# Pharmacokinetics of a single dose of enrofloxacin administered orally to captive Asian elephants (*Elephas maximus*)

Carlos R. Sanchez, DVM; Suzan Z. Murray, DVM; Ramiro Isaza, DVM, MS; Mark G. Papich, DVM, MS

**Objective**—To determine the pharmacokinetics of enrofloxacin after oral administration to captive elephants.

**Animals**—6 clinically normal adult Asian elephants (*Elephas maximus*).

**Procedure**—Each elephant received a single dose of enrofloxacin (2.5 mg/kg, PO). Three elephants received their complete diet (pellets and grain) within 2 hours after enrofloxacin administration, whereas the other 3 elephants received only hay within 6 hours after enrofloxacin administration. Serum concentrations of enrofloxacin and ciprofloxacin were measured by use of high-performance liquid chromatography.

**Results**—Harmonic mean half-life after oral administration was 18.4 hours for all elephants. Mean ± SD peak serum concentration of enrofloxacin was 1.31 ± 0.40 µg/mL at 5.0 ± 4.2 hours after administration. Mean area under the curve was 20.72 ± 4.25 (µg × h)/mL.

**Conclusions and Clinical Relevance**—Oral administration of enrofloxacin to Asian elephants has a prolonged elimination half-life, compared with the elimination half-life for adult horses. In addition, potentially therapeutic concentrations in elephants were obtained when enrofloxacin was administered orally at a dosage of 2.5 mg/kg. Analysis of these results suggests that enrofloxacin administered with feed in the manner described in this study could be a potentially useful antimicrobial for use in treatment of captive Asian elephants with infections attributable to organisms, such as *Bordetella* spp, *Escherichia coli*, *Mycoplasma* spp, *Pasteurella* spp, *Haemophilus* spp, *Salmonella* spp, and *Staphylococcus* spp. (*Am J Vet Res* 2005;66:1948–1953)

Bacterial infections in captive elephants are common.[1] Some infections attributable to gram-negative bacilli, such as *Escherichia coli*, *Enterobacter* spp, *Klebsiella* spp, *Proteus* spp, and *Pseudomonas* spp, are of medical importance in captive elephants. Furthermore, infections caused by *Salmonella* spp can be fatal in captive elephants.[1] To effectively treat elephants with bacterial infections, it is important to determine appropriate dosages for specific antimicrobial agents. In elephants, antimicrobial dosages have routinely been extrapolated from those used in equine medicine or estimated from allometric formulas.[2,3] Allometric studies[4,5] of enrofloxacin have been performed, but elephants were not included in the analyses. Therefore, pharmacokinetic studies specific for elephants are needed to determine accurate dosages.[6]

Of the reports from pharmacokinetic studies of antimicrobials in elephants, most[3,7-10] describe parenteral administration of the drugs. Although IM injections are widely used, long-term treatment by IM injection may result in formation of sterile abscesses, pain, muscle necrosis and inflammation, and problems with cooperation of the patients.[11]

In the 2 pharmacokinetic studies[8,12] in captive elephants that included the use of orally administered antimicrobials, investigators concluded that trimethoprim-sulfamethoxazole and ampicillin should be administered at least twice daily to achieve effective plasma concentrations. For practical purposes, administration of antimicrobials to captive elephants would be better accepted if it could be accomplished once daily because most zoologic exhibitions only have personnel available for 8- to 10-hour schedules, which makes it impractical to achieve a 12-hour dosing interval. In addition, elephants tend to refuse orally administered drugs; therefore, the possibility of increasing the medication interval from 12 hours to 24 hours is an attractive alternative for zookeepers and veterinarians.

Enrofloxacin, the first fluoroquinolone licensed for veterinary use, has bactericidal actions through inhibition of bacterial DNA replication and transcription.[13-16] Its activity is a concentration-dependent event, making it ideal for once-daily administration. Enrofloxacin has activity against some gram-positive aerobes and a wide range of gram-negative bacilli, including *Klebsiella* spp, *Pseudomonas* spp, and *Salmonella* spp, and other organisms, such as *Mycoplasma* spp, *Staphylococcus* spp, and *Chlamydia* spp.[14,16,17] Consequently, this antimicrobial is clinically useful for treatment of animals with respiratory tract infections, urinary tract infections, and infections resulting from soft tissue injuries.[15-19]

Received September 10, 2004.
Accepted February 24, 2005.
From the Department of Animal Health, Smithsonian National Zoological Park, 3001 Connecticut Ave NW, Washington, DC 20008-2598 (Sanchez, Murray); Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610 (Isaza); and Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Papich).
Supported in part by Friends of National Zoo and Bayer Corporation.
The authors thank Tony Barthel, Marie Galloway, Sean Royals, Deborah Flynn, Deborah Flinkman, Harry Locker, and Cat Monger for assistance with sample collection; Delta Dise for assistance with the high-performance liquid chromatography analysis; and Patti Young for technical assistance.
Address correspondence to Dr. Sanchez.

