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PHARMACOKINETICS OF A SINGLE DOSE OF ORAL AND SUBCUTANEOUS ENROFLOXACIN IN CARIBBEAN FLAMINGOS (*PHOENICOPTERUS RUBER RUBER*)

Melissa R. Nau, D.V.M., James W. Carpenter, M.S., D.V.M., Dipl. A.C.Z.M., Butch KuKanich, D.V.M., Ph.D., Dipl. A.C.V.C.P., and Matt Warner, M.S.

Abstract: Enrofloxacin is a fluoroquinolone antimicrobial that is widely used in veterinary medicine because of its bactericidal activity and safety in a broad range of species. Caribbean flamingos, a member of the order Phoenicopteriformes, are popular in zoological collections and suffer from a variety of conditions that can result from or lead to bacterial infection. In this study, two groups of 7 adult captive Caribbean flamingos received a single dose of 15 mg/kg enrofloxacin, administered either orally or subcutaneously. Plasma concentrations of enrofloxacin and its metabolite, ciprofloxacin, were measured using liquid chromatography and mass spectrometry. Pharmacokinetic analysis was performed using noncompartmental methods. The pharmacokinetic parameters for both routes of administration were similar, with a mean peak plasma concentration (C_{max}) of 5.25 and 5.77 μg/ml, a mean time to peak plasma concentration (T_{max}) of 1.49 and 1.1 hr, a mean area under the curve (AUC) of 49.9 and 47.3 hr·μg/ml, and a mean terminal half-life ($t_{1/2}$) of 5.83 and 6.46 hr for oral and subcutaneous dosing, respectively. Conversion to ciprofloxacin was minimal, with the AUC of ciprofloxacin representing <3% of the enrofloxacin AUC for both routes of administration. Based on the results of the present study, a dose of 15 mg/kg enrofloxacin delivered either orally or subcutaneously in the Caribbean flamingo every 24 hr is recommended for susceptible bacterial pathogens with a minimal inhibitory concentration ≤ 0.25 μg/ml.

Key words: Antimicrobial, Caribbean flamingo, enrofloxacin, pharmacokinetics, *Phoenicopterus ruber ruber.*

INTRODUCTION

Enrofloxacin is a widely used antimicrobial within the veterinary medical profession for avian, mammalian, and reptilian patients. Avian species are commonly owned pets and comprise a large proportion of zoological park animal collections. Despite the ubiquity of avian patients in exotic and zoological veterinary medicine, there is a relative lack of information in the veterinary literature regarding the pharmacokinetics of antimicrobials, including enrofloxacin, in avian species. Available pharmacokinetic studies have provided information specific to several avian species; however, dosing remains anecdotal in the remaining unstudied species.[1–11,13–16,19–23,25,27,33,34] The variable pharmacokinetic data obtained from the previous enrofloxacin studies suggest that extrapolation of recommended dosing protocols from closely related avian species or based on allometric relationships can lead to inaccurate dosing, adverse effects, or insufficient efficacy in the uninvestigated species.

Enrofloxacin is a bactericidal and concentration-dependent fluoroquinolone antimicrobial that has activity against many gram positive and gram negative aerobic bacteria.[28] The bactericidal activity occurs through disruption of bacterial DNA gyrase enzymes, which leads to cell death. Enrofloxacin is primarily excreted through the kidneys, with hepatic excretion occurring to a lesser extent.[28] Metabolism of enrofloxacin varies between species, but the drug may undergo biotransformation to ciprofloxacin, which possesses antimicrobial activity similar to its parent compound.[26] Measurable concentrations of ciprofloxacin after administration of enrofloxacin doses have been demonstrated in multiple psittacine species, chicken, turkey, Muscovy duck (*Cairina moschata*), Japanese quail (*Coturnix japonica*), common pheasant (*Phasianus colchicus*), ostrich (*Struthio camelus*), rhea (*Rhea americana albescens*), sandhill crane (*Grus canadensis*), southern crested caracara (*Caracara plancus*), and African penguin (*Spheniscus demersus*).[1,3,5–11,13–16,19,23,25,33,34]

Phoenicopteriformes, an order made up of six flamingo (*Phoenicopterus*) species, are particularly popular in captive zoological settings, with 14,324 captive flamingos registered with the International Species Information System (ISIS)

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worldwide as of 2008.[24] Pododermatitis and traumatic leg injuries, which appear to be a result of husbandry and climate factors, are prevalent sources of morbidity in captive flamingos.[29,30] Secondary infections and infectious diseases typical of most avian species are common, and infection was reported to be the second most common cause of mortality in one retrospective study.[18] As a result of the lack of pharmacokinetic data published for flamingos, antimicrobial selection and dosing has been empirical and extrapolated from doses used in other avian species.

