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The pharmacokinetics of enrofloxacin in ducks with steatosis after force-feeding

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ABSTRACT

The pharmacokinetics of enrofloxacin (EFC) was investigated in ducks fed with a normal diet, and in force-fed ducks, after a single intravenous (i.v.) and oral (p.o.) administration at doses of 10 mg/kg. Serum concentrations of EFC and ciprofloxacin (as metabolite of EFC) were determined by the HPLC method. The elimination half-lives of EFC after i.v. administration and compartmental pharmacokinetic analysis were 4.62 ± 0.62h and 6.39 ± 2.78 h in healthy and force-fed ducks, respectively. The values of total body clearance were 0.24 ± 0.03 L/h/kg in healthy and 0.18 ± 0.02 L/h/kg in force-fed ducks. The values of the volume of distribution (V_{ss}) were 1.32 ± 0.18 L/kg and 1.31 ± 0.21 L/kg, respectively. After oral administration, maximum serum concentrations were 1.95 ± 0.36 µg/mL reached at 3.67 ± 4.26 h, and 4.25 ± 1.21 µg/mL at 1.25 ± 0.88 h, respectively. The serum concentrations of ciprofloxacin were significantly lower in the force-fed ducks. Longer enrofloxacin residence in force-fed ducks can be expected if compared to normally fed animals.

Key words: pharmacokinetics**,** enrofloxacin, ducks, force-feeding, steatosis

Introduction

Enrofloxacin (EFC), a second generation, broad spectrum fluoroquinolone, developed for use in veterinary medicine, is active against many Gram-positive and Gram-negative microorganisms (*Pasteurella multocida*, *Riemerella anatipestifer*, *E. coli*, *Salmonella* spp., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) and *Mycoplasma* spp. (BROWN, 1996; GARCIA-OVANDO et al., 1999; KNOLL et al., 1999). Its disposition and that of its main metabolite, ciprofloxacin (CFC), have been studied in many domestic and wild avian species: chickens (ANADÓN et al., 1995; BUGYEI et al., 1999; GARCIA-OVANDO

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et al., 1999; KNOLL et al., 1999), turkeys (HARITOVA et al., 2004; DIMITROVA et al., 2007; RUSSO et al., 2012), pheasants and Japanese quail (LASHEV et al., 2015), emu (KUMAR et al., 2015), greater rheas (DE LUKAS et al., 2005), ostrich (DE LUKAS et al., 2013), but the data for ducks (INTORRE et al., 1997; TANSAKUL et al., 2005) and geese (JIANG and SHI, 2013; SHI et al., 2014) are scarce.

Raising ducks for fatty liver production may be accompanied by diseases with bacterial etiology. Their therapy often requires antibiotic use. Although force-feeding does not induce diet-related pathological changes or lead to reversible steatosis when it is carried out according to professional standards (BENARD et al., 2006), during this period many physiological parameters in the birds change, leading to increased body weight, triglyceridemia, and high AST and lipase blood levels (BOGIN et al., 1984). Additionally, force-fed ducks' body weight increases extensively mostly by increased liver mass and body fat, which is a predisposition for changes in the drug behavior of highly lipophilic substances, such as enrofloxacin. Such changes can provoke alterations in its pharmacokinetics when treatment is necessary for disease. These ducks, after force feeding, may also be useful as an experimental model for investigation of animals with excess body mass. This is why the aim of the paper was to investigate the pharmacokinetics of enrofloxacin, and its metabolite ciprofloxacin in force-fed ducks compared to normally fed ducks.

Materials and methods

Drug. A solution of enrofloxacin (Baytril® 5%, Bayer Animal Health GmbH D-51368 Leverkusen, Germany) was used. The original drug form was diluted with distilled water to a concentration of 2.5% and after that was used for oral treatment.

Animals. Twenty-four ducks, divided into two groups, were used in the study. In the first experiment eleven-week old ducks (6 males and 6 females) were included, at the time just before the beginning of force-feeding, weighing 2.91-3.94 kg, and in the second trial there were thirteen-week old ducks (6 males and 6 females), at the end of force-feeding, weighing 4.05-5.45 kg. All of them were hybrids of male Muscovy and female Peking ducks, reared on a private farm. Food and water were provided *ad libitum*. The feed was removed 18 hours before the experiments. Care and handling of animals were in accordance with the provisions for welfare of Regulation (EC) № 882/2004 of the European Parliament and of the Council of 29 April 2004, adopted by the Government of the Republic of Bulgaria in Ordinance № 20 of 01.11.2012. The experiments were approved by the Committee on the Ethical Treatment of Animals at Trakia University.

