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PHARMACOKINETICS OF ORAL FLUNIXIN MEGLUMINE, MELOXICAM, OR GABAPENTIN IN THREE BLACK RHINOCEROS (*DICEROS BICORNIS*)

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Abstract: Pharmacokinetics of single, separate doses of IV flunixin meglumine (1 mg/kg), IV meloxicam (0.5 mg/kg), oral flunixin meglumine (1 mg/kg), oral meloxicam (1 mg/kg), and oral gabapentin (15 mg/kg) in three adult black rhinoceroses (*Diceros bicornis*) were determined from serial blood collection made over 72 h. The concentration versus time profiles were analyzed for each drug and route in each individual rhinoceros, and individual pharmacokinetic parameters were calculated for each medication administered. Meloxicam had near complete bioavailability in each trial, while flunixin meglumine was generally lower. Oral meloxicam was noted with similar half-life values between all animals (range 9.22–14.52 h) tested, while oral gabapentin had a larger range (range 10.25–24.85 h). Oral flunixin meglumine achieved a lower C_{max} (range 170.67–664.38 ng/ml) in this study compared with the mean C_{max} (1,207 ng/ml) reported in a similar study in white rhinoceroses (*Ceratotherium simum*), but some overlap in range of values was noted. Oral flunixin meglumine T_{max} (range 1.05–10.78 h) and half-life (range 3.88–14.85 h) values in black rhinoceroses was similar to mean values reported in white rhinoceroses (3 and 8.3 h, respectively).

INTRODUCTION

Analysis of both pharmacokinetic and pharmacodynamic pharmacologic effects is ideal, when possible, to understand both the metabolism of a product by an organism, and the clinical effect of the product on the organism. Analgesic pharmacodynamic analysis is challenging in veterinary patients because it requires comparison of plasma drug concentration to measurable and objective clinical outcomes. As pharmacodynamic variables are not available for rhinoceroses, it is preferred to predict analgesic effects based on extrapolations of circulating drug concentrations consistent with efficacy in other species, such as domestic horses. However, pharmacokinetic analysis in rhinoceros species is possible and has been reported for flunixin meglumine (FM) and phenylbutazone in white rhinoceroses (WR; *Ceratotherium simum*).[4,8] Due to species-specific differences, such as oxidative stressor sensitivity in black rhinoceroses (BR; *Diceros bicornis*) and differences in the preferred diet between browsing BR and grazing WR, pharmacokinetic analysis of analgesic medications in BR is needed. Single-dose pharmacokinetics of oral and IV FM and meloxicam, and oral gabapentin, were completed in three BR. Selection of these analgesics was guided by reports for use in megavertebrates concurrently with a lack of species-specific pharmacokinetic data.[12] The study protocol was approved by the Lincoln Park Zoo Research Committee and endorsed by the BR Species Survival Plan and rhino Taxon Advisory Group before initiation of the study.

MATERIALS AND METHODS

One female (BR1: 9 yr) and two male (BR2: 28 yr; BR3: 17 yr) adult BR were evaluated by oral medication dosing, while only male BR received IV FM and meloxicam due to BR1 pregnancy. No

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health concerns were noted for any individual based on routine health screening, and no BR received any study drugs in the prior year. Each treatment was dosed alone, no combination treatments were administered, and each treatment was separated by a standard 2-wk washout, based on equid elimination half-lives. Drug doses were guided by recommended equid doses and the most recent weight of each BR. In domestic horses, FM is approved for oral and IV routes, while all routes are extralabel for both gabapentin and meloxicam.

During Trial 1, BR2 and BR3 received FM paste (Intervet International B.V., Whitehouse Station, NJ 08889, USA; 1 mg/kg PO); FM injectable solution (Bimeda-MTC Animal Health, Inc, Cambridge, ON N3C 2W4, Canada; 1 mg/kg IV); meloxicam tablets (15-mg tablets, Unichem Laboratories, Ltd, Bardez, Goa 403 511, India; 1 mg/kg PO); meloxicam injectable solution (Norbrook Laboratories, Ltd, Newry, BT35 6PU County Down, Northern Ireland; 0.5 mg/kg IV); or gabapentin capsules (400-mg capsules, Amneal Pharmaceuticals, Hauppauge, NY 11788, USA; 15 mg/kg PO). Each treatment was completed in BR2 and BR3 and separated by a washout of 2 wk. During Trial 2, BR1, BR2, and BR3 each received oral doses of FM paste, meloxicam tablets, or gabapentin capsules at the same doses. Each treatment was completed in each individual and were separated by a washout of 2 wk.

