Pharmacokinetics after intravenous, subcutaneous, and oral administration of enrofloxacin to alpacas

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Objective—To determine plasma concentrations of enrofloxacin and the active metabolite ciprofloxacin after PO, SC, and IV administration of enrofloxacin to alpacas.

Animals—6 adult female alpacas.

Procedure—A crossover design was used for administration of 3 single-dose treatments of enrofloxacin to alpacas, which was followed by an observational 14-day multiple-dose regimen. Single-dose treatments consisted of IV and SC administration of injectable enrofloxacin (5 mg/kg) and PO administration of enrofloxacin tablets (10 mg/kg) dissolved in grain to form a slurry. Plasma enrofloxacin concentrations were measured by use of high-performance liquid chromatography. The multiple-dose regimen consisted of feeding a mixture of crushed and moistened enrofloxacin tablets mixed with grain. Behavior, appetite, and fecal quality were monitored throughout the 14-day treatment regimen and for 71 additional days following treatment.

Results—Mean half-life following IV, SC, and PO administration was 11.2, 8.7, and 16.1 hours, respectively. For SC and PO administration, mean total systemic availability was 90.18% and 29.31%, respectively; mean maximum plasma concentration was 3.79 and 1.81 µg/mL, respectively; and area under the curve (AUC) was 50.05 and 33.97 (µg × h)/mL, respectively. The SC or PO administration of a single dose of enrofloxacin yielded a ratio for AUC to minimum inhibitory concentration > 100 for many gram-positive and gram-negative bacterial pathogens common to camelids.

Conclusions and Clinical Relevance—The administration of enrofloxacin (5 mg/kg, SC, or 10 mg/kg, PO) may be appropriate for antimicrobial treatment of alpacas. (*Am J Vet Res* 2005;66:767–771)

As the market for South American camelids continues to expand, a deficiency in pharmacokinetic references for antimicrobial dosing in these animals has become more pronounced. Several types of antimicrobial agents are routinely used in camelids to treat a range of common infectious conditions; however, sparse pharmacokinetic data are available for these drugs.[1-3] Furthermore, the practice of extrapolating antimicrobial dosages across species can be invalid.[1] There is a lack of pharmacokinetic data in the literature regarding SC or oral administration of antimicrobials to camelids. Drugs such as penicillins, cephalosporins, and potentiated sulfonamides that are effective after enteral administration to monogastrics are poorly absorbed in ruminants as a result of inactivation or dilution of the drug in the rumen.[1,4] However, in 1 study,[5] researchers documented that oral administration of enrofloxacin to sheep resulted in adequate absorption, a prolonged half-life, and high bioavailability.

Enrofloxacin is a synthetic antimicrobial in the class of fluoroquinolone carboxylic acid derivatives.[6,7] Fluoroquinolone drugs inhibit DNA gyrase formation and are known for their broad-spectrum bactericidal action against gram-negative bacteria, *Mycoplasma* spp, and some gram-positive bacteria.[6-8] Additional attributes of fluoroquinolones include concentration-dependent pharmacokinetics and a substantial postantimicrobial effect; in 1 in vitro study,[9] bacteria were killed or inhibited for 4 to 6 hours after enrofloxacin was removed. Furthermore, surrogate markers of therapeutic efficacy (eg, ratios of the **area under the curve [AUC]** to **minimum inhibitory concentration [MIC]**) have been derived from studies[10,11] in humans and other animals. This information provides guidelines for dosing when pharmacokinetic data are available on absorption and disposition in mammalian species. Enrofloxacin is registered for use in cats and dogs (oral and injectable) and cattle (injectable). There has been a large amount of pharmacokinetic-pharmacodynamic data generated in the past 10 years for fluoroquinolone antimicrobials, including extensive studies in laboratory animals[8,12] and some domestic species.[9,12,13] However, little information has been published regarding enrofloxacin in camelids.[1] Although clinicians have administered fluoroquinolones to camelids, we are not aware of any reports of effectiveness.

