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PHARMACOKINETICS OF CIPROFLOXACIN IN PIGS AFTER SINGLE INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION

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ABSTRACT

The pharmacokinetics of ciprofloxacin in pigs after single intravenous or intramuscular application was followed out. Blood concentrations were assayed using HPLC with UV-detection. By means of the TopFit, v. 2.0. software, the pharmacokinetic parameters were calculated by two pharmacokinetic models – compartmental and non-compartmental.

After *i.v.* application, the respective values of calculated pharmacokinetic parameters were as followed: $t_{1/2\alpha}$ = 0.54 h; $t_{1/2\beta}$ = 5.92 h and $t_{1/2\beta}$ = 5.76 h; MRT = 8.74 h and MRT = 8.41h; $AUC_{0\rightarrow\infty}$= 23.14 μg.h/ml and $AUC_{0\rightarrow\infty}$= 22.24 μg.h/ml; V_{ss}= 4.87 l/kg and $Vd_{(area)}$ = 5.14 l/kg.

After *i.m.* application of ciprofloxacin, the respective values of calculated pharmacokinetic parameters were as followed: $t_{1/2\alpha}$ = 0.46 h; $t_{1/2\beta}$ = 4.83 h and $t_{1/2\beta}$ = 4.61 h; MRT = 9.89 h and MRT = 9.68 h; $t_{1/2abs.}$ = 0.56 h; MAT = 1.15 h and MAT = 1.12 h; C_{max} = 0.714 μg/ml and C_{max} = 0.625 μg/ml; T_{max}= 0.76 h and T_{max}= 0.88 h; $AUC_{0\rightarrow\infty}$ = 17.630 μg.h/ml and $AUC_{0\rightarrow\infty}$ = 16.835 μg.h/ml; F = 76.23% and F = 75.69%.

Key words: ciprofloxacin, pharmacokinetics, pigs.

Introduction

Gram-negative infections in pigs cause serious illnesses. The antimicrobial therapy for their treatment includes the use of chemotherapeutics from the group of fluorinated quinolones. In the veterinary clinical practice, the drug enrofloxacin is commonly prescribed for treatment of Gram-negative and Gram-positive infections in animals. Another fluoroquinolone, permitted for use in chickens and pigs is ciprofloxacin. It is widely applied and investigated in human medicine (Müler *et al.*, 1999; Morlet *et al.*, 2000; Hassan *et al.*, 2007). Pharmacokinetic studies with ciprofloxacin were conduced in animals as well – rats (Dautrey *et al.*, 1999; Tung-Hu Tsaj *et al.*, 2001), chickens (Atta Sharif, 1997; García Ovando, 1999; Anadón *et al*., 2001; Raina *et al.*, 2007; Raina *et al.*, 2008), rabbits (Bashir, 2007; Bashir *et al.*, 2007; Bashir *et al.*, 2008), dogs (Albarellos *et al*., 2006; Boothe *et al.*, 2006; Hendrix and Cox, 2008), cats (Boothe *et al.*, 2006), goats (Iqbal *et al.*, 2007; Raina *et al.*, 2008; Javed *et al.*, 2009; Iqbal *et al.*, 2011), sheep (Javed *et al.*, 2009; Iqbal *et al.*, 2012) and calves (Nows *et al.*, 1988; Saini and Srivastava, 2001; Javed *et al.*, 2009).

The antimicrobial activity of ciprofloxacin against various *Pseudomonas* strains is attributed to the pyperazine ring attached to position 7, while the fluorine atom at position 6 confers activity against Gram-positive microbial pathogens (Vancustem *et al.*, 1990).

The activity spectrum of ciprofloxacin is broad, it exhibits activity against Gram-negative and some Gram-positive pathogens, *Mycoplasma* spp., *Chlamydia* spp. and *Rickettsia* spp. (Hannan *et al.*, 1989; Prescott and Yelding, 1990). It is effective against anaerobic bacteria too (Prabhala *et al*., 1984). The antibacterial effect mechanism is mediated through inhibition of the enzyme topoisomerase, aka DNA-gyrase (Gellert, 1981).

Due to its good solubility in lipids and the low degree of protein binding, ciprofloxacin is characterized with a large volume of distribution, thus allowing high concentrations of the drug to reach numerous tissues and body fluids in the different animal species (Neer, 1988).

The physiological differences among the animal species do not permit extrapolation of dose regiments from one species to another. This was the incentive of our study, aiming to follow out the pharmacokinetic behaviour – absorption, distribution, elimination and bioavailability – of ciprofloxacin after intravenous and intramuscular injection to pigs.

Material and methods

Animals and housing. The pharmacological experiment was performed in 8 clinically healthy, sexually intact pigs, Danube white×Landrace crosses, equal number of both genders. The animals were 10 weeks of age and weighed 14.3–18.9 kg.

