Oral bioavailability and pharmacokinetic characteristics of ketoprofen enantiomers after oral and intravenous administration in Asian elephants (*Elephas maximus*)

Robert P. Hunter, MS, PhD; Ramiro Isaza, MS, DVM, DACZM; David E. Koch, MS

Objective—To assess oral bioavailability (F) and pharmacokinetic characteristics of the *R*- and *S*-enantiomers of ketoprofen administered IV and orally to captive Asian elephants (*Elephas maximus*).

Animals—5 adult Asian elephants.

Procedure—Elephants received single treatments of racemic ketoprofen at a dose of 2.2 mg/kg, administered IV and orally, in a complete crossover design. Blood samples were collected at intervals during the 24 hours following treatment. At least 4 weeks elapsed between drug administrations. Samples were analyzed for *R*- and *S*-ketoprofen with a validated liquid chromatography-mass spectroscopic assay. Pharmacokinetic parameters were determined by use of noncompartmental analysis.

Results—The enantiomers of ketoprofen were absorbed well after oral administration, with median F of 101% for *R*-ketoprofen and 85% for *S*-ketoprofen. Harmonic mean half-life ranged from 3.8 to 5.5 hours, depending on route of administration and enantiomer. The area under the concentration-time curve, mean residence time, apparent volume of distribution, plasma clearance, and maximum plasma concentration values were all significantly different between the 2 enantiomers for both routes of administration.

Conclusions and Clinical Relevance—Ketoprofen has a long terminal half-life and complete absorption in this species. Based on the pharmacokinetic data, a dosage of ketoprofen of 1 mg/kg every 48 hours to 2 mg/kg every 24 hours, PO or IV, is recommended for use in Asian elephants, although the safety and efficacy of ketoprofen during long-term administration in elephants have not been determined. (*Am J Vet Res* 2003;64:109–114)

Publications of pharmacokinetic studies or pharmaceutical plasma concentration data involving elephants are limited, and most of those that are available have focused on antimicrobial preparations[1-7] with few providing information for analgesic or anti-inflammatory agents. Because of the dearth of pharmacokinetic data, dosage regimens for nonsteroidal anti-inflammatory drugs in elephants are based on the hypothesis that pharmaceutical compounds administered to elephants are absorbed, distributed, metabolized, and excreted in approximately the same manner as in horses.[5,8,9] In horses, ketoprofen has an apparent **volume of distribution** (V_d) of 0.15 L/kg, **plasma clearance** (Cl_p) of 0.18 L/h/kg, and **terminal half-life** ($t_{½}$) of 0.5 to 1.5 hours following IV administration,[10-12] and ketoprofen readily distributes into the synovial space of inflamed and noninflamed joints.[11]

The enantiomers of ketoprofen are different chemical entities that induce different pharmacologic and toxicologic effects. The pharmacokinetics of the enantiomers are often more important clinically than the pharmacokinetics of the total drug because of differences in efficacy and toxicity.[13-17] For instance, the *S*-enantiomer of ketoprofen is more efficacious than *R*-ketoprofen, but the latter has been associated with a greater diversity of adverse effects,[14,18,19] although results of 1 study[20] in mice do not support the increase in adverse effects of *R*-ketoprofen. Administration of a racemic mixture constitutes polypharmacy in the most simplistic sense and has no therapeutic rationale,[14,21] but alternative pharmaceutical preparations are often not available. Regulatory authorities in the United States and Europe require pharmacokinetic data for each enantiomer of a drug to be provided for each species for which approval is requested, but this information is published infrequently.

Given the pharmacokinetic properties of ketoprofen and its efficacy in the treatment of inflammation and chronic hoof pain in horses,[11,22] it is suggested that ketoprofen may have therapeutic application in elephants. The purpose of the study reported here was to assess oral **bioavailability (F)** and pharmacokinetic characteristics of the *R*- and *S*-enantiomers of ketoprofen administered IV and orally to captive Asian elephants.

