1 was found to rapidly appear in serum after both IV and oral administration. M1 concentrations paralleled tramadol concentrations in the PO study, suggesting rapid metabolism of tramadol to M1.

After oral administration, the M1:tramadol AUC ratio was found to be 0.68 which is in between what has been reported for dogs and cats (0.42 dogs vs. 0.93 in cats); however, after IV administration the M1:tramadol AUC ratio was found to be 0.01 which is similar to what has been found in the cat (0.02) yet different from that reported in dogs (0.31) (Kukanich & Papich, 2004; Pypendop & Ilkiw, 2008). One can then assume that metabolism of tramadol to M1 is larger in dogs than in monkeys; and that metabolism of tramadol to M1 is very similar between cats and monkeys. The difference between oral and IV administration likely results from a large first-pass effect following oral administration.

In humans, following surgery, minimum effective plasma concentrations of tramadol were found to range from 298 (127-469) ng/mL (Lehmann et al., 1990) to 590 (180-1000) ng/mL (Grond et al., 1999), and minimum effective plasma concentrations of M1 were found to range from 39.6 (10.1-69.1) ng/mL (Lehmann et al., 1990) to 84 (50-134) ng/mL (Grond et al., 1999). If these concentrations apply to rhesus macaques, review of our raw data suggests that oral dosages as high as 4-20× the dose used in this study may be required to prevent pain in this species (*e.g.* dosage range 200-1000 mg/kg to yield tramadol concentrations ≥298 ng/mL and M1 concentrations ≥39.6 ng/mL). Of course, serum concentrations sufficient to provide analgesia in this species are unknown; and species-specific analgesiometric testing is ultimately needed in order to assess tramadol and M1 efficacy in rhesus macaques.

In summary, oral administration of tramadol resulted in greater metabolism of tramadol to M1 than IV administration; while bioavailability of tramadol was poor, if M1 is the active analgesic, this may not be of high clinical relevance. At-will patient compliance to oral administration was highly variable and intensive patient monitoring post-drug administration would be required if oral tramadol is to be used in the clinical veterinary setting. Additional pharmacodynamic studies are needed to explore analgesic efficacy in this species.