Enrofloxacin is approved for use in cats, dogs, poultry, and cattle.[16,19] It has been used in an extralabel manner in a number of species, including nondomestic species.[13-15,20,21] The use of enrofloxacin in elephants has been limited because dosing guidelines have not been established. Other factors that have discouraged its use in elephants are the cost of the treatment and the large volume of solution required when medications are administered parenterally. Oral administration of enrofloxacin has been used to treat elephants that have bacterial infections without causing adverse effects, which has encouraged additional studies[22,23] to define the plasma concentrations and an accurate dosage regimen. Enrofloxacin is absorbed well in ruminants and horses after oral or intragastric adminstration,[24-29] but to our knowledge, specific data on elephants have not been reported. In livestock with a gastrointestinal tract that contains fermenting bacteria, adverse effects, such as changes in fecal consistency attributable to disruption of microorganisms in the gastrointestinal tract, have not resulted from oral administration of enrofloxacin.[25,28] This may be attributable to the poor activity of enrofloxacin against most anaerobic bacteria and many gram-positive microorganisms.[14,16,17] This observation also provides advantages for oral administration of enrofloxacin to elephants.

Studies[25,27,29,30] on oral administration of enrofloxacin to horses indicate that a solution made from the injectable product formulated for use in cattle may yield variable results depending on the feeding status of the horse and method of administration of the solution (gastric intubation vs oral administration). Oral administration of the injectable product formulated for use in cattle may also have clinical effects in horses, such as the development of oral lesions.[29] Because medications in zoologic settings are often hidden or mixed with food and we did not want to risk development of oral lesions from this formulation, our goal was to examine absorption of enrofloxacin tablets when mixed with feed by use of 2 methods. The objective of the study reported here was to evaluate the pharmacokinetics after oral administration of enrofloxacin to Asian elephants (*Elephas maximus*) and provide data needed to generate dosing regimens.

## Materials and Methods

**Animals**—Three adult female Asian elephants (range of estimated ages, 29 to 56 years) housed at the **Smithsonian National Zoological Park (SNZP)** and 3 adult female Asian elephants (range of estimated ages, 53 to 58 years) housed at the **Ringling Brothers and Barnum Bailey Center for Elephant Conservation (RBB)** in Florida were used in the study. Body weight of the elephants ranged from 2,988 to 4,386 kg.

One week before onset of the study, all elephants received a routine physical examination. Laboratory testing was conducted, including a CBC count and serum biochemical analysis. One elephant at the RBB had chronic paralysis of the trunk; however, on the basis of results of the physical examination and laboratory tests, this elephant was considered otherwise healthy. The study design was reviewed and approved by the SNZP Institutional Animal Care and Use Committee and was in compliance with their guidelines.

**Experimental design and collection of samples**—Elephants were fed their typical diet on the day preceding onset of the experiment. On the day the study commenced (day 1), the morning meal was withheld pending collection of samples. A 10-mL blood sample was collected by use of a 12-mL syringe from an auricular vein of each elephant for use in assay calibration and determination of baseline values (time 0). Then, enrofloxacin[a] (approx 2.5 mg/kg) was given orally in the morning. This enrofloxacin dosage was selected on the basis of a dose of enrofloxacin used in a sick elephant at the SNZP from which we were able to obtain serum and determine that it had adequate serum concentrations and on the basis of the empirical dosage reported elsewhere.[23] The dose was calculated to the nearest one-half tablet (each tablet contained 68 mg of enrofloxacin). Tablets were mixed with gruel (pellets, rolled oats, and rice bran mixed with water) and provided to the 3 elephants at the SNZP, whereas tablets were mixed with rolled oats, bran, and molasses to form balls, which were provided to the 3 elephants at the RBB.

Each elephant completely ingested the medicine-containing gruel or balls. Elephants at the SNZP received their typical morning diet, which consisted of hay, pellets, rice bran, wheat bran, and rolled oats, within 2 hours after enrofloxacin administration, whereas elephants at the RBB received hay immediately after enrofloxacin administration but did not receive the remainder of their typical morning feeding until 6 hours after enrofloxacin administration.

Subsequent blood samples were collected by venipuncture of auricular veins on both ears of each elephant. Subsequent samples were collected 30, 45, 60, and 90 minutes and 2, 2.5, 3, 4 (3 elephants at the RBB) or 5 (3 elephants at the NZP), 8, 12, 24, and 36 hours after enrofloxacin administration. Because of difficulties in obtaining a blood sample, the samples for the 3 elephants at the SNZP were obtained at 5 hours after enrofloxacin administration and not at 4 hours after administration.

