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COMPARATIVE ANALYSIS OF ENROFLOXACIN PHARMACOKINETICS IN DOGS AND CATS

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Abstract

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The pharmacokinetics of enrofloxacin in dogs and cats after single intravenous (*i.v.*) and subcutaneous (*s.c.*) application of 5 mg.kg^{-1} enrofloxacin hydrochloride was studied and analyzed. Six dogs and six cats, equal number of both genders, were used. Blood samples were collected immediately after enrofloxacin injection and at post injection hours 0.08, 0.33, 0.66, 1, 2, 4, 6, 8, 10, 12 and 24 h. Serum concentrations of the quinolone and its active metabolite were assayed on a high-performance liquid chromatograph. The pharmacokinetic parameters were calculated with specialized pharmacokinetic software (TopFit, v.2.0.). The statistical analysis (Statistica, v.6.0.) performed both parametric and non-parametric analyses – one way ANOVA and Mann-Whitney U test. There were statistically significant differences in serum concentrations and the pharmacokinetics of the drug in both studied animal species. After *i.v.* application in both species, serum concentrations-time curves fitted the two-compartmental pharmacokinetic model, whereas after *s.c.* – the one-compartmental model. The studied pharmacokinetic parameters differed statistically significantly between dogs and cats for both routes of administration and were characterized by higher biological half-life and mean residence time, higher volume of distribution, higher $AUC_{0\rightarrow\infty}$, C_{max} and T_{max} values, and lower absolute bioavailability of enrofloxacin in cats.

Key words: enrofloxacin, ciprofloxacin, pharmacokinetics, dogs, cats

Introduction

A number of factors are known to influence the systemic behavior of drugs in humans and animals the species, gender, hormonal status, physiological status, age, immune condition etc.

Numerous researches have reported the pharmacokinetics of enrofloxacin in different canine breeds (Walker et al., 1992; Kűng et al., 1993; Kűng and Wanner, 1994; Duval and Budsberg, 1995; Intorre et al., 1995; Meinen et al., 1995; Cester, 1996; Monloui et al., 1997; De Manuelle et al., 1998; Hawkins, 1998; Boeckh, A. et al., 2001; Frazier et al., 2000; Heinen, 2002; Gokhan et al., 2008; Boothe et al., 2009). Those dedicated on this quinolone behaviour in cats are however few (Scheer, 1987; Droumev et al., 2003; Seguin et al., 2004; Gerhardt et al., 2006; Walker and Dowling, 2006).

There are no studies comparing the pharmacokinetics of enrofloxacin, applied at the same dose and concentration in both domestic carnivore species.

The purpose of the study was to perform a comparative analysis of the pharmacokinetics of enrofloxacin and its active metabolite in uniformly treated dogs and cats.

Material and Methods

Animals and housing

The experiments were performed with six clinically healthy adult mixed-breed dogs (3 males and 3 females), weighing 18-25 kg and six (equal number of both genders) clinically healthy adult European shorthair cats with body weight 3.4-4.9 kg. The animals were housed indoors, in individual metal cages with wooden floors with controlled mi-

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croclimatic parameters: ambient temperature 20-22°C, mixed light regimen, relative air humidity of 550-600 g.kg^{-1}. The animals were fed with dry maintenance food for the respective species (Lyubimets, Bulgaria). Two days prior to experiments, the health status of dogs and cats was examined.

Drugs

The pharmacokinetic studies included intravenous (*i.v.*) and subcutaneous (*s. c.*) injection of 50 g.kg^{-1} aqueous solution of enrofloxacin hydrochloridum (Chemos GmbH, Germany), at a dose of 5 mg.kg^{-1}.

Experimental design

A 20-day washout period was allowed between experiments with the two routes of administration. Enrofloxacin was applied *i.v.* in the right *v. cephalica,* whereas the *s. c.* application was performed in the back, between the shoulder blades.

Blood samples (1.5 ml) were collected by venflon cannulae immediately before *i.v.* and *s .c.* infection of the quinolone (hour 0) and by post injection hours 0.08, 0.17, 0.33, 0.66, 1, 2, 4, 6, 8, 10, 12 and 24 h.