Materials and Methods

Elephants—Five adult Asian elephants (3 female, 1 sexually intact male, and 1 castrated male) were used in our study. The health status of the elephants (mean ± SD body weight, 3,004 ± 1,346 kg) was assessed by means of multiple physical examinations, CBCs, and serum biochemical analyses. Physical examinations were performed at least 1 week prior to the start of the study and weekly until study completion. The CBC and serum biochemical panels were performed once per month throughout the study, and all results remained within reference limits.

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From the Zoological Pharmacology Laboratory, Department of Anatomy and Physiology (Hunter, Koch), and the Department of Clinical Sciences (Isaza), College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506-5802.
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Address correspondence to Dr. Hunter.

Experimental design—The elephants were randomly assigned to 1 of 2 groups. Food and water were not withheld from the elephants. The first group received a single IV administration of racemic ketoprofen[a] (2.2 mg/kg) via an ear vein. The second group received a single PO administration of ketoprofen[b] (2.2 mg/kg). From all elephants, blood samples were collected prior to ketoprofen administration and at intervals of 10, 20, 40, 60, and 90 minutes and 2, 3, 4, 5, 6, 8, 12, and 24 hours after ketoprofen administration. For each elephant, phlebotomy and IV administration of ketoprofen were not performed in the same ear. Intravenous catheters were not used because elephants will remove them promptly after placement. To complete the study, each group was treated according to the alternative protocol after a period of at least 4 weeks, and blood samples were obtained in the manner described.

Drug assay—Ketoprofen concentration was determined in elephant plasma samples by use of a liquid chromatography-mass spectroscopy assay. Chromatographic conditions were modified from Eichhold et al.[23] A 250 × 2-mm column[a-c] was used for separation of the enantiomers. All chemicals used were of high-performance liquid chromatography grade. The mobile phase consisted of 20mM ammonium acetate in a mixture of methanol and water (80:20) maintained at a flow rate of 0.3 mL/min. Detection of ketoprofen was achieved by use of a combination of mass spectrometry and **ultraviolet (UV)** spectrometry. The UV detection was accomplished by use of a photodiode array detector.[d] A wavelength of 255 nm was used to quantitate ketoprofen at concentrations > 250 ng/mL. At plasma concentrations of ketoprofen between 10 and 250 ng/mL, quantitation was performed by use of mass spectrometry.[e] Mass spectrometry was also used to screen for circulating metabolites. The mass spectrometer used an atmospheric pressure chemical ionization source in the negative ionization mode. To screen for ketoprofen, a **mass-to-charge ratio (m/z)** of 252.9 was selected, then mass spectrometry with a normalized collision energy of 35% was performed, and the daughter ion of 240.6 was monitored and used for quantitation. Sample vaporization was achieved with an atmospheric pressure chemical ionization vaporizer temperature of 270°C. Ionization was achieved with a source current of 5.0 µA (voltage, 4.5 kV). Other instrument settings were as follows: capillary temperature, 170°C; capillary voltage, –44 V; tube lens offset, 30 V; multipole 1 offset, 5.25 V; multipole 2 offset, 8 V; intermultipole lens voltage, 14 V; and ion trap DC offset voltage, 10 V.

To obtain **quality control (QC)** samples, 100 µL of a stock solution of racemic ketoprofen in water was added to 900 µL of plasma obtained from elephants that had not been treated with ketoprofen to yield 3 different QC solutions with concentrations within the range of the standard curves. These solutions were stored at –20°C, thawed, and extracted in duplicate with the standard curves. Standards were prepared on the days extractions were performed by adding 100 µL of a stock solution of racemic ketoprofen in water to 900 µL of plasma to yield standard concentrations ranging from 10 to 2,500 ng/mL. Accuracy and precision were within ± 15% of actual values, and recovery of both enantiomers was > 80% across the range of the assay. Plasma concentrations of ketoprofen were quantitated by use of peak area ratios and slope-intercept from linear standard curves. Samples in which concentrations of ketoprofen appeared greater than the highest standard curve concentration were assayed again in a smaller volume of plasma.

