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Source: Journal of Zoo and Wildlife Medicine, 49(2):307-314.
Published By: American Association of Zoo Veterinarians
https://doi.org/10.1638/2017-0067.1
URL: http://www.bioone.org/doi/full/10.1638/2017-0067.1

Journal of Zoo and Wildlife Medicine 49(2): 307–314, 2018

PHARMACOKINETICS OF MELOXICAM FOLLOWING A SINGLE ORAL DOSE IN MALAYAN FLYING FOXES (*PTEROPUS VAMPYRUS*)

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Abstract: Meloxicam, a COX-2 selective nonsteroidal anti-inflammatory medication, has been used in many exotic animals at doses extrapolated from domestic animal pharmacokinetic and pharmacodynamic studies. Increasing evidence suggests that significant species differences exist in meloxicam metabolism. Because of this, dose extrapolation from domestic animals may not be appropriate for exotic species. The objective of this study was to investigate the pharmacokinetics of meloxicam in a population of male Malayan flying foxes, *Pteropus vampyrus*, following a single oral dose of 0.2 mg/kg. Using a sparse sampling method based on a pilot study, two blood samples from each of 10 bats were collected over an 8-hr time period. Analysis of meloxicam in plasma samples was conducted using reversed-phase high-performance liquid chromatography. The peak plasma concentration of 598 ± 157.5 ng/ml occurred at 1.0 hr post dosing. The terminal half-life was 1.1 ± 0.1 hr, which indicates that meloxicam is rapidly metabolized in this species. No adverse clinical effects were noted during the study period. A single oral dose of 0.2 mg/kg appears safe for use in male Malayan flying foxes, but due to rapid elimination, frequent dosing may be required to maintain plasma concentrations within a therapeutic range. Multidose studies are needed to determine if plasma accumulation of meloxicam occurs.

Key words: Flying fox, meloxicam, nonsteroidal anti-inflammatory, pharmacokinetics, *Pteropus vampyrus.*

INTRODUCTION

Chiroptera are one of the most diverse orders of mammals, consisting of over 900 different species distributed worldwide in varied habitats.[28] Both megachiropterans and microchiropterans are commonly displayed in zoological parks, and wild bats are critical in maintaining ecosystem health through such activities as insect control and pollination. Chiropterans have been widely studied due to their role as reservoirs of rabies virus, other lyssaviruses, Nipah and Hendra viruses, and their presumed role in SARS-CoV-like virus.[4] The only pharmacokinetic study in chiropterans to date is that of terbinafine in little brown myotis (*Myotis lucifugus*).[11]

The nonsteroidal anti-inflammatory drug (NSAID) meloxicam, is regularly used in both human and veterinary medicine for its analgesic, anti-inflammatory, and antipyretic properties.[13,41] In mammals, meloxicam is a cyclooxengenase-2 (COX-2) preferential NSAID that blocks the production of prostaglandins directly involved in inflammation and pain.[13,33,41] Meloxicam is highly protein bound in most species studied, and extensive human and domestic animal studies have revealed species-specific differences in dosage and frequency required to achieve apparent therapeutic plasma levels.[3,8,9,15,18–22,24,25,31,32,37,38,40,42,44,45,47,50] Zoo veterinarians treat many exotic animal patients with meloxicam, using doses extrapolated from domestic animal studies. There is increasing research into the pharmacokinetics of meloxicam in exotic animals. Many of these studies indicate that there are significant differences in required doses based on order and/or species.[2,5,6,10,14,16,19,26,27,29,30,33,35,36,39,43,51]