The objective of this study was to determine the pharmacokinetic properties of a single dose of enrofloxacin, administered either orally or subcutaneously, in a group of captive Caribbean flamingos (*Phoenicopterus ruber ruber*). Ciprofloxacin after enrofloxacin administration was also measured and evaluated. Using this information, an appropriate dosing regimen for this species can be recommended to guide safe and effective antimicrobial therapy.

MATERIALS AND METHODS

Animals

The study was reviewed and approved by the Institutional Animal Care and Use Committee at Kansas State University. Fourteen adult Caribbean flamingos (8 males and 6 females) were used in the present study. The flamingos ranged in age and weight from 4 to 12 yr and from 2.2 to 3.6 kg. The birds are captive-housed in the Sunset Zoo, Manhattan, Kansas, and have access to both an outdoor exhibit and indoor holding facility. The group is fed a commercial pelleted diet formulated for flamingos (Mazuri, Land O' Lakes Inc., PMI Nutrition International, Saint Paul, Minnesota 55164, USA) and supplemented with mealworms. All individuals underwent complete physical examinations, complete blood count and plasma biochemistry analyses, and fecal examinations. Based on these results, all animals were deemed healthy prior to the study period. The flamingos were kept in the indoor holding facility with free access to food and water for the duration of the study and were released back into the exhibit after final sample collection.

Drug administration and sample collection

The flamingos were manually restrained for all handling during the study period. Body weights were measured immediately before drug administration to ensure accurate dosing for each individual. The flamingos were stratified by weight and randomly assigned a study group, each consisting of seven birds. The two study groups received a single dose of enrofloxacin, delivered either orally or subcutaneously. All flamingos received a dose of 15 mg/kg enrofloxacin (2.27% injectable solution, Bayer HealthCare LLC, Shawnee Mission, Kansas 66201, USA), regardless of route of administration. This injectable form of enrofloxacin was used for oral administration based on its use and stability in compounded oral medications in exotic species.[12,32]

For oral dosing, the total volume of enrofloxacin was administered using a 10 French orogastric tube inserted into the esophagus. The tube was flushed with 3 ml of 0.9% saline to ensure that the complete dose of enrofloxacin was delivered. For subcutaneous administration, the volume of enrofloxacin to be administered was diluted 1 : 4 with 0.9% saline solution. The total volume of fluid was administered subcutaneously in the inguinal region using a 25-ga needle attached to a 12-ml syringe.

A blood sample volume of 0.75 ml was collected before dosing and at each of the following time points: 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hr postadministration. Venipuncture of the medial metatarsal vein was performed to obtain each sample using a 1-ml syringe with a 25-ga needle, preflushed with heparin to prevent clot formation. Samples were immediately placed in lithium heparin microtubes (BD Microtainer, Becton, Dickinson, and Company, Franklin Lakes, New Jersey 07417, USA). The blood tubes were centrifuged at 3500 × g for 10 min, and the plasma was transferred to a cryovial for storage at −70°C until analysis could be performed.

Sample analysis

Plasma samples were analyzed for enrofloxacin and ciprofloxacin using ultra performance liquid chromatography (Waters Acquity, Waters Corp., Milford, Massachusetts 01757, USA) with triple quadrupole mass spectrometry (Waters TQD, Waters Corp.). The mobile phase used a linear gradient (Table 1). Separation was achieved with a C18 column (CSH C18+ 50 × 2.1 mm, 1.7 μm pore size, Waters Corp.) maintained at 55°C. The mass spectrometer monitored the mass/charge (*m/z*) qualifying ions of 360.294 for enrofloxacin, 332.254 for ciprofloxacin, and 386.264 for the internal standard sarafloxacin. The product ions were 245.089 for enrofloxacin, 245.054 for cipro-

Table 1. Mobile phase gradient for the analysis of enrofloxacin and ciprofloxacin in flamingo plasma.