The objectives of the study reported here were to investigate the pharmacokinetics of enrofloxacin when administered to alpacas as a singe bolus by the IV, SC, and oral routes and to generate data that can be used to develop dosing regimens that will result in plasma concentrations in alpacas that are within the therapeutic range. This study was not designed to test drug efficacy; instead, it was designed to enable us to identify

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dosages that can be used for additional studies. Second, we intended to monitor alpacas for any observable effects on health of the digestive tract associated with a 14-day course of oral administration of enrofloxacin.

Materials and Methods

Animals—Six clinically normal adult female alpacas were used in the study. The alpacas weighed between 63 and 78 kg (mean, 70 kg) and were part of The Ohio State University Llama Research Program. The alpacas were housed as a single group in 1 large stall and paddock. Water and hay were available ad libitum, and daily grain rations were provided throughout the study. The study was approved by The Ohio State University Institutional Animal Care and Use Committee.

Experimental procedure—The alpacas were allocated into 3 treatment groups (2 alpacas/group). Alpacas were assigned a number (1 through 6 in ascending order) as they exited the trailer on arrival. Alpacas 1 and 2 constituted group 1, alpacas 3 and 4 constituted group 2, and alpacas 5 and 6 constituted group 3.

Enrofloxacin was administered to each group as 3 single-dose treatments via the IV, SC, and oral routes in a crossover design during a period of 5 weeks. A washout period of at least 2 weeks separated each subsequent treatment. Alpacas were weighed (nearest 1 kg) on the day before each treatment. On the day of treatment, a 14-gauge, 14-cm fluoride-coated catheter was aseptically inserted into a jugular vein and attached to an 83.8-cm extension and 3-way stopcock; the extension and stopcock were secured to the alpaca by use of elastic tape.

For each treatment, enrofloxacin was administered via one of the routes of administration to each group. Treatments consisted of enrofloxacin injectable[a] (5 mg/kg) administered IV via the catheter in the jugular vein and immediately followed by 6 mL of saline (0.9% NaCl) solution containing 10% heparin, enrofloxacin injectable (5 mg/kg) injected SC in the most dorsal region of the shoulders, or enrofloxacin tablets[b] (10 mg/kg) administered PO. The tablets were pulverized and mixed with water-soaked grain to create a slurry that could be easily administered as a drench by use of a 60-mL syringe.

Collection of samples—Blood samples (6 mL) were collected immediately before drug administration (time 0) and 0.17, 0.33, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours after administration. Blood samples were immediately placed in heparin-coated tubes. The catheters inserted in the jugular vein were flushed with heparinized saline solution between subsequent collection of blood samples. At the time of each sample collection, 20 mL of blood was withdrawn to remove the heparinized saline solution from the extension system. The 6-mL sample was collected, and the 20 mL of blood was then injected back into the alpaca. Samples were centrifuged (1,000 × *g* for 15 minutes), and plasma was decanted and stored at −45°C or colder until assayed by use of reverse-phase **high-performance liquid chromatography (HPLC)**.

Determination of drug concentrations—Plasma samples (samples obtained from the alpacas and samples fortified with known amounts of compounds) were assayed concurrently for enrofloxacin and ciprofloxacin concentrations by a validated[14] method by use of HPLC and UV detection. The system consisted of a pump,[c] an automated sampling system,[d] and a UV light detector.[e] A 4.6-mm × 15-cm reverse-phase column[f] was used to separate enrofloxacin and ciprofloxacin from other plasma components. The eluate was monitored by use of the UV detector at a wavelength of 279 nm. Each drug was extracted from the plasma by use of solid-phase extraction cartridges.[g] 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 at 45°C for 25 minutes. The dried product was reconstituted with 200 µL of a mixture (15:85) of methanol:0.1% **trifluoroacetic acid (TFA)** in water. The isocratic mobile phase was 77% deionized water, 23% acetonitrile, and 0.1% TFA, and flow rate was 1 mL/min. Retention time for enrofloxacin and ciprofloxacin was approximately 3.0 and 4.0 minutes, respectively.