Oral medication doses (FM paste, gabapentin capsules, or meloxicam tablets) were mixed with a cup of dry dietary grain and a tablespoon of honey inside a brown paper bag, which was shut and rolled tightly to seal, and the entire unit was placed in the oral cavity during unrestrained training to ensure complete ingestion. Capsules were not opened, and tablets were not crushed for dosing. IV medications were diluted in 250 mL of a 0.9% sodium chloride (Abbott Laboratories, North Chicago, IL 60064, USA) fluid bag and infused through a 21-ga (1-inch) needle (Covidien, Mansfield, MA 02048, USA) on a 103-inch IV infusion set (Henry Schein Animal Health, Dublin, OH 43017, USA), with a 30-inch extension set (Henry Schein Animal Health), into a pedal or radial vein that had been prepared topically with 70% isopropyl alcohol (Medical Chemical Corp, Torrance, CA 90501, USA), 2% chlorhexidine scrub (Henry Schein Animal Health), and diluted 10% povidone iodine solution (Henry Schein Animal Health). IV infusions were performed during unrestrained training and ranged in time from 8 to 17 min.

Following dosing, 10-mL blood samples were collected into red-top serum tubes using either 21- or 25-ga (3/4-inch) winged infusion sets (Becton, Dickinson and Company, Franklin Lakes, NJ 07417, USA) from a radial vein at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 33, 48, 57, and 72 h after oral dosing and 1, 2, 3, 4, 6, 8, 10, 12, 24, 35, 48, 57, and 72 h after IV dosing. After IV dosing, no blood samples were collected from the infused leg for 24 h. After resting at room temperature for 2 h, tubes were centrifuged for 10 min at 2,719 *g* (LW Scientific, Lawrenceville, GA 30046, USA), and serum was aliquoted into ultralow plastic storage tubes (Thermo Fisher Scientific, Inc, Rochester, NY 14625, USA) and frozen at –80°C.

Serum concentrations of gabapentin, FM, and meloxicam were determined using an Accela autosampler and pump and a LTQ-XL mass spectrometer (Thermo Fisher Scientific) for high-pressure liquid chromatography coupled with mass spectrometry detection, with a validated method that has been previously published.[5] All samples were analyzed on the same day. The same standard curve range (5–20,000 ng/mL), limit of quantitation (LOQ; 5 ng/mL), limit of detection (0.1 ng/mL), and quality control concentrations (30, 300, and 3,000 ng/mL) were used for each drug. The difference in calculated and actual concentrations of gabapentin (–14 to 15%), meloxicam (–5 to 15%), and FM (–6 to 13%) varied for spiked plasma quality control samples. Calibration curves exhibited a correlation coefficient (r^2) exceeding 0.995 across the concentration range.

A commercially available software package (Phoenix WinNonlin®, Certara, USA, Princeton, NJ 08540, USA) was used to analyze time–concentration data for each drug and administration route, separately by animal, using noncompartmental methods. Following IV administration (FM and meloxicam), the area under the time–concentration curve (AUC_{0-last}) was calculated by the trapezoidal rule (linear up and ln–linear down), and doses were treated as an IV infusion in the software. The elimination half-life was calculated from the slope of the terminal portion of the time–concentration curve on a ln–linear scale (λ_z) using the equation $0.693/\lambda_z$. The area under the curve (AUC) was extrapolated ($AUC_{0-\infty}$) to infinity by adding C_{last}/λ_z to AUC_{0-last}, where C_{last} is the last measured concentration. The volume based on the terminal phase (V_{dz}) and clearance (Cl) were calculated using standard equations (dose/AUC × λ_z) and dose/AUC, respectively). The mean residence time (MRT) was calculated