Pharmacokinetics—Pharmacokinetic parameters were determined for each elephant by use of noncompartmental analysis.[24,25] Values relating to the IV treatment included calculations of **area under the plasma concentration versus time curve (AUC)** and **area under the first moment curve (AUMC)**. **Mean residence time (MRT)** was calculated by use of the equation MRT = AUMC/AUC. Apparent **volume of distribution at steady-state (V_{dss})** was calculated by use of the equation: V_{dss}(Dose × AUMC)/AUC^2. Plasma clearance was calculated by use of the equation Cl_p = Dose/AUC. **Elimination rate constant (k_{el})** was determined from the slope of the terminal phase of the plasma concentration curve that included a minimum of 3 time points. Terminal half-life was calculated by use of the equation $t_{1/2} = 0.693/k_{el}$. Values relating to the PO treatment included similar calculations of AUC, AUMC, and MRT. **Mean absorption time (MAT)** was calculated by use of the equation MAT = $MRT_{PO} - MRT_{IV}$. Bioavailability was calculated by use of the equation $F = (AUC_{PO}/AUC_{IV}) \times 100$. Lag time was determined directly from the data. All AUCs and AUMCs were calculated by use of the trapezoidal rule with extrapolation to infinity.[f]

Table 1—Pharmacokinetic characteristics of ketoprofen after IV or PO administration of a single dose (2.2 mg/kg) in 5 Asian elephants

	R-ketoprofen			*S*-ketoprofen		
Route and variable	**Mean**	**Median**	**Range**	**Mean**	**Median**	**Range**
IV						
AUC_∞ (h X ng/mL)*	123,645	104,437	86,667– 94,809	77,349	69,691	51,263–132,459
$AUMC_\infty$ (h² X ng/mL)	782,858	838,960	539,521–870,815	337,461	329,118	214,676–428,307
MRT (h)*	6.6	6.8	4.4–8.1	4.6	4.4	3.2–5.8
V_d (L/kg)*	0.066	0.079	0.025–0.086	0.074	0.090	0.027–0.092
Cl_p (L/h/kg)*	0.0096	0.011	0.0056–0.013	0.016	0.016	0.0083–0.021
k_{el} (h^{-1})	0.126	0.131	0.094–0.147	0.138	0.147	0.0917–0.189
$t_{½}$ (h)	5.5†	5.3	4.7–7.3	5.0†	4.7	3.7–7.6
PO						
AUC_∞ (h X ng/mL)*	111,194	112,615	79,869–140,385	57,602	56,450	46,203–73,140
$AUMC_\infty$ (h² X ng/mL)	1,354,887	1,331,269	1,020,596–1,762,836	571,407	566,440	428,676–686,854
MRT (h)*	12	13	11–13	10	10	8.9–11
MAT (h)	5.9	5.2	4.1–8.4	5.6	5.2	3.2–8.1
C_{max} (ng/mL)*	8,176	8,359	5,949–10,017	5,246	5,230	3,640–6,875
T_{max} (h)	8.3	7.9	6.0–12	8.0	7.9	6.0–12.2
F (%)*	91	101	41–119	75	85	35–105
Lag time (h)	0.31	0.33	0.00–0.67	0.31	0.27	0.17–0.68

*For these parameters, median values of the *R*- and *S*-enantiomers of ketoprofen within a given route of administration were significantly (P = 0.0156) different. †Harmonic mean.

AUC = Area under the plasma concentration versus time curve. AUMC = Area under the moment curve. MRT = Mean residence time. V_d = Apparent volume of distribution at steady state. Cl_p = Plasma clearance. k_{el} = Elimination rate constant. $t_{½}$ = Terminal half-life. MAT = Mean absorption time. C_{max} = Maximum plasma concentration. T_{max} = Time C_{max} occurs. F = Absolute bioavailability.