The pigs were housed freely in 4.5×1.9 m pens with brick floors, with common feeding and watering troughs. The animals were divided into 2 groups depending on the gender (4 pigs per pen). The premise with pens was continuously aerated and with mixed light regimen (dark and light), and air humidity 55%. The ambient temperature was 23–24 °C. The animals were fed compound grower feed, and water was available *ad libitum*.

Drugs. In this study, ciprofloxacin hydrochloridum was used, purchased from Actavis Ltd, Sofia, and stored in a refrigerator at 4 °C until use. It was dissolved *ex tempore* in sterile distilled water for parenteral use to obtain 5% solution for intravenous and intramuscular application.

Experimental design. ***Prior to application, the drug solutions were warmed in a water bath to 37 °C. The intravenous application was in the right ear* v. auricularis*, and the intramuscular – in the neck muscles. The tested quinolone, previously dissolved in sterile distilled water, was applied once, either intravenously or intramuscularly at a dose of 10 mg/kg. A 15-day "wash out" period was allowed between both routes of administration for complete elimination of the drug and its metabolites. Blood for analysis after* i.v. *treatment was collected before the treatment and at post treatment hours 0.08, 0.17, 0.33, 0.50, 1, 2, 4, 6, 8, 12 and 24 h. The sampling intervals after* i.m. *application were: 0 h, 0.17, 0.33, 0.50, 1, 2, 4, 6, 8, 12 and 24 h.***

Blood samples. Blood samples were collected from the orbital sinus (*sinus ophthalmicus*) in capped Eppendorf tubes and left for 2 h at room temperature. The serum was separated by centrifugation at 1500×*g* for 15 min. Blood serum samples was stored in capped Eppendorf tubes frozen at –25 °C until analysis.

Sample analysis. ***For assays, ciprofloxacin hydrochloridum substance was used, as well as acetonitrile HPLC grade (Labscan); triethylamine (TEA; Merck); tetrabutyl ammonium hydrochloride 40% (TBA, Merck); phosphoric acid 85% (Merck) and perchloric acid for analysis 70% (Merck). The water used in analyses was treated through a Millipore purifying system.***

Serum ciprofloxacin concentrations of treated pigs were assayed by a highly sensitive automated technique – high-performance liquid chromatography with UV detection. The analysis protocol was that of Imre *et al*. (2003), already used by us, with a slight modification consisting of substituting blood serum for plasma. Serum concentrations were analyzed on a reverse-phase HPLC system Waters equipped with quaternary pump, fluorescence detector, protected and analytical columns Lichrospher (Beckman).

The mobile phase consisted of acetonitrile and water (1:1), supplemented with 3% potassium phosphate buffer, 2% TEA and 2% TBA. Mobile phase pumping rate was 1.2 ml/min.

The HPLC system was connected to a PC with Waters Empower software.

Blood proteins were precipitated by adding two acids – 85% phosphoric acid and 70% perchloric acid to 100 μl serum. Then, serum was homogenised by a vortex mixer and centrifuged for 10 min at 1500×*g*. One hundred μl of supernatant aliquots were injected in the HPLC system.

Assay was validated by the method of external calibration curves from spiked matrix standards. The limit of quantitation (LOQ) for ciprofloxacin was 0.025 μg/ml, and the limit of detection (LOD) – 0.005 μg/ml.

Pharmacokinetic analysis. The TopFit, v. 2.0. software was used for describing the behaviour of the tested fluoroquinolone after single intravenous or intramuscular injection in this pharmacokinetic experiment (Henzel *et al.*, 1993). Two pharmacokinetic models were used – the compartmental and non-compartmental analysis (Gibaldi and Perrier, 2007). The pharmacokinetic modelling was done according to Akaike's criterion (Yamaoka *et al.*, 1978). Determined pharmacokinetic parameters were presented as means (Mean) ± standard error of means (SEM).

The following parameters were determined: rate constants for the distribution (α) and elimination (β) phases; drug transfer rate constants from the central to the peripheral (k_{12}) and from the tissue to the central (k_{21}) compartment; absorption rate constant for i.m. application ($k_{abs.}$), and elimination rate constant (k_{el}). The distribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$), the mean residence time (MRT) and absorption half-life ($t_{1/2abs.}$); the volume of distribution in the central (V_c) and peripheral (V_t) compartments, as well as steady state volume of distribution (V_{ss}) were determined. The total body clearance (Cl_B); back-extrapolated zero serum concentration of the fluoroquinolone (C°p); area under the serum concentration curve from hour 0 to the limit of quantitation ($AUC_{0\rightarrow LOQ}$) and from hour 0 to infinity ($AUC_{0\rightarrow\infty}$); maximum serum drug concentration (C_{max}), and the time to reach maximum serum concentration (T_{max}) were calculated

The absolute bioavailability (F) after intramuscular injection of fluoroquinolone solution was calculated as per the formula:

$$F\ (\%) = [(AUC_{0\rightarrow\infty\ i.m.} \times D_{i.v.})/ [(AUC_{0\rightarrow\infty\ i.v.} \times D_{i.m.})] \times 100.$$

On the basis of mean residence time (MRT) values after *i.v.* and *i.m.* application, individual mean absorption times (MAT) were calculated as:

$$MAT = MRT_{i.m.} - MRT_{i.v.}$$

Results

After intravenous application of ciprofloxacin, serum concentrations were higher than 0.076 μg/ml until the post treatment hour 24. The analysis of individual time *vs* concentration curves showed comparable serum values, usually close to mean values.

