Pharmacokinetics after intravenous and oral administration of enrofloxacin in sheep

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Objective—To compare pharmacokinetics of enrofloxacin administered IV and in various oral preparations to ewes.

Animals—5 mature Katahdin ewes weighing 42 to 50 kg.

Procedure—Ewes received 4 single-dose treatments of enrofloxacin in a nonrandomized crossover design followed by a multiple-dose oral regimen. Single-dose treatments consisted of an IV bolus of enrofloxacin (5 mg/kg), an oral drench (10 mg/kg) made from crushed enrofloxacin tablets, oral administration in feed (10 mg/kg; mixture of crushed enrofloxacin tablets and grain), and another type of oral administration in feed (10 mg/kg; mixture of enrofloxacin solution and grain). The multiple-dose regimen consisted of feeding a mixture of enrofloxacin solution and grain (10 mg/kg, q 24 h, for 7 days). Plasma concentrations of enrofloxacin and ciprofloxacin were measured by use of high-performance liquid chromatography.

Results—Harmonic mean half-life for oral administration was 14.80, 10.80, and 13.07 hours, respectively, for the oral drench, crushed tablets in grain, and enrofloxacin solution in grain. Oral bioavailability for the oral drench, crushed tablets in grain, and enrofloxacin in grain was 47.89, 98.07, and 94.60%, respectively, and median maximum concentration (C_{max}) was 1.61, 2.69, and 2.26 µg/ml, respectively. Median C_{max} of the multiple-dose regimen was 2.99 µg/ml.

Conclusions and Clinical Relevance—Enrofloxacin administered orally to sheep has a prolonged half-life and high oral bioavailability. Oral administration at 10 mg/kg, q 24 h, was sufficient to achieve a plasma concentration of 8 to 10 times the minimum inhibitory concentration (MIC) of any microorganism with an MIC ≤ 0.29 µg/ml. (*Am J Vet Res* 2002; 63:1012–1017)

The use of orally administered antimicrobials in ruminants has been limited, primarily because of the complexity of their digestive system and the associated anatomic-physiologic factors that influence drug absorption. A major concern with oral administration of drugs is the large volume of fluid and digesta in the rumen. This fluid volume can reduce concentration of drugs, and particulate matter can adsorb some drugs, potentially decreasing the amount of drug available for absorption from the abomasum and duodenum.[1] Another major issue affecting absorption is the large amounts of ruminal microbial enzymes that may metabolize or degrade a drug. Because of these factors, the amount of drug available for absorption from the rumen epithelium can be highly variable.

The pharmacokinetics of enrofloxacin have been investigated in many species of mammals such as rabbits,[2] dogs,[3] pigs,[4] horses,[5] and cattle.[6] It has high bioavailability in most species and is rapidly absorbed with peak concentrations evident 30 to 60 minutes after IM, SC, or oral administration.[2-7] However, in a limited number of studies,[8,a] enrofloxacin reportedly had low bioavailability after oral administration in ruminants.

The objective of the study reported here was to investigate the pharmacokinetics of enrofloxacin when administered in various oral preparations to small ruminants. The preparations chosen were those most likely to be administered orally to small ruminants, and the concentrated solution was selected because of its low volume and decreased cost. Although the FDA strictly prohibits the extralabel use of enrofloxacin in animals intended for human consumption, there are specific circumstances in which enrofloxacin may be considered for use as an orally administered antimicrobial in animals not intended for human consumption, such as domestic small ruminants used in research or as pets and exotic small ruminants in zoos and wildlife parks.

Materials and Methods

Animals—Five clinically normal adult Katahdin ewes that weighed between 42 and 50 kg were used in the study. They were housed separately in stalls and had access to hay and water throughout the study period. This study was approved by the North Carolina State University Institutional Animal Care and Use Committee and was in compliance with their guidelines on care and use of animals.

Study design—Four single-dose treatments were administered in a nonrandomized crossover design, which was followed by administration of enrofloxacin for 7 days in a multiple-dose regimen. There was a washout period of at least 2 weeks between successive experiments. The sequence of treatment was not randomized in an attempt to minimize the effect of feed (hay) variability among treatments. The sequence of experiments consisted of an initial IV administration; followed by a single administration via oral drench, crushed tablets mixed with grain, enrofloxacin solution mixed with grain, respectively; and the multiple-dose oral administration. The preparation and administration of the oral forms of enrofloxacin were designed to simulate field conditions.