Painful conditions such as skeletal fluorosis have been reported in several species of megachiropterans.[17,34] Additionally, anecdotal reports of traumatic injuries, osteoarthritis, and surgical procedures are common in captive chiropterans (Emanuelson, Procter, Pope, Wellehan, pers. comm.). However, to date, there are no controlled studies of NSAID pharmacokinetics in chiropterans, and only few anecdotal reports of meloxicam use in any species of bat. At the Oakland Zoo, doses of meloxicam ranging from 0.1 mg/kg po sid to 0.3 mg/kg po bid have been used without apparent adverse effect (Emanuelson and Goodnight, pers. exper.). A case report of ovariohysterectomies in vampire bats (*Desmodus rotundus*) reported perioperative analgesia with meloxicam at doses of 0.29 mg/kg sc or 0.5 mg/kg sc, and postoperative analgesia using meloxicam at 0.2 mg/kg po sid, with no apparent adverse effects.[7] This study investigates the pharmacokinetics of

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meloxicam after a single oral dose in a male population of a megachiropteran species, the Malayan flying fox (*Pteropus vampyrus*).

MATERIALS AND METHODS

Animals and housing

Ten adult male Malayan flying foxes, *Pteropus vampyrus*, ranging in ages from 14 to 18 yr, were used in this study. The bats were housed in Northern California, United States, with three other male *P. vampyrus* and eight male *P. hypomelanus* in a hexagonal outdoor flight pen consisting of 18.3 m sides and a 12 m height, along with two indoor holding pens (7 m length, 5.5 m width and 8.2 m length, 5 m width). Bats were allowed indoor-outdoor access until ambient temperature fell below 8°C, when bats were restricted to the indoor holding area. The outdoor flight pen floor was made of natural substrate composed of a variety of trees and grasses, with wire mesh structures 1.8–2.4 m high for roosting and climbing. Outdoor humidity ranged from 30 to 40% during the majority of the year; however, it was as high as 95% during the rainy 2–3 mo of winter. The indoor holding pen also contained wire mesh structures 1.8 m high, with a concrete floor and occasional varied tree branches provided for enrichment. Ambient indoor temperature was maintained from 18°C to 29°C and humidity 30–60%. Bats were fed a diet of fruits, vegetables, and a commercial supplement (HMS Frugivore and Lubee Bat Supplement, HMS Zoo Diets, Inc., Bluffton, Indiana 46714, USA). Water was provided ad libitum.

All bats were deemed clinically healthy based on visual examination, medical record review, and normal complete blood count and biochemistry panels performed within 4 mo of commencement of the study. No bat in the study received any other medications for 1 mo prior to the study. Bats were weighed (range 0.96–1.70 kg) within 1 wk of drug administration to ensure accurate dosing.

This study was approved by the Oakland Zoo Research Committee.

Experimental design

Bats were dosed with meloxicam oral suspension (Metacam, Boehringer Ingelheim Vetmedica Inc., St. Joseph, Missouri 64506, USA) at 0.2 mg/kg. Meloxicam was administered individually to each bat by zookeepers. Bats were not restrained for dose administration. The full dose of meloxicam liquid was placed into a 1-ml oral dosing syringe, and the outside of the syringe was coated with a thin layer of jelly to entice the bats to lick the syringe. As the bats licked, the keeper pushed the syringe plunger down to ensure bats consumed the full dose of meloxicam. The meloxicam oral suspension appears to be palatable to this bat species, as most bats continued to lick at the syringe after all the medication was dispensed. The bats' normal feeding schedule was maintained throughout the study in order to simulate routine clinical meloxicam use in this collection. Additionally, maintaining this normal feeding schedule minimized hypoglycemia previously noted in bats in this collection after even 1 hr of fasting (Emanuelson and Goodnight, pers. exper.). The bats are offered a variety of fruits and vegetables twice daily. The food items are hung from skewers attached to the climbing mesh and distributed throughout the indoor and outdoor exhibit areas. Additionally, multiple bowls of vegetable and commercial bat supplement mixture are placed throughout the exhibit twice a day. Bats are allowed to forage ad libitum. After dosing, there was no apparent change in food intake by any individual.

