Disposition of Enrofloxacin in Red-tailed Hawks (*Buteo jamaicensis*) and Great Horned Owls (*Bubo virginianus*) after a Single Oral, Intramuscular, or Intravenous Dose

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Original Research

Disposition of Enrofloxacin in Red-tailed Hawks (*Buteo jamaicensis*) and Great Horned Owls (*Bubo virginianus*) after a Single Oral, Intramuscular, or Intravenous Dose

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Abstract: Enrofloxacin is a fluoroquinolone antibiotic that is effective against many of the common gram-negative bacterial pathogens in raptors. This 3-period crossover study was designed to compare the pharmacokinetics of enrofloxacin after oral, intramuscular, or intravenous administration in red-tailed hawks (*Buteo jamaicensis*; n = 8) and great horned owls (*Bubo virginianus*; n = 5). In each study period, birds received a single dose of an injectable formulation of enrofloxacin (15 mg/kg) by 1 of these 3 routes. Oral administration was accomplished by force-feeding each bird a small freshly killed mouse that had received an intraperitoneal injection of enrofloxacin (in-prey). Intramuscular injections were divided into 2 sites in the pectoral musculature. Serial plasma samples were taken before administration and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours after administration. Oral administration resulted in plasma concentrations of enrofloxacin that peaked at 4–8 hours in both species. Plasma concentrations remained at >1 μg/ml until at least 18 hours after administration, although an initial lag time of approximately 2–8 hours occurred for absorption from the gastrointestinal tract. Intramuscular administration resulted in plasma concentrations that peaked at 0.5–2 hours; enrofloxacin levels remained at >1 μg/ml for at least 15 hours. After intravenous administration to red-tailed hawks, enrofloxacin levels remained at >1 μg/ml for at least 15 hours. Two great horned owls showed acute weakness, bradycardia, and peripheral vasoconstriction during intravenous injection. These clinical signs resolved within 1–3 hours with supportive therapy; however, the intravenous route was not evaluated for the other 3 owls. We conclude that oral (in-prey) and intramuscular routes are reliable means of administration of injectable enrofloxacin in red-tailed hawks and great horned owls, using a dosage of 15 mg/kg q24h. Intravenous administration of enrofloxacin can be performed with caution in red-tailed hawks but should not be attempted in great horned owls.

Key words: enrofloxacin, single-dose pharmacokinetics, adverse reactions, red-tailed hawk, *Buteo jamaicensis*, great horned owl, *Bubo virginianus*

Introduction

Few pharmacologic studies have been performed during the past 15 years that provide information regarding antibiotic absorption and clearance in raptors.[1–4] Gram-negative bacteria are common pathogens in raptors[5–8]; therefore, preferred antibiotics have historically included cephalosporins, aminoglycosides, and fluoroquinolones. However, cephalosporins require frequent administration to avian patients,[9,10] and aminoglycosides may cause nephrotoxicity or neuromuscular blockade.[11–13] Moreover, most of the raptors presented for initial evaluation at veterinary hospitals are dehydrated, which increases the risk of iatrogenic renal damage.

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Table 1. Minimum inhibitory concentrations of enrofloxacin for various pathogens.[a]

Pathogen	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Source species	Reference
Acinetobacter species		≤0.25	Barn owl (*Tyto alba*), red-shouldered hawk (*Buteo lineatus*)	Unpublished[b]
Escherichia coli	0.03	0.5	Turkey	23
		<0.128	Not specified	15
	0.015	0.12	Calf	26
Klebsiella pneumoniae		<0.128	Not specified	15
Pasteurella multocida	0.007	0.015	Pig	24
	0.016	0.032	Not specified	15
	≤0.004	0.06	Calf	26
Proteus mirabilis		<1.0	Not specified	15
Pseudomonas aeruginosa	1.02	2.04	Not specified	15
Salmonella arizonae		<1.0	Not specified	15
Salmonella typhimurium	0.03	0.03	Calf	26
Salmonella species	0.015	0.5	Turkey	23
Staphylococcus aureus		≤0.25	Burrowing owl (*Athene cunicularia*), golden eagle (*Aquila chrysaetos*), rough-legged hawk (*Buteo lagopus*)	Unpublished[b]

[a] MIC_{50} indicates minimum inhibitory concentration for 50% of organisms; MIC_{90}, minimum inhibitory concentration for 90% of organisms.

