



# Pharmacokinetics of ketorolac in wild Eastern box turtles (*Terrapene carolina carolina*) after single intramuscular administration

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## Abstract

Ketorolac is a nonsteroidal anti-inflammatory drug that possesses potent analgesic activity comparable to morphine. The opioid shortage in the United States has led to an unreliable supply of opioids for use in rehabilitation facilities, thus underscoring the need for research on the safe and effective use of nonopioid alternatives. The goal of this study was to determine the pharmacokinetics of ketorolac after a single 0.25 mg/kg intramuscular injection administered to injured Eastern box turtles (*Terrapene carolina carolina*). A sparse blood sampling protocol was used to collect samples from 32 wild turtles that presented to the Turtle Rescue Team at North Carolina State University for traumatic injuries. Blood was collected from 0 to 24 hr after injection and analyzed via high-pressure liquid chromatography (HPLC). A nonlinear mixed-effects (NLME) model was fitted to the data to obtain typical values for population parameters. Using this approach, we identified a long half-life ( $T_{1/2}$ ) of 9.78 hr and a volume of distribution ( $V_{ss}$ ) of 0.26 L/kg. We have concluded that this long  $T_{1/2}$  for a dose of 0.25 mg/kg ketorolac-injected IM provides plasma levels above a previously published target level for 24-hour analgesia to allow for once daily dosing.

## 1 | INTRODUCTION

Effective pain management reduces the morbidity and mortality associated with traumatic injury and/or surgery in reptiles (Sladky & Mans, 2012). In comparison with mammals, reptiles possess similar anatomic, biochemical, and functional components for the transmission and central processing of painful stimuli (Stoskopf, 1994). It is a standard of practice to assess the need for analgesia in reptiles based on behavioral and physiologic parameters. It is recommended to provide analgesia in cases where an injury or procedure in a reptile is perceived as painful (Machin, 2001; Perry & Nevarez, 2018; Pollock, 2002; Read, 2004), and many veterinarians consider nonsteroidal anti-inflammatory drugs (NSAIDs) for treating pain in reptiles (Read, 2004; Thompson et al., 2018).

Eastern box turtles are particularly susceptible to anthropogenic morbidity and mortality due to their terrestrial lifestyle. In cases of

traumatic injury, emergent therapy focuses on returning the animal to its preferred temperature zone, maintaining hydration status, preserving cardiorespiratory function, and providing pain management (Martinez-Jimenez & Hernandez-Divers, 2007). Opioids such as morphine are routinely used in chelonians postoperatively and in cases of traumatic injury (Applegate, Drapp, & Lewbart, 2016; Martinez-Jimenez & Hernandez-Divers, 2007). The opioid shortage in the United States has directly affected wildlife rehabilitation facilities such as the Turtle Rescue Team (TRT) at North Carolina State University (see: <https://www.avma.org/News/JAVMANews/Pages/180701a.aspx>). The shortage has led to an inconsistent supply of available morphine, which emphasizes the need for the evaluation of nonopioid alternatives for reptiles (De Oliveira, Theilken, & McCarthy, 2011; Ventola, 2011).

Ketorolac tromethamine is a nonspecific COX inhibitor that possesses a comparable level of analgesia as morphine in humans

(Forrest et al., 2002; Forrest, Heitlinger, & Revell, 1997; O'Hara, Fragen, Kinzer, & Pemberton, 1987). Ketorolac has been used previously for its analgesic and anti-inflammatory properties using dosing regimens extrapolated from other species in Eastern box turtles (*Terrapene carolina carolina*), yellow bellied sliders (*Trachemys scripta scripta*), and loggerhead sea turtles (*Caretta caretta*; Henson & Lewbart, 1988; Jaeger, Wosar, Harms, & Lewbart, 2003; Lewbart, Roe, Sharp, Love, & Harms, 2001). Furthermore, when used for the management of postoperative pain in injured wild turtles, the turtles that received ketorolac following shell fracture repair began eating sooner than control animals (Henson & Lewbart, 1988). During inflammation, COX-1 and COX-2 proteins are upregulated in the tissues of turtles; therefore, traditional NSAIDs such as ketorolac, which blocks both COX isoforms may be more efficacious than COX-2-selective NSAIDs; however, further research evaluating the relative expression or upregulation of the two isoenzymes is necessary before clinical assumptions about the effectiveness of NSAIDs in Eastern box turtles can be made (Royal, Lascelles, Lewbart, Correa, & Jones, 2012).