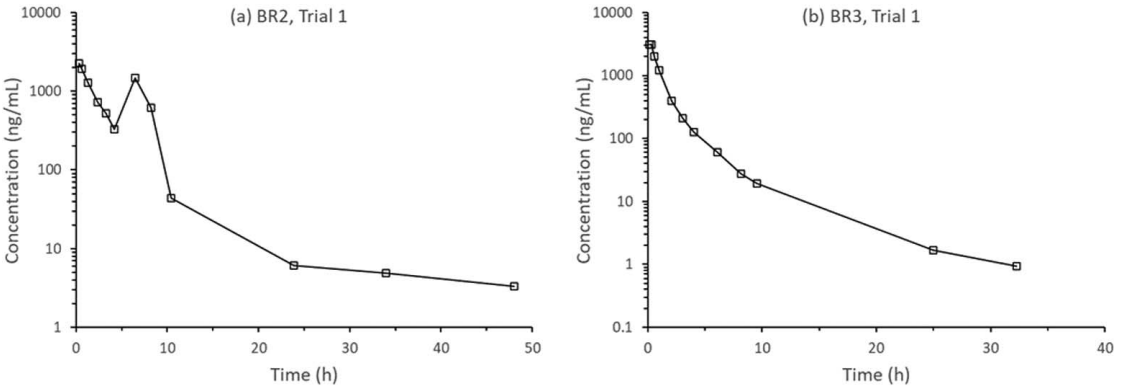

Figure 1. Concentration–time profiles of flunixin meglumine after IV administration in black rhinoceroses (BR; *Diceros bicornis*): (**a**) BR2, Trial 1; and (**b**) BR3, Trial 1.

from the AUC and the area under the first moment curve (AUMC), (AUC/AUMC), and the volume of distribution at steady state (V_{ss}) was then calculated as MRT × CL. For oral administration (FM, meloxicam, and gabapentin), the maximal concentration (C_{max}) and time of maximal concentration (T_{max}) were taken directly from the data. All other oral pharmacokinetic parameters were calculated as described for IV parameters. Oral bioavailability (F) was calculated for animals where IV and oral routes of drugs were administered, according to the following formula:

$$F = \frac{\text{AUC}_{\text{non-IV}} \times \text{dose}_{\text{IV}}}{\text{AUC}_{\text{IV}} \times \text{dose}_{\text{non-IV}}} \times 100.$$

When applicable, dose normalization of exposure-related pharmacokinetic parameters, C_{max} and $AUC_{0-\infty}$, was performed by dividing the parameter by the drug milligram per kilogram dose.

RESULTS

The estimated percentage of successful IV FM (BR2 61% and BR3 80%) and meloxicam (BR2 75% and BR3 92%) doses were noted. Subcutaneous extravasation of the remaining FM and meloxicam doses only occurred in BR2 due to limb movement, resulting in dislodging of the needle. Further IV access attempts were not successful, administered dose was recorded, and the remainder was dosed subcutaneously. Pharmacokinetic data were not dose normalized for extravasation of IV doses. Complete oral dosing of each medication in each BR was noted. No adverse effects were noted following IV or oral drug administration.

Serum drug concentration versus time graphs for IV FM (Fig. 1), IV meloxicam (Fig. 2), oral FM (Fig. 3), oral meloxicam (Fig. 4), and oral gabapentin (Fig. 5) are presented for each BR. Individual pharmacokinetic parameters for FM (Table 1), meloxicam (Table 2), and gabapentin

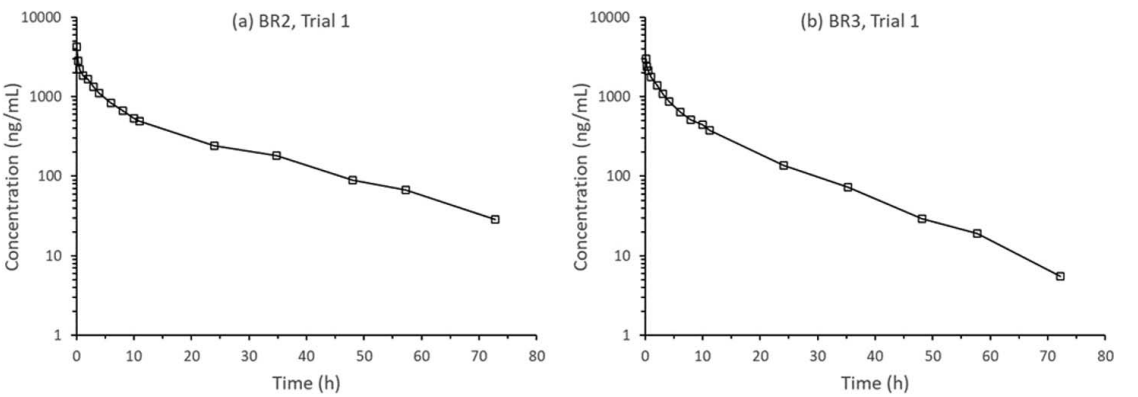

Figure 2. Concentration–time profiles of meloxicam after IV administration in black rhinoceroses (BR; *Diceros bicornis*): (**a**) BR2, Trial 1; and (**b**) BR3, Trial 1.