A pilot study was performed with two bats to assess plasma meloxicam concentrations and confirm length of detected plasma concentrations. All sample collections were performed in a separate pen within the bat night house, to minimize handling time and environmental changes. For each blood sample, bats were anesthetized and maintained with sevoflurane (3%–6%, SevoThesia, Butler Schein Animal Health, Dublin, Ohio 43017, USA) by mask. Total time of anesthesia for blood collection averaged 6.6 min for each bat. Venipuncture was performed in the brachial vein or artery using a 22-ga needle on a 3-ml syringe. Approximately 3 ml of whole blood was collected and immediately placed into lithium heparin tubes. Blood was centrifuged for 3 min at 8,050 *g* within 10 min of collection, and plasma was removed and stored in cryovials at −20°C until analysis. Samples were collected from each bat at $T = 8$, 12, 24, and 48 hr. Additionally, plasma samples from two unmedicated bats were collected and stored by the same methods for use as assay controls. Serum chemistry panel and complete blood cell count were performed on both bats at the end of the pilot study using blood collected at the final sampling time. No abnormalities were noted in the lab work as compared with published reference values.[23] Additionally, upon completion of both studies, all bats appeared behaviorally normal.

Plasma drug analysis

The full study was performed with the same methods as described for the pilot study. Ten bats were medicated orally at 0.2 mg/kg meloxicam, with subsequent blood sample collection. Sparse sampling was used so that each bat was sampled only twice, resulting in three samples representing each time point: $T = 0$, 15 min, 30 min, 1 hr, 2 hr, 4 hr, and 8 hr. Meloxicam was not detected in plasma after 8 hr during the pilot study, so samples were only collected for the full study until $T = 8$ hr. Data from the pilot study was not included in the final pharmacokinetic analysis.

Meloxicam was extracted from plasma using a previously detailed method.[12] Analysis of meloxicam in plasma samples was conducted using reversed-phase high-performance liquid chromatography. The system consisted of a 2695 separations module, a 2487 UV absorbance detector and a computer equipped with Empower software (Waters, Milford, Massachusetts 01757, USA). The compounds were separated on an Xbridge C_{18} (4.6×250 mm, 5 μm) column with a 5 μm Xbridge guard column. The mobile phase was a mixture of A, 10 ml of glacial acetic acid in 1 L of H_2O (pH 3.0 adjusted with sodium hydroxide) and B, acetonitrile (50 : 50). Absorbance was measured at 360 nm with a flow rate of 1 ml/min.

Meloxicam was extracted from plasma samples using liquid-liquid extraction. Previously frozen plasma samples were thawed and vortex-mixed and 100 μl of plasma was transferred to a screw-top tube, and 15 μl of prioxicam (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 sec and then centrifuged for 20 min at 1,070 *g*. The organic phase was transferred to a clean glass tube, and evaporated to dryness with nitrogen. Samples were reconstituted in 250 μl of mobile phase and 100 μl injected into chromatography system.

Standard curves for plasma analysis were prepared by fortifying untreated plasma with meloxicam to produce a linear concentration range of 5–1,500 ng/ml. Calibration samples were prepared exactly as plasma samples. The lower limit of quantification during validation was 5 ng/ml. The intra- and inter-assay variability ranged from 1.1 to 10%; the average recovery for meloxicam was 95%.

Pharmacokinetic analysis

Pharmacokinetic parameters for meloxicam were calculated using Phoenix WinNonlin 6.4 (Certara USA, Inc., Princeton, New Jersey 08540, USA). Values for elimination rate constant (λ_z), plasma half-life ($t_{½}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), mean residence time ($MRT_{0-\infty}$), and area under the plasma concentration time curve ($AUC_{0-\infty}$) from time 0 to infinity were calculated from noncompartmental analysis. The *AUC* was calculated using the log-linear trapezoidal rule. Variability in pharmacokinetic parameters was expressed as the standard deviation. In the case of the half-life, harmonic mean and pseudostandard deviation were used.

Table 1. Pharmacokinetic parameters for meloxicam in 10 Malayan flying foxes (*Pteropus vampyrus*) following a single-dose oral administration of 0.2 mg/kg. Each calculation is based on sampling 3 bats per time point.

