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Pharmacokinetics of Injectable Meloxicam and Buprenorphine in the Naked Mole-Rat (*Heterocephalus glaber*)

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Unique characteristics of the naked mole-rat (NMR) have made it increasingly popular as a laboratory animal model. These rodents are used to study many fields of research including longevity and aging, cancer, circadian rhythm, pain, and metabolism. Currently, the analgesic dosing regimens used in the NMR mirror those used in other rodent species. However, there is no pharmacokinetic (PK) data supporting the use of injectable analgesics in the NMR. Therefore, we conducted 2 independent PK studies to evaluate 2 commonly used analgesics in the NMR: meloxicam (2 mg/kg SC) and buprenorphine (0.1 mg/kg SC). In each study, blood was collected at 8 time points after subcutaneous injection of meloxicam or buprenorphine (0 [predose], 0.25, 0.5, 1, 2, 4, 8, and 24 h). Three NMRs were used per time point for a total of 24 animals per PK study. Plasma concentrations of meloxicam were highest between 0.5 and 1 h postinjection. Levels remained above the extrapolated dog and cat therapeutic threshold levels (390 to 911 ng/mL) for at least 24 h. Plasma concentrations of buprenorphine were highest between 0.25 and 0.5 h postinjection. Levels remained above the human therapeutic threshold (1 ng/mL) for up to 21 h. No skin reactions were seen in association with injection of either drug. In summary, these data support dosing meloxicam (2 mg/kg SC) once every 24 h and buprenorphine (0.1 mg/kg SC) once every 8 to 12 h in the NMR. Further studies should be performed to evaluate the clinical efficacy of these drugs by correlating plasma concentrations with postoperative pain assessments.

Abbreviations and Acronyms: AUC0-∞, area under the plasma concentration–time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration–time curve from time 0 to the last observed concentration; AUMC0-last, area under the plasma concentration–time moment curve from time 0 to the last observed concentration; CL, clearance; COX, cyclooxygenase; MRT0-∞, mean residence time from time 0 to infinity; MRT0-last, mean residence time from time 0 to last observable concentration; NMR, naked mole-rat; NSAID, nonsteroidal antiinflammatory drug; PK, pharmacokinetic; t1/2-λz, elimination half-life; λz, terminal elimination rate constant

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Introduction

One of the most important aspects of laboratory animal medicine is the management of pain and distress. The *Guide for the Care and Use of Laboratory Animals*, Public Health Service policy, and the Animal Welfare Act all include statements mandating that pain and distress experienced by research animals be minimized when possible.[2,27,40] Providing appropriate pain management to laboratory animals is not only required by law but is also one of the core ethical obligations addressed in the 3Rs (replacement, reduction, and refinement) principle, which is used as a guiding foundation for improving laboratory animal welfare throughout the world.[26,34] Furthermore, it has been established that pain and suffering can dramatically alter an animal's behavior, physiology, and immunology, therein creating unpredictable, significant variables that can impair scientific quality, reliability, and reproducibility.[4,29,39] Taken together, these reasons make providing appropriate analgesia intrinsic to the framework of humane and efficacious animal research.

Nonsteroidal antiinflammatory drugs (NSAIDs) are a category of analgesics that are commonly used to treat mild to moderate pain in veterinary medicine. NSAIDS work through the inhibition of cyclooxygenase (COX) enzymes. COX-1 enzymes are present in many tissues throughout the body and generally mediate homeostatic functions such as maintaining the integrity of the gastric mucosa, preserving normal platelet function, and regulating renal blood flow. COX-2 enzymes are activated in damaged or inflamed tissues and generally amplify the inflammatory response, which includes pain, inflammation, and fever. Overall, the analgesic, antiinflammatory, and antipyretic effects of NSAIDs predominantly result from COX-2 inhibition, and the negative side effects such as gastrointestinal toxicity, coagulopathy, and renal and hepatic failure largely result from COX-1 inhibition. Meloxicam is an NSAID that preferentially inhibits COX-2 over COX-1, and therefore it has a decreased risk of negative side effects compared with other, nonselective NSAIDs.[15,17,20,45] Pharmacokinetic (PK) and efficacy studies have proven meloxicam to be an effective analgesic in the mouse, rat, and many other species used in research.[9,21,28,30,46] Based on these studies, commonly referenced