The lack of pharmacokinetic data makes it difficult to determine appropriate doses and dosing intervals for ketorolac in clinical reptile practice. Therefore, the goal of this study was to determine the pharmacokinetics of ketorolac in Eastern box turtles that presented to the TRT with traumatic injuries. Because the turtles were stressed, injured, may have encountered blood loss, and were often of small size, a sparse sampling protocol and nonlinear mixed-effects (NLME) modeling was used.

## 2 | MATERIALS AND METHODS

### 2.1 | Animals

Turtles were entered into the ketorolac treatment protocol and subsequently sampled for this study if they met specific inclusion criteria. Turtles met the criteria if the TRT staff deemed the traumatic injury serious enough to warrant the administration of ketorolac for pain management and if blood samples could be collected without undue stress or discomfort to the patient. Lactated ringers solution (20 ml/kg) was administered subcutaneously to each patient at the time of presentation in order to support fluid balance and cardiorespiratory function. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee at North Carolina State University.

### 2.2 | Procedure

A sampling grid was used for sparse sampling to ensure that sufficient time points were collected for a robust NLME analysis. Turtles were housed individually in 2–20 L containers with a water dish that was filled daily. They were fed and cleaned at least every other day. A controlled temperature (23.4–25.0°C) was maintained in the housing area, and the minimum and maximum temperatures were recorded

daily. Turtles were given ketorolac (Ketorolac Tromethamine, 30 mg/ml, Athenex, Schaumburg, IL 60173, USA; 0.25 mg/kg) as a single intramuscular injection into the left triceps muscle.

### 2.3 | Collection of blood samples

Blood was collected from the right brachial vein at 0 (predose sample), 1, 2, 4, 6, 8, 10, 12, 18, and 24 hr after injection. Sparse sampling was performed on the subjects with the goal of obtaining three samples per individual turtle, plus a sample obtained prior to drug administration for some animals. Approximately 0.4 ml of blood was aseptically collected at each time point using a 1-ml tuberculin syringe with a 25-ga needle. The syringe and needle interiors were rinsed before use with 0.1 ml of 1,000 IU/ml sodium heparin solution (McKesson Medical-Surgical Inc., Jacksonville, FL 32216, USA) as an anticoagulant. Blood was placed into amber polyethylene microcentrifuge tubes (Fisher Scientific, Pittsburgh, PA 15219, USA), which were capped and immediately submerged in ice water. The blood was then centrifuged (2,350 × g) to harvest approximately 0.15 ml of plasma, which was placed into amber polyethylene microcentrifuge tubes via micropipet. The tubes were capped and stored at –70°C until high-pressure liquid chromatography (HPLC) analysis.

### 2.4 | Analysis of ketorolac concentrations

Ketorolac in plasma was quantified using HPLC. Ketorolac was eluted on a C-18 reverse-phase column (Zorbax SB-C18, Agilent) with the detection set at 313 nm and a flow rate of 1.0 ml/min. The mobile phase consisted of 60% 0.005 M ammonium acetate buffer (pH 3.5); 40% acetonitrile.

Blank plasma was fortified with ketorolac and used for quality control and calibration standards. Calibration standards for the calibration curve ranged from 0.05 to 10.0 µg/ml. Fresh calibration standards were prepared for each day's analysis. The calibration curve was linear with a  $r^2$  value of at least 0.99. Blank samples (plasma collected prior to drug administration) from each experimental animal were analyzed to ensure there were no interfering peaks in the chromatogram.

### 2.5 | Pharmacokinetic analysis

A naïve averaged pooled analysis using a two-compartment model was used to obtain initial estimates (results not shown). From these initial estimates, a two-compartment pharmacokinetic model with a single bolus input and nonlinear mixed-effects modeling (NLME) was fitted to these data (Phoenix® NLME™ version 8.0, Certara Inc., St. Louis, MO, USA). The primary pharmacokinetic parameter values typical for the population were obtained from the analysis, in addition to secondary parameters and the random source error variability (interindividual variability, IIV). Our pharmacokinetic methods were similar to those used in other studies from our laboratory (Cerreta, Lewbart, Dise, & Papich, 2018; Rosenberg et al., 2016).