Blood serum was separated by centrifugation at 1500×*g* for 10 min at room temperature and stored at –25°C until the analysis.

Drug analysis

The concentrations of enrofloxacin and its metabolite were assayed by the method of Imre et al. (2003), by a high-performance liquid chromatograph (HPLC) – Hewlett Packard 1090 with fluorescence detector (SPD 10A), and double pump. The mobile phases used were: acetonitrile, methanol, HPLC water (17:3:80, v/v/v) containing 4 g.kg^{-1} triethylamine and 4 g.kg^{-1} orthophosphoric acid (850 g.kg^{-1}, v/v).

The limits of quantitation of enrofloxacin and its active metabolite were 0.005 μg/ml and 0.010 μg/ml, respectively, and the corresponding limits of detection – 0.001 μg/ml and 0.0025 μg/ml.

Pharmacokinetic analysis

The pharmacokinetic parameters of enrofloxacin and ciprofloxacin were determined with the TopFit, v.2.0 software (Heinzel et al., 1993). The most appropriate pharmacokinetic model was selected via the Akaike's information criterion (AIC) (Yamaoka et al., 1978) and the Schwarz test (Schwartz, 1978). For both routes of application, compartmental and non-compartmental pharmacokinetic analysis was run (Gibaldi and Perrier, 2007).

The area under the serum concentrations-time curve ($AUC_{0\rightarrow\infty}$) was calculated by the trapezoid rule. The bioavailability (F) of enrofloxacin applied *s. c.* was determined from the ratio between individual $AUC_{i.m.}$ and $AUC_{i.v}$. ($F = AUC_{i.m.}/AUC_{i.v.}$).

Statistical analysis

All values of serum concentrations of enrofloxacin and its metabolite, and respective pharmacokinetic parameters were evaluated with a statistical software (Statistica®, v. 6.0) using a non-parametric (Mann-Whitney U test) and parametric (One-way ANOVA) tests and presented as mean and SEM. The differences were considered statistically significant at $p<0.05$.

Results

Blood serum drug concentrations

The blood serum concentrations of the applied fluoroquinolone and its active metabolite in both domestic carnivore species are depicted on Figure 1 (for the *i.v.* route) and Figure 2 (for the *s. c.* route). Enrofloxacin and its metabolite were de-

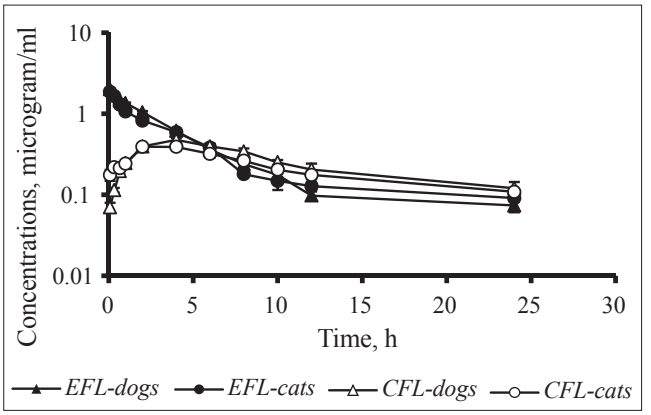

Fig. 1. Serum concentrations of enrofloxacin (EFL) and its active metabolite ciprofloxacin (CFL) after *i.v.* administration of enrofloxacin in dogs and cats

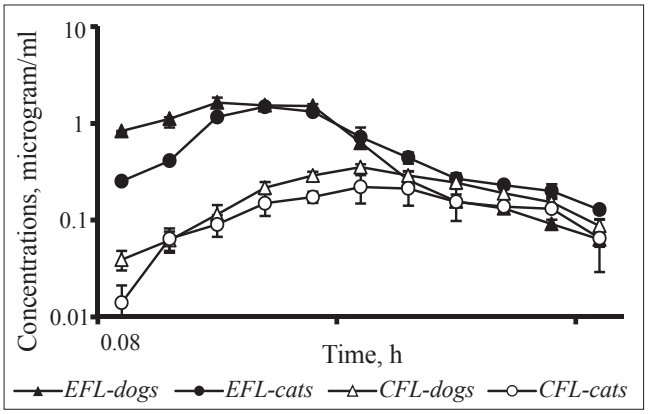

Fig. 2. Serum concentrations of enrofloxacin (EFL) and its active metabolite ciprofloxacin (CFL) after s.c. injection in dogs and cats