Time	Flow	A: 0.1% formic acid in deionized water	B: 0.1% formic acid in 33% methanol	C: Acetonitrile
Initial	0.800	96.0	4.0	0.0
0.15	0.800	3.0	2.0	95.0
0.65	0.800	3.0	2.0	95.0
0.66	0.800	96.0	4.0	0.0
2.00	0.800	96.0	4.0	0.0

floxacin, and 299.129 for sarafloxacin and were used for quantification. The standard curve was calculated with peak area ratios of the analyte to the internal standard.

Plasma standards and quality control samples were made in untreated flamingo plasma. Plasma samples, standards, and quality control samples were extracted using pass-through plates (Ostro, Waters Corp.). Plasma (50 µl) was added to 100 µl of acetonitrile with 500 ng/ml sarafloxacin in the plates and vortexed. Positive pressure was applied to the plates, and the eluent was collected. Deionized water (150 µl) was added to the eluent and vortexed again. The injection volume was 10 µl. The standard curve for enrofloxacin was linear from 0.01 to 10 µg/ml. The mean accuracy and precision (coefficient of variation) of the assay for enrofloxacin on three replicates at 0.01, 0.5, and 10 µg/ml were 98 and 8%, respectively. The standard curve for ciprofloxacin was linear from 0.01 to 5 µg/ml. The mean accuracy and precision of the assay for ciprofloxacin on three replicates at 0.01 and 0.5 µg/ml were 106 and 10%, respectively.

Pharmacokinetic modeling and statistical analysis

Noncompartmental pharmacokinetic analyses were performed with computer software (Phoenix 64, Certara, Princeton, New Jersey 08540, USA). The area under the curve (AUC), percent of the AUC extrapolated to infinity (AUC extrap), plasma clearance per fraction of the dose absorbed, volume of distribution (area method) per fraction of the dose absorbed, and mean residence time were calculated for each animal and are presented as geometric mean, minimum value, and maximum value for each parameter. The maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and concentration at 24 hr (C24) were determined directly from the data. The relative bioavailability of the subcutaneous dose to the oral dose was calculated by dividing the mean subcutaneous AUC by the mean oral AUC and is expressed as a percentage.

RESULTS

No adverse behavioral or physical effects were noted for any of the flamingos throughout the study period as a result of enrofloxacin administration. Enrofloxacin and its metabolite, ciprofloxacin, were detected in all plasma samples after drug administration. The plasma concentrations of enrofloxacin and ciprofloxacin are depicted in Figures 1 and 2, respectively. As illustrated in Figure 1, the curves for oral and subcutaneous dosing are similar for both the absorption and elimination phases. Pharmacokinetic parameters for enrofloxacin and ciprofloxacin are summarized in Tables 2 and 3, respectively. The enrofloxacin pharmacokinetic parameters for both routes of administration were similar, with a mean peak plasma concentration (C_{max}) of 5.25 and 5.77 µg/ml, a mean time to peak plasma concentration (T_{max}) of 1.49 and 1.1 hr, a mean AUC of 49.9 and 47.3 hr·µg/ml, and a mean terminal half-life ($t_{1/2}$) of 5.83 and 6.46 hr for oral and subcutaneous dosing, respectively.

Ciprofloxacin had relatively low peak plasma concentration and AUC for both the oral and subcutaneous routes of administration of enrofloxacin. The total AUC for ciprofloxacin only

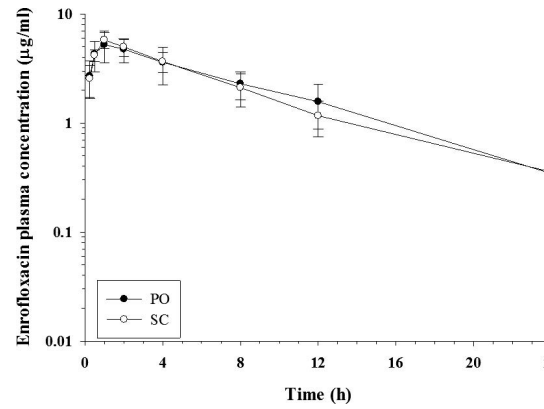

Figure 1. Plasma concentrations of enrofloxacin after oral (p.o.; $n = 7$) or subcutaneous (s.c.; $n = 7$) administration at 15 mg/kg to Caribbean flamingos.