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doses for meloxicam include 2 to 10 mg/kg SC every 8 to 12 h in mice and 1 mg/kg SC every 12 to 24 h in rats.[5,9,18,30,35]

Opioids are a category of analgesics that are commonly used to treat moderate to severe pain in veterinary medicine. Opioids work by mimicking the effects of endogenous opioids and acting as an agonist, antagonist, and/or partial agonist on the μ, δ, and κ opioid receptors. The principal positive effect of opioid use is analgesia, while negative side effects can include respiratory depression, hypothermia, constipation, nausea, and addiction. Opioids can produce variable amounts of both analgesia and negative side effects depending on their action on and affinity to the different opioid receptors. Buprenorphine is a semisynthetic opiate classified as a partial μ receptor agonist and κ receptor antagonist that provides analgesia with minimal respiratory depression.[12,31,38] PK and efficacy studies have proven buprenorphine to be an effective analgesic in the mouse, rat, and many other species used in research.[11,19,25,31,33] Based on these studies, commonly referenced doses for buprenorphine include 0.1 to 0.5 mg/kg every 4 to 6 h in the mouse and 0.05 to 0.1 mg/kg every 6 to 8 h in the rat.[5,9,18,30,35]

Naked mole-rats (NMRs) (*Heterocephalus glaber*) are an emerging nontraditional laboratory animal model and are used in many fields of research including longevity and aging, cancer, circadian rhythm, pain, and metabolism.[6–8,14,16,36,41] As the use of NMRs in research has increased, there is a need to establish data that can guide the medical management of pain in this unique species. PK studies are conducted to determine the absorption, distribution, metabolism, and elimination of test compounds in a living organism. Mathematical models derived from these data allow for the characterization of drug disposition, half-life, elimination constants, and exposure levels.[24,42,44,47] Ultimately, PK studies support our understanding of how different compounds are processed by the body in different species. Currently, analgesic practices used for the NMR mirror those used in other rodent species such as mice and rats, for which there are well-established PK data. Differences in the metabolic activity of the NMR as compared with other mammals have been described in literature, and this may have an effect on drug absorption and kinetics in this species.[8,16,23,37] To date, no PK profiles exist for either meloxicam or buprenorphine in the NMR.

The aim of the project was to perform 2 PK studies in the NMR to assess 2 commonly used analgesics in rodents, injectable meloxicam and buprenorphine. Our hypothesis is that when NMRs are given a dose of meloxicam that is consistent with published mouse and rat dosing recommendations (2 mg/kg SC),[5,9,18,30,35] plasma concentrations of this drug will remain above the proposed therapeutic plasma concentration that has been shown to be effective in dogs and cats, 390 to 911 ng/mL, for 12 to 24 h.[18,21,28] We also hypothesize that when NMRs are given a dose of buprenorphine that is consistent with published mouse and rat dosing recommendations (0.1 mg/kg SC),[1,13,18,19,22,32] plasma concentrations of this drug will remain above the proposed therapeutic plasma concentration that is effective in other species, 1 ng/mL, for 6 to 8 h.[11,19,25,30] The results of this study will ultimately contribute valuable information to support our understanding of pain management in this unique species with the ultimate goal of improving animal welfare.

Materials and Methods

Ethics statement. All procedures were performed under approval from the University of Illinois Chicago Animal Care Committee. All animals were housed in accordance with the *Guide for the Care and Use of Laboratory Animals* , Public Health Service policy, and Animal Welfare Act and Regulations in an AAALAC-accredited facility.[2,27,40]

Animals. Experiments were conducted on clinically normal NMRs (*H. glaber*, n = 48 [29 females and 19 males], age ≥ 1 y, weight = 20 to 70 g). NMRs were housed under seminatural conditions in an artificial burrow system consisting of standard mouse and/or rat microisolation cages interconnected with PVC pipe. These systems were lined with cellulose bedding (Envigo Bioproducts, Madison, WI, 7070C certified diamond dry bedding®) and maintained within an animal housing room on a 14-h light/10-h dark cycle at 80 ± 2 °F and 30% to 70% relative humidity.[3] NMRs were fed a diet consisting primarily of sweet potato/yam and a rotating mix of other seasonal fruits and vegetables. No water was provided, as NMRs obtain all their water from their food.[43] All NMRs used in this study were obtained from an existing in-house colony.