All blood samples were placed in clot-separator tubes and allowed to clot for approximately 2 hours at 22° to 24°C. Tubes were then centrifuged at 1,000 to 1,300 × *g* for 10 minutes. Serum was harvested and stored at –70°C until assayed.

**Analysis of samples**—Serum enrofloxacin concentrations were determined by use of **high-performance liquid chromatography (HPLC)**; ciprofloxacin concentrations were also determined by use of the same methods. Antimicrobial-free serum from untreated elephants was pooled and fortified with known amounts of enrofloxacin and ciprofloxacin to validate the methods. Serum samples (unknown samples and fortified samples) were assayed concurrently to determine enrofloxacin and ciprofloxacin concentrations by use of a validated method of reverse-phase HPLC and UV detection described elsewhere.[28]

The HPLC system consisted of a pump,[b] an automated sampling system,[c] and a UV light detector.[d] A 4.6-mm × 15-cm reverse-phase column[e] was used to separate the compounds of interest from other serum components. The eluate was monitored by use of the UV detector at a wavelength of 279 nm. Enrofloxacin and ciprofloxacin were extracted from the serum by use of solid-phase extraction cartridges.[f] The cartridges were conditioned with 1.0 mL of methanol followed by 1.0 mL of deionized water, and then each sample was washed with a mixture of deionized water:methanol (95:5). Each drug was eluted from the cartridge with 1.0 mL of methanol, which was evaporated under a flow of nitrogen gas at 45°C for 25 minutes. The dried product was reconstituted with 200 µL of a mixture of methanol:0.1% trifluoroacetic acid in water (15:85). The isocratic mobile phase was 77% deionized water, 23% acetonitrile, and 0.1% trifluoroacetic acid, and flow rate was 1 mL/min. Retention time for enrofloxacin and ciprofloxacin was approximately 4.0 and 3.0 minutes, respectively.

Chromatograms were integrated by use of computer software.[g] Calibration curves of peak height versus concentration were calculated by use of linear-regression analysis. New calibration graphs for the range of 0.05 to 5.0 µg/mL for enrofloxacin and 0.05 to 2.0 µg/mL for ciprofloxacin were generated for assays performed each day for pooled elephant serum obtained prior to drug administration and subsequently fortified with drug. Analytic reference standards for enrofloxacin[h] and ciprofloxacin[i] were used to make the calibration standards and to fortify quality-control samples.

Between-day accuracy and precision were measured for enrofloxacin and ciprofloxacin. The precision of the assay was within ± 15% of the mean, accuracy was within ± 15% of the true value, and both were within published guidelines for use in validation studies.[31] The limit of quantification was determined from the signal-to-noise ratio (6:1) for analysis of unfortified serum samples and was 0.05 µg/mL for enrofloxacin and ciprofloxacin.

**Pharmacokinetic analysis**—The pharmacokinetic analysis was performed separately for each elephant by use of a standard 2-stage analysis. Pharmacokinetic values for each elephant were determined by use of noncompartmental pharmacokinetic analysis performed with a computerized pharmacokinetic program.[j] Equations for calculating pharmacokinetic variables were obtained from a textbook.[32] Variables for serum enrofloxacin included the **area under the curve (AUC)** determined by use of the logarithmic-linear trapezoidal method, **peak concentration ($C_{max}$)**, **elimination half-life ($t_{1/2}$)**, apparent volume of distribution at steady state corrected for bioavailability, and clearance corrected for bioavailability. The equation for $t_{1/2}$ was as follows: $t_{1/2}$ = Natural logarithm of 0.5/terminal rate constant. The AUC from zero to infinity was calculated by determining the AUC up to the last time point and then adding the terminal portion estimated from the terminal rate constant. Absolute systemic absorption could not be determined because there were no accompanying data for IV administration.

## Results

Mean ± SD values for enrofloxacin and ciprofloxacin on the serum concentration-versus-time curve for all elephants after oral administration of enrofloxacin were plotted (**Figure 1**). Pharmacokinetic variables for enrofloxacin and ciprofloxacin were calculated (**Table 1**).

