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Pharmacokinetics of buprenorphine following intravenous and intramuscular administration in male rhesus macaques (*Macaca mulatta*)

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Abstract

This study reports the pharmacokinetics of buprenorphine in conscious rhesus macaques (*Macaca mulatta*) after intravenous (IV) and intramuscular (IM) administration. Four healthy, opioid-naïve, socially-housed, adult male macaques were used. Buprenorphine (0.03 mg/kg) was administered intravenously as a bolus or intramuscularly on separate occasions. Blood samples were collected prior to, and up to 24 h, post-administration. Serum buprenorphine concentrations were analyzed with liquid chromatography-mass spectrometry. Noncompartmental pharmacokinetic analysis was performed with commercially available software. Mean residence time in the IV study as compared to the IM study was 177 (159–189) minutes vs. 185 (174–214) minutes, respectively [median (range)]. In the IV study, concentration back extrapolated to time zero was found to be 33.0 (16.8–57.0) ng/mL [median (range)]. On the other hand, the maximum serum concentration found in the IM study was 11.8 (6.30–14.8) ng/mL [median (range)]. Rhesus macaques maintained concentrations greater than 0.10 ng/mL for over 24 h in the IV study and over 12 h in the IM study. Bioavailability was found to be 68.1 (59.3–71.2)% [median (range)]. No significant adverse effects were observed in the monkeys at the 0.03 mg/kg dose of buprenorphine during either study.

Keywords

pharmacokinetics; buprenorphine; macaque; analgesia; opioid

INTRODUCTION

Buprenorphine is a semi-synthetic, highly lipophilic opioid that is derived from the morphine alkaloid thebaine. A Drug Enforcement Agency (DEA) schedule III controlled substance, buprenorphine is a parenteral opioid analgesic licensed for medical use in

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humans. It is approved for veterinary use in many different countries; however, it is currently not approved for veterinary use in the United States. Regardless, buprenorphine is commonly used by veterinarians worldwide (including the United States) to clinically manage acute and chronic pain in animals. Buprenorphine is a partial agonist exerting its activity by binding to the μ and ê opioid receptors in mammals. In rodents, dogs, cats, nonhuman primates, and humans, buprenorphine produces analgesia through partial μ-agonist activity (Nickel, 1987; Roughan & Flecknell, 2002; Lutfy et al., 2003; Lutfy & Cowan, 2004; Johnson et al., 2005; Escher et al., 2007; Abbo et al., 2008).

Buprenorphine is reported to be 25–30 times more potent than morphine (Roughan & Flecknell, 2002). A bell-shaped, dose-response curve has been reported with this opioid; and a ceiling-effect has also been observed (Roughan & Flecknell, 2002; Lutfy & Cowan, 2004; Johnson et al., 2005). Agonist and/or antagonist effects have been found to depend on the species, dose , and individual (Roughan & Flecknell, 2002; Lutfy & Cowan, 2004; Johnson et al., 2005; Cowan, 2007; Escher et al., 2007). Dosing recommendations vary widely between and within species and reflect the complex pharmacology of this drug (Inturrisi, 2002; Roughan & Flecknell, 2002; Lutfy & Cowan, 2004; Johnson et al., 2005; Cowan, 2007).

Buprenorphine has been recommended for acute and chronic pain management in monkeys and has been reported to be used by veterinary clinicians for the perceived long duration of action and subsequently accepted justification for long dosing interval (Flecknell, 1984; Kohn, 1997; Roughan & Flecknell, 2002; Carpenter & Marion, 2013; Nunamaker et al., 2013). The pharmacokinetic profile of IM buprenorphine has recently been published in ketamine-sedated, mixed-species macaques (Nunamaker et al., 2013); however, the pharmacokinetic profile of IV and IM buprenorphine has not been studied in conscious macaques. The purpose of this study was to characterize the disposition of buprenorphine after bolus IV and IM administration in conscious adult male rhesus macaques (*Macaca mulatta*).

MATERIALS AND METHODS

Animals

Four, healthy, opioid-naïve, adult male rhesus macaques (*Macaca mulatta*) of Indian origin were used in this study [10 ± 2 y (mean ± standard deviation); 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, and socially-housed throughout the study. Positive-reinforcement training was used to condition macaques to all of the restraint techniques used in the study (Bliss-Moreau et al., 2013). Macaques were fed a commercial diet (4047 Old World Monkey Chow, Purina Mills, St. Louis, MO), and they were provided daily allocations of produce or mixed grains for enrichment. Water was available *ad libitum*. Monkeys were maintained on 12:12 h light:dark cycles. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of California, Davis.