PK study—groups. NMRs were divided into 2 groups, one meloxicam group and one buprenorphine group. In each group, samples were collected at 8 time points postadministration: 0 (predose), 0.25, 0.5, 1, 2, 4, 8, and 24 h. Three animals were used per time point for both meloxicam and buprenorphine PK analysis, for a total of 48 study animals. The number of time points and animals per time point were chosen with direct input and guidance from an experienced scientist in the field of PK analysis.

PK study—compound administration. Meloxicam (meloxicam injectable solution, 5 mg/mL, 20 mL/vial, packager: Covetrus North America, Dublin, OH, NDC: 11695-6936-2) was diluted with sterile water to a final dose concentration of 0.5 mg/mL used in this study. Buprenorphine (buprenorphine HCl injection, 0.3 mg/mL, 1 mL/vial, packager: Par Pharmaceutical, Chestnut Ridge, NY, NDC: 42023-179-05) was diluted with sterile saline to a final dose concentration of 0.03 mg/mL used in this study. All animals were weighed immediately before compound administration to allow for accurate dosing of medications. The method of dosing was identical for both compounds. Subcutaneous injections were administered as a single bolus without anesthesia to manually restrained NMRs. A 23- to 25-gauge needle was used depending on the size of the NMR. The area of skin on the dorsal surface of neck between the shoulders was pinched into a tent shape and the needle was inserted at the base of this skin tent. Needle positioning was confirmed by tugging slightly upward on the syringe and visualizing subcutaneous placement. The contents of the syringe were fully injected, and the needle was withdrawn. The area of the back where the injection was given was gently rubbed and the animal was returned to its cage. Meloxicam was given at a dose of 2 mg/kg SC once and buprenorphine was given at a dose of 0.1 mg/kg SC once. This injection was considered time point 0. All NMRs were observed by a veterinarian for any clinical signs of adverse reactions such as changes in behavior, mentation, appetite, activity, or injection site reactions immediately after dosing, intermittently between dosing and sample collection, and immediately before sample collection.

PK—sample collection. Terminal caudal vena cava blood collection was performed under isoflurane anesthesia. After confirming anesthetic depth, a 1- to 2-cm full thickness abdominal incision was made. A 25- to 27-gauge needle was used to collect blood from the caudal vena cava, after which blood was immediately transferred to a K2EDTA tube. Blood collection was completed in approximately 3 min and was directly followed by cardiac perfusion for collection of tissues for another study. Postmortem examination was performed by a veterinarian to confirm NMR sex and observe any signs

of gross pathology such as injection site reactions, ulceration, and hemorrhage.

PK study—plasma sample analysis. Prior to study initiation, 5 mL (2.5 mL/assay) of baseline NMR plasma in EDTA tubes was sent to the University of Tennessee College of Veterinary Medicine to calibrate the meloxicam and buprenorphine assays needed for PK analysis. This 5-mL volume was obtained from an existing flash-frozen plasma bank maintained by another principal investigator at the author's institution. All blood samples from the study were collected in K2EDTA tubes and centrifuged for 10 min at 1,025 × *g*. Plasma was stored in a −80 °C freezer until it was sent on dry ice to the University of Tennessee College of Veterinary Medicine for PK analysis.

The analysis of meloxicam in plasma samples was conducted using reversed-phase HPLC method with UV detection. The compounds were separated on an Xbridge C18 (4.6 × 250 mm, 5 µm) column with a mobile phase of 10 mL of glacial acetic acid in 1 L of H_2O (pH 3.0 adjusted with sodium hydroxide) and acetonitrile (50:50). Absorbance was measured at 360 nm with a flow rate of 1 mL/min. Meloxicam was extracted from plasma samples using a liquid–liquid extraction. One hundred microliters of plasma was transferred to a screw top tube, and 15 µL of piroxicam (internal standard, 5 µg/mL) was added followed by 100 µL of 1 M HCl and 2 mL of chloroform. The tubes were vortexed for 60 s and then centrifuged for 20 min at 1,070 × *g*. The organic phase was transferred to a glass tube and evaporated to dryness with nitrogen. Standard curves for plasma analysis were prepared by fortifying untreated plasma with meloxicam to produce a linear concentration range of 5 to 15,000 ng/mL. The intra- and interassay variability was less than 10%, and the average recovery for meloxicam was 93%. The lower limit of quantification during validation was 5 ng/mL.