**TABLE 1** Results of pharmacokinetic analysis with nonlinear mixed-effects modeling using the Phoenix® NLME™ software (Certara, St. Louis, MO, USA)

Parameter	Estimate	Units
$\theta A$	5.30	ug/ml
$\theta \alpha$	1.91	1/hr
$\theta B$	0.52	ug/ml
$\theta \beta$	0.07	1/hr
$C_{MAX}$	5.82	ug/ml
K21	0.23	1/hr
K10	0.58	1/hr
K12	1.17	1/hr
Vc	0.04	L/kg
AUC	10.07	ug*hr/ml
Cl/F	0.02	L/kg/hr
MRT	10.37	hr
$V_{SS}/F$	0.26	L/kg
$\alpha T_{1/2}$	0.36	hr
$\beta T_{1/2}$	9.78	hr

Note.  $\theta A$ , distribution intercept;  $\theta \alpha$ , distribution rate constant;  $\theta B$ , elimination intercept;  $\theta \beta$ , elimination rate constant; ( $\theta$ , theta, is used to indicate that these are the typical values, tv, for the population); AUC, area under the drug concentration curve; Cl, systemic clearance;  $C_{MAX}$ , peak (maximal) plasma concentration; MRT, mean residence time;  $V_{SS}$ , apparent volume of distribution at steady-state; Distribution  $T_{1/2}$  and Elimination  $T_{1/2}$  are the distribution and elimination half-lives, respectively. Note that Cl and  $V_{SS}$  are listed as per fraction absorbed, because this was a non-intravenous dose.

Compartmental analysis of the data from the ketorolac injection was calculated using a 2-compartment model according the following formula:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C is the ketorolac concentration, A is the distribution phase intercept, e is the base of the natural logarithm, t is time after injection,  $\alpha$  is the distribution rate constant, B is the elimination phase intercept, and  $\beta$  is the elimination phase rate constant (terminal phase). Secondary parameters calculated include distribution ( $\alpha$ ) and elimination ( $\beta$ ) half-lives ( $T_{1/2}$ ), microdistribution rate constants, area under the curve (AUC), apparent volume of distribution at steady-state ( $V_{SS}$ ), systemic clearance (CL), and mean residence time (MRT).

Various models were tested with different error structures to determine the best fit base model. The models were parameterized as described above after testing other models. The model was run with the First-Order Conditional Estimation-Extended Least Squares (FOCE-ELS) engine in Phoenix. Model selection was based on goodness of fit plots, diagnostic plots of residuals, scatter plots of predicted vs. observed values, and statistical significance between models using -2LL (twice the negative log likelihood), Akaike information Criterion (AIC), obtained in Phoenix, and CV% of parameter estimates. Inter-individual (between-subject) variability (variance of a parameter among different

subjects) was expressed using an exponential error model according to the equation:

$$P_i = \theta P \times \exp(\eta_i P) \quad (2)$$

where P is the pharmacokinetic parameter of interest for the individual i,  $\theta P$  is  $\theta$  (theta), or the typical value (fixed effect) for the population estimate of the parameter of interest, and  $\eta_i P$  is the  $\eta$  (eta, random effect) for the interindividual (between-subject) differences of the parameter of interest. The  $\eta$  values were assumed to be independent and have a normal distribution with a mean of zero and variance of  $\omega^2$ . An additive model described the residual error ( $\epsilon$ ) of the data, where  $\epsilon$  is the residual intra-subject (within subject) variability with a mean of zero and a variance of  $\sigma^2$ , according to the equation:

$$C_{obs} = C_{pred} + \epsilon \quad (3)$$

where  $C_{obs}$  is the observed concentration for the individual and  $C_{pred}$  is the model predicted concentration plus the error value ( $\epsilon$ ).

