Pharmacokinetics of Orally Administered Phenylbutazone in African and Asian Elephants (Loxodonta africana and Elephas maximus)

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PHARMACOKINETICS OF ORALLY ADMINISTERED PHENYLBUTAZONE IN AFRICAN AND ASIAN ELEPHANTS (LOXODONTA AFRICANA AND ELEPHAS MAXIMUS)

Ursula Bechert, D.V.M., Ph.D., J. Mark Christensen, Ph.D., C. Nguyen, Ph.D., R. Neelkant, Ph.D., and E. Bendas, Ph.D.

Abstract: The pharmacokinetic parameters of phenylbutazone were determined in 18 elephants (Loxodonta africana and Elephas maximus) after single-dose oral administration of 2, 3, and 4 mg/kg phenylbutazone, as well as multiple-dose administrations with a 4-wk washout period between trials. After administration of 2 mg/kg phenylbutazone, mean serum concentrations peaked in approximately 7.5 hr at 4.3 ± 2.02 μg/ml and 9.7 hr at 7.1 ± 2.36 μg/ml for African and Asian elephants, respectively, while 3 mg/kg dosages resulted in peak serum concentrations of 7.2 ± 4.06 μg/ml in 8.4 hr and 12.1 ± 3.13 μg/ml in 14 hr. The harmonic mean half-life was long, ranging between 13 and 15 hr and 39 and 45 hr for African and Asian elephants, respectively. There was evidence of enterohepatic cycling of phenylbutazone in Asian elephants. Significant differences (P < 0.0001) in pharmacokinetic values occurred between African and Asian elephants for clearance (27.9 and 7.6 ml/hr/kg, respectively), terminal half-life (15.0 and 38.7 hr, respectively), and mean residence time (22.5 and 55.5 hr, respectively) using 2-mg/kg dosages as an example. This suggests that different treatment regimens for Asian and African elephants should be used. There were no apparent gender differences in these parameters for either elephant species.

Key words: Phenylbutazone, pharmacokinetics, African elephants, Asian elephants, NSAID.

INTRODUCTION

There is a high prevalence of musculoskeletal disorders (e.g., trauma, arthritis) among captive elephants (Loxodonta africana and Elephas maximus) reported to occur in more than 70% of the population in North America in a retrospective study. To treat these and other conditions, nonsteroidal anti-inflammatory agents (NSAIDS), such as phenylbutazone, are used strictly on an empirical basis in elephants. However, results from previous studies with other drugs suggest that metabolic scaling calculations for elephants are unreliable, either under- or overestimating dosage and dosing interval requirements. The enormous body size and dissimilar physiologic metabolism of elephants compared with other species, such as horses and cattle, complicate estimation of dosing requirements based on metabolic scaling calculations.

Phenylbutazone, a pyrazolone NSAID, works primarily through inhibition of the arachidonic acid cascade to decrease production of prostaglandins and thromboxane. It is a potent pain reliever, anti-inflammatory agent. Phenylbutazone has commonly been used in horses to treat bone and joint inflammation, laminitis, and soft-tissue inflammation and in captive elephants has similarly been used to treat inflammatory conditions, such as arthritis. Potential negative side effects from use of phenylbutazone include gastrointestinal ulceration and hemorrhage, especially when used with other anti-inflammatory analgesics, as well as inhibition of T₄ to T₃ conversion and decreased free thyroxine concentrations. In one study with horses, chronic phenylbutazone administration affected articular cartilage metabolism, which might subsequently suppress proteoglycan synthesis and actually potentiate cartilage damage. Other side effects may include kidney damage, suppression of white blood cell production, and aplastic anemia.

Pharmacokinetic properties of phenylbutazone are known to vary significantly among different species, and one author advises to “avoid interspecies extrapolation of pharmacokinetic data... to extrapolate from one species to another is hazardous and increases the likelihood of adverse drug reactions.” The maximum oral dose of phenylbutazone recommended by manufacturers for horses ranges from 1 to 3 mg/kg given t.i.d. Empirical dosages of phenylbutazone administered to captive elephants have ranged between 1 and 2 mg/kg every 24 hr; however, in addition to problems with metabolic scaling, differences in NSAID dosage requirements between African and Asian elephants have been observed.