After oral administration of enrofloxacin, $C_{max}$ ranged from 0.82 to 1.98 µg/mL (mean ± SD, 1.31 ± 0.40 µg/mL). **Time until Cmax ($t_{max}$)** ranged from 1 to 12 hours (mean, 5.0 ± 4.2 hours). Serum enrofloxacin concentrations in the elephants were > 0.75 µg/mL at approximately 1 hour after oral administration. Serum drug concentrations steadily decreased, with a harmonic mean $t_{1/2}$ of 18.4 hours for all elephants (arithmetic mean $t_{1/2}$, 20.42 ± 7.42 hours). The AUC ranged from 15.58 to 26.89 (h × µg)/mL (mean, 20.72 ± 4.25 [h × µg]/mL). Enrofloxacin concentrations were above the **minimum inhibitory concentration (MIC)** for common pathogens in domestic animals.[18,19,33-35] These pathogens include *Bordetella* spp, *E coli*, *Mycoplasma* spp, *Pasteurella* spp, *Haemophilus* spp, *Salmonella* spp, and *Staphylococcus* spp, which are of clinical importance in elephants.

Ciprofloxacin concentrations were detectable but low and variable. Mean ± SD ciprofloxacin $C_{max}$ was only 0.1 ± 0.06 µg/mL at 5 hours after enrofloxacin

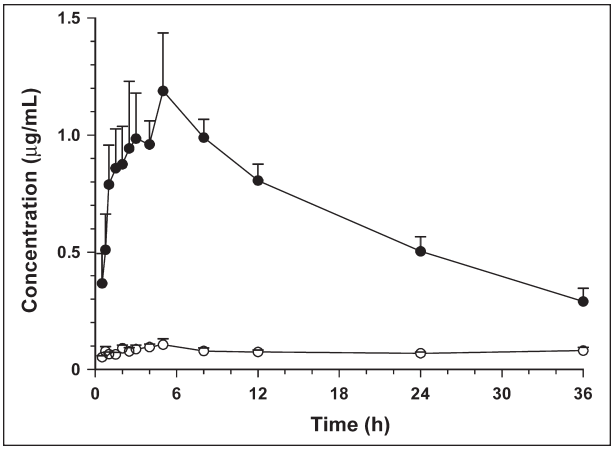


Figure 1—Mean ± SD serum concentrations of enrofloxacin (black circles) and ciprofloxacin (white circles) after oral administration of enrofloxacin at a dosage of approximately 2.5 mg/kg to 6 captive Asian elephants. Time 0 = Time of administration of enrofloxacin.

Table 1—Calculated pharmacokinetic variables for enrofloxacin after oral administration of a single dose (2.5 mg/kg) to 6 captive Asian elephants.

| | Range | | |
|---|---|---|---|
| **Variable** | **RBB (n = 3)** | **SNZP (3)** | **Mean ± SD (6)** |
| Elimination rate (/h) | 0.022–0.49 | 0.032–0.054 | 0.038 ± 0.013 |
| $t_{1/2}$ (h) | 14.05–31.44 | 12.88–21.58 | 18.4* |
| $C_{max}$ (µg/mL) | 0.82–1.24 | 1.39–1.98 | 1.31 ± 0.40 |
| $t_{max}$ (h) | 4.0–12.0 | 1.0–2.6 | 5.0 ± 4.2 |
| $AUC_{0 \text{ to last time point}}$ ([h × mg]/mL) | 15.58–22.03 | 17.15–26.89 | 20.72 ± 4.25 |
| $AUC_{0 \text{ to infinity}}$ ([h × mg]/mL) | 30.14–48.95 | 19.82–38.74 | 34.93 ± 10.20 |
| VD/F (mL/kg) | 1,681–2,726 | 1,886–2,340 | 2,096 ± 375 |
| CL/F (mL/h/kg) | 51.1–83.0 | 64.0–125.9 | 77.5 ± 26.7 |
| AUMC (h × [{h × µg}/mL]) | 710–1,969 | 334–1,161 | 1,141 ± 675 |
| MRT (h) | 23.6–47.7 | 16.9–30.0 | 30.3 ± 11.3 |

*The SD was not calculated for this variable.

RBB = Ringling Brothers and Barnum Bailey Center for Elephant Conservation. SNZP = Smithsonian National Zoological Park. $t_{1/2}$ = Elimination half-life. $C_{max}$ = Maximum serum concentration. $t_{max}$ = Time until $C_{max}$. $AUC_{0 \text{ to last time point}}$ = Area under the serum concentration-versus-time curve (AUC) from time 0 to the last time point. $AUC_{0 \text{ to infinity}}$ = AUC for the entire curve extrapolated to infinity. VD/F = Apparent volume of distribution at steady state corrected for oral bioavailability. CL/F = Clearance corrected for bioavailability. AUMC = Area under the moment curve. MRT = Mean residence time.

administration. Because of these low concentrations, compared with concentrations for the parent drug enrofloxacin, pharmacokinetic analysis was not performed for ciprofloxacin. However, ciprofloxacin concentrations were plotted on the serum concentration-versus-time curve (Figure 1).

