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Important Update:

In order to remain compliant with the most current regulatory guidelines, we have updated the labeling on our SR formulations from Buprenorphine and Meloxicam SR to Buprenorphine and Meloxicam ER. **As of July 1, 2022, SR preparations mentioned in the attached study are now labeled as ER,** with no changes to the formulation of the medication(s).

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Pharmacokinetics of 3 Formulations of Meloxicam in Cynomolgus Macaques (*Macaca fascicularis*)

Cassondra Bauer,[1,*] Patrice Frost,[1] and Stephen Kirschner[2]

Meloxicam is a commonly used COX2-preferential NSAID in both human and veterinary patients. Minimal information has been published regarding appropriate dosing in nonhuman primates. Here we investigated the pharmacokinetic parameters of 3 formulations of meloxicam in cynomolgus macaques. A single dose of meloxicam SR, an extended-release formulation purported to provide therapeutic levels for as long as 72 h, was compared with the intramuscular and oral formulations dosed for 3 consecutive days and as a single dose. The oral formulation, both over 3 d and as a single dose, yielded lower plasma levels and a shorter duration than did intramuscular and sustained-release subcutaneous formulations. The intramuscular formulation, both over 3 d and as a single dose, provided lower plasma levels and a shorter duration than did a sustained-release subcutaneous formulation. The sustained-release formulations generated the highest plasma concentrations for the longest periods of time. None of the formulations caused significant effects on kidney or liver function. Our results indicate that the sustained-release formulation of meloxicam can achieve an adequate steady-state plasma concentration for 2 to 3 d in nonhuman primates. The standard intramuscular formulation provides adequate plasma concentrations for 12 to 24 h, with waxing and waning levels associated with daily dosing. The oral formulation has limited utility in nonhuman primates because of low circulating levels of drug.

Abbreviations: AUC_{∞}, AUC from time 0 to infinity with extrapolation of the terminal phase; AUC_{last}, AUC from time 0 to last measured data point; C_{max}, peak plasma concentration; SR, sustained release; T_{max}, time to peak plasma concentration.

Pain management is an essential component when practicing veterinary medicine as dictated by the Animal Welfare Act.[4] Pain can be caused by many factors involving multiple physiologic pathways both peripherally and centrally. An agreed upon definition of pain can be difficult to achieve, however it is the responsibility of researchers and veterinarians to recognize and alleviate pain.[33] Pain can be categorized as inflammatory and neuropathic, as well as acute and chronic. Therefore, multimodal analgesia is best used to help control pain through several mechanisms. NSAID are key components of multimodal pain management with antiinflammatory, antipyretic, and analgesic properties. Typically, NSAID are paired with an opioid analgesic. NSAID act peripherally through the reduction of the activation and sensitization of nociceptors, and centrally as an analgesic.[48] The antiinflammatory properties occur through the blockage of prostaglandin synthesis by inhibiting cyclooxygenase in the arachidonic cascade. One NSAID available for use is meloxicam ([4-hydroxy-2methyl-N-(5-methyl-2thiazolyl)-2H-1,2-benzothiazine-3carboxamide-1,1-dioxide]). Meloxicam is a preferential inhibitor of cyclooxygenase 2 of the oxicam class. Cyclooxygenase 2 is induced by inflammatory stimuli, whereas cyclooxygenase 1is responsible for physiologic processes.[14,15,18,21,32,35,38,46,49] Despite the wide usage of meloxicam, there is relatively little literature available on the dosage and frequency at which the drug should be administered in nonhuman primates.[3,15]

Nonhuman primates can pose a challenge for the administration of drugs, because they must cooperate or be physically restrained or a remote darting system must be used. Sustained-release (SR) drug alternatives may be preferred, yet must be tested in the species in which their use is intended. Dosages for nonhuman primates cannot always be extrapolated from other species, as evidenced by the determination that cefovecin (Convenia) was long-lasting in dogs but not nonhuman primates.[39,40]

Because nonhuman primates are unable to communicate verbally regarding pain, husbandry, technical, and veterinary staff must oversee the animals for the recognition and alleviation of pain. It is generally accepted that any procedure that would be perceived as painful in a human would also be painful in an animal, because humans and animals share several anatomic and chemical pathways for pain reception.[33] Therefore, it is necessary to provide appropriate therapeutics in painful situations and to initiate preemptive analgesia if possible. Recognizing pain in nonhuman primates first requires that caretakers understand normal behavior and postures of the animals. Technicians and care staff must be trained to recognize some standard indications that primates may exhibit when in pain, including hunched posture, hugging themselves, screaming, facial grimacing, separation from the group, inappetance, decreased fluid intake, shallow or rapid breathing, pale mucous membranes, dehydration, elevated heart rate, increased body temperature, rough hair coat or decreased grooming,[33] puffy eyes, reluctance to move, rejection of infants, or carrying or limping on affected limb. Nonhuman primates are wild animals and therefore are exceptional at hiding mild and moderate pain, and they mask severe pain to the best of their abilities. For this reason, it is imperative that caretakers critically evaluate nonhuman primates after any procedure or injury that is suspected to be painful, to ensure that pain is treated appropriately.

A new formulation of meloxicam for veterinary use is reported by the manufacturer to have adequate analgesic activity

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[1]Texas Biomedical Research Institute, Southwest National Primate Research Center, San Antonio, Texas; [2]Wildlife Pharmaceuticals, Clinical Research and Development, Fort Collins, Colorado.
[*]Corresponding author. Email: cbauer@txbiomed.org

for as long as 72 h in rats and canines. If the long duration of action is also present in nonhuman primates, meloxicam would be an ideal candidate for administration for pain management. Minimizing stress and handling while providing appropriate analgesia can quicken the pace an animal recovers from an injury or surgery, yet few appropriate drug options are available. Using intermittent doses to treat postoperative pain with intermittent doses is often ineffective,[16,17,28,44,48] because sustained concentrations at therapeutic levels are not achieved. Many analgesic options available have not been tested for efficacy in nonhuman primates, and doses are extrapolated from other species (both veterinary and human) coupled with subjective evaluation. The plasma concentrations of meloxicam in rats and dogs are similar to those in humans, but this correlation does not hold true for baboons and other species.[15] This discrepancy warrants further examination to determine appropriate dosages in nonhuman primates.