Chromatograms were integrated by use of computer software.[h] 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 plotted for each assay by fortifying pooled alpaca plasma obtained prior to drug administration. Analytical reference standards for enrofloxacin[i] and ciprofloxacin[j] were used to make the calibration standards and to fortify quality-control samples. Precision was calculated as follows: (SD of 5 fortified samples/mean concentration of those 5 fortified samples) × 100. Precision was within 15% for enrofloxacin and ciprofloxacin concentrations of 0.05, 0.5, and 5.0 µg/mL, respectively. The limit of quantification, defined as the lowest detected concentration resulting in a coefficient of variation < 20%, was 0.05 µg/mL for enrofloxacin and ciprofloxacin.

Table 1—Median (range) values for pharmacokinetic variables determined after administration of a single dose of enrofloxacin (5 mg/kg, IV; 5 mg/kg, SC; and 10 mg/kg, PO) to 6 alpacas.

Variable	IV	SC	PO
AUC_{∞} ([µg × h]/mL)	58.39 (43.21–120.60)	41.90 (33.53–89.00)	32.46 (29.29–42.74)
$AUC_{\%extrapolated}$ (%)	1.42 (0.08–5.44)	1.26 (0.50–4.62)	10.79 (1.87–24.80)
C_{max} (µg/mL)	NA	4.16 (1.45–4.69)	1.42 (0.83–3.97)
$t_{1/2}$ (h)	13.04 (6.26–46.58)	7.83 (3.36–15.64)	15.32 (8.25–25.03)
T_{max} (h)	NA	6.0 (4.0–8.0)	4.0 (0.5–8.0)
Clearance (mL/h/kg)	84.50 (41.46–115.70)	NA	NA
F (%)	NA	90.18 (62.85–117.5)	29.44 (12.14–41.24)
VD_{ss} (L/kg)	0.44 (0.32–1.07)	NA	NA
VD(area) (L/kg)	1.61 (0.42–7.64)	NA	NA
MRT (h)	4.85 (4.48–10.71)	10.33 (7.26–21.62)	21.98 (10.92–35.68)

AUC_{∞} = Area under the plasma concentration-versus-time curve (AUC) from time 0 to infinity; time of administration was designated as time 0. $AUC_{\%extrapolated}$ = Percentage of the AUC that was extrapolated. C_{max} = Maximum concentration. $t_{1/2}$ = Elimination half-life. T_{max} = Time to maximum concentration. F = Bioavailability (ie, fraction of drug absorbed). VD_{ss} = Apparent volume of distribution at steady state. VD(area) = Area of the volume of distribution. MRT = Mean residence time. NA = Not applicable.

Pharmacokinetic analysis—Pharmacokinetic values for each alpaca were determined for IV, SC, and oral drug administration. Noncompartmental pharmacokinetic analysis of the plasma concentrations was performed by use of a computerized pharmacokinetic program.[k] Plasma enrofloxacin calculations included the AUC, **peak concentration (C_{max})**, **elimination half-life ($t_{1/2}$)**, **apparent volume of distribution at steady state (VD_{ss})**, **bioavailability (F)**, and clearance. The AUC was measured by use of the trapezoidal method in which the areas for each trapezoid are summed. In this study, we used the linear-logarithmic trapezoidal method. The **AUC from 0 to infinity (AUC_{∞})** was calculated by determining the AUC up to the last sample point and then adding the terminal portion estimated from the terminal rate constant. The number of time points used to calculate the terminal slope of the curve varied among alpacas. Mean ± SD proportion of the AUC that was extrapolated was 11.4 ± 8.2%, 1.85 ± 1.61%, and 1.65 ± 1.48% for PO, SC, and IV administration, respectively. The C_{max} was determined directly from the data. The $t_{1/2}$ was the natural logarithm of 2 divided by the elimination rate. The value for VD_{SS} was calculated by use of the following equation:

$$VD_{SS} = (AUMC \times dose)/(AUC)^2,$$

where AUMC is the area under the moment curve. **The volume of distribution for enrofloxacin in the plasma (VD[area])** was calculated by use of the following equation:

$$VD(area) = dose/(elimination\ rate \times AUC).$$

Mean residence time (MRT) was calculated as follows: MRT = AUMC/AUC. Clearance was calculated as dose/AUC. The F was calculated by use of the following equation:

$$F = ([AUC_{\{non\text{-}IV\}} \times dose_{\{IV\}}]/[AUC_{\{IV\}} \times dose_{\{non\text{-}IV\}}]) \times 100,$$

where $AUC_{(non\text{-}IV)}$ and $dose_{(non\text{-}IV)}$ are the AUC and dose, respectively, for the non-IV routes of administration (ie, SC and PO).