The analysis of buprenorphine in plasma was conducted using reversed-phase HPLC and single-quadrupole mass spectrometry. The compounds were separated on an XBridge C18 (4.6 × 50 mm, 3.5 µm) column with a mixture of water with 0.1% formic acid and acetonitrile with 0.1% formic acid (90:10). The flow rate was 0.80 mL/min, and the column temperature was ambient, which was 30 °C. The compounds were detected by positive selected ion recording. The scan rate was 2 mV/s, gain 1, capillary voltage 0.8 kV, cone voltage 12, ion source temperature 150 °C, and probe temperature 600 °C. Nitrogen was used as the nebulizing gas. Buprenorphine was detected at 468.32 *m/z* and fentanyl was detected at 337.34 *m/z*. Buprenorphine was extracted from plasma samples using a protein precipitation with 0.1 M zinc sulfate and acetonitrile. Plasma samples (100 µl) were transferred to a 7-mL glass screw top tube, after which 10 µL of internal standard (0.1 µg/mL fentanyl) was added. Two milliliters of acetonitrile and 100 µL of $ZnSO_4$ were added and tubes were capped, vortexed for 30 s, and then centrifuged for 10 min at 1,020 × *g*. The supernatant was removed and placed in a glass tube and evaporated to dryness with nitrogen gas. Samples were reconstituted in 200 µL of mobile phase and 55 µL was injected into the HPLC system. Standard curves for plasma were prepared by spiking untreated plasma with buprenorphine, which produced a linear concentration range of 0.1 to 25 ng/mL. Intra- and interassay variability was less than 10%, and the average recovery of buprenorphine was 100%. The lower limit of quantification is 0.1 ng/mL.

PK study—PK statistical analysis. The plasma concentration–time data following the single subcutaneous dose of either meloxicam (2 mg/kg) or buprenorphine (0.1 mg/kg) were analyzed by noncompartmental methods using R version 4.3.1. The package 'ncappc' was used for pharmacokinetic analysis. The nominal time of blood collection was used for the analysis. The noncompartmental analysis provided estimates of the following parameters for each drug in each group: terminal elimination rate constant (λ_z) and elimination half-life ($t_{1/2\text{-}\lambda z}$), area under the plasma concentration–time curve from time 0 to the last observed concentration ($AUC_{0\text{-last}}$), area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$), area under the plasma concentration–time moment curve from time 0 to the last observed concentration ($AUMC_{0\text{-last}}$), area under the plasma concentration–time moment curve from time 0 to infinity ($AUMC_{0\text{-}\infty}$), clearance (CL), volume of distribution, C_{max}, T_{max} of observing C_{max}, the mean residence time from time 0 to last observable concentration ($MRT_{0\text{-last}}$), and the mean residence time from time 0 to infinity ($MRT_{0\text{-}\infty}$). The λ_z was estimated by linear regression of the terminal exponential portion of the log plasma concentration–time curve. At least 3 time points during a discernible terminal elimination phase and correlation coefficient for the log-linear regression analysis of >0.80 were required for acceptance of the λ_z calculation. The $t_{1/2\text{-}\lambda z}$ was determined by dividing 0.693 (ln 2) by λ_z. The linear trapezoidal method was used to calculate $AUC_{0\text{-last}}$ and $AUMC_{0\text{-last}}$. Extrapolation to infinity was performed by dividing the last observed plasma concentration by λ_z. The $AUC_{0\text{-}\infty}$ and $AUMC_{0\text{-}\infty}$ were obtained as the summing the extrapolated area to $AUC_{0\text{-last}}$ and $AUMC_{0\text{-last}}$, respectively. CL was calculated by dividing dose by $AUC_{0\text{-}\infty}$. The $MRT_{0\text{-last}}$ and $MRT_{0\text{-}\infty}$ were estimated as the ratios of the corresponding area under the moment curve (AUMC) to AUC. The CL was divided by λ_z to estimate the volume of distribution. We also reported the median values of the PK parameters along with their first and third quantiles of the 3 animals per group per drug. The interpolating line, the line between 2 time points t_1 and t_2 with mean plasma concentration y_1 and y_2, was calculated using the formula: $y = y_1 + (t - t_1) \times (y_2 - y_1)/(t_2 - t_1)$.