## Discussion

To our knowledge, the study reported here is the first in which pharmacokinetics of enrofloxacin were evaluated in elephants. In contrast, pharmacokinetics of enrofloxacin have been extensively studied in horses,[24-27,29,30,36,37] which have a gastrointestinal tract that is physiologically and anatomically similar to that of elephants.

In the study reported here, enrofloxacin was absorbed after oral administration, as indicated when the $C_{max}$ of our study was compared with values reported in studies of other animals. Mean ± SD $C_{max}$ was 1.31 ± 0.40 µg/mL for elephants, whereas the $C_{max}$ in horses is 1.85,[25] 1.90,[29] or 2.22 µg/mL[27] after oral administration of dosages that were 3 times as high as the dosage used in our study. Absorption in horses after oral administration ranges from 49% to 66%.[25-27,29] Absorption after oral administration to elephants in our study yielded a mean AUC of 20.72 ± 4.25 (h × µg)/mL, which is higher than the AUC in horses after administration at a dosage 3 times as high,[25,27] except in 1 study[29] in which a compounded formulation was administered via stomach tube to horses from which food was withheld. The possibility that such high absorption was a function of the sample collection regimen or the analytic method cannot be ruled out. Higher $C_{max}$ and AUC values were observed in horses in another study,[26] but those investigators used a bioassay that is known to overestimate enrofloxacin concentrations. Absorption after oral administration to the elephants of the study reported here was particularly encouraging because enrofloxacin was administered in a field setting in which the drug was mixed with feed.

Mean ± SD $t_{max}$ was 5.0 ± 4.2 hours, which is considerably longer than the $t_{max}$ reported[24-27,29,30] for horses (< 2 hours) when the drug is given orally or intragastrically. However, the $t_{max}$ for the elephants of our study was similar to that observed after administration of enrofloxacin tablets to small domestic ruminants[28] and llamas,[21] where $t_{max}$ is approximately 8.0 and 4.0 hours, respectively. There was large variability observed among all the elephants (range of $t_{max}$, 1 to 12 hours). When the elephants were separated into 2 groups on the basis of location (ie, SNZP and RBB), those at the SNZP had a $t_{max}$ with little variation (range, 1 to 2.58 hours) that was similar to the $t_{max}$ reported[24-27,30] for horses. Elephants at the RBB had a considerably more prolonged $t_{max}$ with large variability (range, 4 to 12 hours); these values are similar to the $t_{max}$ reported for small ruminants[28] and llamas.[21]

Enrofloxacin was administered as coated tablets that were mixed with feed; the tablets were not crushed or ground before addition to the feed. The effect of food on absorption of enrofloxacin after oral administration has been reported for other species.[13,26,28,29,38] It is generally accepted that administration of fluoroquinolones with food may have slowed or caused prolonged absorption without affecting the total serum concentration.[13,14] In our study, we observed an inverse effect in which the elephants at the RBB, which received hay immediately after enrofloxacin administration but did not receive their complete morning meal (ie, pellets and grains) until a few hours later, had a more prolonged interval until $C_{max}$. It has been suggested[17] that concurrent administration of food may decrease the oral bioavailability of some fluoroquinolones.

Other diet-related factors, such as differences in water sources, diet composition (including mineral load), amount of food, and feeding regimens between the SNZP and RBB, could all have influenced absorption and, consequently, the $t_{max}$ obtained in our study.[14,15,17] Because the effect of diet on absorption after oral administration was not an objective of our investigation and we had only 3 elephants in each dosing group, additional studies will be necessary to specifically address the influence of diet on absorption of orally administered enrofloxacin in elephants.

Clinically, the variability in $t_{max}$ is of little relevance because the efficacy of enrofloxacin is not based on time at which $C_{max}$ is achieved or the amount of time that the serum concentration is above MIC; rather, it is based on AUC or the $C_{max}$-to-MIC ratio.[14,39-41] In humans and domestic animals, a $C_{max}$-to-MIC ratio ≥ 10:1 or an AUC for the first 24 hours after oral administration-to-MIC ratio ≥ 100 to 125:1 is required for optimal antimicrobial effects and a lower incidence of resistance for fluoroquinolones.[13,14,39,42,43]