In the current study, we evaluated 3 formulations of meloxicam by determining plasma concentration and elimination pharmacokinetics. The drugs were given at subjectively relevant therapeutic dosages. Our goal was to determine whether all 3 formulations achieved quantifiable plasma concentrations and to assess how long the concentrations remained detectable. We investigated 3 routes of administration—subcutaneous, oral, and intramuscular—to determine the adequacy and duration of action for each route. We expected that the sustained-release (SR) formulation of meloxicam would have the longest duration of therapeutic levels with minimal peaks and valleys and that the other formulations would have fluctuations in plasma concentrations. The matrices for meloxicam SR were the same as those used to formulate the buprenorphine SR that was tested and determined to remain at therapeutic levels for at least 5 d in the plasma of cynomolgus and rhesus macaques.[36] The matrices are formulated from a safe, reliable biodegradable polymer and are eliminated via the tricarboxylic acid cycle as carbon dioxide and water. An SR formulation of meloxicam that offered a similar duration of efficacy to that of buprenorphine SR would be most beneficial for managing pain in nonhuman primates. Using such a drug would decrease handling-associated stress to patients and offer stable pain management, improved safety to both the animals and caretakers, and more cost-efficient pain management. The hypothesis we explored was that meloxicam SR would exhibit an extended-release profile, resulting in the maintenance of therapeutic plasma concentrations over time as compared with those of the intermittently dosed oral and intramuscular formulations. We anticipate that this feature will result in a more stable plane of analgesia and effective pain relief in macaques.

Materials and Methods

Animals. Six adult female cynomolgus macaques (age: 8.63 ± 0.88 y; weight: 5.77 ±1.23 kg) and 6 adult male cynomolgus macaques (age: 5.90 ± 1.08 y; weight: 5.82 ± 1.18 kg) were used to complete this investigation. All animals were identified with a unique tattoo number and microchip. All procedures were conducted under an approved protocol from the Texas Biomedical Research Institute Animal Care and Use Committee. All animals were housed in accordance with the *Guide for the Care and Use of Laboratory Animals*,[27] Public Health Service Policy,[37] and Animal Welfare Act[4] and Regulations[5] in an AAALAC-accredited facility. The macaques were housed in visual and auditory contact with conspecifics and were pair-housed when not actively being handled. They received Purina 5 LEO Monkey Diet (15% crude protein, 4% crude fat, 5% crude fiber; Purina Mills, St Louis, MO) once daily and municipal tap water ad libitum. Fresh produce or grains were offered as edible enrichment items daily. Rooms were maintained at 74 °F ± 10 °F and 30% to 70% relative humidity. Air was 100% conditioned with a minimum of 10 changes hourly. Fluorescent lighting was provided on a 12:12-h light:dark cycle (lights on, 0700 to 1900). Animals were housed in squeeze-back cages with a removable divider. All macaques were provided with manipulable enrichment (balls, kongs, toys) as well as auditory enrichment via a radio during the day. All animals were tuberculosis-free as determined by semiannual skin testing. All female macaques were negative for *Trypanasoma cruzi*, and all male macaques were *T. cruzi*-positive, as confirmed by ELISA and PCR testing. All female macaques tested negative for STLV and B virus and positive for SRV; all male macaques were negative for SRV, STLV, and B virus. All female macaques were supplied through an onsite colony, and male macaques were supplied through an outside vendor. All animals received a physical examination by the study veterinarian prior to study selection and were deemed fit for study.

Animal handling. All macaques were handled unanesthetized for the duration of the study. The pole-and-collar method was used.[2,34] During their pretreatment physical examination, all animals were fitted with an appropriately sized primate collar (nylon or aluminum; Primate Products, Miami, FL). All animals were trained by using positive reinforcement to separate and allow a divider to be placed between the paired cagemates. Each then was trained with positive reinforcement to be caught on the pole and transported to the front of their cages. The male macaques were trained to climb from the cage onto a rolling chair-restraint device (Primate Products), to which the collar was secured and on which the limbs could be manipulated. The female macaques were trained to exit their cages on the pole supported by technicians. The macaques were carried to a primate blood-collection stand (Byers Manufacturing, Lawton, MI), where a second technician temporarily restrained them, allowing for blood collection and quick release back to their home cages. Small edible rewards were given each time animals were returned to their home caging. During long interbleed intervals (more than 1 h) and after the completion of all study activities for the day, the dividing panels were removed from the cages, and the pairs were allowed to resocialize.

Drugs. Animals received meloxicam as 0.2 mg/kg IM once daily (Loxicom 5 mg/mL, Norbrook, Newry, Northern Ireland), 0.1 mg/kg PO once daily (Metacam 1.5 mg/mL, Boehringer Ingelheim, St Joseph, MO), and as a single injection (0.6 mg/kg SC) of meloxicam SR (2 matrix formulations; Meloxicam SR 10 mg/mL, ZooPharm, Fort Collins, CO) with a minimum of 6 wk between dosing.

Animals were divided into 2 dosing groups of 6 animals, 3 male and 3 female macaques, in each group. The first group received meloxicam SR subcutaneously followed 6 wk later by oral meloxicam. The second group received meloxicam intramuscularly followed 6 wk later by meloxicam SR (SR1) subcutaneously. Because of unexpected injection site reactions, 6 animals received meloxicam SR again 8 wk after completion of the first 2 rounds. Four macaques from group 1 were used, but 2 animals from the same group were deemed unfit at that time (one had a low hematocrit due to heavy menstruation, and the other had a thickening of the muscle at the previous injection site) and were replaced with 2 animals from group 2. A second formulation of meloxicam SR (SR2), incorporating an adjustment to the polymer delivery matrix formulation, was administered during the second and third rounds of dosing.

Dosages were based on accepted dosages for dogs, information in formularies, and the limited published studies available

for dosages in nonhuman primates.[16,26] The standard dosages included in the package inserts for the intramuscular (0.2 mg/kg) and oral (0.1 mg/kg) formulations were used. The dosage for meloxicam SR (0.6 mg/kg) was calculated based on a cumulative volume administered over 3 d of the injectable intramuscular formulation. This dose was derived after discussion with the manufacturer and review of an unpublished study of the same compound in dogs.

All macaques were weighed prior to each round of dosing to allow for accurate drug dosage. Animals receiving meloxicam SR received a single dose that was designed to release and sustain therapeutic levels of meloxicam throughout a 72-h period. Macaques receiving the oral or intramuscular formulations received a dose once daily for 3 d (0, 23, and 47 h). During the predose blood collection, both thighs were shaved for easy observation of the injection site. For the first dose of each round, the macaques were restrained in their caging by using the squeeze-back until they were immobilized. The subcutaneous and intramuscular injections were administered in the right or left thigh. The oral dosage was administered by using a needleless syringe inserted into the cheek pouch. For subsequent doses (intramuscular and oral), the animals were restrained for blood collection, and intramuscular doses were administered in the opposite thigh from the previous day while the animals were out of their cages. All injection sites were circled with permanent marker for easy identification and observation. All dosage sites and times of administration were documented by the administrator.

