

Pharmacokinetics of meloxicam in red-eared slider turtles (*Trachemys scripta elegans*) after single intravenous and intramuscular injections

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Received May 9, 2015.

Accepted July 29, 2015.

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OBJECTIVE

To determine the pharmacokinetics of meloxicam after single IV and IM injections in red-eared slider turtles (*Trachemys scripta elegans*).

ANIMALS

8 healthy red-eared slider turtles.

PROCEDURES

Turtles received 1 dose of meloxicam (0.2 mg/kg) IV or IM (4 turtles/route), a 30-day washout period was provided, and then turtles received the same dose by the opposite route. Blood samples were collected at predetermined times for measurement of plasma meloxicam concentration. Pharmacokinetic values for each administration route were determined with a 2-compartment open model approach.

RESULTS

For IV administration, mean \pm SD values of major pharmacokinetic variables were 1.02 ± 0.41 hours for distribution half-life, 9.78 ± 2.23 hours for elimination half-life, 215 ± 32 mL/kg for volume of distribution at steady state, 11.27 ± 1.44 $\mu\text{g}\cdot\text{h}/\text{mL}$ for area under the plasma concentration versus time curve, and 18.00 ± 2.32 mL/h/kg for total body clearance. For IM administration, mean values were 0.35 ± 0.06 hours for absorption half-life, 0.72 ± 0.06 $\mu\text{g}/\text{mL}$ for peak plasma concentration, 1.5 ± 0.0 hours for time to peak concentration, 3.73 ± 2.41 hours for distribution half-life, 13.53 ± 1.95 hours for elimination half-life, 11.33 ± 0.92 $\mu\text{g}\cdot\text{h}/\text{mL}$ for area under the plasma concentration versus time curve, and $101 \pm 6\%$ for bioavailability. No adverse reactions were detected.

CONCLUSIONS AND CLINICAL RELEVANCE

Long half-life, high bioavailability, and lack of immediate adverse reactions of meloxicam administered IM at 0.2 mg/kg suggested the possibility of safe and effective clinical use in turtles. Additional studies are needed to establish appropriate administration frequency and clinical efficacy. (*Am J Vet Res* 2016;77:439–444)

Identification and treatment of pain in reptiles is challenging because of these animals' unique physiologic, anatomic, and behavioral characteristics.¹ In a survey² conducted by members of Association of Reptile and Amphibian Veterinarians, 98% of respondents stated that they believed that reptiles feel pain. How-

ever, only 39% of respondents reported use of analgesics for > 50% of reptilian patients. In that study,² reasons for the lack of analgesic use were not identified. However, possible reasons included difficulties with pain detection, insufficient data on the efficacy and adverse effects of analgesics, and lack of experimentally established doses and pharmacokinetics of analgesics for reptiles.¹

Opioids, local anesthetics, and NSAIDs are typically used as analgesics for reptilian patients. Clinical experience suggests that NSAIDs are efficacious for this purpose.³ In turtles, production of the enzymes COX-1 and COX-2 is upregulated during inflammation of muscle tissue.⁴ However, the inhibitory effects of NSAIDs on COX enzymes in turtles have not been reported. Nonsteroidal anti-inflammatory drugs have a slight analgesic effect in amphibians.^{5,6} In the absence of data regarding NSAID use in reptiles, it might be anticipated that analgesic and adverse effects in reptiles would be similar to those in mammals.¹

ABBREVIATIONS

AUC	Area under the plasma concentration-versus-time curve
Cl _T	Total body clearance
C _{max}	Maximum plasma drug concentration
COX	Cyclooxygenase
CV	Coefficient of variation
HPLC	High-performance liquid chromatography
LOD	Limit of detection
LOQ	Limit of quantification
t _{1/2ab}	Absorption half-life
t _{1/2α}	Distribution half-life
t _{1/2β}	Elimination half-life
T _{max}	Time to maximum plasma drug concentration
Vd _{ss}	Apparent volume of distribution at steady state