Instrumentation and drug administration for IV study

On the day of experimentation, conscious macaques were placed in restraint chairs. An IV bolus of 0.03 mg/kg buprenorphine hydrochloride (Buprenex, Reckitt Benckiser, Richmond, VA) was administered into the right cephalic vein of each monkey with a 23 gauge needle attached to a 3 mL syringe. Serial blood samples (1 mL/sample) were collected with 23 gauge needles attached to 3 mL syringes and transferred to 3 mL serum tubes after venipuncture of the left cephalic vein in each monkey. Blood samples were collected prior to buprenorphine administration and 2, 5, 10, 23, 45, 90 min and 3, 6, 12, and 24 h after administration.

Instrumentation and drug administration for IM study

After at least two weeks of rest, conscious macaques were again placed in restraint chairs. An IM bolus of 0.03 mg/kg buprenorphine hydrochloride (Buprenex, Reckitt Benckiser, Richmond, VA) was administered into the right quadriceps of the hind leg of each monkey with a 23 gauge needle attached to a 3 mL syringe. Serial blood samples (1 mL/sample) were collected with 23 gauge needles attached to 3 mL syringes and transferred to 3 mL serum tubes after venipuncture of the left cephalic vein in each monkey. Blood samples were collected prior to buprenorphine administration and 2, 5, 7, 10, 23, 45, 90 min and 2, 3, 6, 8, 12, and 24 h after administration.

Side-effect observations

Macaques were visually monitored for side-effects by continuous, cage-side observation for 2 h following initial drug administration. Macaques were then visually monitored for side-effects during 5–10 min focal observations at 3, 6, 8, 12, 24, 48, and 72 h after initial drug administration. Experienced nonhuman primate handlers watched for nonspecific signs of sedation, injection-site pruritus, whole-body pruritus, depression, vomiting, diarrhea, constipation, anorexia/poor appetite, and phlebotomy complications (*e.g.* bruising, hematoma formation, etc.).

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 1462x*g* (Allegra 6R Centrifuge, Beckman Coulter, Brea, CA) and was stored at −70°C until analysis for buprenorphine concentration. The concentration of buprenorphine in each sample was determined by the internal-standard (buprenorphine d3, Toronto Research Chemicals, Ontario, Canada) method using the peak area ratio and linear regression analysis. The response for buprenorphine was linear and gave correlation coefficients (R^2) of 0.99 or better. The technique was optimized to provide a limit of quantitation of 0.10 ng/mL. Quantitative analyses were performed on a triple-quadrupole mass spectrometer (TSQ Quantrum Ultra, Thermo Scientific, San Jose, CA) equipped with a heated electrospray ionization probe. Data was processed by using LCQuan software (version 2.6, Thermo Scientific). The triple-quadrupole mass spectrometer was coupled with a chromatographic system (1100 LC system, Agilent, Santa Clara, CA). Chromatographic separation used an activated charcoal column ($ACEC_{18}$, 100x2.1 mm, 3.0-μm column; MacMod, Chadds Ford,

PA) and linear gradient of acetonitrile in water with a constant 0.20 % formic acid at a flow rate of 0.35 mL/min (Burdick and Jackson, Muskegon, MI). Prior to analysis, the serum proteins, controls, and calibrators were extracted by solid-phase extraction (Polychrom Clin II cartridges, SPEware, Baldwin, CA). Intra-day and inter-day accuracy (% nominal concentration) was 88 and 91%, respectively, for 0.30 ng/mL. Intra-day and inter-day precision (% relative standard deviation) was 13 and 11%, respectively, for 0.30 ng/mL. Accuracy between 85 and 115% and precision below 15% were deemed acceptable. For both the IV and IM studies, the lower limit of detection (LOD) and of quantitation (LOQ) was 0.05 and 0.10 ng/mL, respectively. The LOQ was selected based on the linearity of the assay, the acceptable accuracy and precision at 3 times the signal:noise, and the presence of a calibrator meeting the acceptance criteria (difference between known and measured concentration of 3%) at 0.05 ng/mL.