For IV administration, injectable enrofloxacin[b] (concentration, 22.7 mg/ml; administered at a rate of 5 mg/kg) was administered as a bolus in the right jugular vein via a butterfly

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catheter. An IV catheter was aseptically inserted in the contralateral jugular vein, and 10-ml blood samples were collected 10, 20, 30, 40, and 60 minutes and 2, 4, 6, 8, 12, 24, 36, and 48 hours after administration. Samples were collected in evacuated glass tubes that contained sodium heparin. Samples were centrifuged at 1,000 × g and stored at –70 C until analyzed.

For all of the single-dose oral administrations, food was withheld from the sheep for 12 hours prior to dosing to facilitate administration or consumption of the drug, but the sheep had access to hay immediately after dosing and throughout the remainder of the study. The enrofloxacin mixtures appeared to be quite palatable and were consumed by all sheep in each treatment within 5 minutes of administration.

For the single-dose oral drench, a suspension of enrofloxacin-water-fructose was administered orally via a dosing syringe. Tablets (68 mg/tablet; dosage rounded to the nearest half tablet) were crushed and thoroughly mixed in a suspension of 15 ml of water and 15 ml of fructose syrup. Each sheep received 10 mg of enrofloxacin/kg, PO. Blood samples were collected in the same manner and at the same time intervals as for the IV administration.

For the tablets-grain administration, enrofloxacin (10 mg/kg) in the form of crushed tablets (68 mg/tablet; dosage rounded to the nearest half tablet) was thoroughly mixed with 15 ml of fructose syrup and 227 g of grain. Sheep were fed the enrofloxacin-grain mixture, and blood samples were collected as previously described.

For the solution-grain administration, enrofloxacin (10 mg/kg) in the form of enrofloxacin solution[c] was thoroughly mixed with 15 ml of fructose syrup and 227 g of grain. Sheep were fed the enrofloxacin-grain mixture, and blood samples were collected from an indwelling IV cannula inserted in a jugular vein but at intervals of 10, 20, 30, 40, 60, and 90 minutes and 2, 4, 6, 8, 12, 18, 24, 28, 36, 48, and 72 hours after administration.

For the multiple-dose administration, enrofloxacin (10 mg/kg) in the form of enrofloxacin solution[c] was thoroughly mixed with 15 ml of fructose syrup and 227 g of grain. This enrofloxacin-grain mixture was fed to the sheep at 24-hour intervals for 7 consecutive days. Blood samples were collected from an indwelling IV cannula inserted in a jugular vein before (trough concentration) and 8 hours after administration (peak concentration) for 6 days. Blood samples were collected 0, 2, 4, 6, 8, 12, and 24 hours following the last dose on day 7.

Analysis of enrofloxacin and ciprofloxacin concentrations—Plasma samples were assayed simultaneously for enrofloxacin and ciprofloxacin concentrations by use of reverse-phase high pressure liquid chromatography. The system consisted of a pump,[d] an automated sampling system,[e] and a UV light detector.[f] A 4.0- mm × 20- cm reverse-phase column[g] was used to separate the drugs from other plasma components for samples from the first 3 experiments, and a 4.6- mm × 15-cm reverse-phase column[h] was used for samples from the last 2 experiments. The eluate was monitored by use of UV light at 279 nm. Each drug was extracted from the plasma by use of solid-phase extraction cartridges.[i] 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 15:85 mixture 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 generated with computer software.[j] 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 (0.05 to 20.0 µg/ml for samples after IV administration) for enrofloxacin and 0.05 to 2.0 µg/ml for ciprofloxacin were made for each assay by use of pooled sheep plasma. Analytical reference standards for enrofloxacin[k] and ciprofloxacin[l] were used to make calibration standards and to validate methods.

Precision was calculated as follows: (SD of 5 fortified samples/mean concentration of those 5 fortified samples) × 100. Precision was 14.99, 12.23, 15.14, and 4.51% for enrofloxacin concentrations of 0.05, 0.5, 5.0, and 20 µg/ml, respectively. Precision was 8.42, 12.47, and 16.19% for ciprofloxacin concentrations of 0.05, 0.5, and 2.0 µg/ml, respectively. The limit of quantitation, defined as the lowest detected concentration resulting in a coefficient of variation < 20%, was 0.05 µg/ml for both enrofloxacin and ciprofloxacin.