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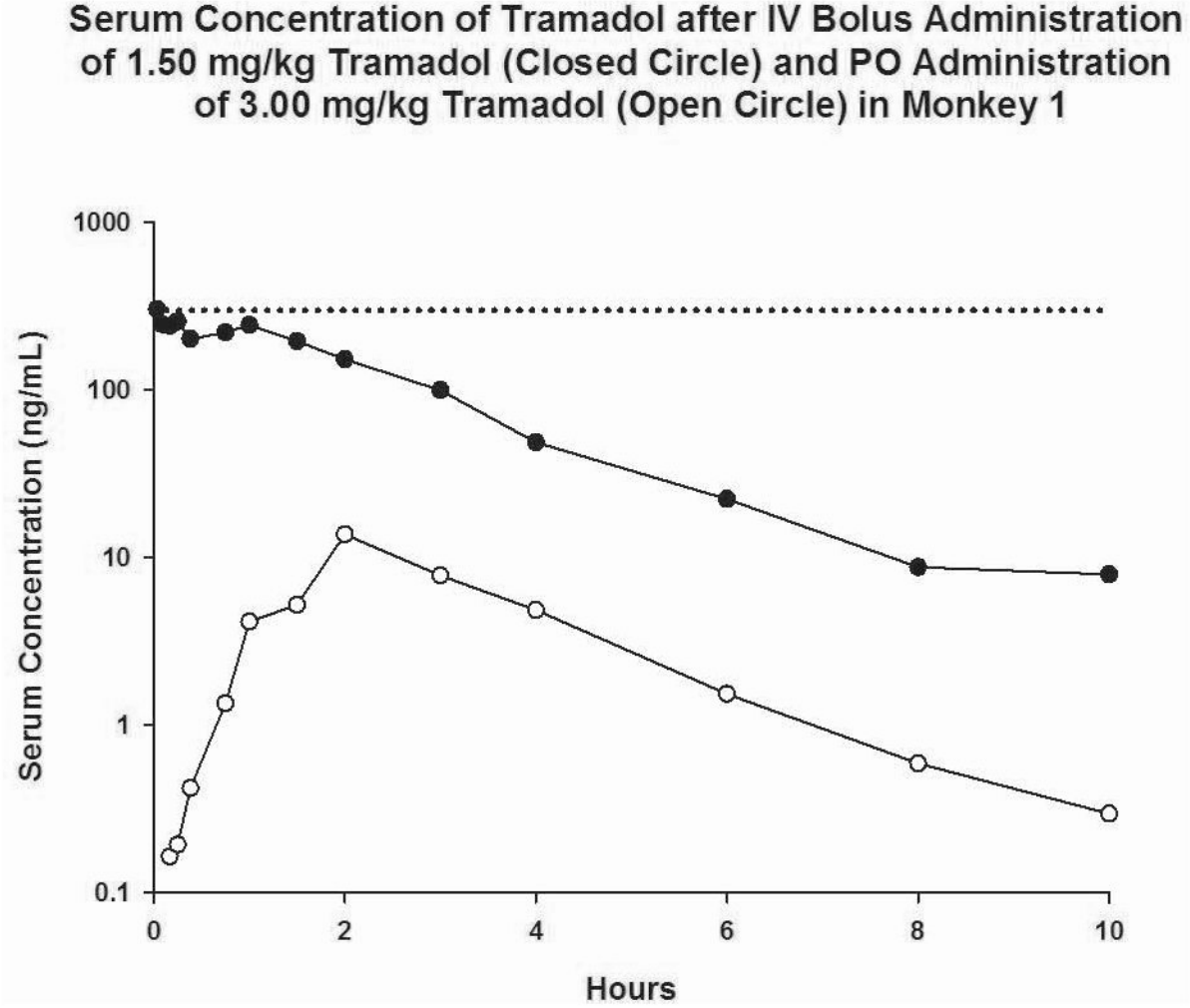