Study design. The first experiment was performed with 12 ducks at the time before the beginning of force-feeding. The birds were randomly divided into two groups of 6 (3 male and 3 female) each. The first group was treated intravenously (in the brachial

vein) and the second - orally (by administration into the crop) at a dose of 10 mg/kg enrofloxacin. In the second experiment, the 12 ducks at the end of fattening period were also divided into two groups of 6 (3 males and 3 females) birds each. They were treated as described above. Before treatment, serum levels related to liver function, AST, ALT, cholesterol, triglycerides and LDH, of all birds were tested.

Sampling collection. Blood samples (each 0.8 mL) were obtained from the v. brachialis of each bird without anticoagulant. After intravenous treatment, only the contralateral vein was used. Times for sampling after i.v. treatment were 0.083, 0.25, 0.5, 1, 3, 6, 9, 12, 18 and 24 h, respectively, and after p.o. administration 0.25, 0.5, 1, 3, 6, 9, 12, 18 and 24 h. All blood samples were centrifuged for 15 min at 1800 *g* and the serum was separated. The obtained serum samples were stored at -20 °C for no longer than 2 weeks until analysis.

Analytical method. Serum concentrations of enrofloxacin and its metabolite ciprofloxacin were assayed by the HPLC method (HARITOVA et al., 2012). The system consisted of a Hipersil Spherisorb ODS-2(C18)-250 × 4.6-mm 5 µm column, a Surveyor LC Pump Plus, a Surveyor fluorescence detector, and a Surveyor Autosampler Plus (Thermo Fisher Scientific Inc., USA). The mobile phase was prepared with acetonitrile and 0.05 M potassium dihydrogen phosphate (25:75, v/v), and the pH was adjusted to 3.5 with phosphoric acid (85%). The flow rate was 0.6 mL/min. Excitation and emission wavelengths were set at 277 nm and 418 nm. Peak area integrations were measured by the ChromQuest Chromatography Data System (Thermo Fisher Scientific Inc., USA). The external standards were enrofloxacin (enrofoxacin hydrochloride, Biovet® Pestera, Bulgaria) and ciprofloxacin (ciprofloxacin hydrochloride, Actavis®, Bulgaria). Standard solutions were prepared in drug-free duck serum at concentrations of 50, 100, 250, 500, 750 and 1000 ng/mL. Serum samples (100 µL) were diluted with 400 µL of 0.1M phosphate buffer with pH 7.4, and vortexed for 0.5 min. After adding 3 mL of dichloromethane, the samples were mixed again for 1 min and centrifuged for 6 min at 1000 *g*. The organic phase was collected and was evaporated in a vacuum evaporator at 40 °C. The residue was dissolved in 100 µL demineralized water, and aliquots of 20 µL were injected into the HPLC system. The limit of quantification was 50 ng/mL for ciprofloxacin and 10 ng/mL for enrofloxacin. The standard curves were linear over the tested range between LOQ and 1000 ng/mL ($r^2 = 0.999$) and enrofloxacin did not interfere with ciprofloxacin. The accuracy was between 82 and 102% for the range of concentrations used. Inter-assay and intra-assay precisions were 2.47 and 1.20, respectively.

Pharmacokinetic analysis. The analysis was carried out using specialized software (Phoenix 6.2.1; Pharsight, Mountain View, CA, USA). Compartmental analysis was used for the data after i.v. administration of enrofloxacin. The best fit was determined according to Akaike's Information Criterion. Non-compartmental analysis was used for the data