Percentage accuracy was calculated as follows: 100 – ([{true value – calculated value}/true value] × 100). Percentage accuracy was 96.52, 97.80, 99.90, and 98.20% for enrofloxacin concentrations of 0.05, 0.5, 5.0, and 20 µg/ml, respectively. Percentage accuracy was 94.91, 97.08, and 86.97% for ciprofloxacin concentrations of 0.05, 0.5, and 2.0 µg/ml, respectively. Recovery from plasma was 75% for enrofloxacin and 60% for ciprofloxacin. The percentage of enrofloxacin metabolized to ciprofloxacin was calculated by use of values for **area under the curve (AUC)**. The **AUC to the limit of quantitation ($AUC_{0\text{-}LOQ}$)** for each drug was used in the following equation: ($AUC_{0\text{-}LOQ}$ ciprofloxacin/[$AUC_{0\text{-}LOQ}$ ciprofloxacin + $AUC_{0\text{-}LOQ}$ enrofloxacin]) × 100.

Pharmacokinetic analysis—Compartmental models were fitted to the plasma concentration-versus-time curves for each sheep by use of a computer program.[m] Using the Aikake information criteria,[9] a 2-compartment model with a weighting scheme of $1/Y^2$ (to decrease unequal variances across time; Y is the plasma drug concentration) resulted in the best fit of the concentration-versus-time curve data for all the sheep after IV administration. Using the same criteria, a 1-compartment model with first-order input was the best fit for all data after oral administration.

The **total area under the curve ($AUC_{0\text{-}\infty}$)** for 1- and 2-compartment models was determined by use of the trapezoidal rule with extrapolation to infinity, using C_{48}/λ_2, where C_{48} is the plasma concentration at 48 hours, and λ_2 is the terminal rate constant. The $AUC_{0\text{-}LOQ}$ was used to determine the percentage of enrofloxacin metabolized to ciprofloxacin, because some ciprofloxacin concentrations were equivalent to or less than the limit of quantitation.

Volume of distribution at steady state (Vd_{ss}) was calculated by use of **area under the moment curve (AUMC)** as follows: Vd_{ss} = (dose × AUMC)/$(AUC)^2$. In this equation, AUMC was $AUMC_{0\text{-}\infty}$ as determined by use of the trapezoidal method. **Apparent volume of distribution as determined by use of the area method (Vd_{area})** was calculated as follows: Vd_{area} = dose/(λ_2 × AUC). **Total body clearance (Cl_T)** for the data after IV administration was calculated as follows: Cl_T = Dose/$AUC_{0\text{-}\infty}$.

Mean residence time (MRT) was calculated by use of statistical moment theory, using the following equation: MRT = $AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}$. **Mean absorption time (MAT)** of an orally administered dose was calculated as the difference between the MRT of IV and PO administration by use of the following equation: MAT = $MRT_{PO} - MRT_{IV}$. **Bioavailability (F)**, defined as the fraction of drug absorbed systemically, was derived from the difference between the AUC and doses by use of the following equation: F = (AUC_{PO} /AUC_{IV}) × ($Dose_{IV}/Dose_{PO}$).

The IV **distribution half-life ($t_{1/2\alpha}$)** was defined as $0.693/\alpha$, where α is the distribution rate constant. The **elimination half-life ($t_{1/2\beta}$)** was defined as $0.693/\beta$, where β is the elimination rate constant. Variables generated from each of the oral administration experiments revealed evidence of flip-flop kinetics, because the **ratio of the elimination rate**

Table 1—Median (range) values for pharmacokinetic variables describing the disposition of enrofloxacin in 5 sheep after a single IV administration (5 mg/kg) and after oral administration of a single dose (10 mg/kg) of 3 forms of enrofloxacin