### 3 | RESULTS

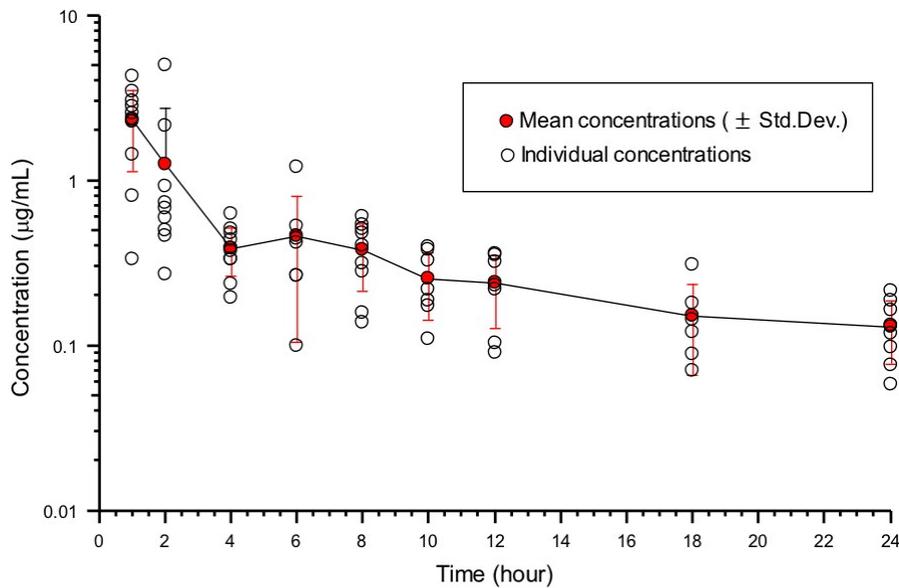
#### 3.1 | Population

A total of 32 adult Eastern box turtles (*Terrapene carolina carolina*) were included in this study. The turtles (18 males and 14 females) weighed  $324 \pm 81.2$  (mean, SD). The dose of ketorolac administered was calculated based on the turtles' weight at presentation. All turtles presented to the NCSU TRT for traumatic injuries. Twenty-eight turtles were presented for vehicular trauma, three for animal attack trauma, and one for trauma secondary to horticultural equipment.