Parameter	Meloxicam mean ± SD
$t_{1/2}$ (h)[a]	1.1 ± 0.1
λ_z[b] (1/h)	0.6 ± 0.06
T_{max} (h)[c]	1.0 ± 0.0
C_{max} (ng/ml)[d]	598 ± 157.5
$AUC_{0-\infty}$ (h*ng/ml)[e]	1437.3 ± 449.4
$MRT_{0-\infty}$ (h)[f]	2.0 ± 0.5

[a] Terminal half-life, harmonic mean.
[b] Elimination rate constant.
[c] Maximum plasma concentration.
[d] Time to maximum plasma concentration.
[e] Area under the plasma concentration time curve from 0 to infinity.
[f] Mean residence time.

RESULTS

Meloxicam was easily delivered to all bats voluntarily via oral dosing syringe. No adverse clinical effects directly related to meloxicam dosing were seen in the bats during or after the study.

Pharmacokinetic parameters for a single oral dose of meloxicam at 0.2 mg/kg to male Malayan flying foxes are presented in Table 1, and the mean meloxicam plasma concentration vs time curve is presented in Figure 1 as a log-linear graph. The mean ± SD time to maximum plasma concentration (T_{max}), terminal half-life ($t_{½}$), and maximum plasma concentration (C_{max}) were 1.0 ± 0.0 hr, 1.1 ± 0.1 hr, and 598 ± 157.5 ng/ml, respectively. The area under the plasma concentration curve from time 0 to infinity ($AUC_{0\text{-as a }\infty}$) was 1,437.3 ± 449.4 h*ng/ml and the mean residence time ($MRT_{0-\infty}$) was 2.0 ± 0.5 hr.

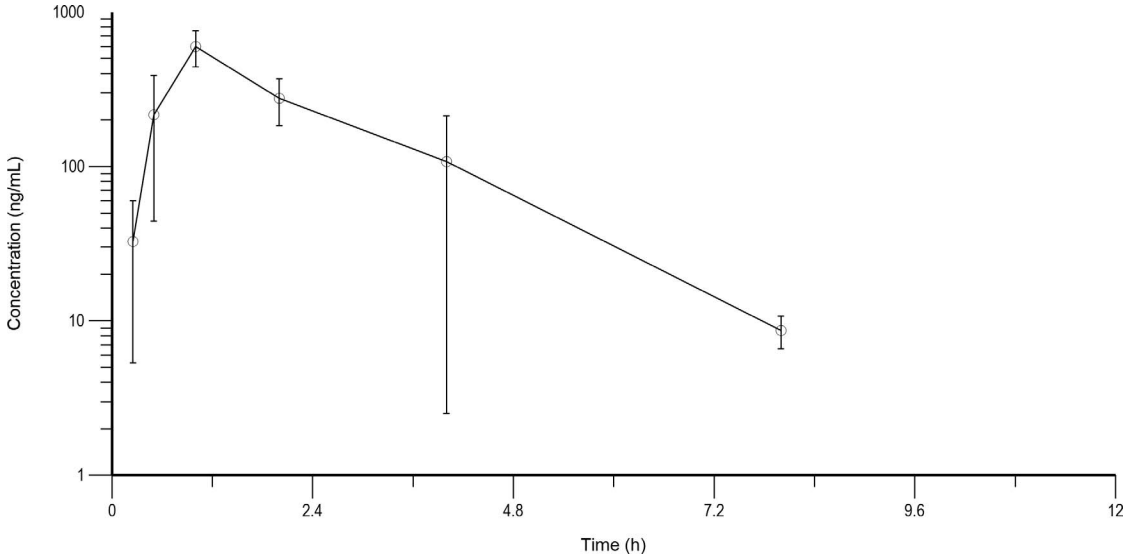

Figure 1. Log-linear mean plasma concentration (ng/ml) of meloxicam in 10 Malayan flying foxes (*Pteropus vampyrus*) following a single-dose oral administration of 0.2 mg/kg. Each calculation is based on sampling 3 bats per time point.