Pharmacokinetic analysis

Pharmacokinetic analyses were conducted by using WinNonlin 6.1 (Pharsight, Cary, NC). Changes in serum concentrations of buprenorphine over time were evaluated by noncompartmental analysis. Standard pharmacokinetic equations were used to determine pharmacokinetic parameters (Gibaldi & Perrier, 1982; Gabrielsson & Weiner, 1997). All parameters are reported as median (range).

RESULTS

No significant adverse effects were noted after administration of 0.03 mg/kg buprenorphine through either IV or IM route. After IV and IM administration of buprenorphine, macaques appeared slightly sedated; however, all animals were quick to respond to any visual or auditory stimuli during this period (up to 30 min IV and up to 45 min IM). No injection site or whole body pruritis (*e.g.* scratch and/or nose wipe) was noted. No additional side-effects were visually appreciated after drug administration.

In rhesus macaques, IV bolus of 0.03 mg/kg buprenorphine was found to result in a mean residence time of 177 (159–189) min when calculated for the duration of the study (0–24 h). The concentration back extrapolated to time zero was 33.0 (16.8–57.0) ng/mL after IV administration. The area under the serum drug time-concentration curve (0–24 h) was found to be 2,188 (2,026–2,353) min*ng/mL for the IV study. On the other hand, IM administration of 0.03 mg/kg buprenorphine was found to result in a mean residence time (0–24 h) of 185 (174–214) min and a maximum serum concentration of 11.8 (6.30–14.8) ng/mL. The area under the serum drug time-concentration curve (0–24 h) was found to be 1,519 (1,202–1,796) min*ng/mL for the IM study. Pharmacokinetic parameters for buprenorphine are summarized in Table 1 (IV bolus) and Table 2 (IM administration).

Buprenorphine drug concentrations were maintained above 0.50 ng/mL for 3–6 h after IV administration and 6 h after IM administration (Table 3). Buprenorphine concentrations were maintained above 0.10 ng/mL for 24 h in the IV study and 12 h in the IM study. Buprenorphine concentrations were higher than LOD (0.05 ng/mL) for the duration of each study (24h) in all monkeys (Figure 1) Bioavailability was found to be 68.1 (59.3–71.2)%

[median (range)] after IM administration. Overall, buprenorphine disposition was characterized by moderate clearance and a relatively large volume of distribution.

DISCUSSION

This study reports the pharmacokinetic profiles of buprenorphine in conscious adult male rhesus macaques (*Macaca mulatta*) after IV bolus and IM administration of 0.03 mg/kg buprenorphine. The pharmacokinetic parameters reported here provide bioavailability for IM buprenorphine and document time-concentration data important for design of any future species-specific buprenorphine analgesiometric studies.

Buprenorphine is an extensively protein-bound opioid that exerts analgesic effects through partial μ-agonist activity in nonhuman primates (Garrett & Chandran, 1985; Roughan & Flecknell, 2002). In this study, time to peak concentration (7 min) suggests relatively rapid drug absorption after intramuscular administration in male macaques. Bioavailability was found to be incomplete (median 68% following IM administration) which is comparable to that reported in horses (range 51–88%) (Davis et al., 2012) and moderately higher than that reported in cats (45.7%) (Steagall et al., 2013). Only minor inter-individual bioavailability variation (59.3–71.2%) was observed in this study and is believed to reflect the strict inclusion criteria used when selecting animals for study (*i.e.* use of an age-, gender-, size-, subspecies-, and body mass distribution-matched cohort) and the small number of animals included (n=4).

IV administration was found to predict a very slow terminal phase (45.6 h), resulting in a very long terminal $t_{1/2}$ with high variability between individuals (12.1–95.6 h). At the time of study design, no species-specific knowledge was available to assist in study design. Based on review of veterinary and human literature, we estimated blood collection up to 24 h would capture samples 3–5 times the terminal $t_{1/2}$ (Lloyd-Jones et al., 1980; Robertson et al., 2005; Escher et al., 2007; Abbo et al., 2008). Unfortunately, we found our samples did not include collections 3–5 times past the terminal $t_{1/2}$ in the IV study. As such, terminal $t_{1/2}$ calculations were perceived to be compromised and were not included in this report. A prolonged $t_{1/2}$ may be present in this species and increased sampling collections are required in order to better clarify terminal $t_{1/2}$ development. If a slow terminal phase is indeed present, it may be of little clinical relevance, since concentrations during that phase would likely be below therapeutic range.