For effective management of pain and inflammation in elephants, administration of phenylbutazone should occur when drug absorption is maxi-
Table 1. Demographic characteristics of 10 African and 8 Asian elephant participants.

<table>
<thead>
<tr>
<th>Species</th>
<th>Gender</th>
<th>No.</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>Facility</th>
<th>Single-dose trials (mg/kg)</th>
<th>Multiple-dose trials</th>
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<tr>
<td></td>
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<td>18</td>
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<td></td>
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<tr>
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<td></td>
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<tr>
<td></td>
<td>♂ Af Fe 2</td>
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<tr>
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<tr>
<td></td>
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<tr>
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<td>43</td>
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<td></td>
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<td>2, 3, and 4 Completed</td>
<td></td>
<td></td>
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</tbody>
</table>

* Bowmanville, Ontario, Canada.
*b Greenbrier, Arkansas.
© Salinas, California.
*d Kansas City, Missouri.
© Rochester, New York.
† Portland, Oregon.

The objective of this study was to determine appropriate dosing regimens for both African and Asian elephants based on noncompartmental pharmacokinetic analyses of phenylbutazone administered in both single and multiple doses.

MATERIALS AND METHODS

Animals

Eighteen healthy captive elephants (five male and five female African; four male and four female Asian) were used in this study (Table 1). Animals ranged in age from 14 to 43 yr and in weight from 3,218 to 4,318 kg for African and 3,200 to 6,136 kg for Asian elephants, and all animals were maintained in captivity in six facilities located in Canada and the USA. Phenylbutazone (Sigma Chemical Company, St. Louis, Missouri 63178, USA) was given orally with food treats (e.g., apples, bread, peanut butter), and blood samples were collected from ear veins using 20-gauge butterfly catheters.

Study design

Pilot studies were conducted using empirically derived dosing regimens to ensure that proper ranges for dosage and dosing frequency determinations would be utilized. Based on these results, single-dose trials using 2-, 3-, and 4-mg/kg dosages were initiated. Washout periods between trials were 4 wk in duration to allow for complete elimination of residual drug metabolites. Blood samples were collected at −5, 30, and 60 min; 2, 12, and 24 hr; and 2, 4, 6, 8, 10, and 12 days post administration. The −5 min samples were negative for detectable phenylbutazone after the 4-wk washout periods. Blood samples were placed into glass tubes and centrifuged for 10 min at 13,000 g. Serum was decanted into plastic screw-cap vials and kept frozen at −20°C until time of analysis.

The optimal dosing frequency was determined by extrapolating serum concentrations of phenylbutazone from single-dose trials to steady-state levels. Based on these results, multiple-dose trials were initiated and consisted of 2-mg/kg doses given every 24 hr to African elephants and 3-mg/kg doses given every 48 hr to Asian elephants. Blood samples were collected hourly for 4 hr after each of three administrations and then every 6 hr plus 1 hr prior to the next administration for the 2-mg/kg dose. For the 3-mg/kg dose, blood samples were collected 3, 4, 12, 16, 28, 35, and 45 hr post administration plus 1 hr prior to the next administration for each of three administrations.
Phenylbutazone analysis

Serum phenylbutazone concentrations were quantified by high-performance liquid chromatography (HPLC) after sample preparation. To prepare samples, 0.5 ml of serum was added to 100 µl of internal standard (25 µg/mL of gemfibrozil), 1 ml of phosphate buffer (pH 7.4), and 1.5 ml of filtered water. The mixture was then vortexed for 30 sec and passed through a C18 solid phase extraction column that had been prewashed with 1 ml methanol and 1 ml filtered water. The residue was washed with 1.5 ml phosphate buffer (pH 7.4), 1.5 ml filtered water at 20 p.s.i., and then 0.15 ml acetonitrile. The column was vacuum dried, and the residue was eluted twice with 1.5 ml methanol, combined, and then vacuum dried again.