Table 1
Serum concentrations of enrofloxacin and its active metabolite ciprofloxacin (μg/ml) after *i.v.* administration of 50 g.kg^{-1} enrofloxacin solution at a dose of 5 mg.kg^{1} in dogs and cats (mean±SEM).

Time, h	Enrofloxacin		Ciprofloxacin (metabolite)	
	Dogs$^{\#}$ (n = 6)	Cats (n = 6)	Dogs$^{\#}$ (n = 6)	Cats (n = 6)
0.08	2.014±0.055	1.860±0.079 (920.35 g.kg^{-1}) *	0.070±0.010	0.176±0.027 (2510.43 g.kg^{-1}) **; ♦♦
0.33	1.693±0.023	1.660±0.056 (980.05 g.kg^{-1}) *; ♦	0.114±0.008	0.218±0.029 (1910.23 g.kg^{-1}) **; ♦♦
0.66	1.477±0.0362	1.296±0.057 (870.75 g.kg^{-1}) *; ♦	0.196±0.013	0.214±0.013 (1090.18 g.kg^{-1})
1	1.358±0.028	1.067±0.058 (780.57 g.kg^{-1}) *; ♦♦	0.246±0.017	0.243±0.008 (980.78 g.kg^{-1})
2	1.044±0.042	0.825±0.045 (790.02 g.kg^{-1}) *; ♦♦	0.395±0.012	0.392±0.030 (990.24 g.kg^{-1})
4	0.615±0.042	0.592±0.027 (960.26 g.kg^{-1})	0.476±0.028	0.390±0.036 (810.94 g.kg^{-1})
6	0.360±0.060	0.383±0.033 (1060.39 g.kg^{-1})	0.396±0.031	0.321±0.031 (810.06 g.kg^{-1})
8	0.240±0.044	0.180±0.012 (750.00 g.kg^{-1})	0.343±0.031	0.263±0.017 (680.80 g.kg^{-1}) ♦
10	0.176±0.029	0.149±0.034 (840.66 g.kg^{-1})	0.252±0.018	0.204±0.016 (800.95 g.kg^{-1})
12	0.098±0.012	0.128±0.015 (1300.61 g.kg^{-1})	0.206±0.038	0.176±0.021 (850.43 g.kg^{-1})
24	0.074±0.013	0.091±0.009 (1220.97 g.kg^{-1}) ♦♦	0.121±0.023	0.109±0.008 (900.08 g.kg^{-1})

Table 2
Serum concentrations of enrofloxacin and its active metabolite ciprofloxacin (μg/ml) after *s.c.* administration of 50 g.kg^{-1} enrofloxacin solution at a dose of 5 mg.kg^{-1} in dogs and cats (mean±SEM)