Multiple-dose administration—At the conclusion of the pharmacokinetic portion of the study, enrofloxacin was administered to alpacas in accordance with a multiple-dose regimen to identify observable effects on flora of the gastrointestinal tract. Each alpaca was administered enrofloxacin (10 mg/kg, PO, q 24 h) in the form of nonflavored tablets crushed and slightly moistened for better adherence to grain. The grain-drug mixture was readily consumed by all alpacas daily for 14 days. Beginning with the first day of administration, fecal output from each alpaca was monitored by caretakers daily for 21 days.

Results

Single-dose administration—Pharmacokinetic variables were calculated for enrofloxacin and ciprofloxacin after IV, SC, and PO administration of a single dose of enrofloxacin (**Table 1**). Mean ± SD plasma concentration-versus-time curves following IV, SC, and PO administrations were plotted for enrofloxacin and ciprofloxacin (**Figure 1**). Plasma concentration-versus-time curves for the IV, SC, and PO routes of administration had similar slopes. Mean $t_{1/2}$ for IV, SC, and PO routes of administration was 11.2, 8.7, and 16.1 hours, respectively, and varied considerably among alpacas after oral administration. Mean F for SC and PO administration was 90.18% and 29.31%, respectively. For SC and PO administration, mean C_{max} for enrofloxacin was 3.79 and 1.81 µg/mL, respectively, and AUC was 50.05 and 33.97 (µg × h)/mL, respectively. Measurement of plasma ciprofloxacin revealed that this metabolite accounted for little of the total active drug. For SC and oral administration, mean C_{max} of ciprofloxacin was 0.06 and 0.15 µg/mL, respectively, and mean AUC was 0.46 and 0.77 (µg × h)/mL, respectively.