The samples were reconstituted with 0.5 ml mobile phase (40% acetonitrile, 60% 0.1 M acetic acid; pH 3.5) and vortexed for 1 min, followed by centrifugation for 5 min at 3,400 g. The reconstituted solution (100 µl) was injected onto an HPLC C-18 column at a flow rate of 1.5 ml/min. The HPLC system consisted of a pump (Model M-600 A, Water Associates, Inc., Milford, Massachusetts 01757, USA), an auto injector (Model 712, Water Associates, Inc., Milford, Massachusetts), a variable wavelength detector set at 229 nm (Model SP8773XR, Spectra Physics, San Associates, Inc.), and an automated data integrator (Hewlett Packard Model 3390A, San Jose, California 95154, USA), and an automated data integrator (Hewlett Packard Model 3390A, San Jose, California 95154, USA).

Serum concentrations of phenylbutazone were calculated from known standard concentrations (0.25–50 µg/mL), and a correlation coefficient for calibration curves was calculated ($r^2 = 0.98$, range 0.96–0.999). Assay sensitivity was 0.1 µg/ml with a 12.8% intra-assay coefficient of variation. The interassay coefficient of variation was 11.69%. Concentrations of oxyphenbutazone and $\gamma$-hydroxyphenylbutazone, active metabolites of phenylbutazone, were observed, but often sample concentration values were too low for accurate determination.

Pharmacokinetic and statistical analyses

Pharmacokinetic data were modeled and fitted using the software program Win NONLIN (2002 Version 3.2, PharSight, Mountain View, California 94040, USA) using noncompartmental analysis. Parameters determined for each elephant included the maximal concentration ($C_{\text{max}}$), time of maximal concentration ($T_{\text{max}}$), volume of distribution ($V/F$), area under the curve (AUC), mean residence time (MRT), clearance rate (Cl/F), terminal half-life ($T_{1/2}$), and the elimination rate constant ($K_{el}$). The elimination half-life for phenylbutazone ($T_{1/2,el}$) was determined by dividing the natural logarithm of 2 (0.693) by $K_{el}$.

Pharmacokinetic parameters were calculated for each elephant and each group of elephants based on species and gender (mean ± SD). The correlation between body weight and peak phenylbutazone concentrations as well as age and $T_{1/2}$ was analyzed by standard regression analysis (Excel, Microsoft, Redmond, Washington 98052, USA). Statistical comparisons between Asian and African elephants were done using an analysis of variance mixed effects model:

$$\log(y_{ijkl}) = \alpha + \beta_i + \gamma_j + \epsilon_{ijkl}$$

where $y_{ijkl}$ represents the measured pharmacokinetic parameter on the $k$th dose in the $j$th zoo for the $i$th elephant of $l$th species. The random elephant effect is $\epsilon_{ijkl}$, $\alpha$ is a fixed zoo effect, $\beta_i$ is the effect of the $i$th dose, $\gamma_j$ is the effect of species, and $\epsilon_{ijkl}$ is the normally distributed random error with mean value zero. The parameter for zoo was included in the model to account for potential variability introduced by six geographically disparate zoos or private facilities. Statistical software was used for analysis (SAS, Version 8.0, InnaPhase Corporation, Cary, North Carolina 27513, USA).

Steady-state, single-dose linear kinetic analyses consisted of paired $t$-tests to compare Asian and African elephant AUC and clearance values. Estimates to predict appropriate doses and dosing intervals for phenylbutazone were based on pharmacokinetic results and literature values of identified therapeutic serum concentrations.