Results

Both meloxicam and buprenorphine were administered to all NMRs (n = 48) successfully on the first attempt. Overall, no adverse effects such as injection site reactions,[22,45] changes in behavior, mentation, appetite, or activity were observed during the period between injection and sample collection in the NMRs.

Meloxicam (2 mg/kg SC) reached a C_{max} of 7,705 ng/mL at a T_{max} of 0.5 h postinjection. The $t_{1/2\text{-}\lambda z}$ of meloxicam was 7.1 h and the $AUC_{0\text{-}\infty}$ was 78,778.52 ng h/mL. The λ_z was 10%/h and the CL from the plasma was 0.52 mL/h (Table 1). The mean concentration curve exceeded the upper limit of the assumed therapeutic threshold (911 ng/mL) at 0.0381 h, and the interpolated line did not fall below the lower limit of the threshold (390 ng/mL) within 24 h (Figure 1).

Buprenorphine (0.1 mg/kg SC) reached a C_{max} of 15.27 ng/mL at a T_{max} of 0.5 h postinjection. The $t_{1/2\lambda z}$ was 5.55 h and the $AUC_{0\text{-}\infty}$ was 73.39 ng h/mL. The λ_z of buprenorphine was 12%/h and the CL from the plasma was 8,348.07 mL/h (Table 1). The mean concentration curve for buprenorphine exceeded the assumed therapeutic threshold (1 ng/mL) at 0.0279 h, and the interpolated line fell below this threshold at 21.6703 h (Figure 2).

Discussion

Several testing methods can be used to help establish species-specific dosing regimens of drugs. These tests include PK studies, toxicity studies, analgesiometric tests, and post-surgical pain assessments. PK studies alone are not used to evaluate the clinical physiologic effects of drugs; however,

Table 1. Noncompartmental PK analysis of meloxicam (2 mg/kg) and buprenorphine (0.1 mg/kg) given subcutaneously to NMRs

PK parameter	Meloxicam (median [IQR])[a]	Buprenorphine (median [IQR])[a]
C_{max} (ng/mL)	7,705 (7,435.9–7,989.26)	15.27 (15.14–18.35)
T_{max} (h)	0.5 (0.5–0.75)	0.5 (0.38–0.5)
C_{last} (ng/mL)	753.58 (727.17–996.29)	0.54 (0.43–0.74)
T_{last} (h)	24 (24–24)	24 (24–24)
$AUC_{0\text{-}last}$ (ng/mL h)	62,942.75 (62,364.53–67,273.94)	61.29 (60.51–79.02)
$AUC_{0\text{-}\infty}$ (ng/mL h)	78,778.52 (74,694.66–79,309.11)	73.39 (69.48–86.08)
AUC (% extrapolated)	10.86 (9.98–16.74)	6.53 (4.28–12.57)
$AUMC_{0\text{-}last}$ (ng/mL)	499,040.51 (483,678.36–541,387.1)	477.43 (425.63–545.21)
$AUMC_{0\text{-}\infty}$ (ng/mL)	829,326.88 (779,851.18–1,012,351.96)	673.79 (592.32–838.13)
$MRT_{0\text{-}last}$ (h)	8.08 (7.76–8.11)	6.34 (6.22–7.16)
$MRT_{0\text{-}\infty}$ (h)	10.53 (10.44–12.75)	7.79 (7.31–10.73)
R-Squared	0.96 (0.87–0.97)	0.98 (0.96–0.98)
Correlation	−0.98 (−0.99–0.93)	−0.99 (−0.99–0.98)
λ_z (/h)	0.1 (0.08–0.1)	0.12 (0.1–0.14)
$t_{1/2\lambda z}$ (h)	7.1 (7.07–8.6)	5.55 (4.92–7.78)
Volume (mL)	7.56 (6.43–82.59)	51,745.39 (28,273.56–118,221.68)
CL (mL/h)	0.52 (0.52–8)	8,348.07 (4,474.09–10,566.47)

[a]PK Parameter data are reported as median values of the PK parameters along with their first and third quantiles of the 3 animals per group per drug. For more information on acquisition of data, see the section Materials and Methods.

they do provide critical data on how drugs are absorbed, metabolized, and excreted in different species. These data, when used in combination with other clinical testing modalities, are essential to the determination of safe and efficacious drug dosing regimens.