Recently, the pharmacokinetic profile of IM buprenorphine (0.01 mg/kg and 0.03 mg/kg) was published in ketamine-sedated, mixed-species male macaques (*Macaca mulatta* + *Macaca fasicularis*) (Nunamaker et al., 2013). Time-concentration data collected separately from both species were combined for pharmacokinetic analysis. Ketamine sedation was recognized to potentially affect reported buprenorphine pharmacokinetics through shared CYP3A4 metabolism of buprenorphine and ketamine (Hijazi & Boulieu, 2002; Moody et al., 2002; Restrepo et al., 2009). After further review, weights in the Nunamaker *et. al.* study adult male macaques ranged from 4.3 kg–10.5 kg as compared to 15–19 kg for our macaques. No body condition scores were reported to facilitate comparison of body mass distribution between the two sets of study animals. Blood samples were collected up to 24 h

post-drug administration in both studies. At equal doses and administration routes (0.03 mg/kg buprenorphine hydrochloride IM), Nunamaker and colleagues reported 40.7±48.7 ng/mL and 0.50±0.50 h for maximal plasma buprenorphine concentration and time to reach maximum plasma buprenorphine concentration [mean±SD] as compared to our findings of 11.0 ng/mL (6.30–14.8) and 0.12 (0.08–0.75) h [median (range)] for maximal serum buprenorphine concentration and time to reach maximum serum buprenorphine. Mean residence time of the buprenorphine molecule within the body over 24 h was found to be similar between the two studies [3.40±1.20 h (mean ± SD) in Nunamaker *et. al.* study vs. 3.08 (2.90–3.57) h (median (range)) in our study]. Differences between studies could have been a result of differences in weight and/or body condition between and within studies as well as potential confounding effects associated with repeated administration of ketamine during the Nunamaker *et. al.* pharmacokinetic trials (Nunamaker et al., 2013).

While Nunamaker and colleagues reported no statistically significant differences between pharmacokinetic data collected in *Macaca mulatta* and *Macaca fasicularis*, interpretation of mixed-species pharmacokinetic data should be done with caution. Buprenorphine has been reported to be metabolized by N-dealkylation to form the active metabolite norbuprenorphine, and both buprenorphine and norbuprenorphine undergo glucuronidation. In humans, the cytochrome p450 enzymes (CYPs) responsible for N-dealkylation of buprenorphine to norbuprenorphine include 3A4, 2C8, 3A5, and 3A7, with 3A4 activity accounting for 65% of the biotransformation and 2C8 for approximately 30% (Picard et al., 2005). In addition, another oxidative pathway resulting in the formation of hydroxybuprenorphine and hydroxynorbuprenorphine has been found involving CYPs 2C9, 2C18, 2C19, and 3A (Picard et al., 2005). Significant differences have been found in hepatic metabolism between rhesus macaques, cynomolgus macaques and humans (Iwasaki & Uno, 2009; Uno et al., 2010; Uno et al., 2011); and these differences may significantly affect cross-species application of clinical pharmalogical data. For example, while cynomolgus macaques have eleven CYPs that exhibit high degrees of homology to human CYPs, one entire CYP family has been found only in cynomolgus macaques with little to no degree of homology to human CYPs (*e.g.* CYP responsible for cynomolgus and rhesus macaque pitavastatin metabolism is not found in humans) (Iwasaki & Uno, 2009; Uno et al., 2010). At the same time, CYP 2C93, a macaque CYP not found in humans, has been found to be involved with drug metabolism in rhesus macaques and not cynomolgus macaques (Uno et al., 2011). While the implications for the metabolism of buprenorphine are not entirely clear, these differences imply that the application of pharmacokinetic data across species, even those as closely related as cynomolgus and rhesus macaques, should be done with caution. Species-specific data is preferable particularly when using pharmacokinetic data to facilitate development of analgesia protocols. As such, the data in this study should be applied to rhesus macaques only.