RESULTS

Serum concentrations of phenylbutazone versus time after administration of single doses of 2, 3, and 4 mg/kg are presented in Figure 1 (samples for 2- and 4-mg/kg doses in Asian elephants were not collected beyond 150 hr). In Asian elephants, a second peak in serum concentrations of phenylbutazone was observed in every elephant at every dose.
centrations at only 30%. Peak butazone but at much lower levels, with peak con-
phenbutazone mirrored concentrations of phenyl-
In African elephants, serum concentrations of oxy-
concentrations in both Asian and African elephants.
In African elephants, serum concentrations of oxy-
butazone were much lower than phenylbutazone
-marked differences in pharmacokinetic values between African and Asian
to difficulties encountered during administration
were not included because no or very little drug
were not quantifiable in the serum, most likely due to difficulties encountered during administration (Table 1). There were significant differences in pharmacokinetic values between African and Asian elephants for AUC (P < 0.0001), CI/F (P < 0.0003), T_{1/2} (P < 0.0001), C_{max} (P < 0.0071), V_d (P < 0.0138), and MRT (P < 0.0001). The AUC increased progressively with increasing doses for each species, but the average range for African el-
was 68–171 µg/hr/ml versus 261–489 µg/
hr/ml for Asian elephants. The V_d was slightly higher in African elephants (mean range: 590–605
ml/kg) compared with Asian elephants (mean range: 423–477 ml/kg). Average values for Cl and
T_{1/2} were also quite disparate between the two species (e.g., Cl of approximately 28-ml/hr/kg in Af-
Serum concentrations of phenylbutazone versus time profiles for Asian and African elephant mul-
to vary considerably, especially when access to feed (such as hay) was provided, which delayed
This also appears to be true in Af-
Absorption of phenylbutazone has been shown to affect absorption of phenylbutazone in elephants.
The fraction of phenylbutazone bound to plasma

Figure 2. Cartesian plots to illustrate second peak in serum concentration-time profiles of phenylbutazone in Asian elephants.

DISCUSSION
Phenylbutazone showed linear pharmacokinetics in both African and Asian elephants; however, the differences in parameters between species were re-
different rates of absorption and drug metabolism attest to evolutionary-based divergence of physiologic systems between these two elephant species.

Absorption of phenylbutazone has been shown to vary considerably, especially when access to feed (such as hay) was provided, which delayed
time to peak concentrations in horses by 6 to 12
hr^28,45 or more. This also appears to be true in Af-
only be confirmed, access to food (and potentially
around time of administration appears to affect absorption of phenylbutazone in elephants.
Figure 3. Concentration-time profiles of phenylbutazone after oral administration of (a) 2-, (b) 3-, and (c) 4-mg/kg dosages in African compared with Asian elephants.
proteins is 98–99%, which is similar across all species studied to date and represents NSAIDs' normally highly protein-bound nature. Protein binding decreases with increasing concentrations of drug. A study conducted with lactating dairy cows suggests that phenylbutazone either binds to milk proteins or is actively transported into milk because its concentration in milk was greater than that expected with simple partitioning from plasma into milk. It is not known if phenylbutazone similarly binds to milk proteins in elephants, but females with nursing calves should probably not receive this drug.

Phenylbutazone follows zero-order (dose-dependent) elimination kinetics in dogs and horses and typically has a longer $T_{1/2,el}$ as the dose increases. The $T_{1/2,el}$ for phenylbutazone in cattle ranges from 35.9 hr to 62.6 hr but is much less in horses, ranging from 3.5 hr to 5.5 hr. Hepatic biotransformation results in secondary metabolites (mainly oxyphenbutazone and $\gamma$-hydroxy-phenylbutazone), and it has been suggested that elimination of phenylbutazone is inhibited by oxyphenbutazone. This could contribute to the relatively long $T_{1/2}$ observed in elephants (14–45 hr). The plasma $T_{1/2}$ in horses has also been shown to increase as drug dosage levels increase, and this may indicate that the kinetics of phenylbutazone are dose dependent. Phenylbutazone is primarily metabolized in the liver, and this process (hepatic mixed function oxidase activity) can become saturated, leading to decreased metabolic rates. Enterohepatic cycling occurs by biliary excretion and intestinal reabsorption of solutes and is typically associated with multiple peaks and a longer apparent half-life in concentration time profiles. It is through this process that higher dosages are likely to be associated with greater serum concentrations of drug over prolonged periods.