We are not aware of studies on the optimum $C_{max}$-to-MIC ratio or AUC-to-MIC ratio for evaluation of efficacy of enrofloxacin in elephants. By use of the $C_{max}$-to-MIC ratio criteria and on the basis of the reported MICs for bacterial isolates obtained from horses[35,44] and small animals,[33] the dosage of 2.5 mg/kg, PO, used in the study reported here (which yielded a $C_{max}$ of 1.31 µg/mL) would be adequate for bacteria with an **MIC at which 90% of isolates are inhibited ($MIC_{90}$)** of ≤ 0.13 µg/mL, such as *E coli* isolates and *Salmonella* (group B) isolates for which the $MIC_{90}$ is 0.03 µg/mL. Even organisms with a higher MIC, such as *Staphylococcus* spp ($MIC_{90}$, 0.12 µg/mL), are likely to be susceptible to this dose of enrofloxacin. More resistant bacteria, such as *Pseudomonas aeruginosa*, *Rhodococcus equi*, *Streptococcus equi*, and *Streptococcus zooepidemicus*, typically have MIC values > 0.15 µg/mL and may not respond as favorably to the dosage of 2.5 mg/kg. The National Committee for Clinical Laboratory Standards (ie, NCCLS) breakpoint for enrofloxacin for susceptible bacterial isolates derived from dogs and cats is an MIC ≤ 0.5 µg/mL. Bacterial isolates derived from cattle are considered susceptible when the MIC is ≤ 0.25 µg/mL. Breakpoints for susceptibility have not been derived for isolates derived from other animals.[45]

In our study, oral administration of 2.5 mg of enrofloxacin/kg yielded a mean ± SD AUC of 20.72 ± 4.25 (h × µg)/mL, which was slightly increased from the value reported[24,25,27] for adult horses when enrofloxacin is administered orally or intragastrically

at 5 or 7.5 mg/kg. The AUC in the study reported here has an AUC-to-MIC ratio > 100 for organisms with an $MIC_{90}$ of ≤ 0.16 µg/mL. By use of the AUC-to-MIC ratio criteria and on the basis of the same MICs for equine isolates used to calculate the $C_{max}$-to-MIC ratio, the susceptible organisms with this approach are similar.

The $t_{1/2}$ (18.23 hours) for elephants in our study was almost twice the $t_{1/2}$ observed in adult horses when enrofloxacin was given orally at dosages of 5 or 7.5 mg/kg[24,25,27] but similar to the $t_{1/2}$ of enrofloxacin when given orally at a dosage of 10 mg/kg to foals.[30] Enrofloxacin has been scaled allometrically in mammals,[4,5] and it is possible that the slower metabolic rate of elephants may account for such a long $t_{1/2}$.

Although pharmacokinetic variables were not calculated for ciprofloxacin, the values were considered low, which is similar to an observation in foals.[30] Other animals (eg, pigs) also have low concentrations of ciprofloxacin after administration of enrofloxacin.[46] The factors (eg, diet or hepatic activity) that account for species differences in metabolism of enrofloxacin to ciprofloxacin are not known. Low concentrations of ciprofloxacin identified in our study would contribute an additive (albeit small) effect to the antimicrobial activity.[13,28,38,k]

Oral administration of enrofloxacin in the form of 68-mg coated tablets to captive Asian elephants resulted in serum drug concentrations as high or higher than those attained after oral administration of higher doses to domestic mammals, such as horses. In elephants, enrofloxacin had a long $t_{1/2}$, compared with the $t_{1/2}$ for enrofloxacin in other mammals. The serum concentrations attained when enrofloxacin is administered orally at a dosage of 2.5 mg/kg once daily are potentially therapeutic. Analysis of results of the study reported here suggests that oral administration of enrofloxacin mixed with feed in the manner described is potentially useful for treatment of captive Asian elephants with infections caused by enrofloxacin-susceptible organisms, such as *Bordetella* spp, *E coli*, *Mycoplasma* spp, *Pasteurella* spp, *Haemophilus* spp, *Salmonella* spp, and *Staphylococcus* spp. Administration of enrofloxacin at the suggested dosage in clinical trials is necessary before we can conclude that treatment is effective.

a. Baytril, 68-mg coated tablets, Bayer Corp, Shawnee Mission, Kan.
b. Agilent quaternary pump, Agilent Technologies, Wilmington, Del.
c. Agilent series 1100, Agilent Technologies, Wilmington, Del.
d. Agilent 1100 series UV detector, Agilent Technologies, Wilmington, Del.
e. Zorbax SB C-8, Mac Mod, Chadds Ford, Pa.
f. Oasis, Waters Corp, Milford, Mass.
g. HP ChemStation software, series 1100 software, Agilent Technologies, Wilmington, Del.
h. Enrofloxacin analytical reference standard, Bayer Corp, Shawnee Mission, Kan.
i. Ciprofloxacin analytical reference standard, US Pharmacopeia, Rockville, Md.
j. WinNolin, version 4.0, Pharsight Corp, Mountain View, Calif.
k. Pirro R, Scheer M, de Jong A. Additive in vitro activity of enrofloxacin and its main metabolite ciprofloxacin (abstr), in *Proceedings*. 14th Annu Cong Eur Soc Vet Dermatol 1997;199.