[b] Unpublished data from the Clinical Microbiology Laboratory, Veterinary Medical Teaching Hospital, University of California at Davis.

Enrofloxacin (Baytril, Bayer Corp, Shawnee Mission, KS, USA) is a fluoroquinolone antibiotic that is known for its minimal adverse effects.[14] Enrofloxacin is partially metabolized (in some species) to ciprofloxacin and excreted via the kidney and liver, but neither nephrotoxicity nor hepatotoxicity have been seen with approved dosages in the animal species studied. Nevertheless, patients with renal or hepatic dysfunction should be monitored while receiving enrofloxacin, and dosage adjustment is recommended to prevent drug accumulation. Anecdotal evidence exists that enrofloxacin may be seizurogenic in epileptic dogs.[15] Moreover, injection site irritation has occurred in avian patients receiving enrofloxacin by the intramuscular route.[16] High dosages of quinolones have produced arthropathies in young large mammals[17–19] and nestling pigeons,[20] as well as delayed feather development in nestling pigeons,[20] but these effects have not been reported in other bird species despite widespread use of enrofloxacin in young psittacine birds.

Other important characteristics of enrofloxacin are its broad antimicrobial spectrum, especially against gram-negative organisms, widespread tissue distribution, and lack of substantial development of bacterial resistance.[21,22] Many of the bacteria considered potentially pathogenic in raptor species (namely, *Acinetobacter* species, *Aeromonas* species, *Escherichia coli*, *Klebsiella* species, *Pasteurella multocida*, *Proteus mirabilis*, *Salmonella* species, and *Staphylococcus* species) are sensitive to enrofloxacin in vitro (Table 1),[14,15,23–25] and extralabel use of enrofloxacin has been a popular tool of avian veterinarians for the past several years. The enrofloxacin dosage for hawks and owls has been derived from anecdotal reports or extrapolation from pharmacokinetic studies performed in other avian species (Table 2).[27–29]

This study was designed to compare the pharmacokinetics of single-dose enrofloxacin administration among intravenous, oral, and intramuscular routes, with the goal of determining dosage regimens for raptors. At raptor rehabilitation centers, the route of administration is often determined by available manpower and the desire to limit frequency of restraint; therefore, the feasibility and efficacy of the oral (in-prey) route was of special interest. Disposition of enrofloxacin in similarly sized falconiform species (red-tailed hawk, *Buteo jamaicensis*) and strigiform species (great horned owl, *Bubo virginianus*) was evaluated to determine whether the presence (in hawks) or absence (in owls) of a crop, as well as other differences between their digestive

Table 2. Dosage recommendations for enrofloxacin in various avian species, made on the basis of pharmacokinetic studies.

Species	Dosage	Reference
Houbara bustard (*Chlamydotis undulata macqueenii*)	10 mg/kg PO (oral suspension) q12h	29
African grey parrot (*Psittacus erithacus*)	190–750 mg/L[a] in drinking water	30
	15 mg/kg PO or IM q12h	27
Senegal parrot (*Poicephalus senegalus*)	15 mg/kg PO or IM q8–12h	31
Emu (*Dromaius novaehollandiae*)	2.2 mg/kg IV q12h	32
Domestic duckling	50 mg/L in drinking water first day, 25 mg/L in drinking water subsequent days	33
Chicken	50 mg/L in drinking water	34
	10 mg/kg PO q24h	35
Turkey	50 mg/L in drinking water	34
Pigeon (*Columba livia domestica*)	100 mg/L in drinking water	20

[a] mg/L is equivalent to parts per million (ppm).

tract anatomy, would affect the pharmacokinetics of oral administration.

Materials and Methods

Eight adult red-tailed hawks and 5 adult great horned owls from the California Raptor Center were included in this study. At the start of the study, hawks weighed 0.96–1.54 kg and owls weighed 0.96–1.33 kg. All birds were in good health, other than the chronic musculoskeletal or ocular abnormalities preventing their release, on the basis of physical examination, complete blood count, and serum biochemistry analysis. Birds were housed in outdoor enclosures, fed day-old chicks or adult mice, and offered water ad libitum before enrofloxacin administration. During each study period, birds were offered mice at 12 hours before enrofloxacin administration and at 13, 25, and 49 hours after enrofloxacin administration. Husbandry and experimental protocols for this study were approved by the Animal Use and Care Administrative Advisory Committee of the University of California, Davis.