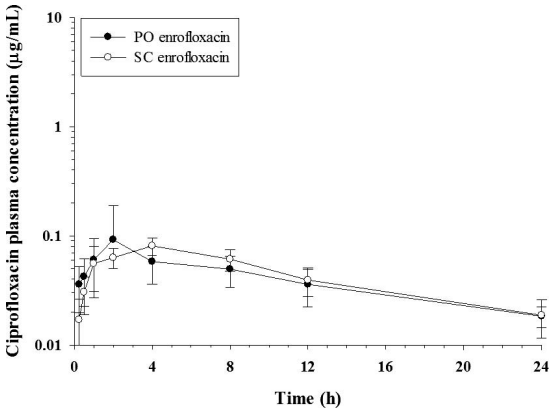

Figure 2. Plasma concentrations of ciprofloxacin after administration of a single dose of enrofloxacin orally (p.o.; $n = 7$) or subcutaneously (s.c.; $n = 7$) at 15 mg/kg to Caribbean flamingos.

represented 2.6 and 2.75% of the enrofloxacin AUC for oral and subcutaneous dosing, respectively.

DISCUSSION

This study evaluated the pharmacokinetic properties of a single dose of enrofloxacin, administered either orally or subcutaneously, in a group of captive Caribbean flamingos. Based on the results of this study, enrofloxacin is consistently absorbed when administered orally and subcutaneously. Because an intravenous dose was not evaluated, absolute bioavailability assessment was not possible. However, the consistent plasma concentrations observed between both routes resulted in a subcutaneous relative bioavailability of 95%. In other studies evaluating the administration of oral enrofloxacin in birds, the absolute bioavailability has been reported to be >60% for several species, with the highest reported being 98–113% in African penguins.[1,2,4,10,11,17,20,25,33] However, the oral bioavailability of enrofloxacin in Japanese quail has been shown to be quite poor, with values as low as 15.16 and 26.4% reported.[19,25] This dramatic difference highlights the possibility for species-specific differences in absorption of oral enrofloxacin, as well as the need for further studies in additional species to ensure appropriate dosing protocols. At the time of the present study, there are no reported absolute bioavailability measurements for enrofloxacin delivered subcutaneously in birds.

Peak enrofloxacin plasma concentrations were similar for the oral and subcutaneous routes in Caribbean flamingos, reaching a mean value of 5.25 and 5.77 µg/ml at 1.49 and 1.1 hr, respectively. Based on these results, the flamingos in the present study appear to have reached relatively high peak plasma concentrations quite quickly for both routes of administration, when compared with other avian species. The mean peak plasma concentrations of enrofloxacin administered at an equivalent dose in other birds varied from 1.09 µg/ml after intravenous administration in ostriches to 6.7 µg/ml after intravenous administration in red-tailed hawks (*Buteo jamaicensis*).[9,20] The T_{max} for oral administration of enrofloxacin in Caribbean flamingos was relatively short compared with other species, with the reported values for T_{max} ranging from 0.35 hr in Japanese quail to 7.69 hr in male turkeys, both receiving an oral dose of

Table 2. Pharmacokinetic data for enrofloxacin following oral ($n = 7$) or subcutaneous ($n = 7$) administration of a single 15 mg/kg dose to Caribbean flamingos (geometric mean, minimum [Min], and maximum [Max] values).

	Oral			Subcutaneous		
Parameter[a]	Mean	Min	Max	Mean	Min	Max
AUC extrap (%)	5.3	1.3	9.7	6.4	3.1	11.2
AUC (hr·µg/ml)	49.9	34.3	66.7	47.3	30.8	64.0
Cl/F (ml/min per kg)	5.01	3.75	7.29	5.28	3.91	8.13
C_{max} (µg/ml)	5.25	3.88	8.43	5.77	4.51	7.19
$t_{½}$ (hr)	5.83	3.74	7.62	6.46	4.83	8.95
λz (1/hr)	0.119	0.091	0.186	0.107	0.078	0.143
MRT (hr)	8.50	6.26	9.57	8.29	6.04	9.82
T_{max} (hr)	1.49	1.00	4.00	1.10	1.00	2.00
Vz/F (L/kg)	2.53	1.59	4.49	2.95	1.92	4.36
C24 (µg/ml)	0.317	0.124	0.536	0.324	0.124	0.537

[a] AUC extrap indicates % AUC extrapolated to infinity; AUC, area under the curve extrapolated to infinity; Cl/F, clearance per fraction of the dose absorbed; C_{max}, maximum plasma concentration; $t_{½}$, terminal half-life; λz, terminal rate constant; MRT, mean residence time extrapolated to infinity; T_{max}, time to C_{max}; Vz/F, volume of distribution (area method) per fraction of the dose absorbed; C24, plasma concentration 24 hr after dose administration.