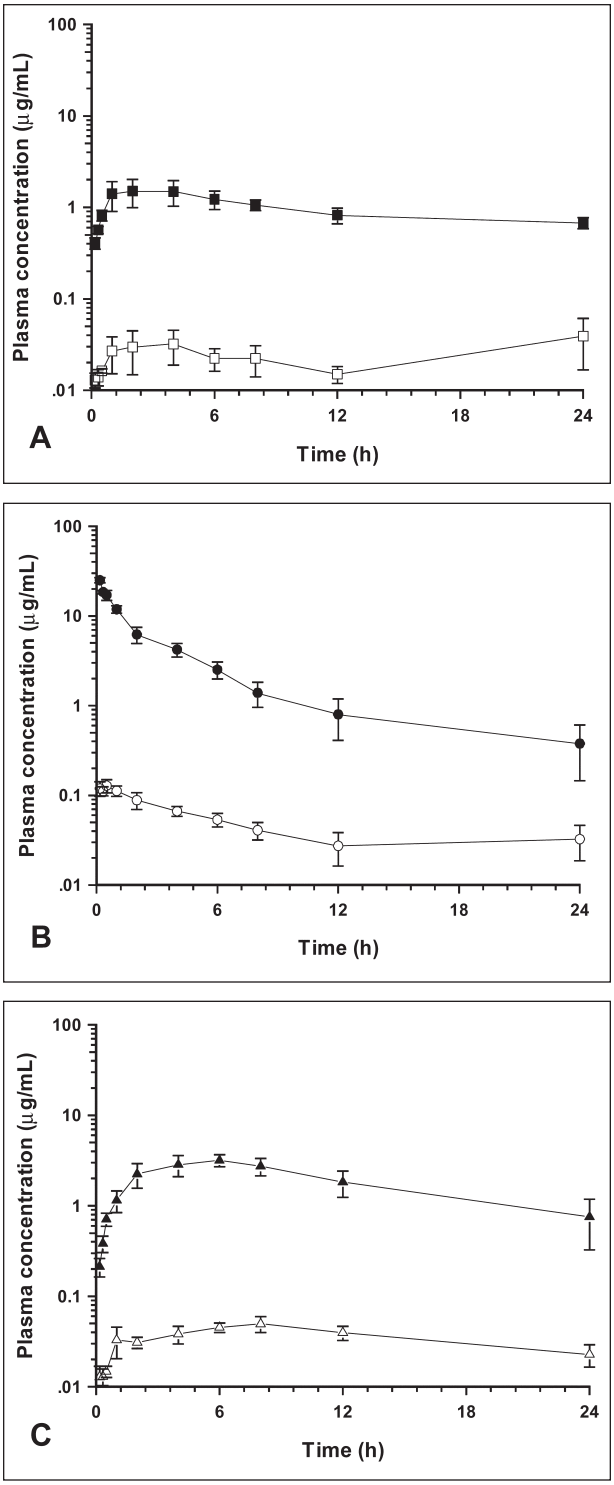

Figure 1—Mean ± SD plasma concentrations of enrofloxacin (black symbols) and ciprofloxacin (white symbols) for 6 alpacas after administration of a single dose of enrofloxacin (A, 5 mg/kg, IV; B, 5 mg/kg, SC; and C, 10 mg/kg, PO). Time 0 = Time of administration of enrofloxacin.

Multiple-dose administration—We did not detect changes in consistency, color, or general volume of fecal output during the 21-day observation period for administration of multiple doses of enrofloxacin.

Discussion

Analysis of our results indicated that absorption of enrofloxacin after SC administration to alpacas was nearly complete (90%) and consistent with values reported for camels (92%).[15] Absorption after PO administration was considerably lower (30%), compared with absorption for the SC route; however, because the dose for PO administration was higher than that for IV or SC administration, the PO route of administration also yielded desired plasma concentrations, as determined on the basis of MICs. In 1 study[5] in sheep, investigators found that crushed tablets fed free choice with grain resulted in superior systemic drug absorption (98%), compared with absorption of tablets crushed and force-fed with water as a drench (48%). Those investigators proposed that dilution of the drug in the liquid fraction of the rumen may be a possible factor in the poorer absorption following drench administration. On the basis of these findings, more complete absorption may be anticipated with clinical use of PO administration of enrofloxacin in alpacas. For PO dosing in the study reported here, the drench preparation was chosen as the best method of administration given the time constraints, and feed was added to the drench to simulate more realistic treatment preparations. A dosage of 10 mg/kg was chosen because it was anticipated that absorption would be low and a higher dosage than for the IV or SC routes was necessary to result in adequate plasma concentrations.

When predicting in vivo efficacy of concentration-dependent antimicrobials such as the fluoroquinolones, C_{max} and AUC are the surrogate markers most often associated with successful treatment. For the fluoroquinolone antimicrobials, the ratio of C_{max} to MIC or the ratio of AUC to MIC may predict successful antibacterial effects. There is some correlation between these variables. A peak concentration that is at least 8 to 10 times the MIC or an AUC:MIC > 100 to 125 has been associated with an optimum antibacterial effect.[8,16-18] Analysis of the evidence from our use of the fluoroquinolones in immunocompetent animals suggests that an AUC:MIC of 50 to 60 is likely to be effective.[19] High values for C_{max}:MIC have been associated with less development of antimicrobial resistance.[17]