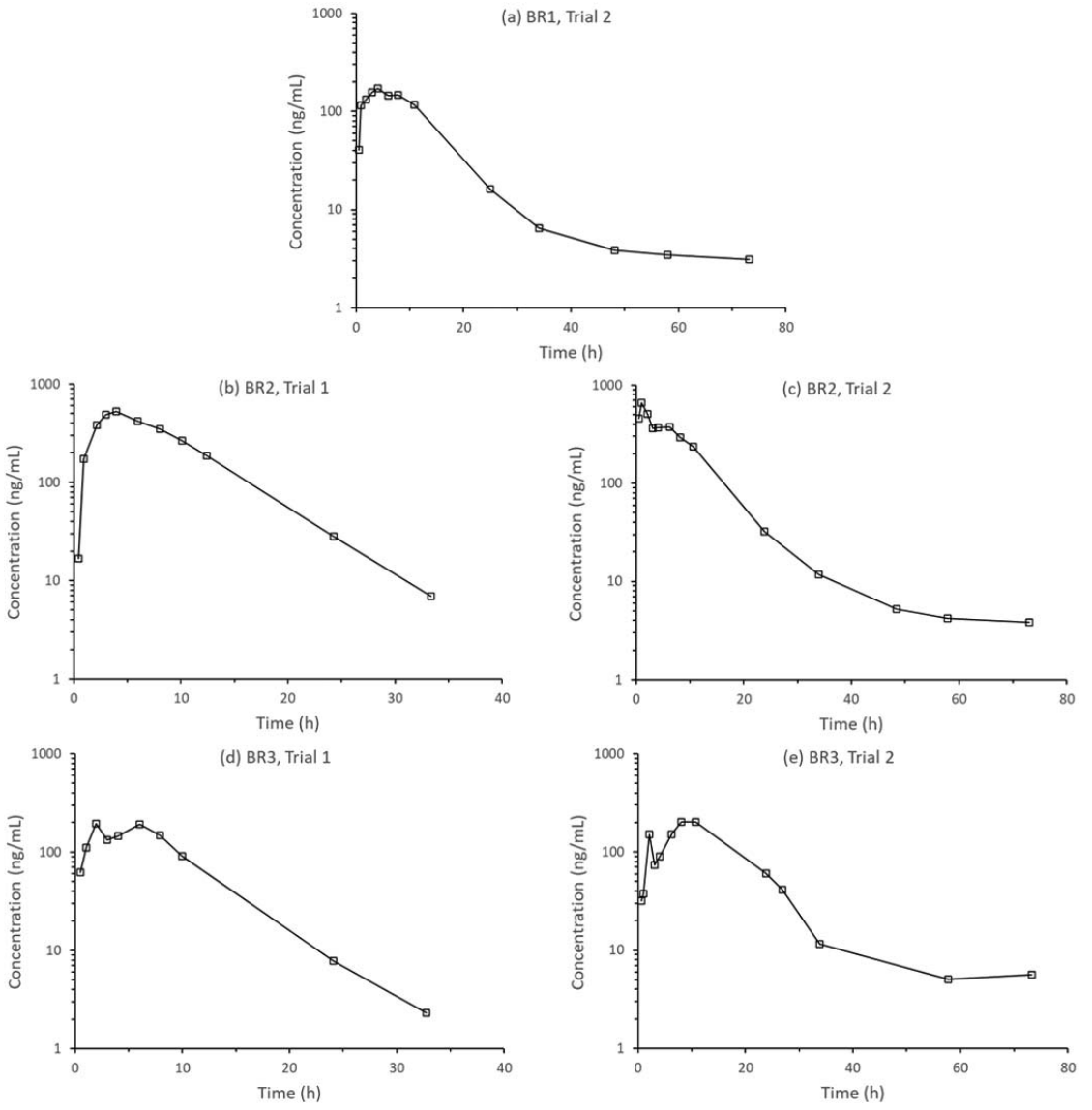

Figure 3. Concentration–time profiles of flunixin meglumine after oral administration in black rhinoceroses (BR; *Diceros bicornis*): (**a**) BR1, Trial 2; (**b**) BR2, Trial 1; (**c**) BR2, Trial 2; (**d**) BR3, Trial 1; and (**e**) BR3, Trial 2.