Statistical analyses—Pharmacokinetic values obtained for *R*-ketoprofen and *S*-ketoprofen following administration by either route were compared by use of Wilcoxon matched-pairs signed-rank tests.[26] Differences were considered significant at values of $P < 0.05$. Values are reported as mean, median, and range. Values for V_d, Cl_p, and $t_{½}$ after IV administration of each enantiomer were plotted (log–log) with similar values from other species to establish allometric relation-

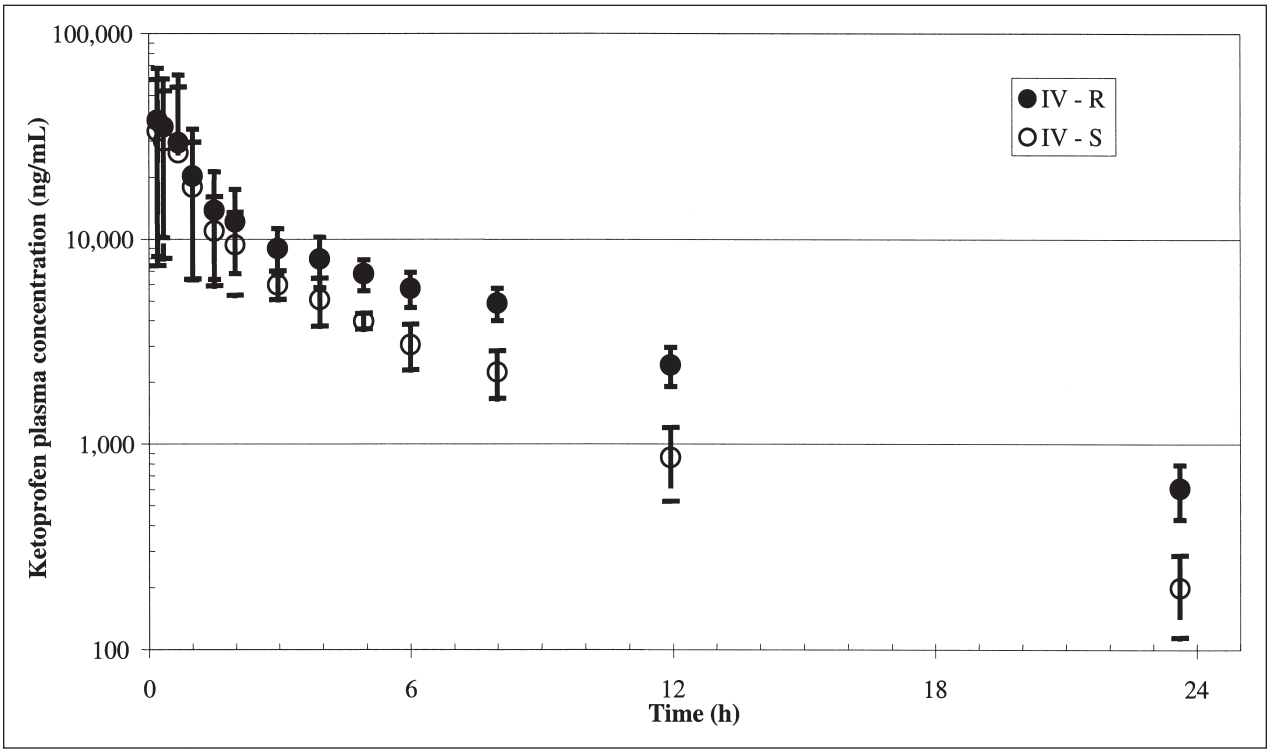

Figure 1— Mean (± SD) plasma concentrations of *R*- and *S*-enantiomers after administration of a single dose of racemic ketoprofen (2.2 mg/kg, IV) in 5 Asian elephants.