Published case reports and veterinary drug reference manuals reflect empirical dosing recommendations for buprenorphine in nonhuman primates (Flecknell, 1983; Kohn, 1997; Coulter et al., 2009; Krugner-Higby et al., 2009; Kelly et al., 2012). While significant differences can be found between metabolism in human and nonhuman primates, the rhesus macaque continues to be accepted as a translational model for human physiology, disease,

and behavior (O'sullivan et al., 2013; Schmitz & Korioth-Schmitz, 2013). Human literature was reviewed, and we found published analgesiometric studies suggesting that maintaining buprenorphine concentrations ≥0.10 ng/mL is sufficient to produce analgesia in humans (Evans & Easthope, 2003; Sittl et al., 2003; Johnson et al., 2005; Escher et al., 2007). We found that buprenorphine drug concentrations were maintained above 0.10 ng/mL for at least 24 h after IV administration and for at least 12 h after IM administration 0.03 mg/kg buprenorphine hydrochloride in our macaques (Table 3). Additional species-specific rhesus macaque pharmacodynamic and analgesiometric time-concentration data is ultimately needed in order to provide evidence-based dosing recommendations to the veterinary community. Despite obvious need for such research, clinicians must continue to recognize that responses to opioid analgesia are dependent on individual patient variability of response, degree of pain, concurrent medications, and chronicity of pain.

In conclusion, buprenorphine disposition in adult, male rhesus macaques (*Macaca mulatta*) was found to be characterized by moderate clearance and a relatively large volume of distribution. Additional pharmacokinetic studies are needed to characterize terminal $t_{1/2}$ in this species.

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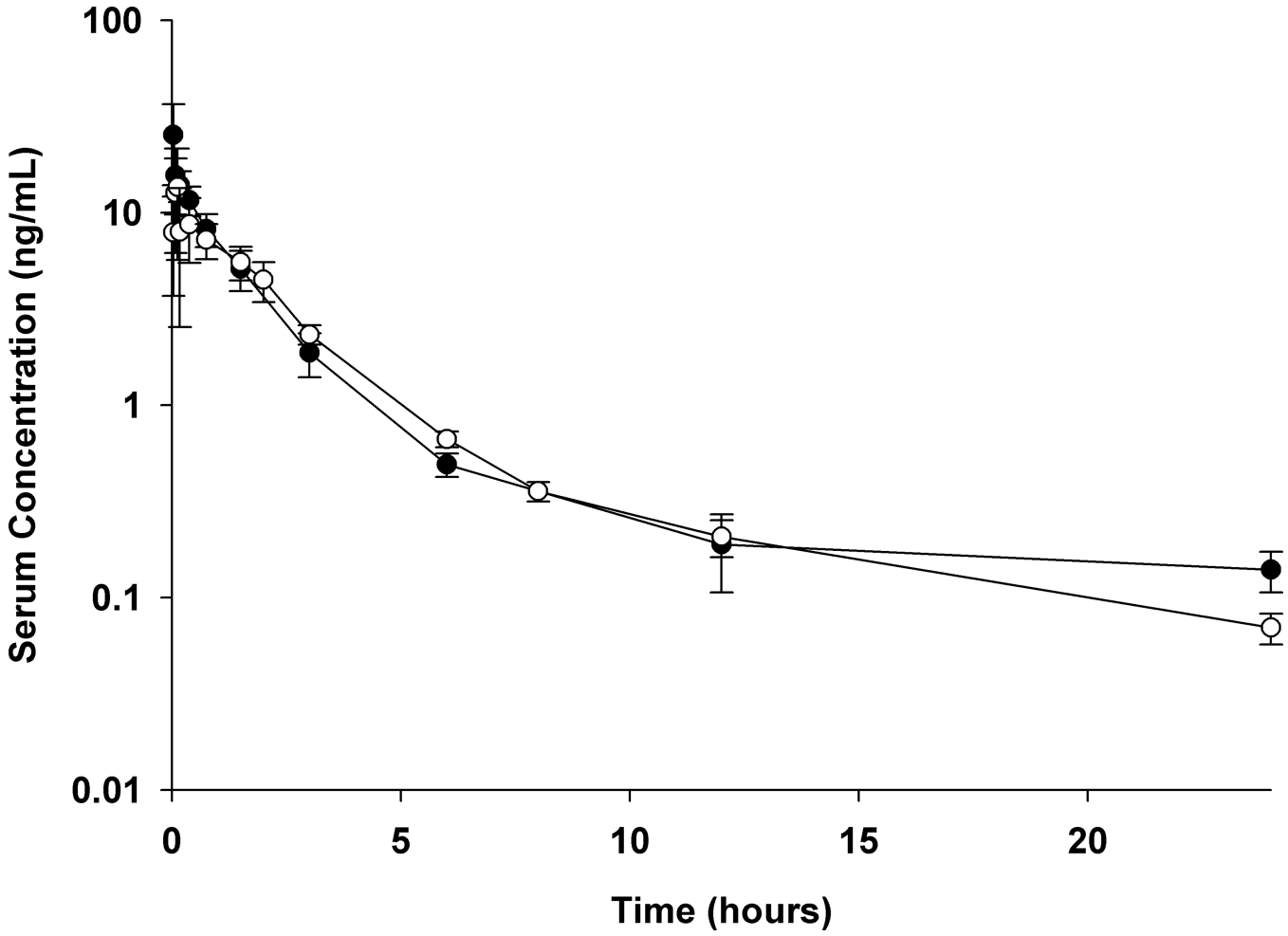