Sample collection. Blood samples were collected at 16 time points for each round of drug administration. A 2-mL blood sample was collected into EDTA at each of the 15 designated time points to determine plasma concentration of meloxicam. Blood collection time points included predose (0 h) and 0.25, 0.5, 1, 4, 8, 12, 23, 24, 36, 47, 48, 72, 96, and 120 h after dose administration. All times were based on the first dose. Animals were handled unanesthetized and had access to food and water at all times throughout the study. For predose (0 h) and day 7 samples, 5 mL blood was collected for a routine CBC (EDTA-treated) and chemistry panel (serum). On day 7, macaques were reweighed, and samples for CBC and chemistry analysis were collected. After sample collection, blood tubes were placed into a rack and were taken to an onsite clinical pathology laboratory for plasma separation within an hour of blood draw during business hours. The samples collected at night were placed in a refrigerator and taken to the lab for plasma separation first thing the next morning. In the laboratory, the samples were centrifuged at 2000 × *g* for 10 to 15 min. The plasma was collected into 2 aliquots and stored at −80 °C until shipment on dry ice for analysis (Protea Biosciences, Morgantown, WV).

Animal observations. Animals underwent cageside observations at baseline (predose) and at 1, 4, 8, 12, 23, 24, 36, 47, 48, 72, 96, and 120 after dosing. All times were based on the first dose. The same set of technicians conducted all observations to minimize interobserver differences. Observations included ingestion of water, stool production, attitude and behavior, food intake, regurgitation or vomiting, and urination. Any other changes from baseline were noted on the same observation form. All injection sites were examined for redness, heat, swelling, ulceration, and necrosis when animals were out of their cages during each blood collection time point. Macaques receiving multiple injections (intramuscular meloxicam) had all injection sites observed for the same criteria.

Health evaluation. Although all animals were confirmed to be healthy through physical examinations prior to study selection, the health of the macaques was continually monitored throughout the study. All macaques were screened by physical examination prior to study selection and were deemed to be healthy. All animals were housed in large indoor–outdoor groups prior to study selection. Viral status of all animals was determined prior to onset of the study. After selection, the macaques were relocated to indoor housing and were observed and placed into compatible pairs by the behavior department. During this time, all macaques had a minimum of 6 wk of training for the pole and collar and respective restraint method (chair for males, blood collection stand for females). Animals were weighed 3 d before dosing started and 7 d post dose administration for all rounds of dosing. During the washout period, animals were weighed biweekly during cage change. Additional physical examinations were performed as deemed necessary by the study veterinarian. Throughout the study, animals had twice-daily cageside observations to monitor food consumption and overall animal health.

Sample analysis. All CBC and chemistry samples were processed at an on-site clinical pathology laboratory. CBC were performed on a UniCel DxH 800 machine (Beckman Coulter, Brea, CA), and chemistries were performed on a UniCel DxC 600 machine (Beckman Coulter). All plasma samples were analyzed for quantification of meloxicam drug concentrations at Protea Biosciences (Morgantown, WV) by using HPLC–mass spectrometry. The samples were thawed on the bench top at room temperature, vortexed for at least 1 min, and aliquotted into 1.5-mL microcentrifuge tubes by using a 50-µL sample volume. Next, 50 µL of a working solution of the internal standard (250 ng/mL meloxicam-d_3 in 50:50 methanol:water) was added. The proteins were precipitated by adding 150 µL acetonitrile. All tubes then were capped, vortexed for 3 min on a multitube vortexer, and centrifuged for 10 min at 20,000 × *g*. Water (100 µL) was added to each sample well of a 96-well plate (U96 PP 2 mL, Nunc, Waltham, MA). Supernatant from each sample (100 µL) was added to the water in the 96-well plate. The plate was sealed with a pre-slit Capmat (Nunc), vortexed for 1 min on a multitube vortexer, and stored at 4 °C until analysis. Analysis was performed on a LC-20A HLPC (Shimadzu, Tokyo, Japan) and Triple-Quad 4000 (ABSciex, Toronto, Canada). The column used was an Amplus column (150 × 2.1 mm C18–16 [2.6 µm]; Protea Biosciences, Morgantown, WV) at a temperature of 40 °C. The lower limit of quantitation of the assay was 10 ng/mL, and the upper limit of quantitation was 4000 ng/mL.

Data analysis. Statistical analysis for meloxicam pharmacokinetics was performed and reviewed by Protea Biosciences (Morgantown, WV) by using Watson LIMS (Laboratory Information Management System; Thermo Scientific, Waltham, MA). Pharmacokinetic analysis was performed on plasma concentration–time data obtained after oral, intramuscular, or subcutaneous administration. AUC, clearance, peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), elimination half-life, volume of distribution, and mean residence time for each formulation were calculated. C_{max} and T_{max} were determined directly from the concentration–time data.

Pharmacokinetic parameters were derived by using noncompartmental analysis. $AUC_{0\text{-}Tlast}$ was determined by using the linear trapezoidal rule. The area was extrapolated to infinity (AUC_{∞}) by using the rate constant of the terminal elimination phase. The rate constant was derived from the slope of the terminal log-linear portion of the concentration–time curve by using a minimum of 3 measurable time points after C_{max} was reached. $T_{1/2}$ was determined by dividing the rate constant of terminal elimination into the natural logarithm of 2. For intramuscular

and oral formulations, the half-life was calculated from the first injection. Clearance was calculated by dose divided by AUC_{∞}. The volume of distribution at steady state (Vd_{ss}) was calculated by dividing the dose by the product of AUC_{∞} and the rate constant of terminal elimination. Elimination phase parameters were not estimated if the R^2 value was less than 0.99. The mean residence time was calculated as the area under the first moment curve extrapolated to infinity divided by AUC_{∞}. Data were analyzed by drug formulation (oral, intramuscular, SR1, SR2) and further segregated by sex within each formulation. The C_{max} and T_{max} for a single dose of intramuscular or oral meloxicam was determined directly from the concentration–time data. The elimination half-life was used to determine plasma levels of a single dose beyond 23 h.