(Table 3) are reported. The oral FM half-life ranged from 3.9–14.9 h, while the IV FM half-life was 27.6 h in BR2 and 4.8 h in BR3. This disparity was likely due to partial dose extravasation in BR2, resulting in slower systemic drug absorption. Oral FM bioavailability ranged from 52.1–94.2%. The oral meloxicam half-life ranged from 9.2–14.5 h, while the IV meloxicam half-life was 14.4 h in BR2 and 9.4 h in BR3. Oral meloxicam bioavailability ranged from 91.9–119%. Oral gabapentin half-life ranged from 10.3–24.9 h. Concentrations of IV and oral (Trial 1) FM decreased below LOQ by 72 h. Concentrations of IV meloxicam, oral FM (Trial 2), oral meloxicam, and oral gabapentin remained quantifiable at 72 h.

DISCUSSION

Linear, instead of metabolic or allometric, scaling of pharmaceutical doses from domestic to megavertebrate species should be carefully considered.[9] Dose extrapolation based on species pharmacokinetics (allometric scaling) or based on metabolic rate (metabolic scaling) have been postulated as safer alternatives to consider.[10]

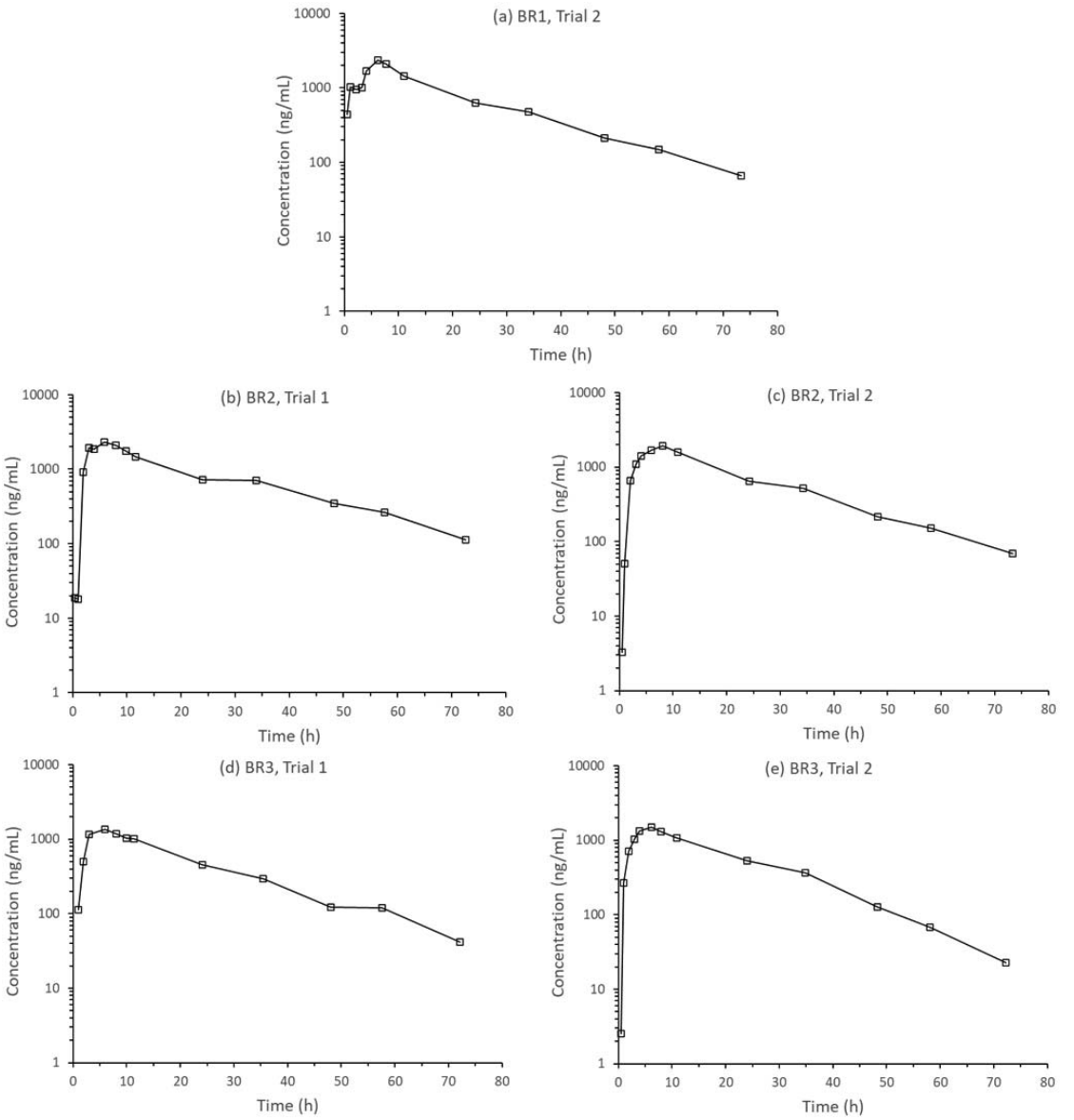

Figure 4. Concentration–time profiles of meloxicam after oral administration in black rhinoceroses (BR; *Diceros bicornis*): (**a**) BR1, Trial 2; (**b**) BR2, Trial 1; (**c**) BR2, Trial 2; (**d**) BR3, Trial 1; and (**e**) BR3, Trial 2.