Figure 1.

Mean (± standard deviation) serum buprenorphine concentrations in 4 male rhesus macaques after IV bolus and IM administration of 0.03 mg/kg buprenorphine.

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Table 1

Individual pharmacokinetic parameters buprenorphine in conscious male rhesus macaques (*n*=4) after IV bolus administration of 0.03 mg/kg.

Parameter	Unit	Rhesus Macaque 1	Rhesus Macaque 2	Rhesus Macaque 3	Rhesus Macaque 4	Median (Range)
MRT_{0-24}	*min*	189	159	165	189	177 (159–189)
AUC_{0-24}	*min*ng/mL*	2,026	2,353	2,058	2,318	2,188 (2,026–2,353)
$AUMC_{0-24}$	*min*min*ng/mL*	258,772	229,261	273,982	400,972	266,377 (229,261–400,972)
Cl	*mL/min/kg*	14.8	12.7	14.6	12.9	13.8 (12.7–14.8)
C_0	*ng/mL*	16.8	25.0	57.0	41.0	33.0 (16.8–57.0)
V_{ss}	*mL/kg*	32,816	49,119	14,166	5,000	23,491 (5,000–49,119)

MRT, mean residence. *AUC*, area under the serum time-concentration curve. *AUMC*, total area under the first moment-time curve. *Cl*, clearance. C_0, amount of buprenorphine in a given volume of serum. V_{SS}, apparent volume of distribution at steady-state.

Table 2

Individual pharmacokinetic parameters for buprenorphine in conscious male rhesus macaques (*n*=4) after IM bolus administration of 0.03 mg/kg.

Parameter	Unit	Rhesus Macaque 1	Rhesus Macaque 2	Rhesus Macaque 3	Rhesus Macaque 4	Median (Range)
MRT_{0-24}	*min*	214	174	186	183	185 (174–214)
AUC_{0-24}	*min*ng/mL*	1,202	1,572	1,466	1,796	1,519 (1,202–1,796)
$AUMC_{0-24}$	*min*min*ng/mL*	257,764	273,722	272,372	327,747	273,047 (257,764–327,747)
C_{max}	*ng/mL*	6.30	11.0	14.8	12.5	11.8 (6.30–14.8)
T_{max}	*min*	45.0	7.00	7.00	5.00	7.00 (5.00–45.00)

MRT, mean residence time. *AUC*, area under the serum time-concentration curve. *AUMC*, total area under the first moment-time curve. C_{max}, maximal serum concentration. T_{max}, time to reach maximum serum concentration.

Table 3

Time in hours each male rhesus macaque remained above 1.00 ng/mL, 0.50 ng/mL, 0.25 ng/mL, and 0.10 ng/mL of buprenorphine throughout the 0.03 mg/kg buprenorphine IV and IM pharmacokinetic studies.

Buprenorphine Concentration	Rhesus Macaque 1		Rhesus Macaque 2		Rhesus Macaque 3		Rhesus Macaque 4	
	IV	IM	IV	IM	IV	IM	IV	IM
≥1.00 ng/mL	3	3	3	3	3	3	3	3
≥0.50 ng/mL	6	6	3	6	3	6	6	6
≥0.25 ng/mL	6	8	6	8	6	8	12	12
≥0.10 ng/mL	24	12	24	12	24	12	24	12