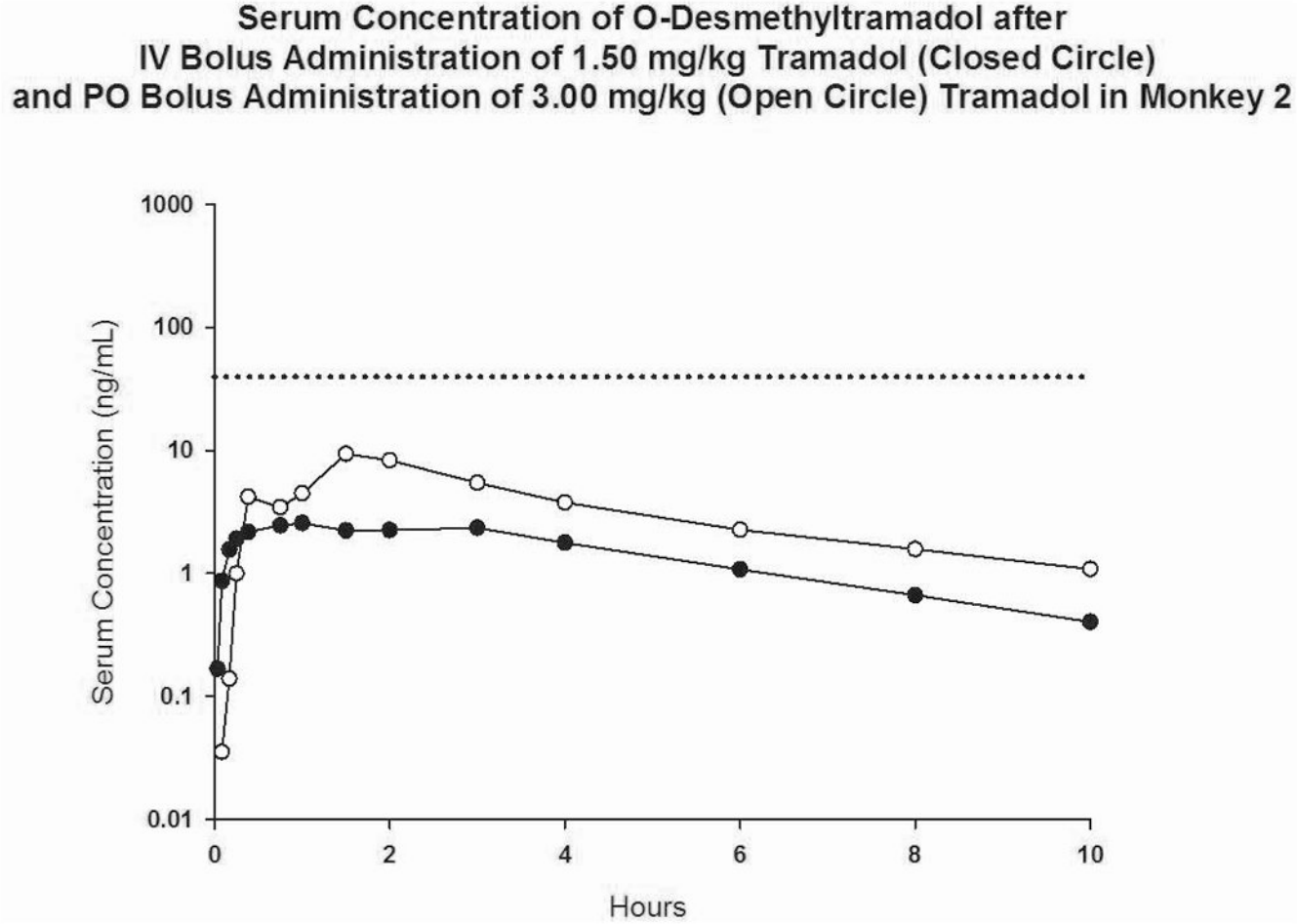
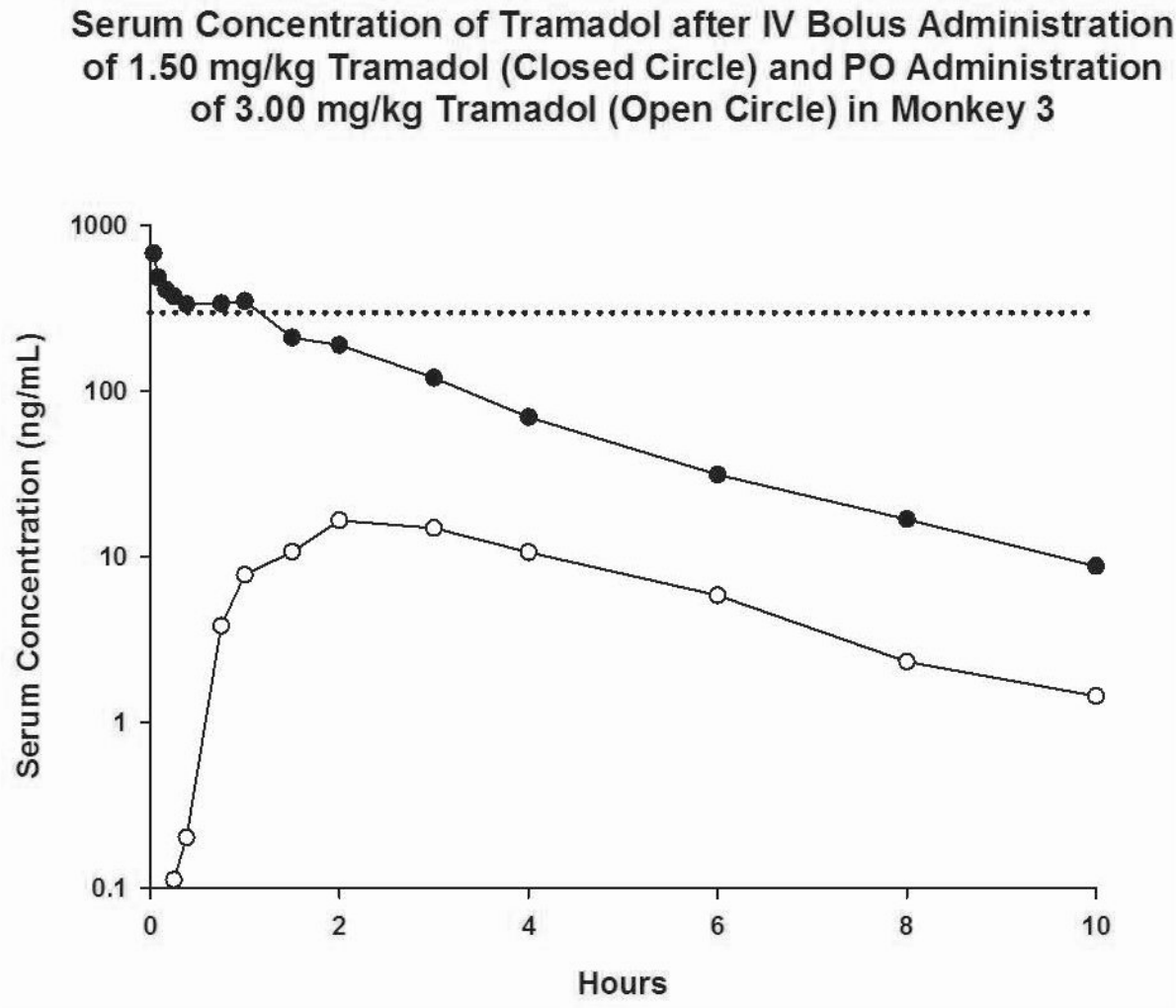