Drugs that undergo extensive hepatic metabolism, like FM, are poor candidates for allometric or metabolic scaling, and linear scaling may, thus, be acceptable.[13,16] Oral bioavailability determination was a study goal, and although administration was challenging, meloxicam and FM were administered intravenously. Accurate pharmacokinetic values were calculated based on detailed notes of successful IV administration. Near-complete meloxicam oral bioavailability was observed, based on comparison of dose-normalized $AUC_{0-\infty}$ values, while FM had variable bioavailability. Partial meloxicam subcutaneous extravasation in BR2 occurred, but complete absorption was suspected based on the concentration versus time graph (Fig. 2). Feeding during oral trials may have resulted in prolonged absorption of drugs, which has also been reported in equine oral meloxicam and FM studies.[19,21] The concentration versus time graphs for oral FM in BR3 (Fig. 3) had secondary peaks, which may be due to irregular gastric emptying or enterohepatic

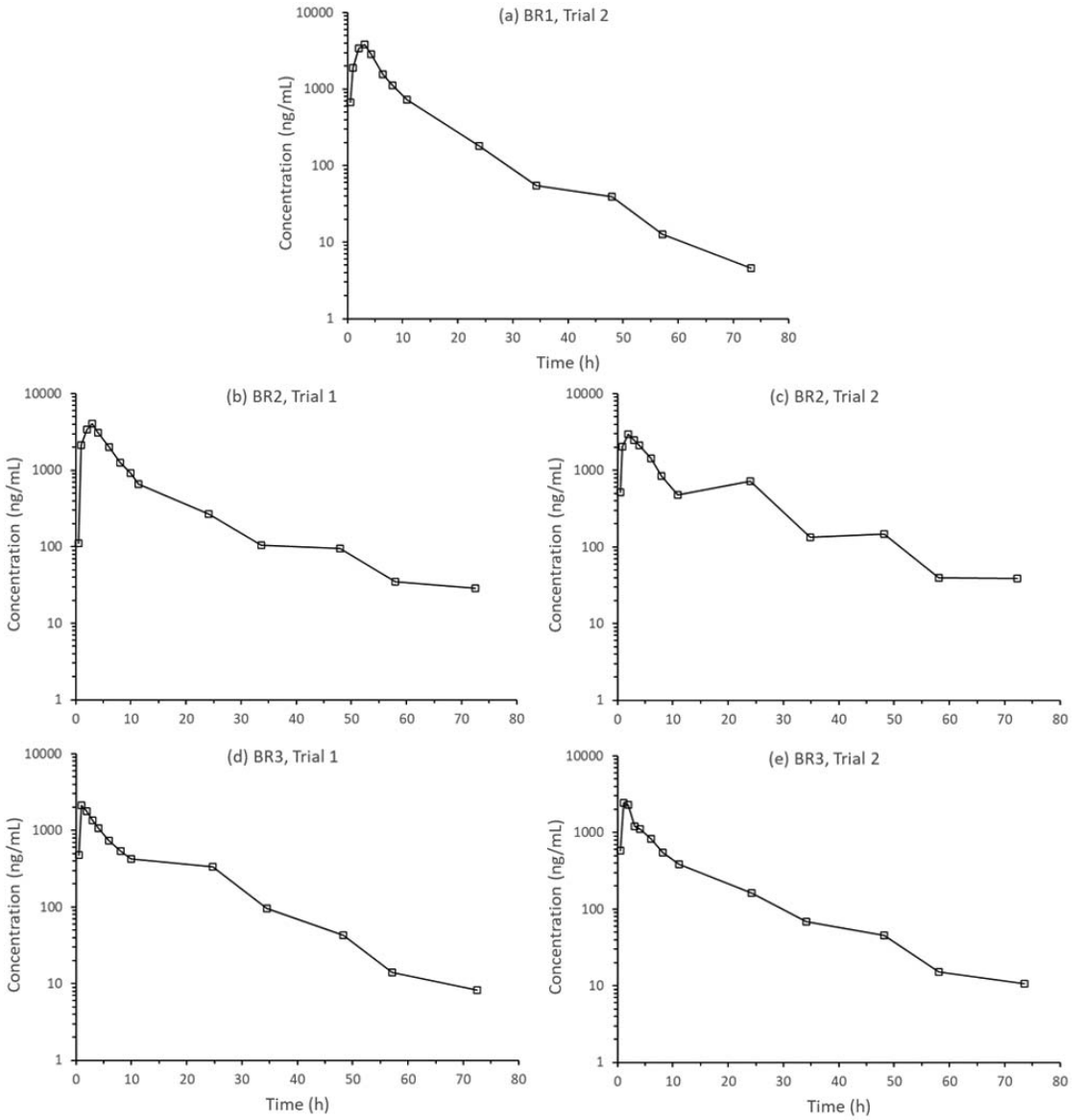

Figure 5. Concentration–time profiles of gabapentin after oral administration in black rhinoceroses (BR; *Diceros bicornis*): (**a**) BR1, Trial 2; (**b**) BR2, Trial 1; (**c**) BR2, Trial 2; (**d**) BR3, Trial 1; and (**e**) BR3, Trial 2.

recycling, and both can cause delays of drug absorption or plasma elimination.[14] FM enterohepatic recycling has been reported in many species, including cattle (*Bos taurus*),[15] goats (*Capra hircus*),[11] cats (*Felis catus*),[7] dromedary camels (*Camelus dromedarius*),[20] WR,[4] and Asian elephants (*Elephas maximus*).[1]

Oral FM (1 mg/kg) pharmacokinetics in WR have been reported, and the mean C_{max} (1,207 ng/mL) was greater than values measured in BR, but lower than horses, at the same dose.[3,4,21] However, T_{max} (3 h) and half-life (8.3 h) were both similar to values in BR.[4] Rhinoceros FM pharmacokinetic variation could be due to species-specific physiology and anatomy, similar to pharmacokinetic variations between Asian and African (*Loxodonta africana*) elephants.[2] WR had decreased food access prior to FM dosing, while study BR were dosed oral FM with food and had regular diet access during the study, which could cause