after i.v. and p.o. administration of the drug. The area under the serum-concentration-time curve (AUC) was calculated by the trapezoids method between the times 0 and 24 h. The following pharmacokinetic parameters were computed: $AUC_{0\rightarrow\infty}$ − area under curve from time 0 to infinite; $AUC_{0\rightarrow24}$ − area under the serum concentration-time curve from time zero to last time (24 h); $t_{1/2\alpha}$ − distribution half- life; $t_{1/2\beta}$ − elimination half-life; Cl_B − total body clearance; $MRT_{0\rightarrow\infty}$ − mean residence time from time 0 to infinite; $MRT_{0\rightarrow24}$ − mean residence time zero to last time (24 h); V_c – volume of distribution in the central compartment; V_{ss} − volume of distribution at steady state; $Vd_{(area)}$ − area volume of distribution; $t_{1/2\lambda}$ − terminal half-life (non-compartmental analysis); C_{max} – maximum serum levels; T_{max} – time of C_{max}; F − bioavailability; $MAT_{0\infty}$ − mean absorption time from time 0 to infinite; $MAT_{0\rightarrow24}$ − mean absorption time from time zero to last time (24 h) (TOUTAIN and BOUSQUET-MELOU, 2004). PK-PD indices $AUC_{0\text{-}24h}$/MIC and C_{max}/MIC were calculated on the basis of MIC (0.01 µg/mL) and MBC (0.06 µg/mL) values for *E. coli* O78/H12 (HARITOVA et al., 2011).

Statistical analysis. The results are expressed as mean values ± standard deviations (SD). Descriptive statistics were performed with Statistica for Windows (Statistica 6.0.1, USA). The Mann–Whitney U test was used and $P<0.05$ was considered to be significant.

Results

The values of the selected biochemical parameters of normally and force-fed ducks are shown in Table 1. Cholesterol, triglycerides and LDH were significantly increased after force feeding.

Table 1. Values of some biochemical parameters of normal and force-fed ducks (mean ± SD).

Parameter	Unit	Before force-feeding	After force-feeding	Reference values
Glucose	mmol/L	10.62 ± 3.18	11.24 ± 0.85	10.9-16.6[1]
Cholesterol	mmol/L	4.74 ± 0.61	13.48 ± 2.84*	3.3-7.2[1]
Triglycerides	mmol/L	0.44 ± 0.10	2.04 ± 1.24*	0.583 ± 0.123[3]
AST	U/L	46.71 ± 15.95	73.73 ± 34.34	28.3[2]
ALT	U/L	25.71 ± 5.97	54.09 ± 38.57	33.4[2]
LDH	U/L	648 ± 206	1500 ± 783*	104-978[1]

*Statistically significant difference between data on ducks before force-feeding and ducks with steatosis at $P<0.05$; [1]STOJKOVSKI, 2001; [2]FAIRBROTHER et al., 1990; [3]HERMIER et al., 2003.

The serum concentration-time profiles of enrofloxacin and its main metabolite ciprofloxacin after single i.v. and p.o. administration of 10 mg/kg enrofloxacin are shown in Fig. 1 and 2. The EFC curves after i.v. administration were best described by the two-compartment model. Its elimination half-life was longer and the AUC values were higher

in force-fed birds. The values of body clearance were lower after feeding. The values of V_c were higher, but these of Vd_{area} and V_{ss} did not differ between the two groups (Table 2).

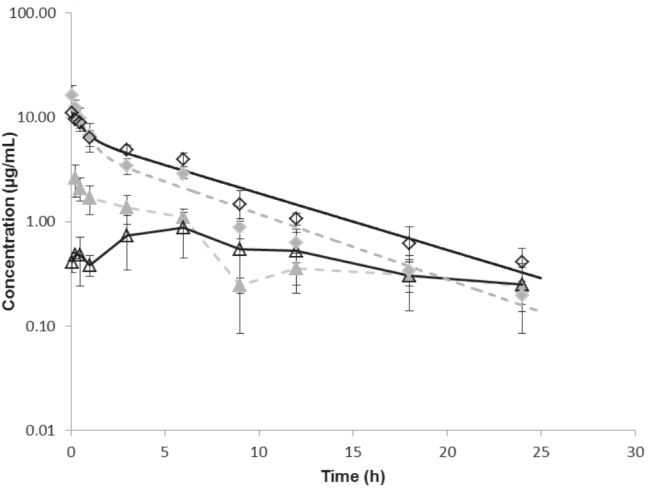

Fig. 1. Serum concentrations of enrofloxacin (◇◆) and ciprofloxacin (△▲) after a single intravenous dose of 10 mg/kg enrofloxacin in intact (---) and force-fed (—) ducks (mean ± SD)

After p.o. treatment, the non-compartment model was used for analysis of the data. The maximum serum concentrations were statistically significantly higher and were reached earlier in the force-fed ducks (Table 2). In the same group, the mean absorption time was insignificantly shorter. The absolute oral bioavailability of EFC was not changed significantly, but the relative oral bioavailability ($F_{relative} = 100.AUC_{fed}/AUC_{normal}$) was higher (121%). The serum concentrations of ciprofloxacin as a metabolite after both administrations of EFC remained above the detection limit for at least 24h (Fig. 1 and 2). The ciprofloxacin/enrofloxacin ratios of AUC values were lower after both administrations in the force-fed birds (Table 2).