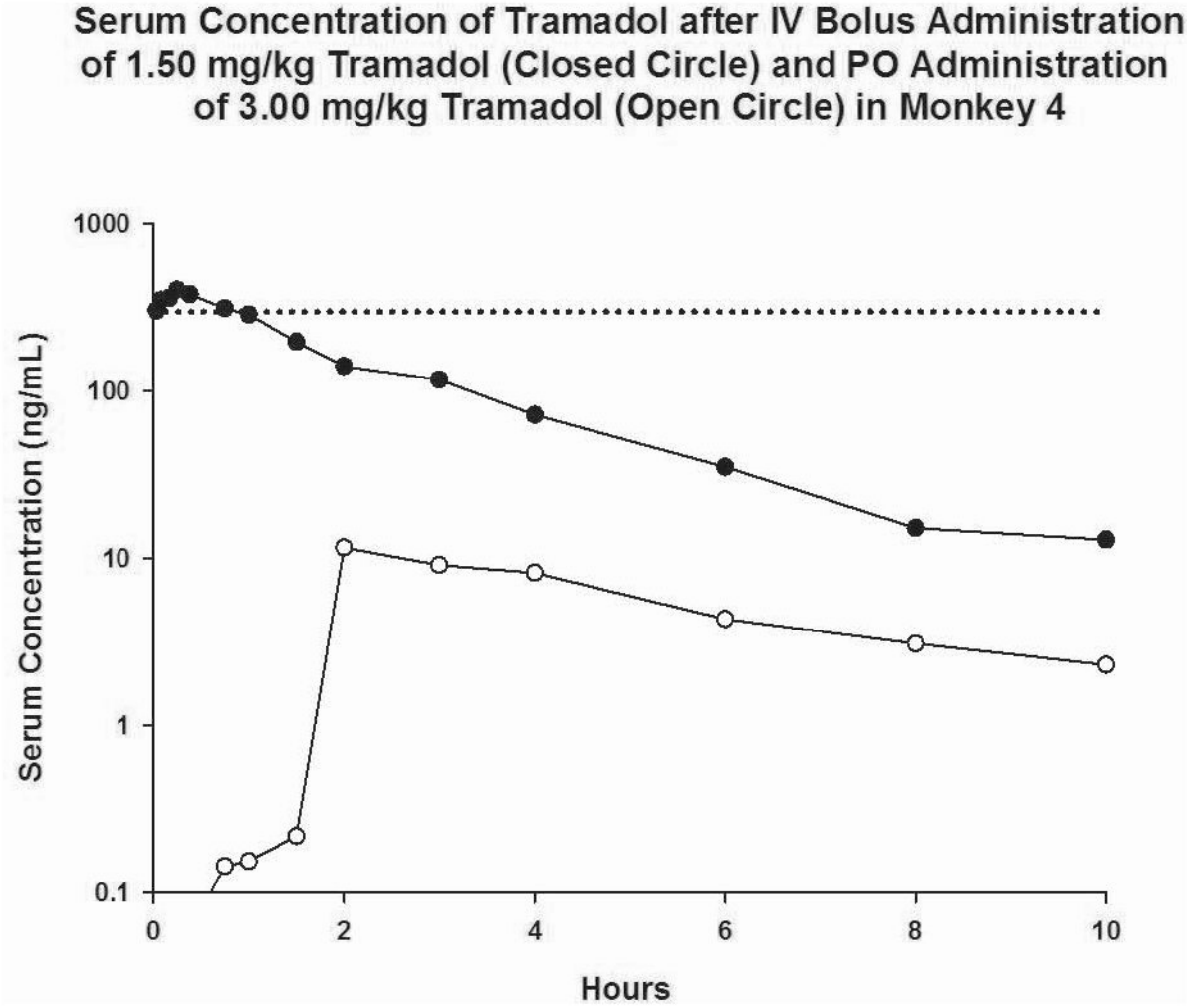