Untreated pain and inflammation impair homeostasis and immune function and inhibit healing in animals. Treatment of pain is therefore important to facilitate healing and prevent or limit the actions of detrimental neurohumoral responses to pain.⁷ In turtles, which have long life spans over which several painful or inflammatory events may occur, NSAIDs may be useful.^{1,7} Meloxicam is a COX-2 selective NSAID that has been used extensively for its anti-inflammatory, analgesic, and antipyretic activity in some domestic animal species.^{8–11} The pharmacokinetics of meloxicam has been evaluated in several species, including baboons,^a mice,^a horses,^{12,13} donkeys,¹³ sheep,^{14,15} goats,^{14,16,17} cattle,^{18,19} dogs,^{20,21,a} vultures,²² green iguanas,²³ cats,^{24,25} piglets,^{26,a} camels,²⁷ llamas,²⁸ and rabbits.^{29–31} Because no data are available for red-eared slider turtles (*Trachemys scripta elegans*), the dosage of meloxicam used in that species is routinely extrapolated from dosages for other species (ie, 0.1 to 0.2 mg/kg, q 24 to 48 h).^{1,7} However, important differences exist among species in the pharmacokinetics of meloxicam, so before dosage recommendations can be made for red-eared slider turtles specifically, the pharmacokinetic profile of meloxicam in that species must be determined. The purpose of the study reported here was to determine the pharmacokinetics of meloxicam in red-eared slider turtles after IV and IM injection of a single dose of 0.2 mg/kg.

Materials and Methods

Animals

Eight healthy red-eared slider turtles weighing between 0.3 and 0.5 kg were used for the study. Turtles were acquired from a retail pet supply store^b and allowed to acclimate to the study environment for 1 month before the study began. Health status was confirmed by physical examination. Four turtles were housed in each of two 450-L aquariums at room temperature (23° to 25°C). Each aquarium had a custom-built mechanical and biological filtration system,^c and water quality was evaluated twice per week by use of test kits.^d Optimal water quality was maintained with respect to pH (6.8 to 7.5) and O₂ (> 6 mg/L), ammonia (< 0.5 mg/L), nitrate (< 10 mg/L), and nitrite (< 0.5 mg/L) concentrations. Water quality was maintained by changing 25% of the aquarium water on a weekly basis and by adding water conditioners. Temperatures of the aquarium water and basking area were maintained at 24° and 30°C, respectively. Turtles were fed a commercial pelleted diet^e every other day. The Ethics Committee of the Faculty of Veterinary Medicine, University of Selcuk approved the use of turtles for this study and all study protocols.

Experimental design

A crossover study design was used, in which each turtle was randomly assigned (by drawing of cards) to receive each of 2 treatments in a particular order. Meloxicam^f (0.2 mg/kg) was then administered IV (4

turtles; left jugular vein) or IM (4 turtles; left deltoid muscle) to each turtle as assigned. After a 30-day wash-out period, treatment administration was repeated via the opposite administration route.

Blood sample collection

Blood samples (approx 0.4 mL) were collected from each turtle by use of 26-gauge, 0.5-inch needles immediately before meloxicam administration (0 hours) and 0.5, 1, 1.5, 3, 6, 9, 12, 24, 36, and 48 hours after administration. Collection sites alternated between the right and left dorsal cervical sinuses. Blood samples were collected into 1-mL insulin syringes that had been rinsed before use with 0.05 mL of heparin sodium solution^g (1,000 U/mL) as anticoagulant. Samples were subsequently transferred into centrifuge tubes and centrifuged at 2,000 X g for 10 minutes. Plasma was harvested and frozen at -70°C^h until analysis. All plasma samples were analyzed for meloxicam content within 1 month after treatments concluded.