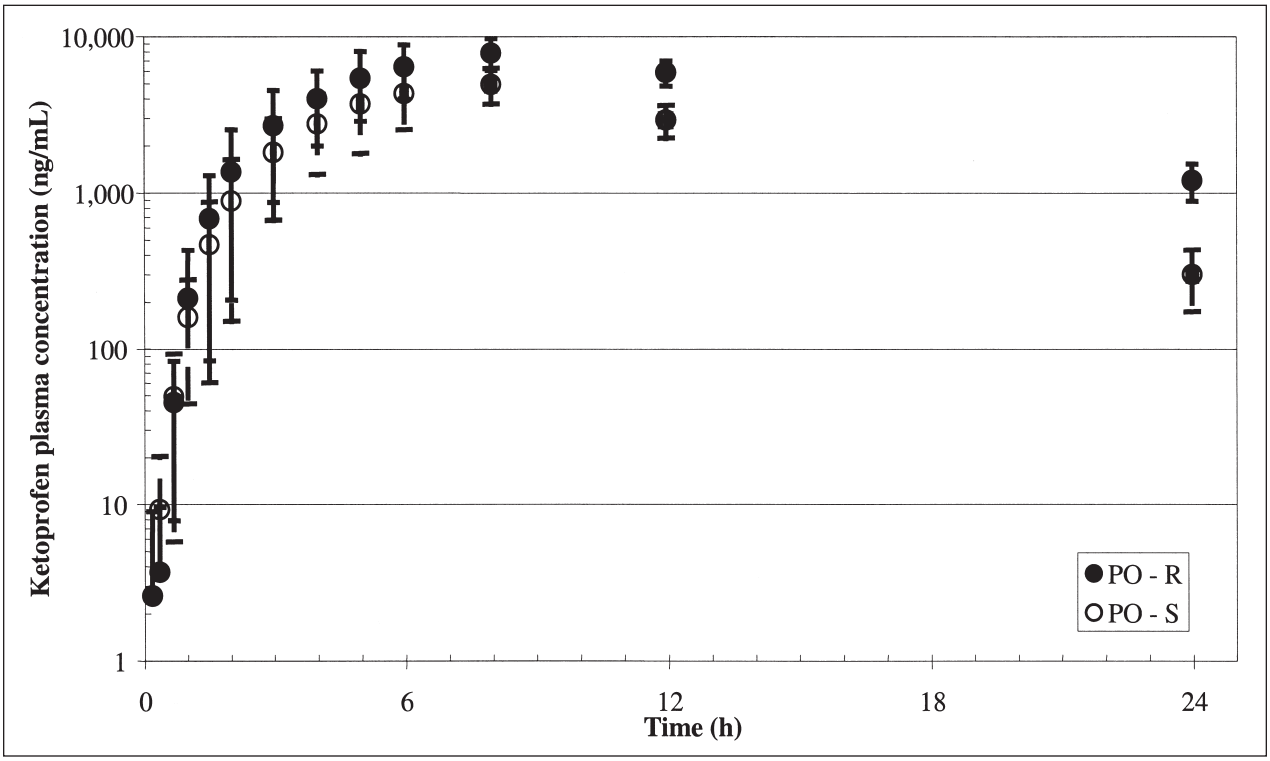

Figure 2— Mean (± SD) plasma concentrations of *R*- and *S*-enantiomers after administration of a single dose of ketoprofen (2.2 mg/kg, PO) in 5 Asian elephants.

ships.[27-35] A test for normality was not performed, as it is inappropriate to assume that data obtained from 5 animals are normally distributed.

Results

Pharmacokinetic data obtained for each route of administration and both enantiomers were tabulated (**Table 1**). Both enantiomers of ketoprofen were absorbed well after PO administration with a median F of 101% for *R*-ketoprofen and 85% for *S*-ketoprofen. Median AUC of *R*-ketoprofen, after both IV and PO administration, was almost twice the median AUC value of *S*-ketoprofen (**Fig 1 and 2**). Median MRT values after administration via the IV and PO routes were significantly greater for *R*-ketoprofen, compared with *S*-ketoprofen. For the IV route, median V_d and Cl_p values were significantly different for the 2 enantiomers. Oral administration resulted in 60% greater **maximum plasma concentration** (C_{max}) for *R*-ketoprofen than for *S*-ketoprofen.