Table 3. Pharmacokinetic data for ciprofloxacin following oral ($n = 7$) or subcutaneous ($n = 7$) administration of enrofloxacin at 15 mg/kg to Caribbean flamingos (geometric mean, minimum [Min], and maximum [Max] values).

	Oral			Subcutaneous		
Parameter[a]	Mean	Min	Max	Mean	Min	Max
AUC (hr·μg/ml)	1.3	1.0	1.7	1.3	0.8	1.8
C_{max} (μg/ml)	0.09	0.05	0.30	0.08	0.06	0.10
T_{max} (hr)	2	0.25	8	3.2813	1	4
C24 (μg/ml)	0.018	0.016	0.027	0.017	0.010	0.029

[a] AUC indicates area under the curve extrapolated to infinity; C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; C24, plasma concentration 24 hr after dose administration.

10 mg/kg.[11,19] Only two studies have reported pharmacokinetic data for subcutaneous administration of enrofloxacin in avian species. Plasma concentrations of enrofloxacin reached peak concentration more rapidly in Caribbean flamingos than the other species studied, including ostriches and turkeys with a mean T_{max} of 1.45 and 1.87 hr, respectively.[5,9]

The AUC for enrofloxacin in Caribbean flamingos was similar between the oral and subcutaneous routes, with a mean AUC of 49.9 and 47.3 hr·μg/ml, respectively. When compared with previously reported values in other avian species for the same single 15 mg/kg dose of enrofloxacin delivered orally, the flamingos fall within the middle of the range, which spans from 6.73 hr·μg/ml in African grey parrots (*Psittacus erithacus*) to 92.9 hr·μg/ml in African penguins receiving a pilled dose.[13,33] The AUC for enrofloxacin in flamingos is most similar to that reported for the great horned owl (*Bubo virginianus*) and red-tailed hawk, where an equivalent 15 mg/kg oral dose resulted in a mean AUC of 44 and 47.2 hr·μg/ml, respectively.[20] Only one other study, of ostriches, has evaluated the AUC for the same 15 mg/kg dose of enrofloxacin delivered subcutaneously. The AUC for ostriches was reported to be 8.15 hr·μg/ml, which is much lower than the value for the flamingos in this study.[9]

The terminal half-life of enrofloxacin has been shown to be highly variable across the avian species studied, ranging from as short as 0.78 hr for intravenous administration of a 5 mg/kg dose in ostriches to as long as 19.4 hr for intravenous administration of a 15 mg/kg dose in red-tailed hawks.[8,20] The terminal half-life for Caribbean flamingos fell within the lower portion of this range and was slightly shorter for the oral versus subcutaneous route of administration, with $t_{1/2}$ values of 5.83 and 6.46 hr, respectively. This relationship is similar to that reported for turkeys, in a study where the pharmacokinetics of a 10 mg/kg dose of enrofloxacin delivered by either the oral or subcutaneous routes were compared. In turkeys, the elimination half-life of enrofloxacin was also slightly shorter for the oral route than the subcutaneous route, with mean $t_{1/2}$ values of 5.27 and 6.22 hr, respectively.[5]

A portion of enrofloxacin was metabolized into ciprofloxacin in flamingos, with the mean AUC for ciprofloxacin representing <3% of the enrofloxacin AUC for both routes of administration. Low concentrations of ciprofloxacin do not likely contribute substantially to the antimicrobial effects of the enrofloxacin administered to the flamingos in this study. The low level of conversion to ciprofloxacin, although much lower than most reported values for other avian species, is most similar to that reported for the turkey, with a conversion of 3–4% after both oral and subcutaneous administration in one study by Cagnardi et al.[5] Very low concentrations of ciprofloxacin were measured after enrofloxacin administration (i.v., p.o.) in penguins.[33] Other avian species, including the turkey in two studies by Dimitrova et al.,[10,11] ostrich, Muscovy duck, chicken (oral dosing), Japanese quail (intravenous dosing), greater rhea, and ostrich, exhibited ≤15% conversion.[6–9,16,17,19,23,25] The highest reported conversion of 30% occurred in chickens receiving an intravenous dose of enrofloxacin.[17] This variability in metabolism of enrofloxacin to ciprofloxacin across avian species may be related to species-specific metabolic pathways, differences in absorption and metabolism between routes of administration for each species, or differences in study design (i.e., dosing protocols) for each species.