Time, h	Enrofloxacin		Ciprofloxacin (metabolite)	
	Dogs$^{\#}$ (n = 6)	Cats (n = 6)	Dogs$^{\#}$ (n = 6)	Cats (n = 6)
0.08	0.834±0.042	0.252±0.014 (300.21 g.kg^{-1}) *; ♦	0.039±0.009	0.014±0.007 (350.89 g.kg^{-1}) *; ♦
0.33	1.116±0.208	0.411±0.015 (360.82 g.kg^{-1}) ♦	0.062±0.014	0.064±0.018 (1030.23 g.kg^{-1})
0.66	1.645±0.077	1.165±0.015 (700.82 g.kg^{-1}) **; ♦	0.114±0.029	0.090±0.023 (780.95 g.kg^{-1})
1	1.534±0.063	1.485±0.058 (960.81 g.kg^{-1})	0.216±0.031	0.149±0.039 (680.98 g.kg^{-1}) *; ♦
2	1.512±0.276	1.319±0.026 (870.24 g.kg^{-1})	0.289±0.028	0.1 73±0.023 (590.86 g.kg^{-1}) **; ♦♦
4	0.628±0.062	0.718±0.041 (1140.33 g.kg^{-1})	0.352±0.026	0.220±0.072 (620.50 g.kg^{-1}) *; ♦♦
6	0.259±0.028	0.442±0.060 (1700.66 g.kg^{-1}) *; ♦	0.289±0.030	0.212±0.071 (730.36 g.kg^{-1})
8	0.156±0.019	0.268±0.037 (1710.79 g.kg^{-1}) *; ♦	0.244±0.028	0.154±0.056 (630.11 g.kg^{-1})
10	0.132±0.010	0.230±0.019 (1740.24 g.kg^{-1}) *; ♦	0.189±0.019	0.138±0.007 (730.02 g.kg^{-1})
12	0.091±0.011	0.200±0.034 (2190.78 g.kg^{-1}) **; ♦	0.153±0.020	0.131±0.035 (850.62 g.kg^{-1})
24	0.063±0.010	0.128±0.012 (2030.17 g.kg^{-1}) **; ♦♦	0.087±0.015	0.065±0.036 (740.71 g.kg^{-1})

For ALL Tables
serum concentrations in dogs are used for comparison and equal 1000 g.kg^{-1};
♦ – statistically significant difference vs dogs in ANOVA: ♦ $p < 0.05$; ♦♦ $p < 0.01$;
* – statistically significant vs dogs in Mann-Whitney U test: * $p < 0.05$; ** $p < 0.01$.

tected in the blood serum of the two species between 0.08 and 24 hours after *i.v.* and *s.c.* injection (Tables 1 and 2).

After *i.v.* administration, the serum time-concentrations curves fitted a two-compartmental pharmacokinetic model, while after *s.c.* – one-compartmental model.

Serum ciprofloxacin concentrations after *i.v.* and *s.c.* application of enrofloxacin in dogs and cats are shown in Tables 1 and 2.

Pharmacokinetic analysis

The observed statistically significant differences in pharmacokinetic parameters between dogs and cats for both routes of enrofloxacin administration, demonstrated by longer biological half-life and mean residence time, larger volume of distribution, higher $AUC_{0\to\infty}$, C_{max} and T_{max} values; lower absolute bioavailability of enrofloxacin in cats, are presented in Tables 3 and 4.

Table 3
Some pharmacokinetic parameters of enrofloxacin after single *i.v.* administration of enrofloxacin at a dose of 5 mg.kg^{-1} in dogs and cats (mean±SEM)

Parameter	Units	Compartmental method		Noncompartmental analysis	
		Dogs$^{\#}$ (n = 6)	Cats (n = 6)	Dogs$^{\#}$ (n = 6)	**Cats** (n = 6)
K_{12}	h^{-1}	1.4330±0.362	0.6147±0.064 (420.90 g.kg^{-1}) ♦♦	–	–
K_{21}	h^{-1}	3.5533±0.735	1.1913±0.213 (530.79 g.kg^{-1})***; ♦♦♦**	–	–
$t_{1/2\alpha}$	h	0.150±0.033	0.402±0.062 (2680.00 g.kg^{-1}) ***; ♦♦**	–	–
$t_{1/2\beta}$	h	2.797±0.332	3.908±0.352 (1390.72 g.kg^{-1}) ♦	4.673±0.290	5.625±0.25 (1200.37 g.kg^{-1}) *; ♦
MRT	h	4.023±0.464	5.230±0.355 (1300.00 g.kg-1) ♦	5.840±0.467	7.410±0.412 (1260.88 g.kg^{-1}) ***; ♦**
V_c	l/kg	2.403±0.104	2.490±0.072 (1030.62 g.kg^{-1})	–	–
V_t	l/kg	0.863±0.072	1.513±0.191 (1750.32 g.kg^{-1}) ***;♦**	–	–
V_{ss}	l/kg	3.08±0.068	3.890±0.189 (1260.30 g.kg^{-1}) ***; ♦♦**	3.617±0.092	4.660±0.234 (1280.84 g.kg^{-1})****; ♦♦**
Cl_B	ml/min/kg	2.365±0.955	12.793±0.746 (1030.46 g.kg^{-1})	6.38±0.736	10.647±0.708 (1000.08 g.kg^{-1})
$AUC_{0\to\infty}$	μg.h/ml	6.950±0.571	7.900±0.514 (1130.67 g.kg^{-1})	8.045±0.601	9.330±0.517 (1150.97 g.kg^{-1})