Allometric equations for V_d, Cl_p, and $t_{½}$ of each enantiomer versus body weight for 8 or 9 mammalian species[27-35] were generated (data not shown). None of the pharmacokinetic parameters was scalable allometrically across the range of mammalian species evaluated.

(The metabolite hydroxy ketoprofen was identified in the plasma of each elephant **Fig 3**) with m/z of 255, with 2 daughter fragments of 211 and 243 m/z, respectively. These fragments are similar to the metabolites identified in horses and camels.[12,36] Another metabolite with m/z of 315 was also detected in the plasma of each elephant, independent of route of ketoprofen administration. This may have been a glycine conjugate (Fig 3) that has also been reported for 2-phenylproprionic acid in dogs,[37] but the identity of this compound was not confirmed.

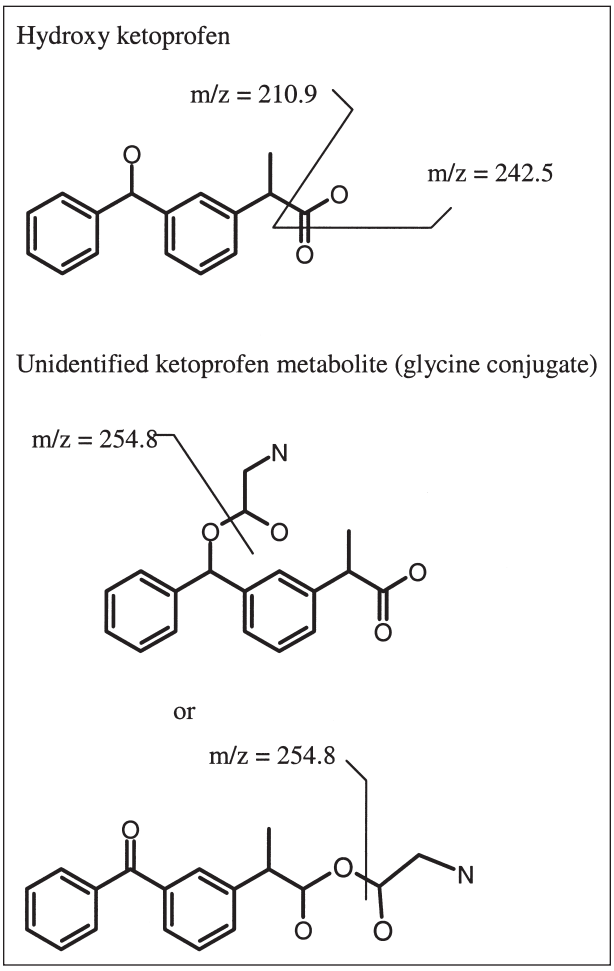

Figure 3—Structures of the 2 ketoprofen metabolites detected in elephant plasma; mass-to-charge ratio (m/z).

Discussion

The pharmacokinetic data indicated that both enantiomers of ketoprofen were absorbed well after PO administration in Asian elephants, with median F for both *R*- and *S*-ketoprofen > 85%. The *S*-enantiomer was cleared from the plasma much more rapidly than *R*-ketoprofen after IV administration. This differs greatly from findings in horses,[10-12,31,38] the species on which elephant pharmaceutical dosage regimens are typically based.[5,8,9] A retrospective study of the medical records of the North American captive elephant population established that foot problems affect > 50% of the population.[39] Arthritis and other chronic foot problems are important problems in adult elephants[40] and in combination are a major cause of death in the captive elephant population.