Statistical analysis for blood work parameters and body weight was conducted by using Excel (Microsoft, Redmond, WA) and Minitab 16 (version 16.2.4, Minitab, State College, PA). Predose (day 0) and day 7 CBC counts and chemistry panels were compared for significant differences. *t* tests were completed for each parameter investigated. Pharmacokinetic parameters were compared by drug formulation to determine significant differences. Kruskal–Wallis tests were conducted to determine parameters for which a difference was present. Subsequent Mann–Whitney tests were conducted on the parameters that differed significantly. Significance was set at a *P* value of less than 0.05. For Mann–Whitney tests, Bonferroni corrections were applied, and for an overall significance of less than 0.05, the *P* value had to be less than 0.0083.

Results

Adverse effects. Adverse effects were seen only in the first group of 6 macaques that received meloxicam SR (SR1). Three of these animals (1 male, 2 female) had injection site reactions. The reaction was noticeable within the first hour after dose administration and ranged from mild reddening of the skin (2 animals) to sloughing of the superficial tissues (1 animal), with healing after approximately 1 wk (Figure 1). During the second round of dosing, the female macaque that had the most severe reaction during the first round had an abscess that opened and drained at the previous injection site. She was treated by drainage of the abscess and cleaning of the area, and the abscess resolved. The abscess did not appear to affect her overall health, and she showed no decline in appetite, attitude, or use of the limb. All subsequent meloxicam SR dosing was conducted using a modified matrix formulation (SR2; ZooPharm, Fort Collins, CO) at the same concentration and dose as for SR1. No adverse reactions were seen with the second matrix formulation.

Pharmacokinetics. Plasma concentration statistics are summarized in Table 1 for all formulations. The last quantifiable meloxicam concentration occurred as early as 96 h for the daily intramuscular formulation (3 doses), 96 h for the daily oral formulation (3 doses), 72 h for the single SR1 dose, and 48 h for the single SR2 dose. The following macaques still had quantifiable levels of drug at 120 h (the last sampling time point): 4 animals with the intramuscular formulation, 3 with SR1, 3 with oral, and 2 with SR2. The plasma concentration had a linear elimination curve and was dose-independent. The overall AUC for 3 daily injections of the intramuscular formulation (Figures 2 through 4) and a single injection (Figure 5) of the SR meloxicam (SR1 and SR2) had similar values. The 3 doses of the oral formulation resulted in an AUC 28.8% to 44.6% of that seen with the other formulations (Figures 2 and 3). The half-life of all formulations was approximately the same, with those of the SR formulations slightly shorter than that of the oral or intramuscular formulation. The C_{max} was higher for the SR formulations than the intramuscular formulation, which was higher than the oral formulation. The T_{max} for the sustained release formulation was longer than that for a single dose of intramuscular formulation, and shorter than that for the oral formulation. All formulations had similar volumes of distribution, with that of the intramuscular formulation less than and of the oral formulation greater than those of the SR formulations.

The Kruskal–Wallis tests identified significant differences among formulations in the following parameters: AUC_{∞}, AUC_{last}, clearance, C_{max}, volume of distribution relative to bioavailability, T_{max}, mean residence time, C_{max}, T_{max}, and volume of distribution at steady state. Bonferroni corrections were applied, and Mann–Whitney tests were used to compare all formulations. Pairwise determinations of significance are reported in Table 2. Although AUC_{∞} and AUC_{last} were identified demonstrating significant differences in the Kruskal–Wallis test, after corrections were applied, no significant differences remained between formulations in pairwise comparisons. Results are reported for 3-d daily dosing of the intramuscular and oral formulation. For the parameters for which single-dose parameters were identified (C_{max} and T_{max}) results are also reported. Half-lives and rate constants showed no significant differences. No significant differences were seen for any parameter or formulation when male macaques were compared with female.

Animal health. All animals remained healthy over the course of the study. Injection site reactions occurred in 3 animals and resolved without additional treatment. Only localized reactions were seen at any injection site, with most animals having no reaction. Body weight fluctuated comparably to other animals that have moved from outdoor group housing to indoor pair or single housing. Throughout the study, all animals maintained a normal appetite, stool, and thirst.

Blood work. The significant differences noted on blood work can be attributed to the volume of blood drawn during the study. RBC, Hct, and Hgb were lower on day 7 than day 0 for all formulations (Table 3). There were no significant differences in creatine phosphokinase and all kidney (BUN, creatinine, BUN:creatinine ratio) and liver parameters (total protein, albumin, globulin, ALT, AST, ASP, GGT, LDH, and total bilirubin) when pre- and post-dosing data from the same animal were compared.

Observations. Subjective evaluation of all macaques revealed no deviations from baseline throughout the study. There were no changes noted in appetite, urination, defecation, water intake, or behavior. All pairs remained socially housed throughout the study, with no adverse effects noted due to animal manipulation. Macaques remained cooperative to handling, becoming more amenable to handling as the study progressed. Animals did not exhibit overt signs of stress during handling, including dosing and bleeding, and displayed affiliative reactions, such as lip smacking and cooing, to the personnel handling them.

Discussion

NSAID dosages for use in nonhuman primates are typically derived from dosages published for canine or human patients, and there is little information available regarding dosing in nonhuman primates. Because of its specificity for cyclooxygenase 2, meloxicam has a relatively high therapeutic index and low ulcerogenic potential,[15] minimal effects on prostaglandin E_2 production, improved gastrointestinal tolerability,[6,9,35] no inhibition of platelet aggregation,[3,13,24] and no inhibition of proteoglycan synthesis.[35] Despite these characteristics, caution should be exercised in the use of meloxicam. Meloxicam is extensively bound