Enterohepatic cycling has been observed for a variety of compounds in numerous species (e.g., NSAIDs flurbiprofen and ibuprofen in rats and piroxicam in rabbits, hormones estrone in bulls and humans, testosterone in dogs). However, enterohepatic cycling of phenylbutazone is species specific, and some animals (e.g., llamas, pigs) do not exhibit evidence of cycling.

Asian, but not African, elephants experienced a second peak in serum concentrations of phenylbutazone, suggesting that enterohepatic cycling is occurring. Because the second peaks occurred during different times in individuals, mean concentration time curves do not fully and clearly show the extent of this. The multiple dose concentration versus time
Table 2. Pharmacokinetic parameters of phenylbutazone after oral administration of 2-, 3-, and 4-mg/kg doses in African and Asian elephants (mean ± SD).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>2 mg/kg</th>
<th>3 mg/kg</th>
<th>4 mg/kg</th>
<th>ANOVA*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>African (n = 8)</td>
<td>Asian (n = 7)</td>
<td>African (n = 10)</td>
<td>Asian (n = 7)</td>
</tr>
<tr>
<td><strong>Cmax (μg/ml)</strong></td>
<td>4.26 ± 2.02</td>
<td>7.14 ± 2.36</td>
<td>7.22 ± 4.06</td>
<td>12.08 ± 3.13</td>
</tr>
<tr>
<td><strong>Tmax (hr)</strong></td>
<td>7.56 ± 4.88</td>
<td>9.71 ± 3.90</td>
<td>8.44 ± 4.42</td>
<td>14.00 ± 9.39</td>
</tr>
<tr>
<td><strong>T1/2 (hr)</strong></td>
<td>15.05 ± 7.88</td>
<td>38.74 ± 24.27</td>
<td>13.3 ± 3.02</td>
<td>44.64 ± 21.55</td>
</tr>
<tr>
<td><strong>Vd/F (ml/kg)</strong></td>
<td>605.8 ± 319.49</td>
<td>423.3 ± 172.24</td>
<td>590.6 ± 235.49</td>
<td>460.3 ± 89.51</td>
</tr>
<tr>
<td><strong>Cl/F (ml/hr/kg)</strong></td>
<td>27.98 ± 15.69</td>
<td>7.63 ± 3.20</td>
<td>26.86 ± 8.76</td>
<td>7.77 ± 3.10</td>
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<tr>
<td><strong>AUC (g/hr/ml)</strong></td>
<td>68.0 ± 29.56</td>
<td>261.1 ± 137.25</td>
<td>116.0 ± 47.84</td>
<td>387.4 ± 17.93</td>
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<tr>
<td><strong>MRT (hr)</strong></td>
<td>22.52 ± 10.89</td>
<td>55.51 ± 27.61</td>
<td>21.85 ± 3.66</td>
<td>54.48 ± 19.45</td>
</tr>
</tbody>
</table>

* ANOVA, analysis of variance; Cmax, maximal concentration; Tmax, time of maximal concentration; T1/2, terminal half-life; Vd/F, volume of distribution; Cl/F, clearance rate; AUC, area under the curve; MRT, mean residence time.

b P value represents the statistical difference between African and Asian elephants.

Harmonic means.
study, accelerated elimination of phenylbutazone in uremic patients was thought to be caused by altered drug distribution related to decreased serum protein binding.\(^9\) Consideration of an elephant's general health status, especially with respect to the gastrointestinal system and organs of elimination, as well as normal physiologic state (e.g., pregnancy, musth), should be given prior to administering phenylbutazone. Additionally, concomitant administration of other drugs, especially other NSAIDS and anticoagulants, should be noted because phenylbutazone can amplify the effects of these drugs\(^{39,47}\) presumably through competitive plasma protein binding.

Effects of age on phenylbutazone pharmacokinetics have been observed in several species, including goats.\(^{10}\) Clearance of phenylbutazone in horses was found to be age dependent, with decreased Cl in older individuals,\(^{22}\) and the $T_{1/2}$ for phenylbutazone in cattle varies among age groups as well.\(^{21,42,49}\) Similar findings were observed in a previous study with elephants with respect to Cl of ibuprofen and age,\(^{1}\) and a correlation between age and phenylbutazone $T_{1/2}$ was also demonstrated in this study for both Asian and African elephants ($P < 0.5$). These results suggest that the dose of phenylbutazone in elderly elephants should be reduced.