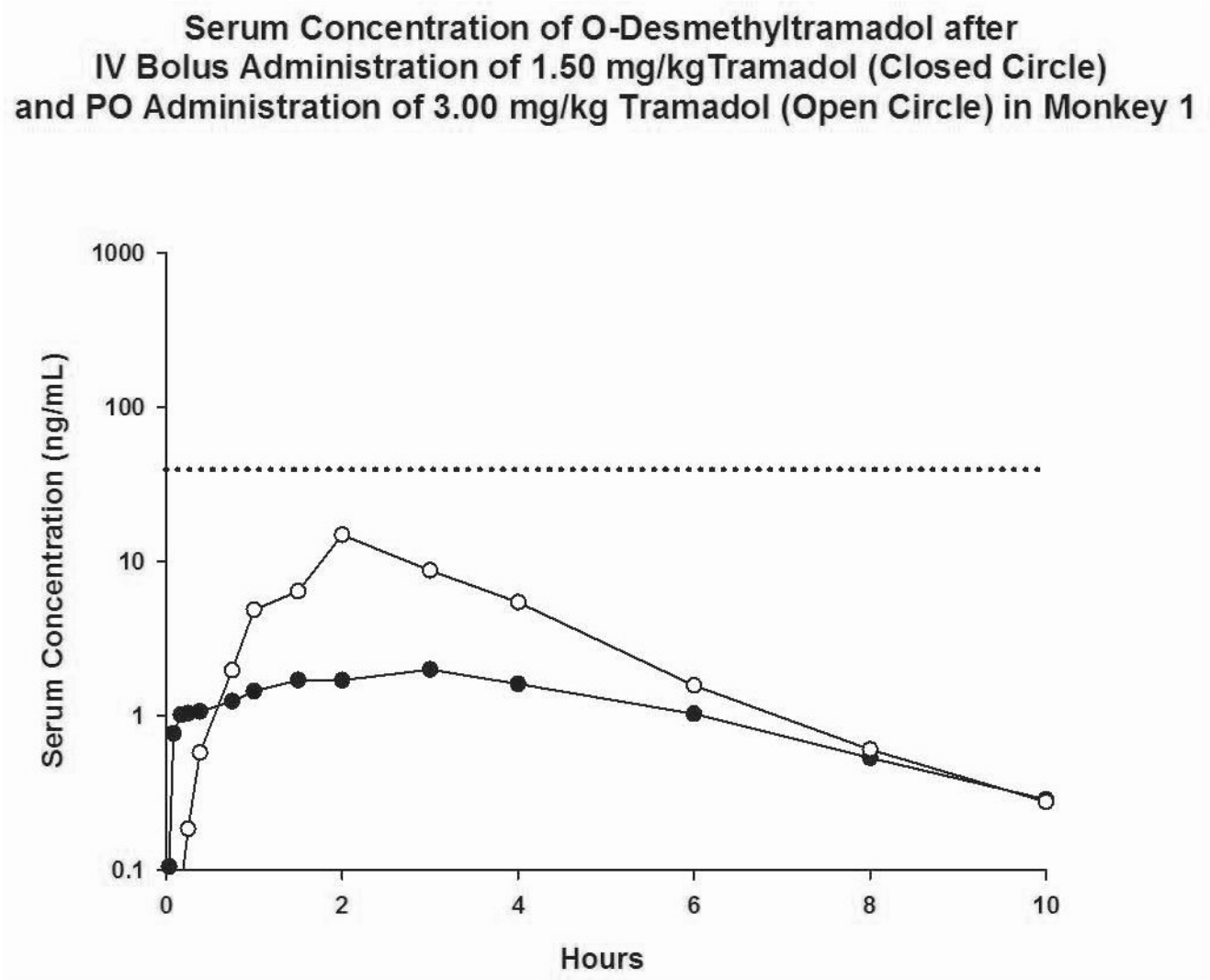
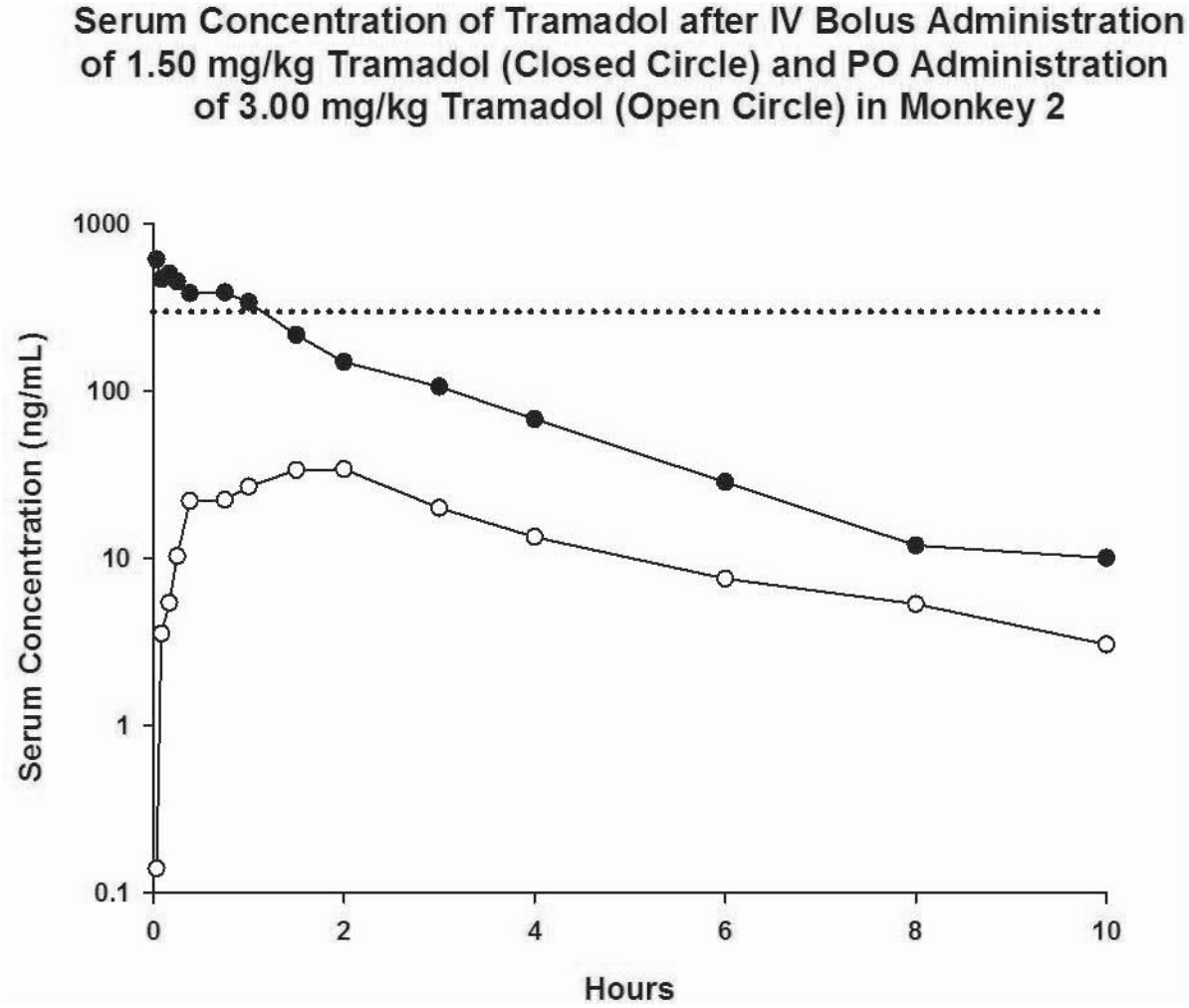