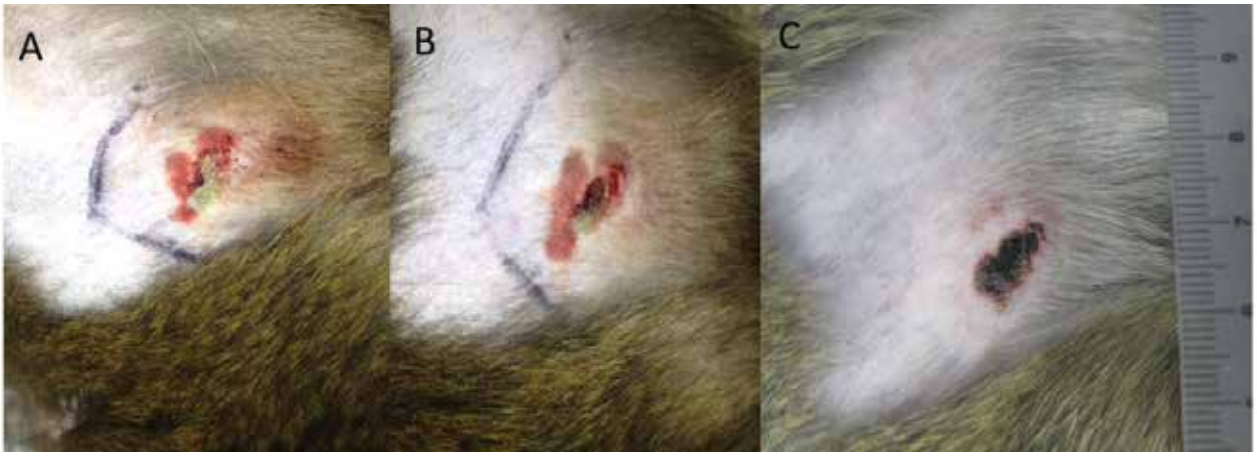

Figure 1. The macaque (female) with the worst injection site reaction during the first round of meloxicam SR administration (SR1). (A) 1 h, (B) 4 h, and (C) 72 h after injection.

Table 1. Meloxicam pharmacokinetics

	Oral			Intramuscular		
	Overall	Male	Female	Overall	Male	Female
AUC_{last} (ng×h/mL)	31222.9 ± 2417.9	33984.1	29842.3	108387.0 ± 30145.8	85413.5	131360.0
AUC_{∞} (ng×h/mL)	31900.6 ± 2485.5	34770.6	30465.6	109758.0 ± 31297.0	85943.5	133572.0
Clearance (mL/kg/h)	3.147 ± 0.234	2.876	3.282	1.949 ± 0.602	2.387	1.511
C_{max} (ng/mL)	507.933 ± 80.308	479.900	521.950	2467.500 ± 630.486	1979.000	2956.000
Rate constant of terminal elimination (1/h)	0.050 ± 0.008	0.049	0.051	0.052 ± 0.007	0.057	0.047
Elimination half-life (h)	14.076 ± 2.029	14.134	14.048	13.631 ± 2.140	12.139	15.124
T_{max} (h)	29.333 ± 22.745	36.000	26.000	42.000 ± 12.000	48.000	36.000
Apparent volume of distribution (mL/kg)	63.913 ± 10.651	58.659	66.540	37.324 ± 8.365	41.994	32.654
Mean residence time (h)	49.733 ± 7.677	52.968	48.116	40.990 ± 2.961	39.391	42.590
Volume of distribution (mL/kg)	156.061 ± 23.728	152.336	157.924	79.189 ± 22.642	94.411	63.967
	$n = 3$	$n = 1$	$n = 2$	$n = 4$	$n = 2$	$n = 2$
T_{max} 1 dose (h)	4.000	4.000	4.000	0.417	0.333	0.500
C_{max} 1 dose (ng/mL)	440.683	384.867	496.500	2134.167	2538.667	1842.000
	$n = 6$	$n = 3$	$n = 3$	$n = 6$	$n = 3$	$n = 3$
		SR1			SR2	
	Overall	Male	Female	Overall	Male	Female
AUC_{last} (ng×h/mL)	80407.4 ± 13067.3	76519.9 ± 12957.2	84294.8 ± 14617.2	69978.0 ± 20514.1	72354.1 ± 19473.9	67601.9 ± 23087.6
AUC_{∞} (ng×h/mL)	80995.8 ± 13224.5	77058.9 ± 12785.8	84932.7 ± 15074.7	70421.1 ± 20520.6	72824.9 ± 19518.0	68017.4 ± 23056.2
Clearance (mL/kg/h)	7.576 ± 1.235	7.919 ± 1.201	7.233 ± 1.420	9.135 ± 2.346	8.711 ± 2.156	9.559 ± 2.651
C_{max} (ng/mL)	3183.170 ± 447.764	3476.330 ± 276.524	2890.000 ± 480.567	3942.170 ± 711.324	3865.000 ± 629.050	4019.330 ± 838.549
Rate constant of terminal elimination (1/h)	0.055 ± 0.011	0.059 ± 0.011	0.051 ± 0.010	0.057 ± 0.008	0.057 ± 0.008	0.056 ± 0.009
Elimination half-life (h)	13.144 ± 2.858	12.107 ± 2.568	14.180 ± 3.256	12.437 ± 1.742	12.325 ± 1.767	12.549 ± 1.877
T_{max} (h)	4.167 ± 2.229	3.000 ± 1.732	5.333 ± 2.309	2.250 ± 2.854	3.125 ± 3.787	1.375 ± 1.321
Apparent volume of distribution (mL/kg)	140.107 ± 14.616	135.381 ± 5.837	144.833 ± 20.809	161.622 ± 40.463	151.546 ± 26.719	171.785 ± 51.383
Mean residence time (h)	20.798 ± 6.300	17.416 ± 2.700	24.181 ± 7.589	16.570 ± 3.531	17.492 ± 3.708	15.647 ± 3.412
Volume of distribution (mL/kg)	152.213 ± 58.667	135.770 ± 3.154	168.656 ± 28.739	145.365 ± 26.632	146.420 ± 18.314	144.311 ± 34.508
	$n = 6$	$n = 3$	$n = 3$	$n = 12$	$n = 6$	$n = 6$

Oral (0.1 mg/kg) and intramuscular (0.2 mg/kg) values (mean ± 1 SD) are calculated on the basis of 3-d consecutive dosing. SR1 and SR2 values (mean ± 1 SD) are calculated on the basis of a single subcutaneous injection (0.6 mg/kg). Single-dose T_{max} and C_{max} were determined from sampling for the intramuscular and oral routes for comparison of single injections of all formulations.

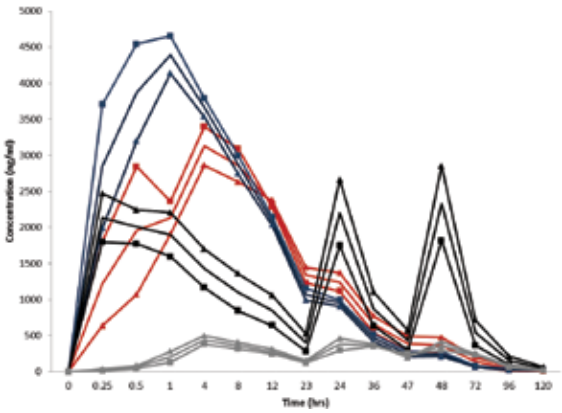

Figure 2. Plasma concentration of meloxicam after single injections of 2 meloxicam SR formulations (SR1 [red] and SR2 [blue]) and 3 consecutive daily intramuscular (black) and oral (gray) doses of meloxicam (0, 23, and 47 h). Plasma concentrations are reported for each sex (male, squares; female, triangles) individually and for all animals combined (lines with no symbols). All groups contained 3 male and 3 female macaques, except SR2 had 6 animals of each sex.