The minimum effective concentration for phenylbutazone is not known for any species,\(^{32}\) but for horses a target range of 5–15 $\mu$g/ml has been suggested.\(^{22}\) In this study, average steady state serum concentrations of phenylbutazone in Asian elephants given 3-mg/kg doses every 48 hr were 6.9 ± 2.49 $\mu$g/ml. The response to phenylbutazone treatment for chronic musculoskeletal pain suggests that this 3-mg/kg dose for Asian elephants is effective. A 32-yr-old female Asian elephant at the Rio Grande Zoo in Albuquerque, New Mexico, was treated with phenylbutazone to manage left hind limb lameness (Richard, pers. comm.). She was

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**Figure 4.** Concentration-time profiles of phenylbutazone after oral administration of multiple 2- and 3-mg/kg dosages in African and Asian elephants, respectively (arrows represent time of administrations).
Table 3. Steady-state pharmacokinetic parameters (mean ± SD) of phenylbutazone after oral multiple dosing in African elephants (2 mg/kg dose every 24 hr) and Asian elephants (3 mg/kg dose every 48 hr).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>African elephants (2 mg/kg q 24 hr; n = 10)</th>
<th>Asian elephants (3 mg/kg q 48 hr; n = 7)</th>
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<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>5.4 ± 2.67</td>
<td>15.6 ± 10.40</td>
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<tr>
<td>Cmin (µg/ml)</td>
<td>1.1 ± 0.39</td>
<td>1.2 ± 1.36</td>
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<tr>
<td>Cavg (µg/ml)</td>
<td>3.0 ± 1.60</td>
<td>6.9 ± 2.49</td>
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<tr>
<td>Tmax (hr)</td>
<td>11.8 ± 4.29</td>
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</tr>
<tr>
<td>Cl/F (ml/hr/kg)</td>
<td>28.3 ± 36.25</td>
<td>9.1 ± 13.69</td>
</tr>
<tr>
<td>AUC (g/ml)</td>
<td>70.6 ± 36.56</td>
<td>330.0 ± 116.21</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>25.0 ± 13.37</td>
<td>55.8 ± 4.50</td>
</tr>
<tr>
<td>T½ (hr)</td>
<td>13.4 ± 1.96</td>
<td>38.7 ± 2.81</td>
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</tbody>
</table>

* Cmax, maximal concentration; Cmin, minimal concentration; Cavg, average concentration; Tmax, time of maximal concentration; Cl/F, clearance rate; AUC, area under the curve; MRT, mean residence time; T½, terminal half-life.

Acknowledgments: The authors thank the dedicated veterinary and elephant keeper staffs at the Kansas City Zoo, Riddle’s Elephant Sanctuary, the

CONCLUSIONS

The pharmacokinetic parameters of phenylbutazone differed significantly for Cmax, T½, Vd, Cl, AUC, and MRT between African and Asian elephants. Asian elephants exhibited enterohepatic cycling of phenylbutazone, which extended Cl rates significantly. Potentially therapeutic doses of phenylbutazone for Asian elephants appear to be 3 mg/kg given every 48 hr and 2 mg/kg given every 24 hr for African elephants. Larger sample sizes are required to confirm the differences observed relative to age. Gender, health status, and physiologic state should also be considered when calculating phenylbutazone dosage regimens for individual elephants. Although no side effects were seen during this study, trials exploring long-term administration of phenylbutazone were not conducted, so confirmation of the safety of phenylbutazone when used at these recommended dosage levels for treatment of chronic conditions could not be determined. Veterinarians are advised to maintain awareness of the potential for occasional upper gastrointestinal bleeding and blood dyscrasias and to monitor hepatic and renal function during the course of long-term phenylbutazone administration. Additionally, concurrent administration of other drugs should be evaluated for their possible effects on the metabolism and potentiating effects of phenylbutazone.

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**LITERATURE CITED**


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