Fluoroquinolones are concentration-dependent antimicrobials, for which peak plasma concentration and total drug exposure are correlated with antimicrobial activity, rather than maintenance of a minimum plasma concentration.[12,31] To predict the efficacy of a fluoroquinolone, it is recom-

mended to achieve a peak plasma concentration of at least 8–10 times the minimal inhibitory concentration (MIC) of the targeted bacterial pathogen; in other words, achieving a C_{max} : MIC > 8–10. Similarly, the AUC is recommended to be at least 100–125 times the MIC, or AUC : MIC > 100–125.[12,31] However, these recommendations may overestimate the needed drug exposure, because they were initially derived from critically ill human patients. Nonetheless, these recommendations can be used as targets until clinical trial data are available. In companion birds, most susceptible bacterial pathogens have been reported to have MIC values ≤0.25 μg/ml for enrofloxacin.[12–14] Although MIC data are lacking in many avian species, other studies have used MIC values identified for poultry and domestic mammals, typically ≤0.25–0.5 μg/ml, as a frame of reference for predicting the efficacy of enrofloxacin.[3,5,6,8–10,17,20,22,23,33,34] One study reported a MIC of ≤0.5 μg/ml for 72% of the *Proteus, Escherichia coli, Salmonella,* and *Klebsiella* strains and 48% of the *Streptococcus* and *Staphylococcus* strains isolated from multiple species of wild bustards.[2]

Using C_{max} : MIC > 8 for a bacterial MIC of 0.25 μg/ml, the C_{max} target would be 2 μg/ml. This target was exceeded for all flamingos for both the oral and subcutaneous routes of administration (Table 2). For a MIC value of 0.5 μg/ml, the C_{max} target would be 4 μg/ml. Although the mean C_{max} values for both routes of administration exceeded this target, only five of the seven birds in the oral administration group were >4 μg/ml, whereas all birds in the subcutaneous group achieved the target concentration.

When using AUC : MIC > 100 for a bacterial MIC of 0.25 μg/ml, the AUC target would be 25 hr·μg/ml. Again, this target was exceeded for all flamingos for both routes of administration (Table 2). For the higher MIC value of 0.5 μg/ml, the AUC target would be 50 hr·μg/ml. The mean AUC values were slightly under this target for both groups. However, when looking at individual flamingos, five of the seven birds receiving an oral dose and three of the seven birds receiving a subcutaneous dose resulted in AUC values above the target of 50 hr·μg/ml. Thus, the predicted efficacy of the present dose of enrofloxacin was consistently met for bacterial pathogens with MIC ≤ 0.25 μg/ml, with a more variable effect for pathogens with MIC ≥ 0.5 μg/ml in this study.

Based on the results of the present study, a dose of 15 mg/kg enrofloxacin delivered either orally or subcutaneously in the Caribbean flamingo every 24 hr is recommended for susceptible bacterial pathogens with MIC ≤ 0.25 μg/ml. Because of the similarities in the pharmacokinetics of the two routes of administration, it appears to be possible to use the two routes interchangeably, according to clinician preference, level of animal cooperation, and disease states. Absorption of enrofloxacin may be affected by multiple variables depending on the route of administration, such as type or amount of food within the stomach at the time of oral medication administration, as well as inflammation, hematoma formation, or even development of secondary infection associated with repeated subcutaneous administration. For both routes, the plasma enrofloxacin concentration decreased by >90% at 24 hr postadministration in Caribbean flamingos. This indicates that accumulation of the drug in the plasma would be minimal and would not be likely to have a substantial effect if multiple doses were administered at 24-hr intervals. However, further studies to evaluate the pharmacokinetic effect of multiple doses would be valuable to guide long-term treatment protocols. Further research to evaluate the absolute bioavailability of oral enrofloxacin, the use of alternative formulations of enrofloxacin, and the pharmacokinetics of additional antimicrobials would be indicated to continue to improve medical management of the Caribbean flamingo in the zoological setting.

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