HPLC

Meloxicam concentration in plasma was determined by use of HPLC in accordance with methods described elsewhere,^{32,33} with minor modifications. The HPLC systemⁱ was composed of a pump, degasser, autosampler, column oven, and UV-visible spectrophotometer. Meloxicam was detected at a wavelength of 354 nm. Column and autosampler temperatures were kept at 40°C and room temperature, respectively. A C18 analytical column^j (250 mm X 4.6 mm; internal diameter, 5 µm) was used for separation. The mobile phase consisted of 40% buffer (20mM KH₂PO₄^k; pH, 3.5) and 60% acetonitrile.^l Mobile phase was filtered through a 0.45-µm nylon membrane filter^m and by sonicationⁿ for 30 minutes. The flow rate was 1 mL/min, and the injection volume was 25 µL. Data were analyzed by use of computer software.^o

Calibration standards and quality control samples

A standard stock solution of meloxicam sodium^p (1 mg/mL) was prepared in water and stored at -70°C. Working solutions were made by appropriate dilutions (0.01 to 40 µg/mL) of the stock solution with water. Calibration standards of meloxicam were prepared at concentrations of 0, 0.01, 0.02, 0.04, 0.1, 0.2, 0.4, 1, 2, and 4 µg/mL by spiking 180 µL of plasma from untreated turtles (ie, blank plasma) with 20 µL of the appropriate standard solution. Quality control samples were prepared in drug-free plasma samples to achieve low (0.04 µg/mL), medium (0.4 µg/mL), and high (4 µg/mL) concentrations of meloxicam standard.

Sample preparation

For each plasma sample, 200 µL was transferred into a microcentrifuge tube and 400 µL of methanol^l with 0.1% formic acid^k was added. Contents were mixed for a 30 seconds, then samples were centri-

fused at 25,000 X g for 10 minutes at 24°C. After centrifugation, the clear supernatant was transferred into an autosampler vial and a 25-µL aliquot was injected into the HPLC system.

Method validation

Selectivity, sensitivity, linearity, absolute recovery, accuracy, and precision of the HPLC method were assessed by use of spiked plasma samples. Selectivity or lack of interference from plasma was evaluated by extraction of meloxicam standard from spiked blank plasma samples from 8 turtles. To demonstrate linearity of results, calibration standards (0.01 to 4 µg/mL) were prepared and assayed in triplicate on 6 days. Sensitivity of the HPLC method was assessed by consideration of the LOD and LOQ, which were determined by evaluation of signal-to-noise ratios of plasma samples spiked with meloxicam standard at concentrations of 0.004 to 0.1 µg/mL. The LOD was defined as the lowest concentration with a signal-to-noise ratio ≥ 3 . The LOQ was defined as the lowest concentration of analyte with a signal-to-noise ratio ≥ 10 . Percentage of meloxicam recovered was calculated by comparing peak areas for quality control samples with peak areas for working solutions prepared in water. For determination of precision and accuracy, quality control samples containing predefined low, medium, and high concentrations of meloxicam standard were analyzed in 6 replicates within 6 days. Intra- and interday precision and accuracy were determined by calculation of the CV and percentage bias, respectively. Percentage bias was calculated as the mean of the measured quality control concentration relative to the theoretical value.

Pharmacokinetic analysis

A statistical software program^q was used to analyze plasma concentration data for each turtle after meloxicam administration by both routes. For IV and IM data, the appropriate pharmacokinetic model was determined by visual examination of individual plasma concentration versus time curves and by application of the Akaike information criterion,³⁴ resulting in the following 2-compartmental model being chosen for data analysis:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p is the concentration of drug in plasma at time t , A is the intercept of the distribution phase, B is the intercept of the elimination phase, α is the distribution rate constant, β is the elimination rate constant, and e is the base of natural logarithm.