Table 1. Pharmacokinetic parameters after 1 mg/kg oral or 1 mg/kg IV administration of flunixin meglumine in black rhinoceroses (BR; *Diceros bicornis*).[a]

Pharmacokinetic parameter	BR1 (female)	BR2 (male)			BR3 (male)		
	PO Trial 2	PO Trial 1	PO Trial 2	IV Trial 1	PO Trial 1	PO Trial 2	IV Trial 1
C_{max} (ng/ml)	171	528	664	—	197	204	—
T_{max} (h)	4.1	4.0	1.1	—	1.9	10.8	—
Half-life (h)	5.6	4.4	6.6	27.6	3.9	14.9	4.8
V_{dz} (ml/kg)	—	—	—	2,485	—	—	1,343
Cl (ml/kg per h)	—	—	—	62.4	—	—	193
$AUC_{0-\infty}$ (ng × h/ml)	2,565	5,637	6,055	9,789	2,175	3,930	4,172
MRT (h)	9.8	8.6	8.8	5.9	7.5	17.3	1.8
V_{ss} (ml/kg)	—	—	—	365	—	—	341
F (%)	—	57.6	61.9	—	52.1	94.2	v

[a] C_{max}, maximal concentration; T_{max}, time of maximal concentration; V_{dz}, apparent volume of distribution based on the terminal phase; Cl, total body clearance; $AUC_{0-\infty}$, area under the curve extrapolated to infinity; MRT, mean residence time; V_{ss}, volume of distribution at steady state; F, oral bioavailability.

Table 2. Pharmacokinetic parameters after 1 mg/kg oral or 0.5 mg/kg IV administration of meloxicam in black rhinoceroses (BR; *Diceros bicornis*).[a]

Pharmacokinetic parameter	BR1 (female)	BR2 (male)			BR3 (male)		
	PO Trial 2	PO Trial 1	PO Trial 2	IV Trial 1	PO Trial 1	PO Trial 2	IV Trial 1
C_{max} (ng/ml)[b]	2,347	2,310	1,926	—	1,354	1,493	—
T_{max} (h)	6.1	5.9	8.0	—	5.9	6.1	—
Half-life (h)	14.2	14.2	14.5	14.4	13.4	9.2	9.4
V_{dz} (ml/kg)	—	—	—	437	—	—	398
Cl (ml/kg per h)	—	—	—	21.0	—	—	29.5
$AUC_{0-\infty}$ (ng × h/ml)[b]	44,802	53,952	43,758	22,757	29,797	31,496	15,599
$AUC_{0-\infty}$ (ng × h/ml; dose normalized[c])	—	—	—	45,515	—	—	31,198
MRT (h)	22.0	25.6	23.5	17.5	21.9	19.6	11.3
V_{ss} (ml/kg)	—	—	—	368	—	—	334
F (%)	—	119	91.9	—	95.5	101	—