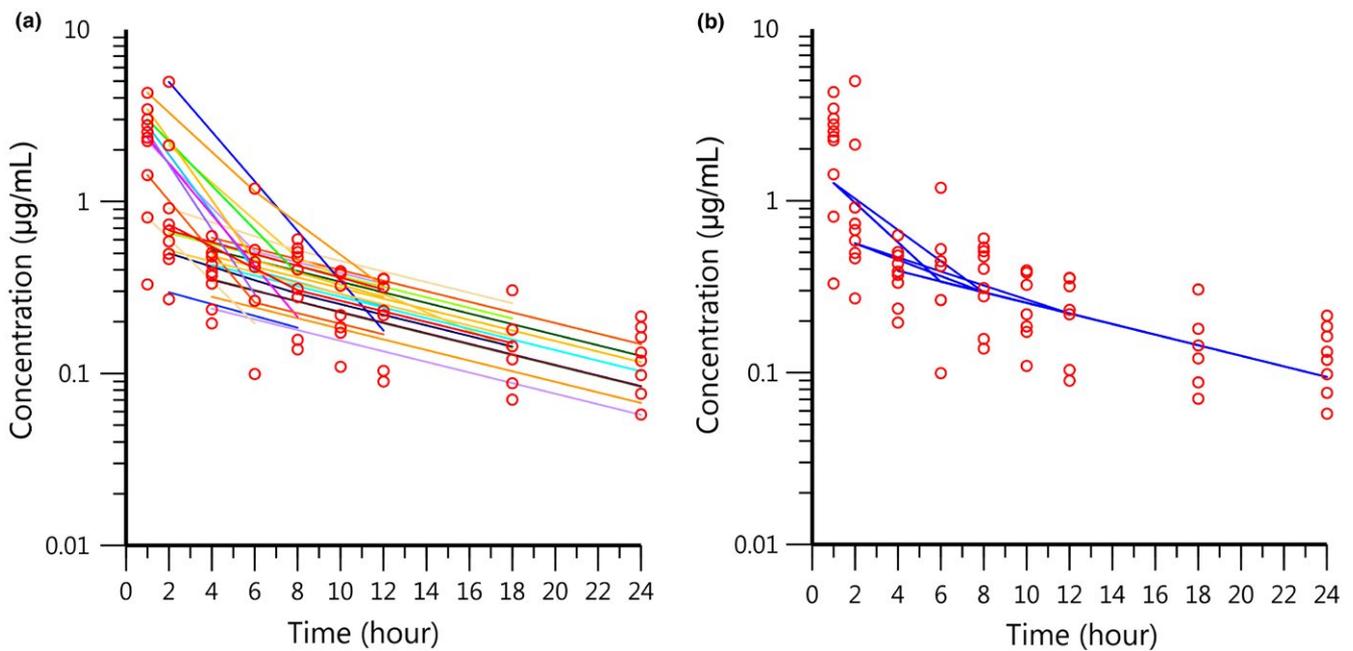
#### 3.2 | Pharmacokinetics

Ketorolac from IM injection produced a high peak concentration followed by rapid distribution and an elimination half-life of 9.78 hr. The population-based pharmacokinetic parameters determined by NLME modeling are summarized in Table 1. Plasma drug concentrations are shown for each individual sample, and the average for the entire group in Figure 1. The fitted lines from the pharmacokinetic analysis are shown in Figure 2, with the model fitted to each individual in panel (a) of Figure 2, and the model fitted after accounting for interindividual variability shown in panel (b). Note the improvement in the model after accounting for between-subject variability.

Diagnostic plots are shown in Figure 3. The plots in Figure 3 show the predicted points vs. dependent variables for the population (PRED) and for individuals (IPRED). Except for a few points in the PRED vs. dependent variable (DV) plot, there is general symmetry with equal number of points above and below the line of unity. The IPRED vs. DV plot shows the individual-specific predicted values vs. DV. This plot (right side of Figure 3) shows that,



**FIGURE 1** Plasma concentrations from 0 to 24 hr of ketorolac after administration at a dose of 0.25 mg/kg IM in 32 Eastern box turtles. Mean concentrations are shown with solid points ( $\pm$ SD), and individual points are shown with open circles



**FIGURE 2** Plot of ketorolac plasma concentrations in individual Eastern box turtles (each open circle represents a sample), with individual fitted lines (a) shown on spaghetti plot and individuals fitted to the population model accounting for between-subject variability (b)

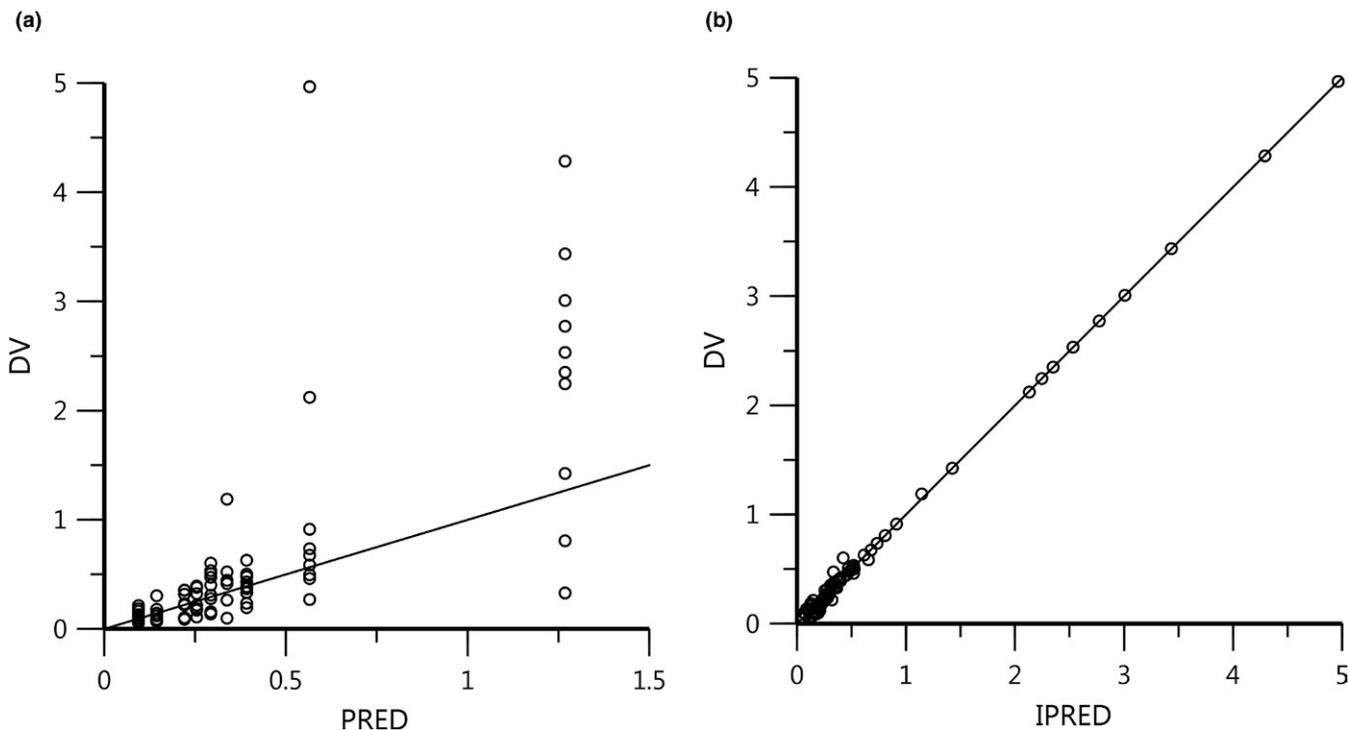
after accounting for between-subject differences, there is a large improvement compared to the PRED vs. DV plot. In a perfect model fit, all points would fall on a line with unit slope indicating perfect correspondence.