Variable	IV	Oral drench	Tablets-grain	Solution-grain
$t_{1/2}\lambda_1$ (h)*	NA	0.56	0.94	2.0
$t_{1/2}\lambda_2$ (h)*	NA	14.80	10.80	13.07
$t_{1/2\alpha}$ (h)*	1.06	NA	NA	NA
$t_{1/2\beta}$ (h)*	4.77	NA	NA	NA
$AUC_{0-\infty}$ ([μg · h]/ml)	31.19 (23.46–42.09)	30.58 (19.26–44.60)	57.52 (28.59–105.20)	56.63 (43.71–88.19)
MRT (h)	5.00 (2.30–7.45)	19.47 (12.75–27.80)	19.95 (18.99–33.70)	19.24 (18.67–20.36)
MAT (h)	NA	14.95 (6.07–21.10)	18.99 (18.99–33.71)	15.87 (11.99–16.19)
T_{max} (h)	NA	5.50 (1.00–12.00)	8.00 (8.00–24.00)	8.00 (6.00–12.00)
C_{max} (μg/ml)	NA	1.61 (0.50–4.35)	2.69 (0.59–5.70)	2.26 (1.70–3.55)
F (%)	NA	47.89 (35.46–76.00)	98.07 (48.17–154.20)	94.60 (54.65–48.58)
α (/h)	0.55 (0.14–0.85)	NA	NA	NA
β (/h)	0.13 (0.12–0.38)	NA	NA	NA
λ_1 (/h)	NA	0.05 (0.02–0.08)	0.06 (0.02–0.11)	0.05 (0.04–0.13)
λ_2 (/hr)	NA	1.21 (0.15–1.83)	0.70 (0.26–0.89)	0.35 (0.13–0.42)
Cl_T (ml/[h · kg])	202.04 (130.83–220.78)	NA	NA	NA
Vd_{ss} (L/kg)	0 .97 (0.44–1.64)	NA	NA	NA
Vd_{area} (L/kg)	1.15 (0.69–2.65)	NA	NA	NA

*Value reported is harmonic mean.

$t_{1/2}\lambda_1$ = Initial half-life after oral administration. $t_{1/2}\lambda_2$ = Terminal half-life after oral administration. $t_{1/2\alpha}$ = IV distribution half-life. $t_{1/2\beta}$ = IV elimination half-life. $AUC_{0-\infty}$ = Total area under the plasma concentration-versus-time curve from time 0 to infinity. MRT = Mean residence time. MAT = Mean absorption time. T_{max} = Time to maximum concentration. C_{max} = Maximum concentration. F = Bioavailability (fraction of drug absorbed). α = Distribution rate constant (IV). β = Elimination rate constant (IV). λ_1 = Absorption rate constant. λ_2 = Elimination rate constant. Cl_T = Total body clearance. Vd_{ss} = Apparent volume of distribution at steady state. Vd_{area} = Apparent volume of distribution as determined by use of the area method. NA = Not applicable.

constant to the absorption rate constant (λ_2:λ_1)[10] exceeded 3, and all MAT values were greater than the value for MRT_{IV}.[11]

Variables for the oral administrations were derived by use of a 1-compartment model with a weighting scheme of $1/Y^2$. **Maximum concentration (C_{max})** and **time to maximum concentration (T_{max})** were determined from the plot of each sheep's concentration-versus-time curves. Pharmacokinetic variables were reported as median and range except for $t_{1/2}$, which was reported as a harmonic mean. Comparisons among normally distributed primary variables such as α and β (compartmental), and λ_2 and AUC (noncompartmental) were conducted by use of ANOVA.[12] The Mann-Whitney analysis (Wilcoxon rank-sum test)[13] was applied to secondary variables whose distribution was unknown, such as $t_{1/2}$, Vd_{ss}, and Cl_T.[14] Significance was defined as $P < 0.05$ for all statistical analyses.

Results

Results for IV and PO administrations were tabulated (**Table 1**). Mean ± SD plasma concentration-versus-time curves of enrofloxacin (**Fig 1**) and ciprofloxacin (**Fig 2**) for IV, oral drench, tablets-grain, and solution-grain administrations were determined. Mean ± SD plasma enrofloxacin and ciprofloxacin peak and trough concentrations of the multiple-day experiment were determined (**Fig 3**).

The $t_{1/2}$ values of the oral administrations (14.80, 10.88, and 13.07 hours for the oral drench, tablets-grain, and solution-grain, respectively) all differed significantly from the IV $t_{1/2\beta}$ of 4.77 hours. There was not a significant difference between the $AUC_{0-\infty}$ values for tablets-grain and solution-grain mixtures, but both of these values differed significantly from that for the oral drench. Mean percentage of extrapolated $AUC_{0-\infty}$ was 2.7% for the IV administration and 9.12, 8.14, and 7.0% for the oral drench, tablets-grain, and solution-grain mixtures, respectively. Comparison of T_{max} and MAT among the experiments (oral drench, 5.50 and 14.95 hours; tablets-grain, 8.00 and 18.99 hours; and solution-grain, 8.00 and 15.87 hours) did not reveal significant differences. There also was not a significant difference between mean ± SD AUC_{0-24} on day 7 of the multiple-dose treatment (52.55 ± 12.15 [μg · h]/ml) and mean $AUC_{0-\infty}$ for the single-dose administration of solution-grain mixture (57.55 ± 17.78