$t_{1/2\alpha}$ – distribution half-life; $t_{1/2\beta}$ – elimination half-life; MRT – mean residence time; K_{12} and K_{21} – hybrid rate constants between the central and peripheral compartments; V_{ss} – steady-state volume of distribution; V_c – volume of distribution in the central compartment; V_t – volume of distribution in the peripheral compartment; Cl_B – total body clearance; $AUC_{0\to\infty}$ – area under the serum concentration curve from time 0 to infinity

Table 4
Some pharmacokinetic parameters of enrofloxacin after single *s.c.* administration of enrofloxacin at a dose of 5 mg.kg^{-1} in dogs and cats (mean±SEM)

Parameter	Units	Compartmental method		Noncompartmental analysis	
		Dogs$^{\#}$ (n = 6)	Cats (n = 6)	Dogs$^{\#}$ (n = 6)	**Cats** (n = 6)
$t_{1/2abs.}$	h	0.140±0.027	0.870±0.449 (6210.43 g.kg^{-1}) **	–	–
$t_{1/2\beta}$	h	2.122±0.147	5.120±2.664 (2410.28 g.kg^{-1})	4.580±0.183	6.138±0.186 (1340.02 g.kg^{-1})****; ♦♦♦**
MRT	h	3.400±0.195	7.488±2.781 (2200.24 g.kg^{-1})	5.678±0.287	9.655±1.296 (1700.04 g.kg^{-1}) ****; ♦**
$AUC_{0\to\infty}$	μg.h/ml	5.955±0.499	5.683±0.237 (950.43 g.kg^{-1})	6.470±0.441	6.333±0.448 (970.88 g.kg^{-1})
T_{max}	h	0.702±0.041	1.232±0.029 (1750.50 g.kg^{-1}) **	0.660±0.000	1.000±0.000 (1510.52 g.kg^{-1})
C_{max}	μg/ml	1.232±0.029	1.498±0.043 (1210.59 g.kg^{-1})	1.645±0.077	1.780±0.060 (1080.21 g.kg^{-1})
F	**%**	5.622±4.278	72.207±3.094 (840.33 g.kg^{-1}) *; ♦	8.625±4.060	70.809±2.672 (900.06 g.kg^{-1}) *; ♦

$t_{1/2abs.}$ – absorption half-life; $t_{1/2\beta}$ – elimination half-life; MRT – mean residence time; $Vd_{(area)}$ – volume of distribution; $AUC_{0\to\infty}$ – area under the serum concentration curve from time 0 to infinity; C_{max} – maximum serum concentration; T_{max} – time to reach maximum serum concentration; F – absolute bioavailability;

Table 5
Some pharmacokinetic parameters of the active metabolite ciprofloxacin after single *i.v.* and *s.c.* injection of 5 mg.kg^{-1} enrofloxacin in dogs and cats – *noncompartmental analysis* (mean± SEM)