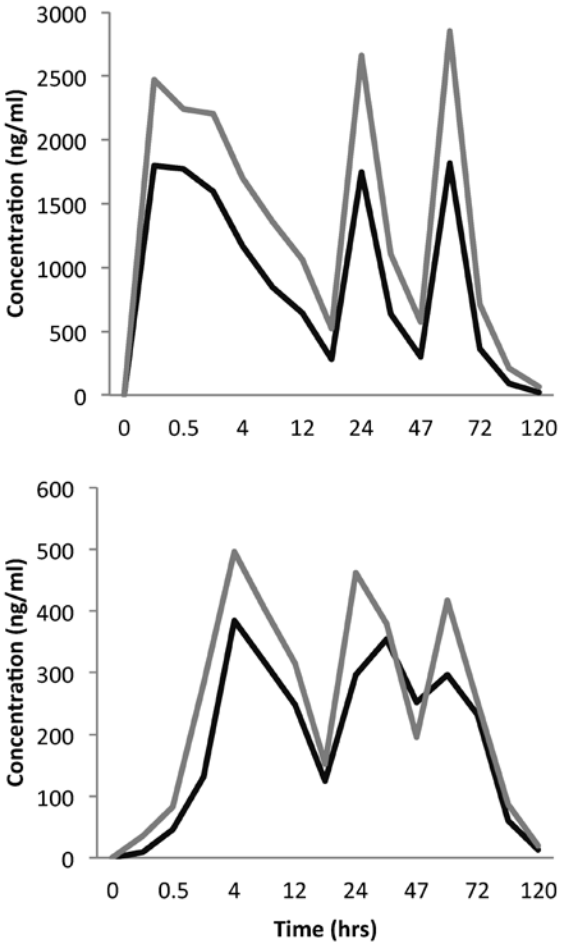

Figure 3. Plasma concentration levels for intramuscular (top) and oral (bottom) meloxicam. Both formulations showed higher concentration levels in female (gray lines; $n = 3$) than male (black lines; $n = 3$) macaques. The oral formulation began to achieve a steady-state concentration over time, whereas the intramuscular formulation did not show this pattern. Both formulations rapidly declined following cessation of dosing.

to plasma proteins, especially albumin,[1,24,32,35,46] leading to a low volume of distribution. In a rat model, meloxicam preferentially localized in areas of inflammation after oral administration.[35]

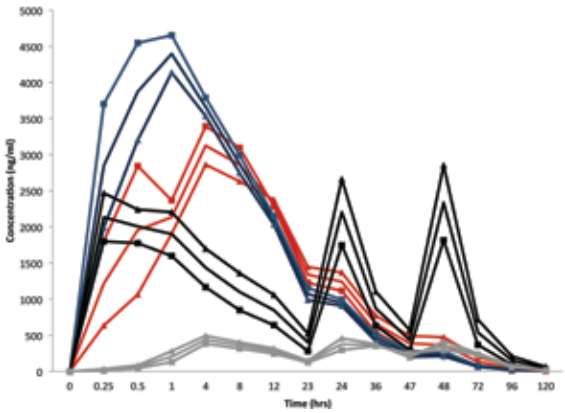

Figure 4. Plasma concentration of meloxicam SR1 (gray line; 3 female [triangles] and 3 male [squares] macaques) and SR2 (black line; 6 female and 6 male macaques) after a single subcutaneous dose. Initial concentrations were high but rapidly were metabolized to lower concentrations, leveling off to slow declines at approximately 48 to 72 h.

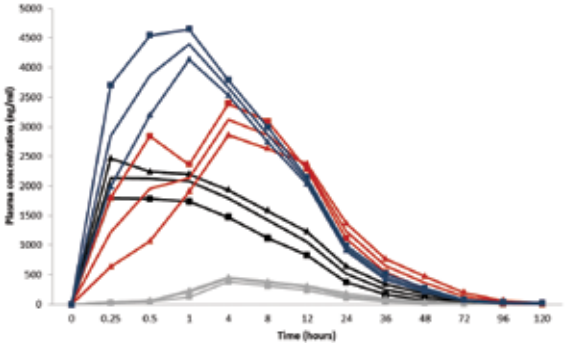

Figure 5. Meloxicam plasma concentrations after a single dosage of meloxicam SR (SR1 [red] and SR2 [blue]), intramuscular [black], and oral [gray] formulations. The plasma concentrations are reported for each sex [female, triangles; male, squares) individually and for all animals combined. All groups contained 3 male and 3 female macaques, except SR2 had 6 animals of each sex.

Humans demonstrate evidence of gastrointestinal recycling or enterohepatic recirculation of meloxicam, which may account for the slow elimination and a second maximal plasma concentration peak.[12,24,46] Subjects in the current study did not replicate the second peak of maximal plasma concentration seen in other studies, and this feature may be a difference between nonhuman primates and other species. Previous studies have shown food and antacid intake do not affect the rate of absorption of orally administered meloxicam.[10,19,24,35,46] Biotransformation through oxidation in the liver creates 4 inactive metabolites,[10,12,15,35] which are primarily excreted through the urine and feces.[6,15,24,46] Meloxicam can safely be used in patients with moderate renal or hepatic insufficiency,[9,12,19,24,46] making this drug an appealing option for veterinary patients who may be of unknown status or compromised.