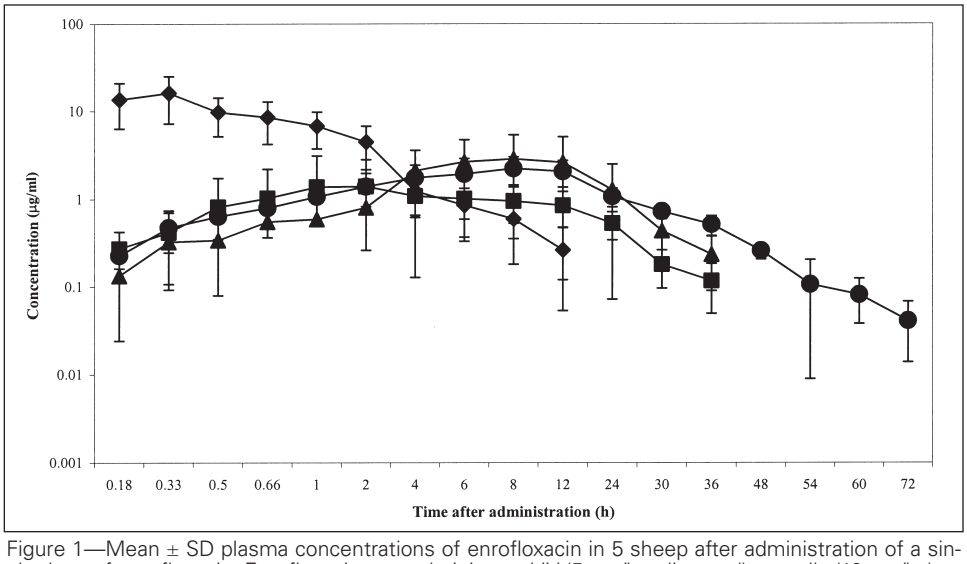

Figure 1—Mean ± SD plasma concentrations of enrofloxacin in 5 sheep after administration of a single dose of enrofloxacin. Enrofloxacin was administered IV (5 mg/kg; diamond) or orally (10 mg/kg) as an oral drench (square), crushed enrofloxacin tablets mixed with grain (triangle), and enrofloxacin solution mixed with grain (circle).

[μg · h]/ml). Therefore, Cl_T and F did not change on day 7 of the multiple-dose treatment.

The lowest median value of C_{max} during the single-dose experiments was 1.61 μg/ml for the oral drench, and the highest value was 2.69 μg/ml for the tablets-grain mixture. Median and range values for C_{max} during the multiple-dose experiment were 2.99 and 2.02 to 5.69 μg/ml, respectively, and median and range trough values were 1.90 and 1.00 to 2.02 μg/ml, respectively.

Mean percentage of enrofloxacin metabolized to ciprofloxacin was 3.10 ± 0.47% for the IV administration, 11.80 ± 0.06% for the oral drench, 8.47 ± 0.40% for the tablets-grain mixture, and 6.32 ± 0.90% for the solution-grain mixture. Mean C_{max} of ciprofloxacin did not exceed 0.20 μg/ml in any of the experiments; consequently, there was only a minor contribution from ciprofloxacin to the total antimicrobial activity of enrofloxacin. Median F of enrofloxacin was 47.89,