Two commonly used analgesics used in laboratory animal medicine are meloxicam and buprenorphine. Previous studies have evaluated the PK profiles and clinical efficacy of these analgesics in laboratory animal species, including the dog, cat, mouse, and rat, but none has been performed using the NMR. The aim of this study was to establish a PK profile for both meloxicam (2 mg/kg SC) and buprenorphine (0.1 mg/kg SC) in the NMR. Determining the clinical efficacy of meloxicam and buprenorphine in the NMR was not the intent of this study; however, these doses have been used at our institution to clinically manage pain in this species.

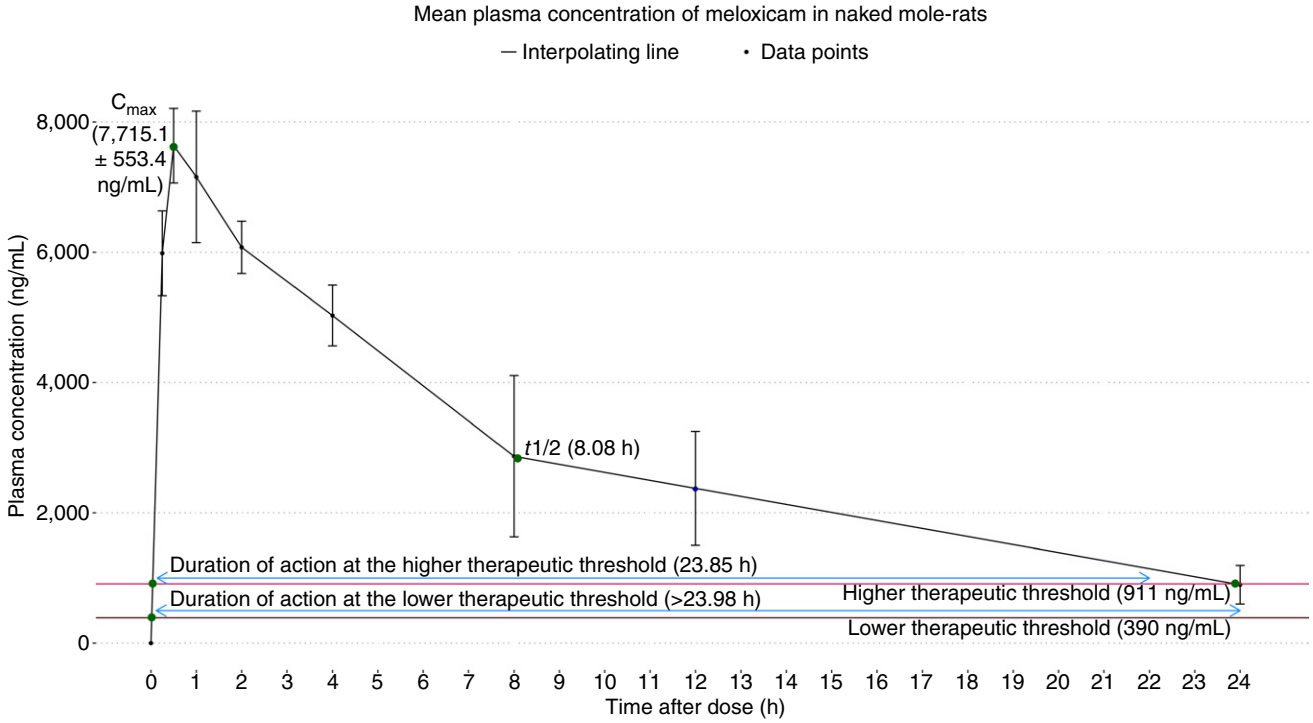

Figure 1. Plasma concentrations of meloxicam in NMRs after subcutaneous administration of a single dose (2 mg/kg). PK data are reported in terms of mean and SD in this plot. Black dots represent data points, black brackets represent SD, and the black line connecting the data points represents the values calculated by linear interpolation. The blue diamond represents the calculated mean concentration at 12 h. The red horizontal line represents the higher therapeutic threshold, and the brown horizontal line represents the lower therapeutic threshold. The assumed therapeutic threshold range is 390 to 911 ng/mL. The horizontal blue lines represent the estimated duration of action of the drug, respective to the higher and lower threshold limits.