The study was performed from June to July 1997 (hawks) and from December 1997 to January 1998 (owls). This study was a 3-period crossover study, with 3- to 4-week washout periods between treatments, such that each bird received enrofloxacin by all 3 routes (oral, intramuscular, and intravenous). The schedule was subsequently modified for great horned owls because of adverse reactions seen in this species after intravenous enrofloxacin administration.

In each study period, birds received a single dose of enrofloxacin (15 mg/kg; Baytril 2.27% injection, Bayer), administered by insulin syringe with 26-gauge needle, by one of the following routes: in the peritoneal cavity of a small freshly killed mouse that was then force-fed to the bird (oral); divided into 2 sites in the pectoral musculature (intramuscular); or in the jugular vein, medial metatarsal vein, or basilic vein (intravenous).

Blood samples (0.5 ml each) were collected from each bird before enrofloxacin administration and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours after administration. Venipuncture sites included the medial metatarsal vein, the basilic vein, and the right jugular vein. Blood was collected using 1-ml insulin syringes with 26-gauge needles and was placed into vials containing lithium heparin. Blood samples were centrifuged within 45 minutes of collection at 4000 rpm for 6 minutes. Supernatant plasma was collected and stored at −80°C until assays could be performed (maximum of 2 months).

Plasma samples were analyzed for enrofloxacin using high-performance liquid chromatography as described by DeManuelle and coworkers.[36] The detection limit for enrofloxacin was 0.1 μg/ml.

Pharmacokinetic and Statistical Analysis

Plasma enrofloxacin concentration was analyzed using nonlinear regression (WINNONLIN, Scientific Consulting Inc/Pharsight, Palo Alto, CA, USA). Data for the intravenous route (hawks only) were analyzed using a 2-compartment model with bolus administration and first-order elimination (model 8 of WINNONLIN). Data for the intramuscular route in both hawks and owls were analyzed using a 2-compartment model with first-order input and elimination (model 13). Data for the oral route were analyzed using a 1-compartment model with a lag

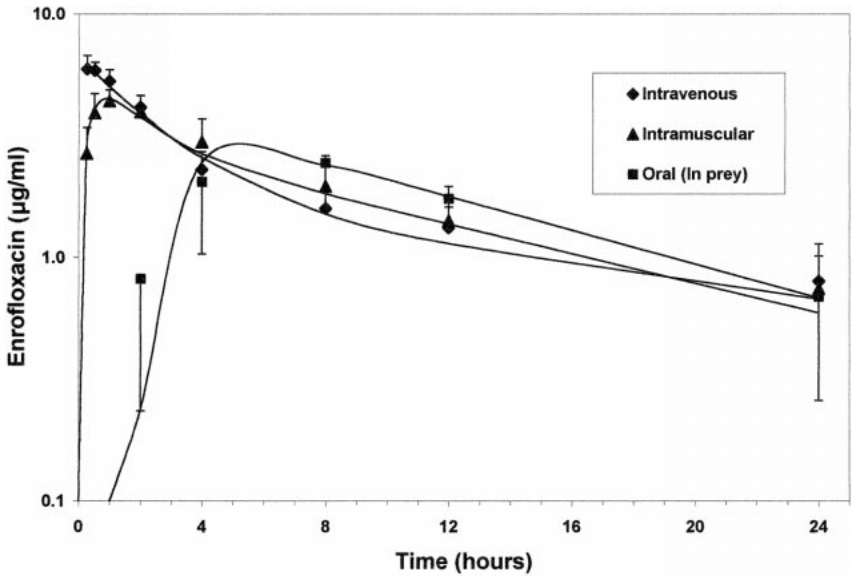

Figure 1. Mean plasma concentrations of enrofloxacin (indicated by symbols) in 8 healthy red-tailed hawks after intravenous, intramuscular, or oral (in-prey) administration of a single dose of 15 mg/kg. Curves were calculated using standard pharmacokinetic models as described in the text and in Table 3.

time, first-order absorption, and first-order elimination (model 4). A single-compartment model was used in this analysis because the lag time for the absorption of enrofloxacin was greater than the time that the distributive compartments were apparent.