Meloxicam is absorbed slowly, with peak plasma concentration in humans occurring 6 to 10 h after dosing.[10,19] In nonhuman primates, the absorption was more rapid, with the peak plasma concentration occurring at 4 h after a single oral dose, approximately a half-hour after a single intramuscular injection, and approximately a half-hour after subcutaneous injection of an SR formulation (Table 1, Figure 2). The absorption of meloxicam is independent of the dose, leading to a linear pharmacokinetic profile.[6,35,46] In humans, the plasma half-life is approximately 20 h, with a steady-state plasma concentration being achieved

Table 2. Pairwise comparisons of formulations for each pharmacokinetic parameter

	AUC_{∞}	AUC_{last}	CL/F	C_{max}	Vz/F	T_{max}	Mean residence time	V_d
SR1, SR2	NS	NS	NS	0.0131	NS	NS	NS	NS
SR1, IM	NS	NS	0.0142	NS/ 0.0131	0.0142	0.0142/ **0.0047**	0.0142	0.0142
SR1, PO	0.0282	0.0282	0.0282	0.0282/ **0.0051**	0.0282	NS/ NS	0.0282	NS
SR2, IM	0.0338	0.0338	**0.0044**	0.0091/ **0.0009**	**0.0044**	**0.0044/** 0.0235	**0.0044**	**0.0064**
SR2, PO	0.0115	0.0115	0.0115	0.0115/ **0.0009**	0.0115	0.0304/ 0.0409	0.0115	NS
IM, PO	NS	NS	NS	NS/ **0.0051**	NS	NS/ **0.0031**	NS	NS

CL, clearance, F, bioavailability; NS, not significant; V_z, volume of distribution; V_d, volume of distribution at steady state
Comparisons with intramuscular (IM) and oral (PO) formulations are based on 3 doses. Parameters in which information on a single dosage is available (C_{max} and T_{max}) are reported in the following format: 3 doses/ single dose. All *P* values less than 0.05 are reported; with Bonferroni corrections to reduce type I error, a *P* value less than 0.0083 (values bolded) is considered significant.
All values for comparisons of the terminal elimination rate constant and elimination half-life were nonsignificant.

Table 3. *P* values of differences in hematologic parameters before (day 0) and after (day 7) dosing.

	RBC count	Hemoglobin	Hematocrit	Platelet count
SR1	0.001	0.001	0.009	nonsignificant
SR2	<0.001	<0.001	<0.001	nonsignificant
IM	0.002	0.001	0.001	0.040
PO	0.017	nonsignificant	0.031	0.040

after 3 to 5 d.[10,12,19,20,24,46] In rats, a steady state also was reached after 3 to 5 d.[35] The current study reported a half-life of 12.4 to 15.1 h, depending on the formulation and sex, with no apparent steady-state reached within the time evaluated.

Pharmacokinetic values in various species have been explored and show marked variation (Table 4), leading to distinct interspecies differences in recommended meloxicam dosage.[7,8,15,22,30,32,35,41,42,43,47] In one study with 3 male baboons, meloxicam reached the mean peak plasma concentration at approximately 6 h after the administration of a 10-mg/kg PO dose.[15] This dose is 1.5 times that required to reach peak plasma concentration after a single dose of the slowest formulation (oral) in the current study. Because the baboons did not fall within the investigator's study objectives, additional investigation into their pharmacokinetic profile was halted.[15] In the current study, all elimination half-lives were shorter than that seen in humans and were approximately double that seen in the baboon study (Table 4). In cynomolgus macaques, peak plasma concentrations were reached 0.42 h and 4 h after a single dose was given (intramuscular and oral, respectively). The elimination half-life in many animals is considerably shorter than that seen in humans: 2.5 to 3.4 h in pigs,[23] 2.7 h in ponies,[30] 8.5 h in horses,[43] 10.9 h in sheep, and 6.7 h in goats.[41] The elimination half-life in cynomolgus macaques ranged from 12.4 to 15.1 h. It is reasonable to assume that animals with a shorter elimination half-life would have less plasma accumulation and be less likely to reach a steady state. If a steady state was reached, it would take longer than was investigated in the current study to achieve. The nadir prior to administration of dose 3 was slightly higher than that before administering dose 2, indicating that a steady-state plasma level might be achieved if dosing were continued long-term. This association was shown to be true of the oral formulation but not the intramuscular formulation (Figure 3). However, because the half-life in humans was almost double that of macaques, twice-daily dosing or a higher dose level may be indicated for macaques to achieve a steady-state plasma level. Both SR formulations appeared to remain at elevated levels for durations ranging from 48 to 72 h (Figure 4).

Previous studies have shown that meloxicam has a more rapid onset of action when given intramuscularly compared with orally.[22] When administered intramuscularly in humans, meloxicam reached peak plasma concentrations within 1.5 h rather than the 5 to 6 h reported for oral administration.[22] In the current study, peak plasma concentration with a single intramuscular dose was achieved in 0.42 h (range, 0.25 to 1 h) rather than 4 h when administered orally. Intramuscular and subcutaneous injections had a faster onset of action than did the oral form (Figure 5, Table 1). The oral formulation had low relative plasma concentrations at all time points, lending to uncertainty regarding whether therapeutic levels were reached or maintained (Figure 5). The intramuscular injections in humans are tolerated well, with only minor local reaction (redness) and minimal elevations in creatine kinase.[22] In the current study, there were no injection reactions, including redness, noted when meloxicam was given intramuscularly. There were no significant differences in the predose and postdose creatine kinase values, indicating no lasting muscle damage.

In humans and rats, a sex-associated difference exists in the metabolism of meloxicam, with females having a longer elimination half-life than males.[15] This pattern remained true for the macaques in the current study for all formulations, but these differences were nonsignificant. Meloxicam can be transmitted through the placenta and milk,[15] so care should be used with administration to lactating or pregnant animals. A marked sex-associated difference has been noted in plasma drug concentrations in dogs[47] and humans,[20] with males having lower plasma concentrations relative to females. This trend was seen in our cynomolgus macaques, with the exception of SR meloxicam (SR1 and SR2; Figures 3 and 4), but was nonsignificant. Additional studies with increased sample sizes may reveal significance.