PK-PD indices, based on the MIC value of enrofloxacin and ciprofloxacin of 0.01 µg/mL, are presented in Table 3. C_{max}/MIC values were almost two-folds higher in force-fed ducks. A similar tendency was observed for AUC_{0-24h}/MIC. Both PK-PD indices were higher than the breakpoint value of 10 for C_{max}/MIC and of 125 for AUC_{0-24h}/MIC. The values of C_{max}/MBC and AUC_{0-24h}/MBC were higher than these breakpoints, where MBC was 0.06 µg/mL (Table 3).

Table 2. Pharmacokinetic parameters (Mean ± SD) of enrofloxacin and its metabolite ciprofloxacin in ducks after single i.v. and p.o. administration at a dose of 10 mg/kg bw

Parameter	Unit	Before force-feeding		With steatosis	
Two-compartmental analysis, i.v. administration					
		Enrofloxacin	Ciprofloxacin	Enrofloxacin	Ciprofloxacin
$AUC_{0\rightarrow\infty}$	µg. h/mL	41.76 ± 4.82	-	55.8 ± 6.68*	-
$t_{1/2\alpha}$	h	0.46 ± 0.35	-	0.43 ± 0.34	-
$t_{1/2\beta}$	h	4.62 ± 0.62	-	6.39 ± 2.78*	-
CL_B	L/h/kg	0.24 ± 0.03	-	0.18 ± 0.02*	-
V_c	L/kg	0.58 ± 0.13	-	0.90 ± 0.13*	-
V_{ss}	L/kg	1.32 ± 0.18	-	1.31 ± 0.21	-
$Vd_{(area)}$	L/kg	1.60 ± 0.17	-	1.66 ± 0.74	-
Non-compartmental analysis, i.v. administration					
$AUC_{0\rightarrow24h}$	µg. h/mL	41.73 ± 4.72	14.62 ± 2.37	54.05 ± 4.85	11.92 ± 5.39
$AUC_{0\rightarrow\infty}$	µg. h/mL	44.66 ± 4.61	na	58.96 ± 6.48	na
$MRT_{0\rightarrow24h}$	h	4.30 ± 0.51	na	5.68 ± 0.63	na
$MRT_{0\rightarrow\infty}$	h	5.96 ± 0.82	14.06 ± 10.26	8.19 ± 1.99	22.01 ± 6.21
$t_{1/2\lambda}$	h		12.36 ± 9.32		15.58 ± 5.39
C_{max}	µg/mL		2.9 ± 0.58		0.92 ± 0.41
T_{max}	h		0.42 ± 0.30		4.25 ± 2.59
AUC_c/AUC_e		0.35		0.22	
Non-compartmental analysis, p.o. administration					
$t_{1/2\lambda}$	h	7.35 ± 1.71	15.42 ± 2.74	7.46 ± 2.99	10.5 ± 3.46
C_{max}	µg/mL	1.95 ± 0.36	0.51 ± 0.12	4.25 ± 1.21*	0.67 ± 0.2
T_{max}	h	3.67 ± 4.26	8.25 ± 5.81	1.25 ± 0.88	5.13 ± 4.35
$AUC_{0\rightarrow24h}$	µg.h/mL	21.75 ± 4.07	6.96 ± 0.87	26.24 ± 3.38	7.77 ± 1.47
$AUC_{0\rightarrow\infty}$	µg. h/mL	25.42 ± 4.35	na	27.80 ± 4.21	9.33 ± 1.35
$MRT_{0\rightarrow24h}$	h	7.95 ± 0.74	na	5.43 ± 1.05	na
$MRT_{0\rightarrow\infty}$	h	11.49 ± 1.94	22.52 ± 4.23	7.08 ± 2.24	14.96 ± 3.33
$MAT_{0\rightarrow24h}$	h	3.65 ± 0.71		1.0 ± 1.32	
$MAT_{0\rightarrow\infty}$	h	5.53 ± 1.46		2.46 ± 2.4	
F	%	52.28 ± 8.55		49.02 ± 8.99	
AUC_c/AUC_e		0.32		0.30	