Results

Plasma concentrations of enrofloxacin over time after single-dose administration of 15 mg/kg are shown in Figure 1 (red-tailed hawks) and Figure 2 (great horned owls). The mean maximum plasma enrofloxacin concentration (C_{max}) after intramuscular administration was 4.52 µg/ml for hawks and 3.81 µg/ml for owls, occurring 0.5–2 hours after injection (Table 3). The C_{max} after oral administration in hawks was 2.8 µg/ml, occurring 4–8 hours after force-feeding; C_{max} in owls was 2.63 µg/ml, occurring up to 12 hours after force-feeding. Both raptor species showed similar rates of elimination of enrofloxacin from the systemic circulation, regardless of route of administration (Table 3). Comparisons of plasma concentrations between species are shown in Figure 3 (intramuscular route) and Figure 4 (oral route).

The values for pharmacokinetic variables describing distribution and elimination of enrofloxacin in hawks and owls are reported in Table 3. The slopes of all elimination-phase curves were similar within each species regardless of route of administration. A significant 3-way interaction was found among species, route of administration, and time using a repeated measures analysis of variance ($P = .0022$). However, overall, no species effect was found ($P = .54$).

When enrofloxacin was administered in the basilic vein of a great horned owl, the bird showed acute weakness and stupor after receiving a dose of approximately 7.5 mg/kg, apparently as a direct effect of intravenous enrofloxacin administration. Peripheral vasoconstriction and bradycardia also occurred, followed by variable tachycardia. The owl's clinical signs resolved 3 hours later, after treatment with intravenous and subcutaneous lactated Ringer's solution, atropine, and oxygen. To investigate whether this was an idiosyncratic drug reaction, the 22.7 mg/ml formulation was diluted to 7.6 mg/ml using sterile saline and administered to a second owl. This bird exhibited signs similar to those of the first, also after receiving enrofloxacin at 7.5 mg/kg IV, and recovered within 1 hour with supportive therapy.

Discussion

We found that oral (in-prey) and intramuscular routes are reliable means of administration of injectable enrofloxacin in red-tailed hawks and great horned owls, using a dosage of 15 mg/kg q24h. The intravenous route can also be used in red-tailed hawks at this dosage. Plasma enrofloxacin concentrations remained >1 µg/ml for at least 15 hours after intravenous administration in hawks and for at least 15 hours after intramuscular administration in both hawks and owls. Although an initial lag time of approximately 2–8 hours occurred for absorption

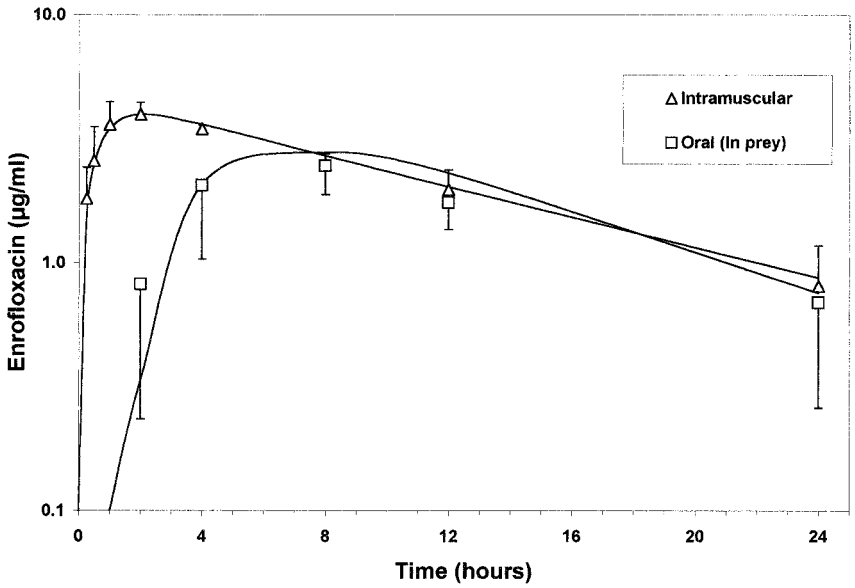

Figure 2. Mean plasma concentrations of enrofloxacin (indicated by symbols) in 5 healthy great horned owls after intramuscular or oral (in-prey) administration of a single dose of 15 mg/kg. Curves were calculated using standard pharmacokinetic models as described in the text and in Table 3.

from the gastrointestinal tract, in-prey administration resulted in plasma enrofloxacin concentrations remaining >1 µg/ml until at least 18 hours after administration in both species. As shown in Table 1, the 90% inhibitory concentration for enrofloxacin of many pathogens in raptors is <1 µg/ml.