[a] C_{max}, maximal concentration; T_{max}, time of maximal concentration; V_{dz}, apparent volume of distribution based on the terminal phase; Cl, total body clearance; $AUC_{0-\infty}$, area under the curve extrapolated to infinity; MRT, mean residence time; V_{ss}, volume of distribution at steady state; F, oral bioavailability.

[b] Dose normalization unnecessary due to 1.0 mg/kg dosing for PO trials.

[c] Dose normalized based on 0.5 mg/kg dosing for IV trials.

Table 3. Pharmacokinetic parameters after 15 mg/kg oral administration of gabapentin in black rhinoceroses (BR; *Diceros bicornis*).[a]

Pharmacokinetic parameter	BR1 (female)	BR2 (male)		BR3 (male)	
	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
C_{max} (ng/ml)	3,807	4,059	2,953	2,130	2,454
C_{max} (dose normalized[b]; ng/ml)	254	271	197	142	164
T_{max} (h)	3.1	3	1.9	1.0	1.1
Half-life (h)	10.3	21.3	24.9	15.0	18.3
$AUC_{0-\infty}$ (ng × h/ml)	27,826	32,720	32,286	18,457	16,868
$AUC_{0-\infty}$ (ng × h/ml; dose normalized[b])	1,855	2,181	2,152	1,230	1,125
MRT (h)	9.2	13.9	19.6	14.2	13.1

[a] C_{max}, maximal concentration; T_{max}, time of maximal concentration; $AUC_{0-\infty}$, area under the curve extrapolated to infinity; MRT, mean residence time.

[b] Dose normalized based on 15 mg/kg dose.

decreased or delayed BR gastrointestinal absorption of FM.[4] Equine oral FM studies have demonstrated that fed horses had lower C_{max}, and later T_{max}, than unfed horses, with no change in half-life.[21]

This study evaluated individual BR pharmacokinetics; mean, median, and range values were not calculated due to small sample size and individual variation, such as age or sex. No BR pharmacodynamic data were collected. BR pharmacokinetic data were dose normalized, which allows comparison to similar dose-normalized equine data. Additionally, BR drug concentrations can be compared with published effective drug concentrations from equine pharmacodynamic studies, with caution to not assume dose efficacy in BR. However, efficacy of NSAID may not be proportional to plasma concentrations, and effective analgesia may occur at low concentrations.[6,17] The PK-PD modeling of experimentally induced equine carpal arthritis treated with FM reported drug concentrations that correlated to pharmacodynamic efficacy for two variables, stride length and rest angle, at 930 ± 350 ng/ml and 240 ± 130 ng/ml, respectively.[17] Only BR2 reached the effective rest angle serum value in both trials, while no BR reached the value for stride length. The IV meloxicam PK-PD equine modeling reported mean drug concentrations that correlated to pharmacodynamic efficacy for stride length and clinical lameness score as 130 ng/ml and 195 ng/ml, respectively.[18] All BR trials had serum concentrations above these values for more than 24 h after dosing oral meloxicam at 1.0 mg/kg. No pharmacodynamic studies to report an effective gabapentin plasma concentration have been performed in horses to date.

Megavertebrate analgesic pharmacodynamic analysis has not been performed, although a survey of perceived benefit is available for rhinoceroses and elephants.[12] Good perceived efficacy in BR for gabapentin (2.5–5.0 mg/kg oral), FM (0.2–1.6 mg/kg oral), and meloxicam (0.2 mg/kg oral) in greater one-horned rhinoceroses (*Rhinoceros unicornis*) was described.[12] This study used higher doses of gabapentin and meloxicam in BR than described in the survey, which was published after completion of this study. BR analgesic pharmacokinetic results should not be interpreted as dose recommendations or proof of efficacy but instead may help guide BR analgesic selection. This study was limited by a small sample size, resulting in individual pharmacokinetic values instead of calculation of species means. Recommendations for future BR analgesic pharmacokinetic studies include a larger sample size and multidose analysis.

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