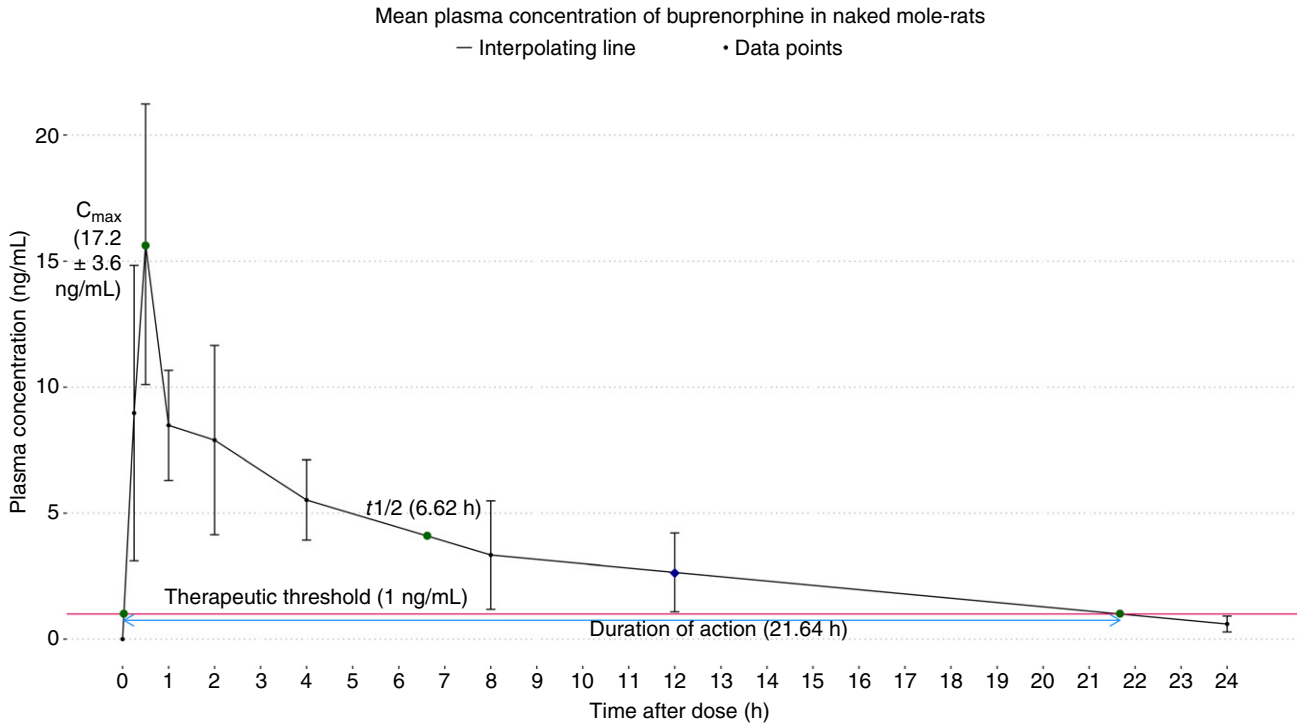

Figure 2. Plasma concentrations of buprenorphine in NMRs after subcutaneous administration of a single dose (0.1 mg/kg). PK data are reported in terms of mean and SD in this plot. Black dots represent data points, black brackets represent SD, and the black line connecting the data points represents the values calculated by linear interpolation. The blue diamond represents the calculated mean concentration at 12 h. The red horizontal line represents the assumed therapeutic threshold (1 ng/mL). The horizontal blue line represents the estimated duration of action of the drug.

Unique physiologic differences between species can lead to significant effects on drug pharmacokinetics. This point is exemplified by the different CL rates of meloxicam between mice, rats, and, as our study shows, NMRs. In a previous study, mice that received meloxicam (1.6 mg/kg SC) displayed a CL of 155 mL/h and rats receiving this same dose displayed a CL of 15 mL/h.[9,10] Our study used a slightly higher dose of meloxicam (2 mg/kg SC) and reported a CL of 0.52 mL/h in the NMR. Therefore, when comparing these studies, the CL of meloxicam in the mouse is approximately 10-fold higher than the rat and approximately 300-fold higher than the NMR. This is just one example of how a single pharmacokinetic variable can differ substantially between species. Therefore, it is considered best practice to perform species-specific pharmacokinetic studies even when using drugs, such as meloxicam and buprenorphine, that are well established in our more commonly used research animals.