#### 4 | DISCUSSION

The pharmacokinetic analysis from this study demonstrated that ketorolac is well absorbed from IM injection in a population of turtles presented to the TRT for traumatic injury. Since we do not know the

impact of the renal portal system on ketorolac, all IM injections were given in the forelimbs to avoid any potential effects. Plasma drug concentrations are sustained for at least 24 hr after a single 0.25 mg/kg intramuscular dose. The half-life of 9.78 hr is longer than both intramuscular administration in humans (3–7 hr) and intravenous administration in dogs (4–5 hr) and horses (0.4–0.8 hr; Ferraresi et al., 2014; Jung, Mroszczak, & Bynum, 1988; Pasloske, Renaud, Burger, & Conlon, 1999), which maintains concentrations throughout a 24-hour interval.

The therapeutic plasma drug concentration is undetermined in turtles, but the concentrations maintained in these turtles for 24 hr were in a range considered therapeutic in humans. Subjectively, the



**FIGURE 3** Diagnostic plots for nonlinear mixed-effects modeling of ketorolac in Eastern box turtles. The population predicted values (PRED) are plotted against the dependent variable (DV) on the left panel (a), and the individual prediction (IPRED) is shown plotted against the DV on the right panel (b). The individual prediction (right panel) is improved by incorporating between-subject variability (interindividual variation) as the major source of variability. Each point on the graphs represents an observed concentration

authors observed an improvement in appetite and activity level for the duration of the turtles' rehabilitation period, which appeared to coincide with the analgesic effects observed in previous studies in turtles (Henson & Lewbart, 1988; Jaeger et al., 2003). However, further research is necessary to determine the analgesic efficacy of ketorolac in this species. No adverse effects were observed from administration of ketorolac tromethamine in these turtles. Twenty-five turtles were returned successfully to the wild after treatment and rehabilitation. The remaining seven turtles required further healing of their shell fractures and are currently in rehabilitation prior to release. We verified the apparent lack of adverse effects during the recovery period with follow-up physical examination 30 days after ketorolac treatment. Our experience agrees with previous studies in dogs that demonstrated safety and efficacy of use (Cagnardi et al., 2013; Mathews, Paley, Foster, Valliant, & Young, 1996). Further studies are needed to evaluate the safety and adverse effects of repeated ketorolac administration.

Our pharmacokinetic analysis used NLME, which is ideal for small reptiles in which only sparse sampling (four samples per animal) is practical to avoid undue stress, excess blood loss, and discomfort to the animals. Furthermore, the NLME analysis improved pharmacokinetic model fit by accounting for interindividual variation (random effect).

In conclusion, intramuscular administration of ketorolac demonstrated favorable pharmacokinetic profiles and subjectively resulted in effects on the turtles in our hospitalized population. This study allowed us to develop a clinical dosing regimen to evaluate analgesic

effects for future studies using ketorolac tromethamine at a dose of 0.25 mg/kg IM, once daily for Eastern box turtles.

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#### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

#### AUTHOR CONTRIBUTIONS

AJC read and approved the final manuscript and contributed to designing study, collecting, samples, drug analysis, and manuscript preparation and review. CAM read and approved the final manuscript and contributed to collecting, samples, drug analysis, and manuscript preparation and review. GAL read and approved the final manuscript and contributed to designing study, results analysis, and manuscript preparation and review. DRD read and approved the final manuscript and contributed to designing study, collecting, samples, drug analysis, and manuscript review. MGP read and approved

the final manuscript and contributed to designing study, supervised the study, designed the drug analysis protocol, data analysis, and manuscript preparation and review.

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