Values for C_{max} and T_{max} after IM administration of meloxicam were obtained directly from the plasma concentration versus time curve for each turtle. Half-lives were calculated by use of the following equations:

$$\begin{aligned} t_{1/2ab} &= \ln(2)/k_{ab} \\ t_{1/2\alpha} &= \ln(2)/\alpha \\ t_{1/2\beta} &= \ln(2)/\beta \end{aligned}$$

where $\ln(2)$ is the natural logarithm of 2, and k_{ab} , α , and β are the absorption, distribution, and elimination rate constants, respectively. The AUC and area under the first moment curve were calculated by use of the trapezoidal method, with extrapolation to infinity.³⁵ For data pertaining to IV administration of meloxicam, Vd_{ss} was estimated as follows:

$$Vd_{ss} = \text{dose} \times \text{area under the first moment curve} / \text{AUC}^2$$

The Cl_T was calculated by dividing the dose by the AUC. Bioavailability (F) was calculated by means of the following formula:

$$F = (\text{AUC}_{IM} / \text{AUC}_{IV}) \times 100$$

Statistical analysis

All data are reported as mean \pm SD. Harmonic means were calculated for $t_{1/2ab}$, $t_{1/2\alpha}$, and $t_{1/2\beta}$. The Wilcoxon rank sum test was used to identify significant differences between administration routes in $t_{1/2\alpha}$ and $t_{1/2\beta}$. The paired t test was used to test for differences between administration routes in other pharmacokinetic data. Values of $P < 0.05$ were considered significant. Statistical software^r was used for statistical analysis.

Results

Animals

All turtles received a single dose of meloxicam (0.2 mg/kg) via both administration routes (IM and IV). No general adverse reactions were identified in any turtle during physical examinations performed after treatment administration.

HPLC method

No interference from biological compounds in plasma was evident during assessment of the validity of the HPLC method for measurement of plasma meloxicam concentration. Retention time of meloxicam in turtle plasma was approximately 6.9 minutes. The calibration curve had excellent linearity ($r^2 > 0.9997$). The LOD of the method was 0.01 µg/mL, and the LOQ was 0.02 µg/mL. The CV was $< 20\%$. Mean percentage recovery values for meloxicam in plasma samples spiked at concentrations of 0.04, 0.4, and 4 µg/mL were $100.76 \pm 3.21\%$, $98.54 \pm 4.37\%$, and $97.64 \pm 2.78\%$, respectively.

Intraday variability in results for 3 plasma samples run 6 times on the same day was low, with CVs (indicating precision) ranging from 1.24% to 5.42% and bias (indicating accuracy) from -6.12% to 4.79%. Interday variability in results for 6 replicates run on 6 days was good, with CVs ranging from 0.98% to 5.67% and bias from -7.36% to 5.14%.

Pharmacokinetics of meloxicam

Plasma meloxicam concentrations decreased in a biexponential manner with time via both administration routes (**Figure 1**). Mean \pm SD values of pharma-

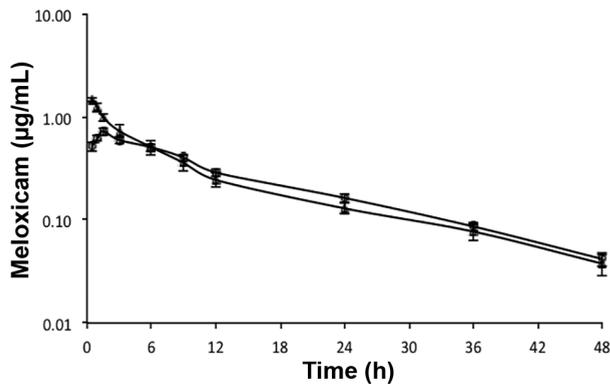


Figure 1—Semilogarithmic plots of mean plasma meloxicam concentrations in 8 red-eared slider turtles (*Trachemys scripta elegans*) at various points after IV (triangles) or IM (circles) administration of a single 0.2 mg/kg dose. Error bars represent SD.

Table 1—Pharmacokinetic values for a single dose of meloxicam (0.2 mg/kg) administered IV and IM to 8 red-eared slider turtles (*Trachemys scripta elegans*) in a crossover study design.