NSAID classically have more potent analgesic and antipyretic effects than an antiinflammatory effect.[29,44] Antiinflammatory therapy is characterized by marked interindividual differences in response to therapy.[31] Therefore, it is important to have a clinical goal in mind when treating with NSAID. Each patient should be observed for the desired effects according to that goal. Because of the wide response to therapy, there is no definitive plasma concentration level that can be deemed to be therapeutic within and across species. Few studies published have attempted to define

Table 4. Published pharmacokinetic values for meloxicam in various species

Species	Route	Dosage	*N*	AUC_{∞} (ng×h/mL)	CL (mL/kg/h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)	Vz/f (mL/kg)	MRT (h)	V_d mL/kg	Reference
Cynomolgus	IM	0.2 mg/kg × 3 doses	4	109758.0 ± 31297.0	1.9 ± 0.6	2467.5 ± 630.5	13.6 ± 2.1	42.0 ± 12.0	37.3 ± 8.4	41. 0 ± 3.0	79.2 ± 22.6	this study
Cynomolgus	IM	0.2 mg/kg	6			2134.2	13.6 ± 2.1	0.4				this study
Cynomolgus	PO	0.1 mg/kg × 3 doses	3	31900.6 ± 2485.5	3.1 ± 0.2	507.9 ± 80.3	14.1 ± 2.0	29.3 ± 22.8	63.9 ± 10.7	49.7 ± 7.7	156.1 ± 23.7	this study
Cynomolgus	PO	0.1 mg/kg	6			440.7	14.1 ± 2.0	4				this study
Beagles	PO	0.31 mg/kg	6	24800 ± 8560	12.6 ± 6	780 ± 1	17.5 ± 5.4	4.0 ± 0.0	320 ± 100	24.4 ± 6.6		49
Rabbits	PO	0.3 mg/kg	5	2570 ± 210	120 ± 10	140 ± 20	8.2 ± 2.2	6.4 ± 0.8			1460 ± 480	47
Rabbit	PO	1.5 mg/kg	5	5200 ± 1290	330 ± 60	300 ± 90	8.4 ± 1.2	6.8 ± 0.5			4140 ± 1030	47
Horses	PO	0.6 mg/kg	8			2580 ± 580		1.5 ± 1.1		7.22 ± 1.69		43
Dogs	PO	0.2 mg/kg				464	24	7.5				11
Male mice	PO	10 mg/kg	5	60700	164	18100	4.8	0.7	1130	3.89		15
Female mice	PO	10 mg/kg	5	89500	112	20700	4.5	0.6	718	4.48		15
Male rats	PO	1.0 mg/kg	5	83300	23	2350	50.0	4.4	2360	31.8		15
Female rats	PO	1.0 mg/kg	5	201000	10	3230	52.4	6.8	886	53.4		15
Beagles	PO	0.2 mg/kg	6	22900	9		23.7		300	40		15
Minipigs	PO	10 mg/kg	3	214000	47	15350	145	3	9850	67.5		15
Male humans	PO	7.5 mg	18		528	1050	20.1	4.9	14700			20
Baboons	PO	10 mg/kg	3	476000	22	34150	6.1	6	202	11.2		15
Beagles	SC	0.2 mg/kg	6	24100	8		23.7		280	35		15
Cat	SC	0.3 mg/kg	6		6.0 ± 1.1	1482 ± 172	37	2.2 ± 0.7			277 ± 96	25
Cynomolgus	SR1	0.6 mg/kg	6	80995.8 ± 13224.5	7.6 ± 1.2	3183.2 ± 447.8	13.1 ± 2.9	4.2 ± 2.2	140.1 ± 14.6	20.80 ± 6.30	152.21 ± 58.67	this study
Cynomolgus	SR2	0.6 mg/kg	12	70421.1 ± 20520.6	9.1 ± 2.4	3942.2 ± 711.3	12.4 ± 1.7	2.3 ± 2.9	161.6 ± 40.5	16.57 ± 3.53	145.37 ± 26.63	this study

CL, clearance, F, bioavailability; IM, intramuscular, NS, not significant; PO, oral; SR, sustained release; V_z, volume of distribution; V_d, volume of distribution at steady state.

a plasma concentration that is therapeutic; in most cases NSAID are dosed to effect. Typically the recommendation is to start at the suggested dose and titrate to achieve maximal effectiveness (Boehringer–Ingelheim; www.metacam.com). In cats, whose pharmacokinetic profile resembles humans,[25,46] 710 to 911 ng/mL was needed for the animals to demonstrate clinical improvement.[25] In horses, reported plasma concentrations required for an improvement in various clinical indicators ranged from 130 ng/mL to 730 ng/mL,[43,45] and the same investigator determined there was no relevant effect seen at a plasma concentration lower than approximately 1.5 ng/mL.[45] Humans were found to have a maximal concentration at steady state of 880 to 1920 ng/mL after 5 to 6 h.[10,35] As evidenced by the wide variety of plasma concentrations in this sampling of studies, it is difficult to pinpoint a therapeutic range that is applicable across all species. A better indicator of appropriate dosing would be to observe a desired effect, given that veterinary patients cannot verbalize.

It is difficult to determine effective dosages because all determinations of pain attenuation in veterinary patients must be done through subjective evaluation. No pain was inflicted in the course of the current study; therefore, subjective evaluations could not be done to ascertain effective attenuation of pain. The dosages used were based on subjective observations of animals that had been treated with meloxicam clinically and in which pain attenuated on the basis of observed behaviors and other subjective indicators. Previous onsite clinical cases include videotaped activity monitoring of an animal with arthritis before and after dosing with meloxicam, repaired lacerations and abrasions, amputations of digits (traumatic and surgical), and as a component of multimodal analgesia after surgery.

Meloxicam also affects prostaglandin levels required for ovulation in female nonhuman primates.[26] A 5-d course of meloxicam around the time of ovulation reduced oocyte release without altering hormones or menstrual cycle length.[26] Meloxicam crosses the placenta and is excreted in milk.[20] These are important factors to consider when selecting an antiinflammatory agent to be used in breeding nonhuman primates.

In the current study, meloxicam levels in plasma were relatively low after the oral formulation. The C_{max} achieved (507.9 ng/mL) is comparable to the level reported for canines,[11] which was determined to be therapeutic. However, given the earlier-referenced studies in which plasma concentrations were tested in relation to various indicators of pain, it is questionable whether a therapeutic level was ever attained in our macaques. If an effective level was reached, it is unclear whether therapeutic levels were maintained. To determine whether the oral formulation provides therapeutic levels of pain management in nonhuman primates, additional pharmacodynamic studies should be performed.

For the intramuscular and SR formulations, C_{max} levels were markedly higher than those for the oral formulation. The levels reached in the current study are similar to those obtained in previous studies with pigs,[23] horses,[43] rats,[15] cats,[25] and humans.[20] These dosages are widely considered therapeutic, lending credence to the possibility that the dosages currently being used in nonhuman primates are similarly therapeutic. Although the duration of action of each formulation depends on the subjects being treated, the general trend suggests that the oral formulation provides a relative short duration of action (8 to 12 h), the intramuscular formulation provides approximately 24 h of action, and the SR formulations provide approximately 48 to 72 h of action. The SR formulations demonstrated more consistent levels in the plasma, as compared with formulations that are dosed daily. To determine the true therapeutic range and duration of action for each formulation in nonhuman primates, additional pharmacodynamic studies need to be conducted.

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