The observed AUCs for oral, SC, and IV routes of administration in the study reported here were similar to those reported for sheep.[5] On the basis of MICs reported for various common pathogens in camelids, 5 mg/kg administered SC or 10 mg/kg administered orally would be appropriate for alpacas. Plasma enrofloxacin measured > 24 hours after administration accounted for little of the total AUC; therefore, AUC_{∞} values were used for calculations. Mean and median AUC_{∞} values for SC administration (50.05 and 41.90 [μg × h]/mL, respectively) were adequate for an AUC:MIC > 100 for organisms with an MIC ≤ 0.5 and 0.42 μg/mL, respectively. Mean and median AUC_{∞} values for PO administration (33.97 and 32.46 [μg × h]/mL) were adequate for an AUC:MIC > 100 for organisms with an MIC ≤ 0.34 and 0.36 μg/mL, respectively. The MIC of enrofloxacin that will result in the death of 90% of organisms for several pathogens of camelids is 0.03 for *Escherichia coli*, *Actinobacillus* spp, *Pasteurella haemolytica*, and *Klebsiella pneumoniae*; 0.15 for *Pasteurella multocida*; 0.25 for *Clostridium perfringens* and *Proteus mirabilis*; 0.13 for *Staphylococcus aureus*[20]; and 0.125 for *Corynebacterium pseudotuberculosis*.[21]

Ciprofloxacin was also included in the pharmacologic analysis because it is the active metabolite of enrofloxacin and therefore contributes to antimicrobial activity. Plasma concentrations of ciprofloxacin were low in the study reported here, indicating that this metabolite accounts for only a small percentage of antimicrobial activity following administration of enrofloxacin to alpacas. The combined mean AUC_{∞} for ciprofloxacin and enrofloxacin following SC and PO administration was 52.11 and 33.93 (h × μg)/mL, respectively. The low concentrations of ciprofloxacin were consistent with those for a study[5] conducted in sheep. We did not determine the reason that animals of these species generate less ciprofloxacin than other animals that have been studied.[11]

The broad-spectrum bactericidal action of enrofloxacin against gram-negative bacteria, in addition to the drug's primary excretion in bile, has raised concerns for health of rumen flora when repeated doses are administered. There were no observable effects on the alpacas throughout a 14-day period of enrofloxacin treatment (10 mg/kg, PO) nor during the observation period following treatment. A pharmacokinetic study[22] in which investigators administered norfloxacin revealed that norfloxacin distributes to the rumen regardless of the route of administration and does not cause substantial effects on the gastrointestinal tract. Furthermore, a study[23] in cattle revealed that repeated oral dosing of enrofloxacin had a minimal effect on rumen flora. In addition, no effects on the gastrointestinal tracts were observed in 5 sheep repeatedly administered enrofloxacin (10 mg/kg) PO.[5] Because enrofloxacin and ciprofloxacin have little activity against protozoa, streptococci, or anaerobic bacteria, it is possible that these organisms in the rumen and digestive tract of the animals in the various studies were not affected by fluoroquinolone administration.

On the basis of the inherent antimicrobial properties of enrofloxacin, the pharmacokinetic values determined for the PO administration in the study reported here, and the MICs of many gram-positive and gram-negative bacterial pathogens common to ruminants, we believe that enrofloxacin administered orally (10 mg/kg, q 24 h) or SC (5 mg/kg, q 24 h) is a safe and appropriate antimicrobial for several common bacterial pathogens of alpacas. Additional studies will be needed to determine the efficacy of enrofloxacin for use in the treatment of alpacas and other camelids.

a. Baytril injectable solution, Bayer Corp, Shawnee Mission, Kan.
b. Baytril 136-mg tablets, Bayer Corp, Shawnee Mission, Kan.
c. Waters 600, Millipore Corp, Milford, Mass.

d. Hewlett-Packard series 1100, Agilent Technologies, Wilmington, Del.
e. Agilent 1100 series UV detector, Agilent Technologies, Wilmington, Del.
f. Zorbax SB C-8, Mac Mod, Chadds Ford, Pa.
g. Oasis, Waters Corp, Milford, Mass.
h. HP ChemStation series 1100 software, Agilent Technologies, Wilmington, Del.
i. Enrofloxacin analytical reference standard, Bayer Corp, Shawnee Mission, Kan.
j. Ciprofloxacin analytical reference standard, US Pharmacopeia, Rockville, Md.
k. WinNolin, version 4.0, Pharsight Corp, Cary, NC.

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