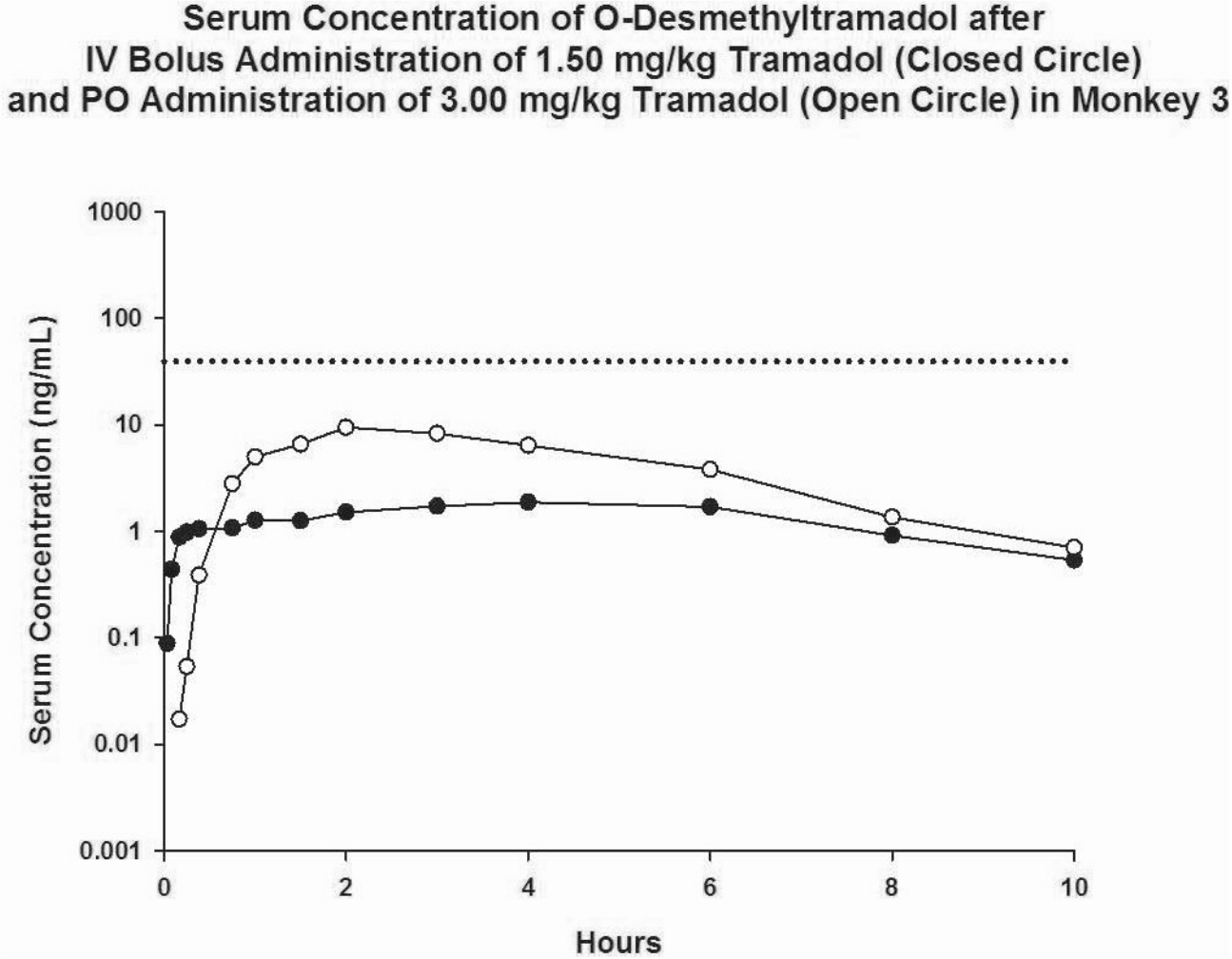