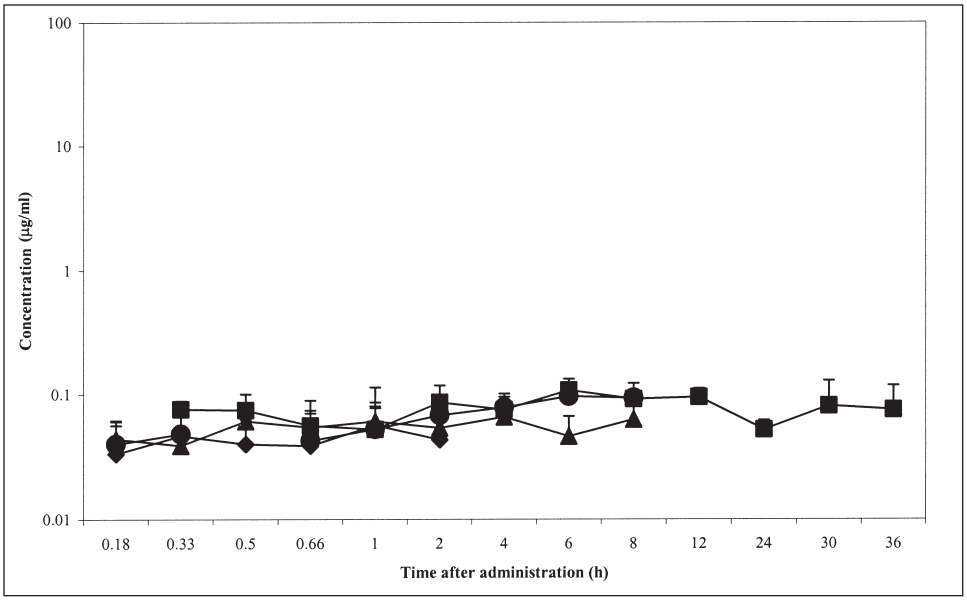

Figure 2—Mean ± SD plasma concentrations of ciprofloxacin in 5 sheep after administration of a single dose of enrofloxacin. *See* Figure 1 for key.

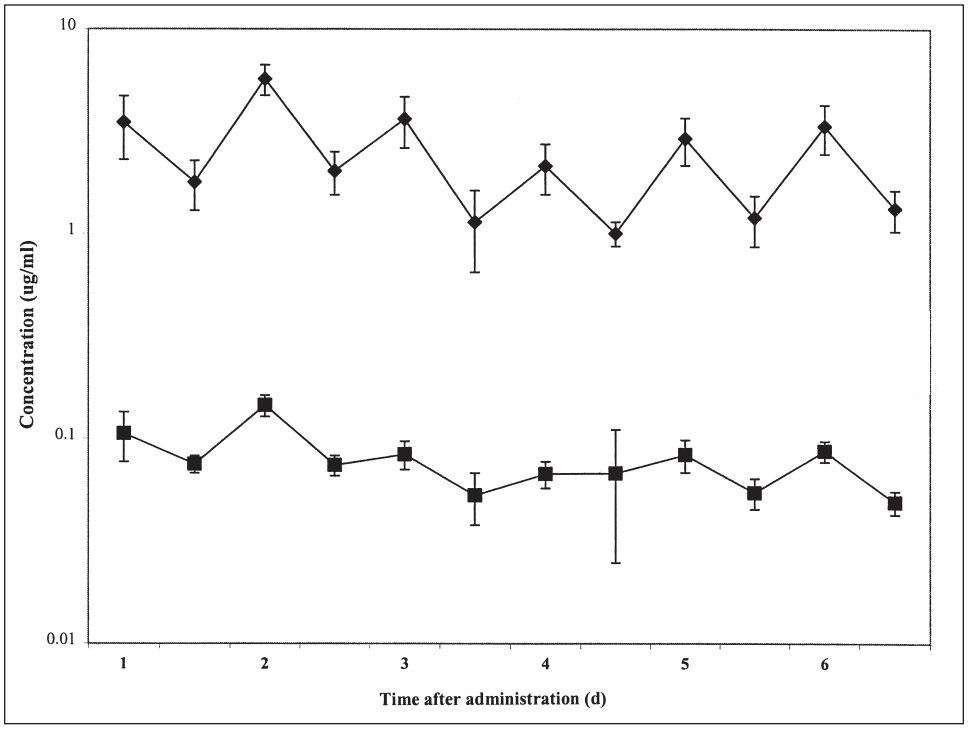

Figure 3—Mean ± SD concentrations of enrofloxacin (diamond) and ciprofloxacin (square) after sequential daily administration of enrofloxacin (10 mg/kg, PO, q 24 h for 7 days) as a solution-grain mixture. Blood samples were obtained daily immediately before and 8 hours after administration.

98.07, and 94.60%, respectively, for the oral drench, tablets-grain, and solution-grain administrations.