Variable	IV	IM
$t_{1/2ab}$ (h)	—	0.35 ± 0.06
$t_{1/2\alpha}$ (h)	$1.02 \pm 0.41^*$	3.73 ± 2.41
$t_{1/2\beta}$ (h)	$9.78 \pm 2.23^*$	13.53 ± 1.95
AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)	11.27 ± 1.44	11.33 ± 0.92
Cl_T (mL/h/kg)	18.00 ± 2.32	—
$V_{d_{ss}}$ (mL/kg)	215 ± 32	—
C_{max} ($\mu\text{g}/\text{mL}$)	—	0.72 ± 0.06
T_{max} (h)	—	1.5 ± 0.0
Bioavailability (%)	—	101 ± 6

Values reported are mean \pm SD; for half-lives, harmonic means were calculated.

*Value differs significantly ($P < 0.05$) from corresponding value for IM administration.

— = Not calculated.

cokinetic parameters estimated from the curve fitting were summarized (**Table 1**). Intramuscular administration resulted in high bioavailability of meloxicam ($101 \pm 6\%$) and a significantly longer $t_{1/2\alpha}$ and $t_{1/2\beta}$ than IV administration.

Discussion

The present investigation revealed that plasma meloxicam concentrations in healthy red-eared slider turtles decreased in a biexponential manner following IV injection, suggesting the presence of distribution and elimination phases and justifying the use of a 2-compartment open model approach to pharmacokinetic analysis. These results were in agreement with the findings of previous studies involving IV administration of meloxicam to calves,¹⁹ sheep, and goats.¹⁴ Plasma concentration profiles for IV administration in the present study revealed a rapid initial distributive phase, followed by a slower elimination phase with an estimated mean $t_{1/2\alpha}$ of 1.02 hours, which was longer than that reported for sheep (0.12 hours).¹⁴

The $t_{1/2\beta}$ was 9.78 hours, which agreed with the $t_{1/2\beta}$ reported for green iguanas (9.93 hours)²³ but was longer than values reported for sheep and goats (7.88

and 6.73 hours, respectively)¹⁴ and shorter than that of Amazon parrots (15.9 hours).³⁶ The extended half-life of meloxicam is likely attributable to a low Cl_T , representing mostly hepatic clearance given that a high degree of protein binding limits glomerular filtration of drug compounds.¹⁹ Such differences among study findings are fairly common and often related to interspecies variation or differences in assay methods used, intervals between blood sample collection, or health and age of study subjects.³⁷ Ambient temperatures can also affect drug pharmacokinetics in some reptile species.^{38–40} In addition, the ambient temperature (24°C) in the present study may have contributed to the extended $t_{1/2\beta}$ of meloxicam in slider turtles.

The $V_{d_{ss}}$ of meloxicam after IV administration was 215 mL/kg in the present study. This value was similar to that reported for IV administration to horses (270 mL/kg),¹³ lower than that reported for green iguanas (458 mL/kg),²³ and higher than that reported for donkeys and camels (93.2 and 92.8 mL/kg, respectively).^{13,27} The $V_{d_{ss}}$ of NSAIDs is consistently small in most animal species and is attributed to the high protein binding of these drugs, which limits their ability to reach extravascular compartments.¹³ Degree of protein binding was not measured in the present study. The Cl_T in the red-eared slider turtles was 18 mL/h/kg, and this value was nearly the same in sheep and Amazon parrots (12 and 12.2 mL/h/kg, respectively),^{14,36} lower in horses and donkeys (34.7 and 187.9 mL/h/kg, respectively),¹³ and higher in camels (1.94 mL/h/kg).²⁷

After IM injection, meloxicam was rapidly absorbed in the turtles, as suggested by the $t_{1/2ab}$ (0.35 hours). This value was similar to that reported for piglets (0.19 hours).²⁶ After IV administration, the initial mean plasma meloxicam concentration (1.47 $\mu\text{g}/\text{mL}$) was measured at 0.5 hours, whereas the mean C_{max} was 0.72 $\mu\text{g}/\text{mL}$ after IM administration. Mean C_{max} was similar to the plasma meloxicam concentration attained 3 hours after IV administration at the same dose. Mean T_{max} after IM administration was 1.5 hours, which was similar to the value reported for piglets (1.1 hours).²⁶ However, this value was greater than that reported for Amazon parrots (0.25 hours).³⁶