Results of our study indicate that *S*-ketoprofen was cleared more rapidly from the plasma than *R*-ketoprofen. This has clinical relevance because *S*-ketoprofen is believed to be the more active form with respect to cyclooxygenase inhibition.[19] After PO administration, C_{max} values were significantly less for *S*-ketoprofen than *R*-ketoprofen; there may be selective excretion of *S*-ketoprofen, or it may inhibit the clearance of *R*-ketoprofen. Another possible explanation for the more rapid plasma clearance of *S*-ketoprofen observed in elephants is chiral inversion, in which *S*-ketoprofen is converted to the *R*-enantiomer. In dogs, hamsters, and rats, > 50% of the ketoprofen dose is converted from *R*-ketoprofen to *S*-ketoprofen.[19] In the same study, conversion of *R*-ketoprofen to *S*-ketoprofen was also reported in mice, gerbils, guinea pigs, rabbits, and cynomolgus monkeys, but this conversion was < 50% of the total ketoprofen dose.[19] Horses and cats also convert *R*-ketoprofen to *S*-ketoprofen.[15,22] This differs from cattle and llamas in which there is no inversion,[28,29] and sheep in which both *R*- and *S*-ketoprofen are interconverted.[30] Selective metabolism of *S*-ketoprofen to either the hydroxy ketoprofen metabolite or the glycine conjugate reported here would also result in increased Cl_p for *S*-ketoprofen. Investigation of conversion of *S*- to *R*-ketoprofen in Asian elephants would require administration of only *S*-ketoprofen to the study animals, but the cost would be prohibitive.

Allometric scaling of therapeutic pharmaceuticals is of interest to zoological veterinarians, because elephants are near the upper limit of the body weight scale. This method can, when used appropriately, provide an estimate for designing dosage regimens. Riviere[25] has reported that only those pharmaceutical agents that are cleared unchanged by the liver or kidneys are scalable allometrically. The variability of chiral

inversion of *R*-ketoprofen and *S*-ketoprofen among species is a complicating factor in scaling the pharmacokinetic variables of ketoprofen enantiomers; overall, allometric scaling does not appear to be appropriate.

The allometric equations for V_d and Cl_p of the 2 ketoprofen enantiomers did not yield acceptable correlations. Plots of $t_{½}$ provided exponents near 0.25 as expected, but they did not yield correlation coefficients to support allometric scaling of either ketoprofen enantiomer. The lack of correlation of V_d and Cl_p may be the result of metabolism of *S*-ketoprofen to *R*-ketoprofen by the elephant kidney, which is different from several other mammalian species; excretion of unchanged ketoprofen by the kidneys; and finally, conversion of ketoprofen to hydroxy ketoprofen or glycine-conjugated ketoprofen and the excretion of these metabolites by the kidneys. The $t_{½}$ of *S*-ketoprofen and *R*-ketoprofen are dependent on several different physiologic processes, and these are probably responsible for the poor allometric scaling of the $t_{½}$ data, even with a large number of evaluated mammalian species, as in Riviere's study.[25]

Comparison of pharmacokinetic values reported in horses and those obtained in elephants identified clinically relevant differences. The Cl_p of both *R*- and *S*-ketoprofen in elephants were a third to a quarter of values published for horses, and V_d was also an order of magnitude smaller.[38] In elephants, the terminal $t_{½}$ was 4 times that of horses. These findings indicate that extrapolation of dosage information for elephants on the basis of equine pharmacokinetic parameters is inappropriate. This study did not attempt to determine the acute or chronic pharmacodynamic or toxic effects of ketoprofen in elephants; ketoprofen has been associated with gastrointestinal irritation, gastric ulceration, and protein-losing enteropathy in dogs.[41] Renal and hepatic toxicosis have also been reported in certain species.[41] Based on results of our study, a dosage of 1 to 2 mg/kg every 24 to 48 hours, IV or PO, in Asian elephants is suggested, although treated elephants should be monitored for possible adverse effects.

[a]Ketofen, Fort Dodge, Princeton, NJ.
[b]ESI Lederle Generics, Madison, NJ.
[c]Chirex 3005, Phenomenex, Torrance, Calif.
[d]UV6000LP, ThermoFinnigan, San Jose, Calif.
[e]LCQ_{DUO}, ThermoFinnigan, San Jose, Calif.
[f]WinNonlin, Pharsight, Mountain View, Calif.

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