Discussion

Analysis of results of the study reported here indicates that enrofloxacin is detectable in the plasma 10 minutes after oral administration and has a prolonged $t_{1/2}$. The IV $t_{1/2\beta}$ (4.77 hours) was consistent with other values reported for sheep (3.88 hours[a] and 3.77 hours[15]); however, Mengozzi et al[15] described much faster Cl_T (550 ml/h/kg) than was reported here (202.04 ml/h/kg). Enrofloxacin administered by use of gavage at a rate of 2.5 mg/kg to Nedji sheep[a] resulted in a shorter $t_{1/2}$ (11.40 hours) and T_{max} (4.5 hours) than those found in our study after an oral drench. In addition, F for the oral drench (47.89%) was less than the value of 60.60% reported by Pozzin et al[a] but higher than the value of 35% found in 10-week-old ruminating calves.[8] We also detected substantial differences in C_{max} and AUC among the oral drench, tablets-grain, and solution-grain experiments.

On the basis of other studies[16,17,a] in which closure of the esophageal groove resulted in higher F for an oral drench, we anticipated that the oral drench would result in higher values of C_{max} and F than for the enrofloxacin-grain experiments. However, C_{max} for the oral drench was lower (1.61 µg/ml), and $AUC_{0-\infty}$ was less (30.58 [µg · h]/ml) than for the enrofloxacin-grain mixtures. We also anticipated a shorter T_{max} for the oral drench on the basis of a faster dissolution rate, but there was not a significant difference in T_{max} among the oral drench and enrofloxacin-grain mixtures. One possible explanation for the lower F could have been a decreased amount of drug administered, because some drug was lost during administration. Another possible factor could have been dilution of the drug in ruminal fluid, which may have had a greater impact on the oral drench than the enrofloxacin-grain mixtures.

The treatment sequence was not randomized in an attempt to reduce the variability attributable to diet (ie, hay) within each treatment. The grain used in the mixtures came from 1 source, and although the hay consumed during all the experiments was the same type, it came from more than 1 source. The composition and quantity of hay was not documented, because the effect of diet was not a study objective. Therefore, because of the lack of randomization, the effect of time, diet (type and quantity of hay), and formulation could not be evaluated separately. Additional studies are necessary to separate and address the influences of diet and formulation on the disposition of orally administered enrofloxacin.

The Vd_{ss} for the IV administration was 0.97 L/kg and is consistent with that reported for most species.[2-6,18] However, the percentage of ciprofloxacin metabolized after IV administration of enrofloxacin (3.10%) was much lower than the 35% reported by other investigators.[15] The percentage of ciprofloxacin metabolized after oral administration of enrofloxacin also was low (6.32 to 11.80%), and the median C_{max} of ciprofloxacin for each of the oral administrations was 0.07, 0.05, 0.09, and 0.08 µg/ml for the oral drench, tablets-grain, solution-grain, and multiple-dose treatments.

When administered orally to Katahdin sheep, enrofloxacin has prolonged absorption with an elimination rate constant that is > 3 times the absorption rate constant. This is suggestive of flip-flop pharmacokinetics in which the rate of absorption, rather than elimination, is the rate-limiting step, and the terminal slope of the time-versus-concentration curves is an estimate of absorption rather than elimination.[10] This phenomenon also has been reported after IM administration of enrofloxacin to adult horses[19] and pigs [4] and after SC and IM administration to cattle.[20] Although the reasons are not clearly understood, the flip-flop effect can lead to a biased estimation of λ_2, resulting in a false increase in systemic bioavailability when comparing parenteral routes to IV administration,[21] and this may have contributed to the high F for the grain mixtures.

Another potential factor resulting in a falsely increased F could have been a mixture of first-order (linear) and zero-order (nonlinear) absorption from the rumen. The oral forms of enrofloxacin used in this study were not sustained-release preparations, so we assumed that there would be first-order absorption when generating the pharmacokinetic models. However, because it can be difficult to determine conclusively whether a drug has strictly first-order absorption kinetics or a mixture of first- and zero-order kinetics,[21] we cannot rule out the possibility of mixed-order absorption. Additional studies will be necessary to more conclusively determine the impact of grain on enrofloxacin absorption. The percentage of extrapolated $AUC_{0-\infty}$ was similar between the IV and oral administrations and did not falsely increase F.