Figure 1.

Figures 1a-1d. Serum tramadol concentrations in 4 rhesus macaques (*Macaca mulatta*) after IV bolus administration of 1.50 mg/kg tramadol (closed circles) and PO administration of 3.00 mg/kg tramadol (open circles). Horizontal dotted line reflects minimum target analgesia concentration of 298 ng/mL reported in humans (Lehmann et al., 1990).







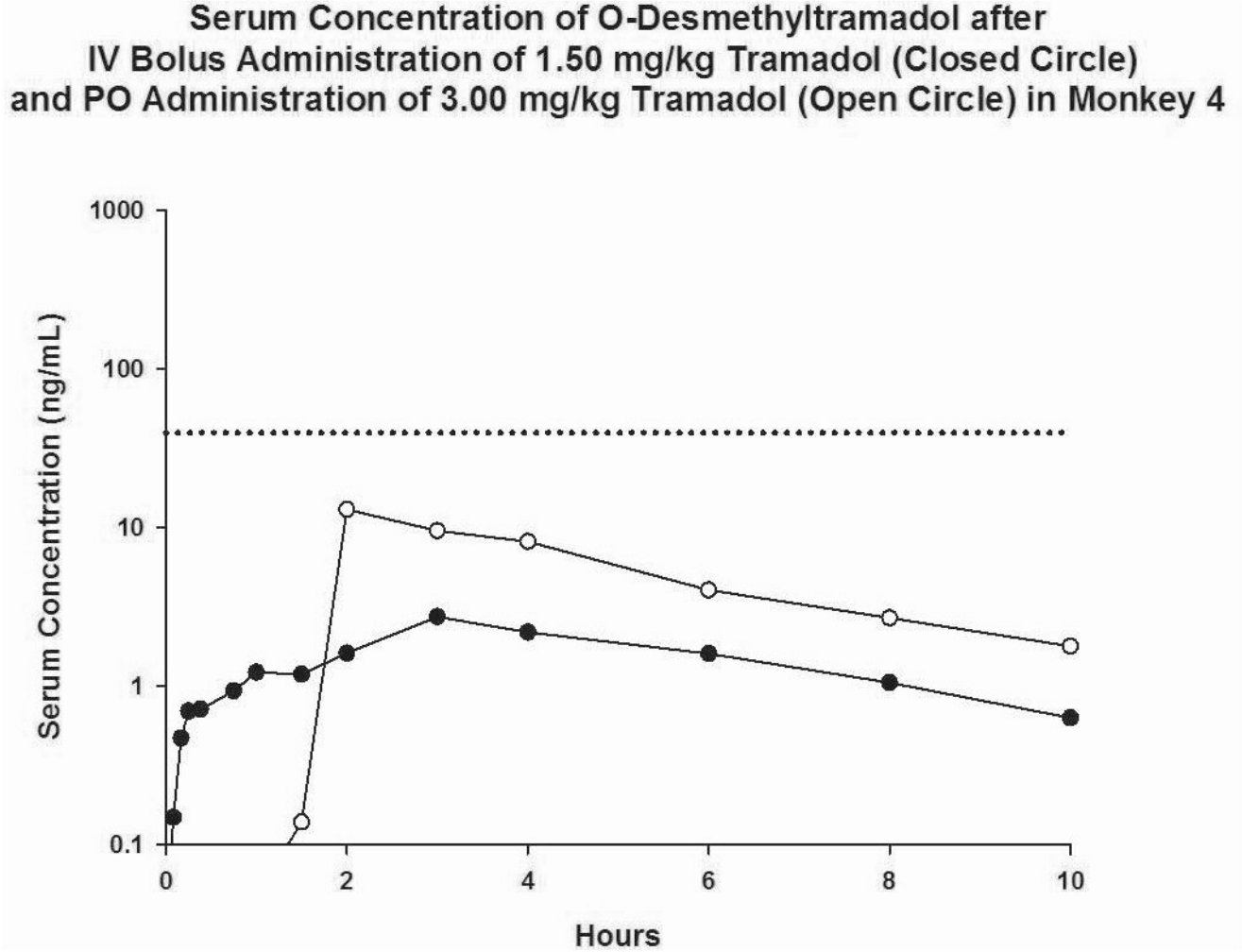


Figure 2.

Figures 2a-2d. Serum O-desmethyltramadol concentrations in 4 rhesus macaques (*Macaca mulatta*) after IV bolus administration of 1.50 mg/kg tramadol (closed circles) and PO administration of 3.00 mg/kg tramadol (open circles). Horizontal dotted line reflects minimum target analgesia concentration of 39.6 ng/mL reported in humans (Lehmann et al., 1990).

Table 1

Pharmacokinetic parameters for tramadol in rhesus macaques (*n*=4) after IV bolus administration of 1.50 mg/kg tramadol.

Parameter	Unit	Rhesus Macaque 1	Rhesus Macaque 2	Rhesus Macaque 3	Rhesus Macaque 4	Median (Range)
MRT_{inf}	*min*	147	136	141	162	144 (136-162)
$AUC_{0\text{-}inf}$	*min*ng/mL*	45,912	62,906	64,094	59,683	61,295 (45,912-61,295)
$AUC_{\%extrap}$	*%*	2.64	2.63	2.15	3.97	2.64 (2.15-3.97)
$AUMC_{0\text{-}inf}$	*min*min*ng/mL*	6,756,194	8,544,034	9,019,645	9,660,646	8,781,840 (6,756,194-9,660,646)
λ_z	*1/min*	0.007	0.006	0.006	0.005	0.006 (0.005-0.007)
$t_{1/2\lambda z}$	*min*	106	115	108	127	111 (106-127)
Cl	*mL/min/kg*	32.7	23.8	23.4	25.1	24.5 (23.4-32.7)
C_0	*ng/mL*	346	733	846	303	540 (303-846)
V_{ss}	*mL/kg*	4,808	3,239	3,293	4,068	3,681 (3,239-4,808)