Parameter	Units	Intravenous application		Subcutaneous application	
		Dogs$^{\#}$ (n = 6)	Cats (n = 6)	Dogs$^{\#}$ (n = 6)	Cats (n = 6)
$t_{1/2\beta}$	h	10.367±1.264	11.567±1.100 (1110.58 g.kg^{-1})	9.932±0.643	11.828±1.876 (1190.09 g.kg^{-1})
MRT	h	15.327±2.166	18.173±1.527 (1180.57 g.kg^{-1})	5.103±0.884	18.098±2.718 (1190.83 g.kg^{-1})
$AUC_{0\rightarrow\infty}$	μg.h/ml	6.925±0.643	7.063±0.224 (1010.99 g.kg^{-1})	4.777±0.510	4.155±0.636 (860.98 g.kg^{-1})
$Vd_{(area)}$	l/kg	10.257±0.700	12.662±0.995 (1230.44 g.kg^{-1})	13.520±1.179	20.038±2.809 (1480.21 g.kg^{-1})
C_{max}	μg/ml	0.476±0.028	0.437±0.030 (910.81 g.kg-1)	0.3522±0.026	0.344±0.021 (970.67 g.kg^{-1})
T_{max}	h	4.000±0.000	2.667±0.422 (660.68 g.kg^{-1})	4.000±0.000	3.500±0.719 (870.50 g.kg^{-1})
MR	%	5.625±2.036	77.065±5.467 (990.00 g.kg^{-1})	68.870±4.539	59.867±9.462 (860.93 g.kg^{-1})

$t_{1/2\beta}$ – elimination half-life; MRT – mean residence time; $AUC_{0\rightarrow\infty}$ – area under the serum concentration curve from time 0 to infinity; $Vd_{(area)}$ – volume of distribution; C_{max} – maximum serum concentration; T_{max} – time to reach maximum serum concentration; MR – metabolic ratio ($AUC_{ciprofloxacin}/AUC_{enrofloxacin}$);
\# serum concentrations in dogs are used for comparison and equal 1000 g.kg^{-1};

Discussion

The lowest blood serum enrofloxacin concentrations after *s. c.* injection in cats were detected by hour 0.08, consisting 300.21 g.kg^{-1} of respective values observed for the same time interval in dogs. For this route of drug application, serum enrofloxacin levels in cats were lower until the 2nd hour, whereas between post administration hours 4 and 24 they were higher than those of dogs were with respective percentages ranging from 2190.78 to 1114.33 g.kg^{-1}.

After intravenous injection of the same dose of the drug, the concentrations of the active metabolite in cats were significantly higher for the first blood sampling intervals (distribution phase), whereas in the latter intervals (elimination phase) they were lower than those in dogs. It is apparent that following *s. c.* treatment, the blood ciprofloxacin concentrations in cats were substantially lower as compared to respective levels in dogs.

After *i.v.* injection of enrofloxacin in both carnivore species, it was established that the distribution half-life ($t_{1/2\alpha}$) of the quinolone in cats was almost three times longer vs that of dogs and that observed differences were statistically significant. In methods of pharmacokinetic analysis (compartmental and noncompartmental), elimination half-life ($t_{1/2\beta}$) and mean residence time (MRT) of the drug in cats were statistically significantly higher, whereas the areas under the serum concentration curve ($AUC_{0\rightarrow\infty}$) was insignificantly higher in cats.

It could be seen that following *s.c.* application, the absorption half-life ($t_{1/2abs}$) of the drug from the injection site increased statistically significantly. For this route of application, the elimination half-life ($t_{1/2\beta}$) and mean residence time (MRT) were considerably longer in cats as compared to dogs. The time needed to reach maximum concentrations after *s c.* enrofloxacin administration (T_{max}) increased statistically significantly. A similar tendency was observed for maximum serum concentrations (C_{max}) which were higher in cats than in dogs. The *s. c.* injection of the same dose in the same muscles resulted in statistically significantly lower absolute bioavailability (F) of enrofloxacin in cats as compared to dogs.

In cats, longer elimination half-life ($t_{1/2\beta}$) and MRT of the active metabolite were observed than respective values in dogs for both routes of treatment.

The maximum serum ciprofloxacin concentrations (C_{max}) in cats after *i.v.* and *s.c.* application were lower than serum concentrations in dogs. The time to reach them (T_{max}) was also shorter in cats than in dogs. A similar tendency was shown for the metabolic ratio (MR), which was lower in cats for both routes of enrofloxacin application.

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