DISCUSSION

The meloxicam dose of 0.2 mg/kg po used in this study was chosen based on one author's (ALG) clinical experience, as this dose has appeared efficacious based on bat behavioral changes after dosing in response to suspected painful conditions. The results of this study indicate that meloxicam at a single dose of 0.2 mg/kg po given to male Malayan flying foxes appears to be rapidly absorbed, with T_{max} of 1.0 hr. The absorption appears to be more rapid than domestic dogs (*Canis lupus familiaris*, single dose 0.2 mg/kg po), humans (single dose of 0.25 mg/kg po) and bottlenose dolphins (*Tursiops truncatus*, single dose 0.1 mg/kg po), which had a T_{max} of 8.5 ± 1.9 hr, 1.5–5 hr, and 11.27 hr, respectively.[3,37,43] The C_{max} (a measure of the peak concentration of meloxicam after administration) at this dose was also different compared with some mammals. Dogs given a single oral dose of 0.2 mg/kg had a greater C_{max} of 820 ± 290 ng/ml, while rabbits given the same dose had a lower C_{max} of 168 ± 63 ng/ml.[5,37] There are several potential explanations for these results. Meloxicam is metabolized in the liver of mammals by cytochrome P450 subgroup enzymes (mostly CYP2C9 and much less by CYP3A4) to four inactive metabolites, and excreted in urine and feces.[13,37] In animal studies, these metabolites have not been shown to have analgesic or anti-inflammatory activity.[13] It is unknown how bats metabolize meloxicam, or the extent and function of cytochrome P450 in bats; thus it is possible that bats produce metabolites that were not measured by this assay and could be pharmacologically active. Additionally, meloxicam is highly protein bound, so plasma levels in bats may not be reflective of the pharmacologic activity of the drug.[13] Anesthesia was used to collect blood samples in this study, therefore an effect of the anesthesia on drug metabolism cannot be ruled out.

Bats were given meloxicam voluntarily via syringe, and appeared to consume the medication readily; however, some bats may not have consumed the entire dose offered, resulting in lower C_{max} values. The meloxicam doses were administered with food (jelly coating the syringe), but it is unlikely that this affected C_{max} as food has not been shown to significantly alter bioavailability in dogs or humans.[41,46] In humans, steady-state blood concentrations after oral dosing are not achieved for 3–4 days, but meloxicam is rapidly and completely absorbed after im dosing.[13] Studies evaluating the pharmacokinetics of meloxicam following iv administration may help to elucidate meloxicam bioavailability in bats.

The $t_{1/2}$, or measurement of the time for meloxicam to lose half of its pharmacologic activity, was similar to that of some birds. Caribbean flamingos (*Pheonicopterus ruber ruber*)

given a single oral dose of 1 mg/kg had a $t_{1/2}$ of 0.695–1.4 hr while Cape Griffon vultures (*Gyps coprotheres*) had a $t_{1/2}$ of 0.33 hr after a single oral dose of 2 mg/kg.[33,39] However, Amazon parrots (*Amazona ventralis*) administered a single dose of 1 mg/kg po demonstrated a much higher variability with a $t_{1/2}$ of 2.9–25 hr.[35] It is possible that bats' adaptations for flight, including the need for rapid energy with minimal weight, may contribute to the rapid metabolism of meloxicam. Species differences in meloxicam absorption, protein binding, or elimination may also contribute to the observed results in this study.

This study did not attempt to evaluate clinical efficacy of meloxicam, but plasma meloxicam concentrations of 570–930 ng/ml (humans), 130–195 ng/ml (horses), and 820 ng/ml (dogs) appear to produce anti-inflammatory effects.[37,47,49] Plasma concentrations in this study reached these levels, possibly indicating that this dose has anti-inflammatory effects for male Malayan flying foxes.