Enrofloxacin was distributed rapidly to the systemic circulation after intramuscular injection. This may be partly because the 15 mg/kg dose was administered as 2 injections of 7.5 mg/kg IM each. Although the absorption rate of an undivided 15 mg/kg IM injection was not evaluated in this study, we assume that enrofloxacin as an undivided dose would also absorb readily into the vasculature of raptors, similar to absorption rates seen in other avian pharmacokinetic studies.

Bioavailability of enrofloxacin in hawks after intramuscular injection (87%) was similar to that reported for houbara bustards (90% at 10 mg/kg IM dose).[29] Bioavailability in owls after intramuscular

Table 3. Pharmacokinetic parameters (mean ± SD) after administration of a single dose of enrofloxacin (15 mg/kg) by the intravenous (IV), intramuscular (IM), or in-prey (per os [PO]) route.[a]

	Red-tailed hawks (n = 8)			Great horned owls (n = 5)	
Parameter	IV	IM	PO	IM	PO
A (µg/ml)	4.9 ± 0.6	4.1 ± 1.5	—	2.2 ± 0.9	—
B (µg/ml)	1.8 ± 0.3	3.2 ± 1.1	—	2.5 ± 1.5	—
α (h^{-1})	0.38 ± 0.05	0.68 ± 0.54	—	0.09 ± 0.02	—
β (h^{-1})	0.04 ± 0.01	0.07 ± 0.02	0.08 ± 0.02	0.06 ± 0.02	0.11 ± 0.0
AUC (µg·h/ml)	62.2 ± 9.9	54.0 ± 20.5	47.2 ± 15.2	65.3 ± 11.0	44.0 ± 10.7
$t_{½\alpha}$ (h)	1.9 ± 0.2	1.5 ± 0.7	—	8.2 ± 2.1	—
$t_{½\beta}$ (h)	19.4 ± 2.4	11.0 ± 2.8	8.9 ± 2.0	11.4 ± 3.6	7.2 ± 3.1
Vd (L/kg)	2.3 ± 0.2	2.4 ± 0.6	4.2 ± 1.0	3.4 ± 0.2	4.2 ± 0.6
T_{lag} (h)	—	—	1.9 ± 0.76	—	1.8 ± 0.7
C_{max} (µg/ml)	6.7 ± 0.7	4.5 ± 0.6	2.8 ± 0.5	3.8 ± 0.3	2.6 ± 0.5
T_{max} (h)	—	1.1 ± 0.4	5.4 ± 1.5	2.1 ± 0.4	7.1 ± 3.0

[a] A indicates the *y* intercept of a calculated curve describing plasma enrofloxacin concentration during the first pharmacokinetic compartment (absorption); B, the *y* intercept of a calculated curve describing plasma enrofloxacin concentration during the second pharmacokinetic compartment (elimination); α, the hybrid rate constant for the distribution phase; β, the hybrid rate constant for the elimination phase; AUC, the area under the plasma concentration-time curve; $t_{½\alpha}$ and $t_{½\beta}$, the half-life for distribution and elimination phases, respectively; Vd, the volume of distribution; T_{lag}, the lag time after oral administration; C_{max}, the peak plasma concentration; T_{max}, the time to C_{max}; and —, not calculated.