*Statistically significant difference between ducks before force-feeding and ducks with steatosis at $P<0.05$; $AUC_{0\rightarrow\infty}$ − area under curve from time 0 to infinite; $AUC_{0\rightarrow24}$ − area under the serum concentration-time curve from time zero to last time (24 h); $t_{1/2\alpha}$ − distribution half-life; $t_{1/2\beta}$ ($t_{1/2\lambda}$) − elimination (terminal) half-life; Cl_B − total body clearance; $MRT_{0\rightarrow\infty}$ − mean residence time from time 0 to infinite; $MRT_{0\rightarrow24}$ − mean residence time zero to last time (24 h); V_c − volume of distribution in the central compartment; V_{ss} − volume of distribution at steady state; $Vd_{(area)}$ − volume of distribution; C_{max} – maximum serum levels; T_{max} – time of C_{max}; F − bio-availability; $MAT_{0\rightarrow\infty}$ − mean absorption time from time 0 to infinite; $MAT_{0\rightarrow24}$ − mean absorption time from time zero to last time (24 h); F − bioavailability; AUC_c/AUC_e - relation between area under serum concentrations of ciprofloxacin and enrofloxacin.; na – not applicable due to extrapolation > 20%.

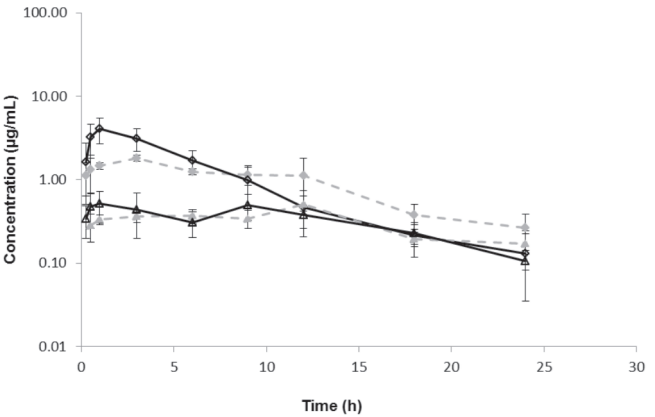

Fig. 2. Serum concentrations of enrofloxacin (◇◆) and ciprofloxacin (△▲) following a single oral dose of 10 mg/kg enrofloxacin in intact (---) and force-fed (—) ducks (mean ± SD)

Table 3. Pharmacokinetic-pharmacodynamic indices of enrofloxacin and its metabolite ciprofloxacin in ducks after single i.v. and p.o. administration at a dose of 10 mg/kg

PK-PD index	Before force-feeding		After force-feeding	
	Enrofloxacin	Enrofloxacin plus ciprofloxacin	Enrofloxacin	Enrofloxacin plus ciprofloxacin
After p.o. administration				
C_{max}/MIC*	195	246	425	492
$AUC_{0 \rightarrow 24h}$/MIC	2175	2871	2624	3401
C_{max}/MBC*	32.5	41	70.8	82
$AUC_{0 \rightarrow 24h}$/MBC	362.5	478.5	437.3	566.8

*MIC = 0.01 µg/mL; MBC = 0.06 µg/mL

Discussion

Although EFC is a well investigated drug and its pharmacokinetics have been the subject of many articles regarding different bird species, the published data for ducks and geese are scarce. In Muscovy ducks Cmax of 0.99 µg/mL were achieved at T_{max} of 1.38 h and MRT was 6.01 h (INTORRE et al., 1997). The value of $t_{1/2\beta}$ in Mallard ducks was 6.47 h and bioavailability of 80.35% was observed (TANSAKUL et al., 2005). These data were similar to the data for the Gallinaceus species and geese (JIANG and SHI, 2013). The data for normally fed ducks in the present investigation were also similar to these, excluding the lower bioavailability in our case.