## References


1. Mikota SK, Sargent EL, Ranglack GS. Causes of death. In: Mikota SK, Sargent EL, Ranglack GS, eds. *Medical management of the elephant*. West Bloomfield, Mich: Indira Publishing House, 1994;219–224.
2. Olsen JH. Antibiotic therapy in elephants. In: Fowler ME, Miller RE, eds. *Zoo and wild animal medicine: current veterinary therapy 4*. Philadelphia: WB Saunders Co, 1999;533–541.
3. Schmidt MJ. Penicillin G and amoxicillin in elephants: a study comparing dose regimens administered with serum levels achieved in healthy elephants. *J Zoo Anim Med* 1978;9:127–136.
4. Bregante MA, Saez P, Aramayona JJ, et al. Comparative pharmacokinetics of enrofloxacin in mice, rats, rabbits, sheep, and cows. *Am J Vet Res* 1999;60:1111–1116.
5. Cox SK, Cottrell MB, Smith L, et al. Allometric analysis of ciprofloxacin and enrofloxacin pharmacokinetics across species. *J Vet Pharmacol Ther* 2004;27:139–146.
6. Vogelman B, Gudmundsson S, Leggett JE, et al. Correlation of antimicrobial pharmacokinetics parameters with therapeutic efficacy in an animal model. *J Infect Dis* 1988;158:831–847.
7. Lodwick LJ, Dubach JM, Phillips LG, et al. Pharmacokinetics of amikacin in African elephants (*Loxodonta africana*). *J Zoo Wildl Med* 1994;25:367–375.
8. Page CD, Mautino M, Derendorf HD, et al. Comparative pharmacokinetics of trimethoprim-sulfamethoxazole administered intravenously and orally to captive elephants. *J Zoo Wildl Med* 1991;22:409–416.
9. Bush M, Raath JP, de Vos V, et al. Serum oxytetracycline levels in free-ranging male African elephants (*Loxodonta africana*) injected with a long-acting formulation. *J Zoo Wildl Med* 1996;27:382–385.
10. Bush M, Stoskopf MK, Raath JP, et al. Serum oxytetracycline concentrations in African elephants (*Loxodonta africana*) calves after long-acting formulation injection. *J Zoo Wildl Med* 2000;31:41–46.
11. Isaza R, Hunter RP. Drug delivery to captive Asian elephants—treating goliath. *Curr Drug Deliv* 2004;1:291–298.
12. Rosin E, Schultz-Darken N, Perry B, et al. Pharmacokinetics of ampicillin administered orally in Asian elephants (*Elephas maximus*). *J Zoo Wildl Med* 1993;24:515–518.
13. Papich MG, Riviere JE. Fluoroquinolone antimicrobial drugs. In: Adams R, ed. *Veterinary pharmacology and therapeutics*. 8th ed. Ames, Iowa: Iowa State University Press, 2001;898–917.
14. Walker RD. Fluoroquinolones. In: Prescott JF, ed. *Antimicrobial therapy in veterinary medicine*. 3rd ed. Ames, Iowa: Iowa State University Press, 2000;315–338.
15. Vancutsem PM, Babish JG, Schwark WS. The fluoroquinolone antimicrobials: structure, antimicrobial activity, pharmacokinetics, clinical use in domestic animals and toxicity. *Cornell Vet* 1990;80:173–186.
16. Plumb DC. Drug monographs. In: Plumb DC, ed. *Veterinary drug handbook*. 3rd ed. Ames, Iowa: Iowa State University Press, 1999;238–241.
17. McKellar QA. Clinical relevance of the pharmacologic properties of fluoroquinolones. *Suppl Compend Contin Educ Pract Vet* 1996;18:14–21.
18. Stegemann M. Microbiology and pharmacology of enrofloxacin in cattle. *Bovine Pract* 1997;31:76–81.
19. Enrofloxacin [package insert]. Shawnee Mission, Kan: Bayer Corp, Agriculture Division, Animal Health, 2001.
20. Gamble KC, Boothe DM, Jensen JM, et al. Pharmacokinetics of a single intravenous enrofloxacin dose in scimitar-horned oryx (*Oryx dammah*). *J Zoo Wildl Med* 1997;28:36–42.
21. Gandolf AR, Papich MG, Bringardner AB, et al. Pharmacokinetics after intravenous, subcutaneous, and oral administration of enrofloxacin in alpacas. *Am J Vet Res* 2005;66:767–771.
22. Schmidt MJ. Antibiotic therapy in elephants. In: Fowler ME, Miller RE, eds. *Zoo and wild animal medicine: current veterinary therapy 4*. Philadelphia: WB Saunders Co, 1999;538.
23. Houck R. Antibiotic therapy in elephants. In: Fowler ME, Miller RE, eds. *Zoo and wild animal medicine: current veterinary therapy 4*. Philadelphia: WB Saunders Co, 1999;538.
24. Langston VC, Sedrish S, Boothe DM. Disposition of single-dose oral enrofloxacin in the horse. *J Vet Pharmacol Ther* 1996;19:316–319.
25. Haines GR, Brown MP, Gronwall RR, et al. Serum concen-