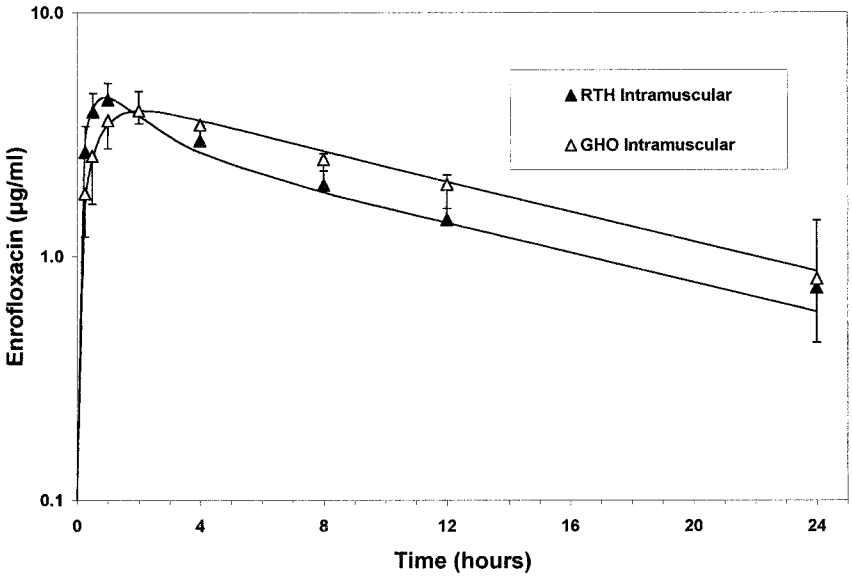

Figure 3. Mean plasma concentrations of enrofloxacin (indicated by symbols) in 8 red-tailed hawks (RTH) and 5 great horned owls (GHO) after intramuscular administration of a single dose of 15 mg/kg. Curves were calculated using standard pharmacokinetic models as described in the text and in Table 3.

injection could not be calculated because of lack of intravenous data, but the area under the concentration-time curve for intramuscular administration to owls was similar to that of hawks (54.0 versus 65.3 µg·h/ml).

Enrofloxacin was absorbed more slowly into the systemic circulation after oral administration than after intramuscular administration, presumably because of the time required for digestion of the prey item. Bioavailability in hawks after oral administration was 76%, similar to bioavailability after inramuscular administration in this species, indicating good absorption of the drug from the gastrointestinal tract. Bioavailability in owls after oral administration could not be calculated, again because of lack of intravenous data, but the area under the concentration-time curve for oral administration to owls was similar to that of hawks.

The disposition of enrofloxacin does not seem to be substantially influenced by the differences in

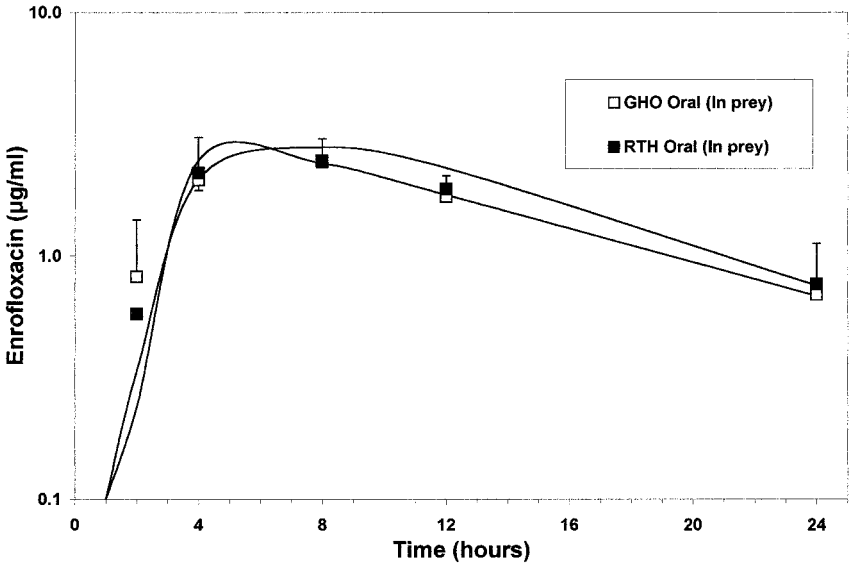

Figure 4. Mean plasma concentrations of enrofloxacin (indicated by symbols) in 8 red-tailed hawks (RTH) and 5 great horned owls (GHO) after oral (in-prey) administration of a single dose of 15 mg/kg. Curves were calculated using standard pharmacokinetic models as described in the text and in Table 3.

anatomy of the gastrointestinal tract between hawks and owls.[37] In-prey administration resulted in similar absorption of enrofloxacin into systemic circulation in red-tailed hawks (a species with a crop) compared with great horned owls (a species without a crop). Elimination of enrofloxacin after oral administration was also similar in hawks and owls. Plasma levels of enrofloxacin after oral administration remained high for long periods of time in both species; therefore, the recommended dosage for oral enrofloxacin administration should be the same for both.

A significant 3-way interaction was found among species (2 levels), route of administration (2 levels), and time after administration (9 levels) in the measurement of plasma enrofloxacin concentration. In other words, differences occurred between plasma enrofloxacin concentrations in hawks and owls that varied in degree depending on the time of sampling and route of administration. The extent of difference between the disposition of enrofloxacin in red-tailed hawks and great horned owls depends on the route of administration and the time in question. However, overall, a species effect did not exist, which supports the recommendation of the same dosage for both species.