Steatosis as a result of force-feeding is the reason for significant changes to liver function, which may be followed by different absorption, distribution or elimination of substances, in accordance with their chemical structure and behavior in the organism. Up to now, data about the pharmacokinetics of drugs in force-fed ducks have not been known, nor has any attempt been made to explain the changes compared to normally fed birds. We assumed that in our case the alterations found in the pharmacokinetics of force-fed ducks were due to the function of fatty liver.

The rate of distribution of EFC in both groups was similar, although the drug showed a higher volume of distribution in the central compartment in the force-fed ducks than in intact birds. The significantly lower clearance in this group of animals may be a prerequisite for the slower elimination of the antibiotic. Reduced drug metabolism, which probably provokes higher blood levels of enrofloxacin, could be another explanation of the observed changes. The registered differences led to higher area under the curves after both routes of administration, and to higher oral relative bioavailability of ENR. Decreased conversion of the parent drug to its main metabolite resulted in half the ratio between the values of area under the curves of ciprofloxacin and enrofloxacin. The present data were similar to the reported retarded elimination of bromosulfophtaleine and indocyanine green in force-fed ducks (BENGONE-NDONG et al., 1996). Insignificantly higher values of C_{max} and AUC were found for enrofloxacin after p.o. treatment in force-fed ducks, which may contribute to the better efficacy of the fluoroquinolones.

The PK-PD integration in both groups of ducks revealed that the applied dose of 10 mg/kg can ensure clinical efficacy for treatment of infections provoked by highly sensitive pathogens with MIC of 0.01 μg/mL and MBC of 0.06 μg/mL, as has been observed in chicken (HARITOVA et al., 2011; MEKALA et al., 2014). The PK-PD indices can be high enough to guarantee clinical success against pathogens with MIC values of 0.125 μg/mL. Higher doses will be necessary for less sensitive bacteria. In order to avoid resistance development, the best strategy requires MIC determination of the specific pathogens in ducks, and administration of enrofloxacin in cases when breakpoint values of C_{max}/MIC>10-12 and for $AUC_{0\text{-}24h}$/MIC>125 are achieved. Additional determination of MBC values can be used for early detection of the risk for resistance selection, if the difference between MBC and MIC is higher than four (HARITOVA et al., 2011). Apparently, high values of PK-PD indices in force-fed ducks do not require additional adjustment of dosage regimen if compared to the normally fed birds. However further studies could be necessary to evaluate the pharmacokinetic behavior of enrofloxacin and its metabolite ciprofloxacin in forced fed ducks after a multiple regimen dosage.

In conclusion, ducks with fat liver absorbed and distributed enrofloxacin better in the body and eliminated it more slowly than normally fed birds. A lower degree of metabolism to ciprofloxacin can be expected in animals with liver steatosis. The observed

differences were not always statistically significant, but alterations in liver function may cause prolonged residence of enrofloxacin in force-fed, compared to normally fed ducks.

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SAŽETAK

Farmakokinetika enrofloksacina (EFC) primijenjenog intravenski i oralno u dozi od 10 mg/kg istražena je u normalno i prisilno hranjenih pataka. Serumske koncentracije EFC i ciprofloksacina (kao metabolita EFC) bile su određene visokotlačnom tekućinskom kromatografijom. Poluvrijeme izlučivanja EFC nakon i.v. primjene i farmakokinetičke analize po odjeljcima iznosilo je 4,62 ± 0,62 h u zdravih, a 6,39 ± 2,78 h u prisilno hranjenih. Vrijednosti ukupnog klirensa lijeka iz organizma bile su 0,24 ± 0,03 L/h/kg u zdravih i 0,18 ± 0,02 L/h/kg u prisilno hranjenih (šopanih). Vrijednosti volumena raspodjele (V_{ss}) bile su 1,32 ± 0,18 L/kg i1,31 ± 0,21 L/kg. Najveće serumske koncentracije nakon oralne primjene bile su dosegnute nakon 3,67 ± 4,26 h, a iznosile su 1,95 ± 0,36 µg/mL, dok su nakon intravenske primjene bile dosegnute nakon 1,25 ± 0,88 h, a iznosile su 4,25 ± 1,21 µg/mL. Serumske koncentracije ciprofloksacina bile su značajno niže u prisilno hranjenih pataka. Duže zadržavanje enrofloksacina može se očekivati u prisilno hranjenih pataka u odnosu na one normalno hranjene.

Ključne riječi: farmakokinetika, enrofloksacin, patke, prisilno hranjenje, steatoza