trations and pharmacokinetics of enrofloxacin after intravenous and intragastric administration to mares. *Can J Vet Res* 2000;64:171–177.

26. Giguère S, Sweeney RW, Bélanger M. Pharmacokinetics of enrofloxacin in adult horses and concentration of the drug in serum, body fluids, and endometrial tissues after repeated intragastrically administered doses. *Am J Vet Res* 1996;57:1025–1030.

27. Boeckh C, Buchanan C, Boeckh A, et al. Pharmacokinetics of the bovine formulation of enrofloxacin (Baytril® 100) in horses. *Vet Ther* 2001;2:129–134.

28. Bermingham EC, Papich MG. Pharmacokinetics after intravenous and oral administration of enrofloxacin in sheep. *Am J Vet Res* 2002;63:1012–1017.

29. Epstein K, Cohen N, Boothe D, et al. Pharmacokinetics, stability, and retrospective analysis of use of an oral gel formulation of the bovine injectable enrofloxacin in horses. *Vet Ther* 2004;5:155–167.

30. Bermingham EC, Papich MG, Vivrett SL. Pharmacokinetics of enrofloxacin administered intravenously and orally to foals. *Am J Vet Res* 2000;61:706–709.

31. Shah VP, Midha KK, Dighe S, et al. Conference report: analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. *Int J Pharm* 1992;82:1–7.

32. Gibaldi N, Perrier D. Appendix A–H. In: Gibaldi M, Perrier D, eds. *Pharmacokinetcs*. 2nd ed. New York: Marcel Dekker Inc, 1982;419–477.

33. Pirro F, Edingloh M, Schmeer N. Bactericidal and inhibitory activity of enrofloxacin and other fluoroquinolones in small animal pathogens. *Suppl Compend Contin Educ Pract Vet* 1999;21:19–25.

34. Greene CE, Budsberg SC. Veterinary use of quinolones. In: Hoper DC, Wolfson JS, eds. *Quinolone antimicrobial agents*. 2nd ed. Washington, DC: American Society for Microbiology, 1993;473–488.

35. Prescott JF, Yielding KM. In vitro susceptibility of selected veterinary bacterial pathogens to ciprofloxacin, enrofloxacin and norfloxacin. *Can J Vet Res* 1990;54:195–197.

36. Giguère S, Bélanger M. Concentration of enrofloxacin in equine tissues after long-term oral administration. *J Vet Pharmacol Ther* 1997;20:402–404.

37. Papich MG, Van Camp SD, Cole JA, et al. Pharmacokinetics and endometrial tissue concentrations of enrofloxacin and the metabolite ciprofloxacin after i.v administration of enrofloxacin to mares. *J Vet Pharmacol Ther* 2002;25:343–350.

38. Küng K, Riond JL, Wanner M. Pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin after intravenous and oral administration of enrofloxacin in dogs. *J Vet Pharmacol Ther* 1993;16:462–468.

39. Lode H, Borner K, Koeppe P. Pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 1998;27:33–39.

40. Drusano GL, Johnson DE, Rosen M, et al. Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model of *Pseudomonas* sepsis. *Antimicrob Agents Chemother* 1993;37:483–490.

41. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993;37:1073–1081.

42. Hyatt JM, McKinnon PS, Zimmer GS, et al. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. *Clin Pharmacokinet* 1995; 28:143–160.

43. Blaser J, Stone BB, Groner MC, et al. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. *Antimicrob Agents Chemother* 1987;31:1054–1060.

44. Ensink JM, van Klingeren B, Houwers DJ, et al. In-vitro susceptibility to antimicrobial drugs of bacterial isolates from horses in The Netherlands. *Equine Vet J* 1993;25:309–313.

45. The National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; approved standard*. 2nd ed. NCCLS document M31-A2. Wayne, Pa: National Committee for Clinical Laboratory Standards, 2002.

46. Nielsen P, Gyrd-Hansen N. Bioavailability of enrofloxacin after oral administration to fed and fasted pigs. *Pharmacol Toxicol* 1997;80:246–250.