MRT_{inf}, mean residence time until infinity; AUC_{inf}, area under the serum concentration-time curve to infinity; $AUC_{0\text{-}inf}$, area under the serum concentration-time curve to infinity; $AUC\%\ extrap$, percent of the area under the serum concentration-time curve extrapolated; $AUMC_{inf}$, total area under the first moment-time curve to infinity; λ_z, slope of the terminal log-linear phase; $t_{1/2\lambda z}$, terminal half-life; *Cl*, clearance; C_0, initial maximum serum concentration; V_{ss}, apparent volume of distribution at steady state.

Table 2

Pharmacokinetic parameters for tramadol in rhesus macaques (*n*=4) after PO administration of 3.00 mg/kg tramadol.

Parameter	Unit	Rhesus Macaque 1	Rhesus Macaque 2	Rhesus Macaque 3	Rhesus Macaque 4	Median (Range)
MRT_{inf}	*min*	199	240	257	390	249 (199-390)
AUC_{inf}	*min*ng/mL*	2,112	8,777	4,497	3,506	4,001 (2,112-8,777)
$AUC_{0\text{-}inf}$	*min*ng/mL*	2,112	8,777	4,497	3,506	4,001 (2,112-8,777)
$AUC_{\%extrap}$	*%*	1.71	7.31	5.56	18.72	6.44 (1.71-18.72)
$AUMC_{inf}$	*min*min*ng/mL*	420,638	2,107,819	1,157,011	1,367,840	1,262,426 (420,638-2,107,819)
λ_z	*1/min*	0.008	0.005	0.006	0.004	0.005 (0.004-0.008)
$t_{1/2\lambda z}$	*min*	84.9	146	120	198	133 (84.9-198)
C_{max}	*ng/mL*	13.7	34.1	16.6	11.6	15.2 (11.6-34.1)
T_{max}	*Min*	120	120	120	120	120 (120-120)
F	%	2.14	5.96	3.57	3.38	3.47 (2.14-5.96)

F, bioavailability; C_{max},maximum serum concentration; T_{max}, time to maximum serum concentration. Refer to Table 1 for remainder of key.

Table 3

Pharmacokinetic parameters for the active metabolite of tramadol, O-desmethyltramadol in rhesus macaques (*n*=4) after IV bolus administration of 1.50 mg/kg tramadol.

Parameter	Unit	Rhesus Macaque 1	Rhesus Macaque 2	Rhesus Macaque 3	Rhesus Macaque 4	Median (Range)
MRT_{inf}	*min*	281	281	339	382	310 (281-382)
AUC_{inf}	*min*ng/mL*	746	960	913	1,072	937 (746-1,072)
$AUC_{0\text{-}inf}$	*min*ng/mL*	746	960	913	1072	937 (746-1072)
$AUC_{\%extrap}$	*%*	8.29	10.2	12.2	17.3	11.2 (8.3-17.3)
$AUMC_{inf}$	*min*min*ng/mL*	209,852	270,396	309,462	409,149	289,929 (209,852-409,149)
λ_z	*1/min*	0.005	0.004	0.005	0.003	0.004 (0.003-0.005)
$t_{1/2\lambda z}$	*min*	149	167	144	204	159 (144-204)
C_{max}	*ng/mL*	2.00	2.57	1.88	2.73	2.28 (1.88-2.73)
T_{max}	*Min*	180	60	240	180	180 (60-240)

Refer to Tables 1 and 2 for key.

Table 4

Pharmacokinetic parameters for the active metabolite of tramadol, O-desmethyltramadol in rhesus macaques (*n*=4) after PO administration of 3.00 mg/kg tramadol.

Parameter	Unit	Rhesus Macaque 1	Rhesus Macaque 2	Rhesus Macaque 3	Rhesus Macaque 4	Median (Range)
MRT_{inf}	*min*	194	282	250	339	266 (194-339)
AUC_{inf}	*min*ng/mL*	2,347	2,336	2,648	3,235	2,497 (2,336-3,235)
$AUC_{0\text{-}inf}$	*min*ng/mL*	2,347	2,336	2,648	3,235	2,497 (2,336-3,235)
$AUC_{\%extrap}$	*%*	1.39	10.8	4.41	13.1	7.61 (1.39-13.1)
$AUMC_{inf}$	*min*min*ng/mL*	454,830	659,387	663,135	1,097,522	661,261 (454,830-1,097,522)
λ_z	*1/min*	0.009	0.004	0.006	0.004	0.005 (0.004-0.009)
$t_{1/2\lambda z}$	*min*	81.5	162	115	165	138 (82-165)
C_{max}	*ng/mL*	14.9	9.37	9.46	13.0	11.2 (9.37-14.9)
T_{max}	*Min*	120	90	120	120	120 (90-120)

Refer to Tables 1 and 2 for key.