The mean half-lives of elimination of enrofloxacin after oral administration to raptors in this study (8.9 hours in hawks; 7.2 hours in owls) were shorter than that reported in chickens (14.2 hours; 10 mg/kg dosage)[35] and longer than that in African grey parrots (2.5–2.7 hours; 3–30 mg/kg).[27] The half-lives after intramuscular administration of enrofloxacin (11.0 hours in hawks; 11.4 hours in owls) were longer than those reported for African grey parrots (2.3 hours; 15 mg/kg)[27] and houbara bustards (5.1 hours; 10 mg/kg).[29] Also, after intravenous enrofloxacin administration, the mean half-life in red-tailed hawks (19.4 hours) was longer than that reported for houbara bustards (6.6 hours; 10 mg/kg)[29] and chickens (10.3 hours; 10 mg/kg).[35]

Fluoroquinolones have a postantibiotic inhibitory effect against most susceptible organisms.[38] Specifically, regrowth of a variety of bacteria in vitro was delayed for up to 3.6 hours after enrofloxacin was removed from the environment.[39] This postantibiotic effect likely contributes to the therapeutic benefit of quinolone use, further increasing the acceptable time interval between drug administrations. Moreover, enrofloxacin concentrations in target tissue may remain at effective levels for a longer time than serum concentrations.[40] Extensive intracellular accumulation in phagocytes and leukocytes occurs after enrofloxacin administration, with concentrations in macrophages reported to be 2–8 times higher than plasma levels.[40] Considering that the plasma enrofloxacin concentration curves determined in our study remained >1 μg/ml for 15–18 hours after administration, it is reasonable to assume that a once daily dosage regimen would be appropriate to treat bacterial infections involving pathogens susceptible at 0.5 μg/ml or below.

Intravenous administration of enrofloxacin to 2 great horned owls at the dosage of 7.5 mg/kg resulted in an immediate and dramatic cardiovascular response that included bradycardia, peripheral vasoconstriction, and stupor. These owls had previously received intramuscular and oral enrofloxacin with no apparent adverse reaction. Although the timing and nature of their response to enrofloxacin was suggestive of anaphylaxis, the clinical picture of an adverse drug reaction or anaphylaxis in mammals usually includes hypotension and vasodilation.[41] The inflammatory cascade in birds possibly includes vasoconstriction instead of vasodilation secondary to the actions of immunoglobulin γ and other specific antibodies and mediators of birds, and the response of the great horned owls to intravenous enrofloxacin possibly was truly one of anaphylaxis. Alternatively, their response could have been a nonimmunologic one, occurring as a result of the pharmacodynamic effects of enrofloxacin or its carrier. Hypotension and other cardiovascular effects have been seen in individuals of other species after administration of chloramphenicol, aminoglycosides, tetracyclines, polymyxins, propylene glycol, and several other drugs.[41] However, adverse cardiovascular reactions to quinolones have not been previously reported in species other than humans (Joy D. Olsen, Bayer Corp, oral communication, September 2000).

Further studies of enrofloxacin use in raptors should include toxicologic evaluation of dosages of 15 mg/kg or greater, as well as cumulative effects of multiple dose administration. The tissue effects of intramuscular injection of enrofloxacin should also be investigated. Sites of intravenous injection should be compared to investigate possible significance of the renal portal system. Additionally, antibacterial efficacy of enrofloxacin in tissues such as kidney, liver, skin, lung, and air sac remains to be evaluated.

This study is the first to document the in-prey route as an effective means of medicating raptors. This route is preferable for emaciated patients with minimal pectoral musculature and when using drugs that induce unacceptable amounts of muscle tissue damage. The in-prey route could also be useful for treatment without manual restraint for raptors who do not tear at their prey before ingesting it. Consid-

ering the long half-lives found in this study and the postantibiotic effect of quinolones, enrofloxacin treatment can be planned for once daily administration of 15 mg/kg, which certainly eases the amount of stress experienced by the patient and by caretakers. An initial dose of enrofloxacin for a newly admitted raptor patient should be parenteral to achieve high concentrations quickly; subsequent treatments can be via the oral route.

Intravenous administration of enrofloxacin seems to be quite dangerous in great horned owls, but the intramuscular route provides high plasma enrofloxacin concentrations within a short period of time and is therefore an acceptable alternative when rapid bactericidal effect is needed.

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