Important values obtained by PK studies include C_{max}, T_{max}, C_{last}, $t_{1/2\lambda z}$, $AUC_{0-\infty}$, λ_z, and CL. C_{max} is the highest reported concentration of drug in the blood, and T_{max} is the time at which C_{max} is achieved. The elimination half-life of a drug, or $t_{1/2\lambda z}$, is the time at which the drug has lost half of its maximum concentration. $AUC_{0-\infty}$, or the area under the curve across time, represents the actual body exposure to a drug after administration of a dose of the drug, which is typically expressed in ng h/mL. The elimination rate, or λ_z, is the fraction of drug eliminated per hour. The C_{last} is the last quantifiable concentration of the drug and, in this study, corresponds with the drug concentration taken at 24 h. The interpolated line is calculated using the formula: $y = y_1 + (t - t_1) \times (y_2 - y_1)/(t_2 - t_1)$, where y equals the mean plasma concentration and t equals time. Using linear interpolation, plasma concentration at any time between 2 determined data points can be predicted and represented on a graph as a line connecting these data points. The therapeutic threshold is the minimum plasma concentration of drug required to provide effective analgesia, and this value is determined by performing efficacy studies using defined doses. The amount of time that drug concentrations remain above the therapeutic threshold is called the therapeutic window, and this determines the duration of action of the drug. Combining PK data and therapeutic threshold data helps support the determination of dosing regimens for appropriate analgesia.[24,44]

The targeted therapeutic plasma meloxicam concentration of 390 to 911 ng/mL has been established in cats and dogs, based on correlations between PK studies and clinical assessment of subjects.[18,21,28] In this study, when NMRs were dosed at time point 0 with meloxicam (2 mg/kg), quantifiable plasma concentrations above the therapeutic threshold were achieved by the first blood sample collection at 0.25 h, and a C_{max} of 7,705 ng/mL was reached at 0.5 h. This quick absorption time and time taken to reach C_{max} supports the use of meloxicam to treat urgent analgesic needs in the NMR. Most notably, the plasma concentration of meloxicam was maintained above the targeted therapeutic threshold through the 24 h time point with levels never falling below the threshold at any time point. The final 24 h time point reported a C_{last} of 753.58 ng/mL, which still fell within the upper range of the targeted therapeutic threshold for meloxicam. As no additional blood samples were collected after this final 24 h time point, the exact duration of action may be even longer than this duration. Overall, if the therapeutic threshold for meloxicam in the NMR is consistent with that of cats and dogs, then these data conservatively support a dosing regimen of 2 mg/kg SC every 24 h in the NMR.

The targeted therapeutic plasma buprenorphine concentration of 1 ng/mL has been suggested in mice, rats, and humans, based on correlations between PK studies and clinical assessment of

subjects.[11,19,25,30] In this study, when NMRs were dosed at time point 0 with buprenorphine (0.1 mg/kg), quantifiable plasma concentrations above the therapeutic threshold were achieved by the first blood sample collection at 0.25 h. In addition, when blood samples were collected at the 0.5 h time point, plasma concentrations of buprenorphine had already reached a C_{max} of 15.27 ng/mL. This quick absorption time and time taken to reach C_{max} supports the use of buprenorphine to treat urgent analgesic needs in the NMR. The plasma concentration of buprenorphine, as displayed by the interpolated line, was maintained above the targeted therapeutic threshold for at least 21 h. The C_{last} (0.54 ng/mL) taken at 24 h was below the targeted therapeutic threshold, but based on the values predicted by linear interpolation, a duration of action of 21.6703 h was suggested. Assuming the therapeutic threshold for buprenorphine in the NMR is 1 ng/dL, then these data conservatively support a dosing regimen of 0.1 mg/kg SC every 8 to 12 h in the NMR.

Overall, the results obtained from this study support giving meloxicam at a dose of 2 mg/kg SC every 24 h and buprenorphine at a dose of 0.1 mg/kg SC every 8 to 12 h in the NMR. To truly establish a dose recommendation, the therapeutic thresholds for both meloxicam and buprenorphine should be confirmed, and further studies should be performed to evaluate the clinical efficacy of these drugs by correlating plasma concentrations with analgesiometric tests or postoperative pain assessments in the NMR. In addition, future studies should be performed to evaluate additional time points to better pinpoint the duration of action, and to further characterize factors such as toxicity, multiple consecutive dose administrations, long-term use, and sustained release formulation pharmacokinetics of both meloxicam and buprenorphine in the NMR.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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