The F calculated from our results were not corrected on the basis of differences in $t_{1/2}$, because the estimates of $t_{1/2}$ were not randomly distributed across treatments, suggesting that prolonged absorption of the drug rather than a change in Cl_T was the cause of the longer $t_{1/2}$ values.[22] Withholding feed for 12 hours prior to drug administration for all 3 single-dose oral administrations probably had little impact on F, because MRT of particle markers in sheep is 39.9 to 51.8 hours.[23]

Disruption of the normal rumen flora is a potential problem after oral administration of enrofloxacin in ruminants, particularly with respect to its activity against Enterobacteriaceae and the fact that it is excreted in high concentrations in the feces.[24] In 1 study,[25] investigators examined the effect of enrofloxacin on ruminal flora in cattle fed enrofloxain (5 mg/kg, PO, q 24 h for 5 days). This resulted in an initial decrease in the density, viability, and activity of protozoa in the ruminal fluid, with a subsequent recovery to typical values within 5 to 7 days after discontinuation of the drug. It was concluded that the drug had minimal effects on rumen fermentation. Although the effect of multiple enrofloxacin doses on the gastrointestinal flora was not evaluated in the study reported here, we did not detect a change in fecal consistency for the ewes during the multiple-dose portion of the study.

Enrofloxacin and ciprofloxacin are fluoroquinolones. Two predictors of clinical efficacy for concentration-dependent antimicrobials are the ratio of C_{max} to the **minimum inhibitory concentration (MIC)** and the **ratio of the 24-hour AUC to the MIC**

(**AUIC**).[26,27] Although the optimum C_{max}:MIC or AUIC for successful treatment of infections in sheep has not been determined, studies[26,27] that involved the use of fluoroquinolones have revealed that the C_{max}:MIC should be between 8 and 10, and AUIC should be ≥ 125. Therefore, the median C_{max} of each single-dose oral treatment was adequate to achieve 8 to 10 times the MIC for any microorganism with a MIC ≤ 0.16 µg/ml, and the median C_{max} of the multiple-dose study (2.99 µg/ml) would be adequate for pathogens with a MIC ≤ 0.29 µg/ml. The smallest mean $AUC_{24\ hours}$ was for the oral drench (20.39 ± 11.40 [µg · h]/ml), which was adequate for an AUIC ≥ 125 for any microorganism with an MIC ≤ 0.16 µg/ml. The MIC that will result in death of 90% of the organisms (**MIC_{90}**) of enrofloxacin for several pathogens of sheep are 0.125 µg/ml for *Corynebacterium pseudotuberculosis*, 0.015 µg/ml for *Haemophilus somnus*, 0.03 µg/ml for *Mannheimia haemolytica*, 0.015 µg/ml for *Pasteurella multocida*,[28] and 0.062 mg/ml for *Escherichia coli*,[29] all of which are less than the critical value for both predictors.

Information on the disposition of orally administered enrofloxacin in ruminants[6,8,a] is limited, but analysis of results of the study reported here suggests that enrofloxacin is an antimicrobial worth consideration for use in the treatment of sheep not intended for human consumption. Oral administration of enrofloxacin to Katahdin sheep is characterized by high F and a prolonged $t_{1/2}$, and a dose of 10 mg/kg, PO, q 24 h was sufficient to achieve potential therapeutic concentrations for most pathogens of sheep.

[a]Pozzin O, Harron DWG, Nation G, et al. Pharmacokinetics of enrofloxacin following intravenous/intramuscular/oral administration in Nedji sheep (abstr). *J Vet Pharmacol Ther* 1997;20(suppl 1):60.
[b]Baytril, Bayer Corp, Shawnee Mission, Kan.
[c]Baytril 100, Bayer Corp, Shawnee Mission, Kan.
[d]Waters 600, Millipore Corp, Milford, Mass.
[e]Hewlett-Packard series 1050, Hewlett-Packard Co, Wilmington, Del.
[f]Hewlett-Packard UV detector, Hewlett-Packard Co, Wilmington, Del.
[g]Zorbax SB-C8, Hewlett-Packard Co, Wilmington, Del.
[h]Luna, Phenomenex, Torrance, Calif.
[i]Oasis, Waters Corp, Milford, Mass.
[j]HP Chem Station, Hewlett-Packard Co, Wilmington, Del.
[k]Baytril, Bayer Corp, Shawnee Mission, Kan.
[l]U. S. Pharmacopeia, Rockville, Md.
[m]WinNonlin Standard, version 2.1, Scientific Consulting Inc, Cary, NC.

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