The T_{max} and $t_{1/2}$ were very rapid at 1.0 hr and 1.1 ± 0.1 hr, respectively, and the *MRT* was only 2.0 ± 0.5 hr, indicating rapid metabolism and elimination of meloxicam in Malayan flying foxes. Plasma concentrations of meloxicam were above 130 ng/ml for less than 5 hr, possibly indicating that clinical effects may not be long lasting in this species of bat. However, meloxicam in other species is extensively protein bound, especially in areas of inflammation, thus clinical effects may last longer than plasma levels indicate.[13] Accumulation of meloxicam with repeated dosing may also occur, thus a multidose study would be useful to examine possible cumulative dosing effects.

Traditionally, meloxicam is given sid in most mammals, and has been used bid in this collection of bats based on clinical efficacy perceptions. Results of this study indicate that oral meloxicam may need to be administered more often than sid or bid in male Malayan flying foxes to achieve sustained clinical efficacy. However, meloxicam accumulates in areas of inflammation, thus clinical effects may persist beyond the 1–2 hr of elimination time.[13] An efficacy study to evaluate bats' changes in pain threshold may better define the dosage and dosing frequency requirements, and clinical effects.

Sparse sampling, based on methods used in rodent toxicokinetic studies, was used for this study.[1,46] This method was developed to decrease the number of samples taken from an individual animal during a study. The goal of sparse sampling is to minimize changes in health that may result from repeated sampling while still obtaining enough samples for adequate statistical significance to be achieved.[1,48] Each bat in this study was sampled at two time points over an 8-hr period, due to concerns that more venipuncture would cause undue stress and adverse effects. All bats appeared clinically normal at the end of the study.

No adverse effects directly related to meloxicam were seen during and since this study was completed; however, prolonged hemorrhage following venipuncture of the first three bats sampled necessitated an alteration in clinical procedures. Typically, venipuncture in this bat collection occurs under anesthesia in the Oakland Zoo Veterinary Hospital large-animal treatment room, with an average temperature of 21.1°C (70°F), and excessive hemorrhage from venipuncture sites has not been observed. At the beginning of the study (the first three bats sampled), the temperature in the holding pen in the bat night house was 28.9°C (84°F). Venipuncture was uncomplicated, but even with manual pressure, hemorrhage continued for several minutes. Additionally, the first two bats hemorrhaged at the venipuncture site upon recovery to consciousness, and the first bat developed a large hematoma. When this same event occurred after venipuncture of the third bat, the bat was carried to the outdoor holding exhibit (temperature 18.3°C [65°F]) under manual restraint with direct pressure on the venipuncture site. Hemostasis was achieved within 2 min. Subsequently, the temperature of the holding pen used for anesthesia and venipuncture for the study was decreased to 23.3°C (74°F) and no further excessive hemorrhage at venipuncture sites was observed.

The hematoma in the first bat resulted in disuse of the wing for 8 wk after the study. The bat was treated with meloxicam 0.2 mg/kg po bid and gabapentin 4 mg/kg po bid (Diamondback Drugs, Scottsdale, Arizona 85251, USA) for 8 wk, along with physical therapy (stretching wing 10 times bid) and recovered fully to normal wing use.

CONCLUSION

This study is the first to evaluate the pharmacokinetics of meloxicam following a single oral dose of 0.2 mg/kg in Malayan flying foxes. In captivity, these bats may sustain injuries and illnesses that require analgesia and anti-inflammatory medication. Based on this study, it appears that Malayan flying foxes are able to absorb and metabolize meloxicam, but the rapid elimination and low C_{max} may indicate that the oral dose needs to be higher and/or given more

frequently than the anecdotally used 0.2 mg/kg po sid–bid. Further studies to evaluate meloxicam and other analgesics in bats will enhance the ability of practitioners to effectively treat painful conditions in this species.

Acknowledgments: Many thanks to the Veterinary and Animal Care staff at Oakland Zoo and Dr. Alex Herman for their participation in this study and dedication to improving the care of and knowledge about bats. Thanks also to Dr. Christopher Bonar for manuscript review.

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Accepted for publication 27 December 2017