Systemic bioavailability of meloxicam in red-eared slider turtles following IM injection in the present study was 101%, which was almost the same as that reported for Amazon parrots (100%).³⁶ Meloxicam was eliminated at a slow rate after IM administration, with a $t_{1/2\beta}$ of 13.53 hours. That value was similar to the $t_{1/2\beta}$ reported for Amazon parrots (15.1 hours)³⁶ and longer than that reported for piglets (2.61 hours).²⁶

Intramuscular administration of meloxicam to the turtles in the present study also resulted in a longer mean $t_{1/2\beta}$ (13.53 hours) than did IV administration. The longer $t_{1/2\beta}$ achieved with IM administration may have been a result of slower absorption caused by the so-called flip-flop phenomenon.

The dose of meloxicam used in the present study (0.2 mg/kg) was chosen on the basis of an-

ecdotal reports^{1,7} and pharmacokinetic data reported for green iguanas.²³ Results suggested that plasma meloxicam concentrations at that dose were > 0.02 µg/mL for approximately 48 hours after IM or IV administration. The therapeutic concentration range needed for meloxicam to provide analgesic and antiinflammatory effects in turtles is unknown. Therapeutic ranges reported for cats and dogs are 883 to 1,298 ng/mL²⁴ and 390 to 466 ng/mL,²¹ respectively. In the present study, because the pharmacodynamics of meloxicam was not evaluated, it is unclear whether plasma concentrations of the drug achieved at the dose and routes administered would have been sufficient to yield analgesic and antiinflammatory effects in turtles. Therefore, studies are needed to determine the safety, pharmacokinetics, and pharmacodynamics of repeated, ascending doses of meloxicam in turtles before adequate and safe doses can be established.

The lack of immediate general adverse reactions in the turtles of the present study as well as the favorable pharmacokinetic properties (ie, long half-life and high bioavailability) of meloxicam administered IM in 1 dose of 0.2 mg/kg suggested the possibility of its safe and effective clinical use in turtles. However, additional studies are needed to establish the appropriate administration frequency and clinical efficacy of meloxicam in this species.

Acknowledgments

Supported by the Coordination of Scientific Research Projects, University of Selcuk (project No. 14401041).

Presented in abstract form at the 32nd World Veterinary Congress, Istanbul, Turkey, September 2015.

Footnotes

- a. Busch U. The pharmacokinetics of meloxicam in animals (abstr). *Scand J Rheumatol* 1994;(suppl 98):119.
- b. Nesil Aquarium, Konya, Turkey.
- c. Sera Fil bioactive external filter (400+UV), GmbH, Heinsberg, Germany.
- d. Sera aqua-test box and oxygen test kit, GmbH, Heinsberg, Germany.
- e. Sera Reptil Raffy P, GmbH, Heinsberg, Germany.
- f. Maxicam (5 mg/mL), Sanovel, Istanbul, Turkey.
- g. Nevparin, Mustafa Nevzat, Istanbul, Turkey.
- h. Ultralow temperature freezer, Operon Co Ltd, Gyeongg-do, Republic of Korea.
- i. Shimadzu, Tokyo, Japan.
- j. Gemini C18 analytical column, Phenomenex, Torrance, Calif.
- k. Merck, Darmstadt, Germany.
- l. VWR International SAS, Fontenay-sous-Bois, France.
- m. Millipore, Bedford, Mass.
- n. Sonicator T 840 DH, Elma, Singen, Germany.
- o. Lcsolution software, version 1.25, Shimadzu, Kyoto, Japan.
- p. Meloxicam sodium salt hydrate (≥ 98% assay purity), Sigma Chemical Co, St Louis, Mo.
- q. Phoenix WinNonlin, version 6.3, Pharsight Corp, Certara, St Louis, Mo.
- r. SPSS, version 16.0, IBM Corp, Armonk, NY.

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