Serum concentration curves in both routes of administration corresponded to two-compartmental open pharmacokinetic model of distribution and elimination, with a rapid distribution phase and a slower elimination phase (Fig. 1).

After intramuscular injection, serum ciprofloxacin concentrations appeared very soon – after 0.17 h and persisted in detectable concentrations over 12 hours (Fig. 1). The maximum levels (C_{max}) were attained very soon after *i.m.* application (by the 1st hour) and in 2 pigs – even earlier – after 0.50 h.

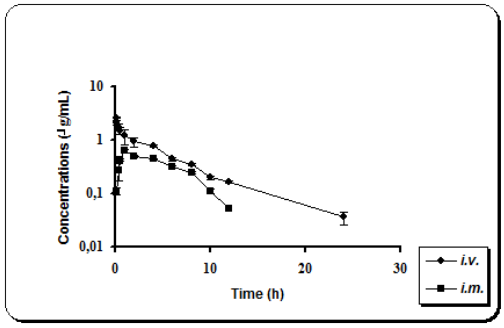

Figure 1: Serum ciprofloxacin concentrations after single intravenous (*i.v.*) and intramuscular (*i.m.*) application in pigs

Table 1: Pharmacokinetic parameters of ciprofloxacin after single intravenous application to pigs at a dose of 10 mg/kg (Mean±SEM)

Parameter	Units	Compartmental method		Parameter	Units	Non-compartmental analysis	
		Mean	SEM			Mean	SEM
$t_{1/2\alpha}$	h	0.54	0.03	$t_{1/2\beta}$	h	5.76	0.09
$t_{1/2\beta}$	h	5.92	0.08	**MRT**	h	8.41	0.08
MRT	h	8.74	0.11	$AUC_{0\rightarrow 24\,h}$	µg.h/mL	21.78	1.04
k_{12}	h^{-1}	2.04	0.08	$AUC_{0\rightarrow\infty}$	µg.h/mL	22.24	2.47
k_{21}	h^{-1}	0.29	0.05	Cl_B	mL/min/ kg	7.16	0.20
k_{el}	h^{-1}	0.26	0.04	V_d	L/kg	5.14	0.09
Cl_B	mL/min/ kg	1.44	0.11	$AUMC_{0\rightarrow\infty}$	µg.h/mL	348.23	5.24
$AUC_{0\rightarrow\infty}$	µg.h/mL	23.14	0.72	r^2	-	0.99	0.08
V_c	L/kg	3.91	0.02				
V_{ss}	L/kg	4.87	0.03				

$t_{1/2\alpha}$ – distribution half-life; $t_{1/2\beta}$ – elimination half-life; MRT – mean residence time; k_{12} – transfer rate constant from the central to the peripheral compartment; k_{21} – transfer rate constant from the peripheral to the central compartment; k_{el} – elimination rate constant; V_{ss} – steady-state volume of distribution; Vc – volume of distribution in the central compartment; Vd – volume of distribution; CL_B – total body clearance; $AUC_{0\rightarrow\infty}$ – area under the serum concentration curve from time 0 to infinity; $AUC_{0\rightarrow 24h}$ – area under the serum concentration curve from hour 0 to hour 24; r^2 – correlation coefficient.

Table 1 presents the pharmacokinetic parameters of ciprofloxacin after its intravenous application to pigs. Similarly to other fluoroquinolones, it is characterised with a long elimination half-life ($t_{1/2\beta}$) and a rapid distribution phase as could be seen from the distribution half-life ($t_{1/2\alpha}$). The fluoroquinolone left rapidly the central compartment and spread at a large volume in body fluids and the other tissues in pigs, as shown by values of k_{12}, k_{21}, V_c and V_{ss}.

The area under the serum concentration curve ($AUC_{0\rightarrow\infty}$) was 23.14±0.18 µg.h/ml (Table 1). The steady-state volume of distribution V_{ss} was rather high – 4.87±0.32 l/kg (Table 1).

Table 2 presents pharmacokinetic parameters depicting ciprofloxacin behaviour after single intramuscular injection. The absorption of the drug from the neck muscles of pigs was rapid and maximum serum concentrations are attained within a short time as seen from $t_{1/2abs.}$, T_{max} and C_{max}. Maximum serum concentrations (C_{max}) for this route of application, determined by the two pharmacokinetic models were 0.714 µg/ml and 0.625 µg/ml, respectively and appeared after 0.76 h and 0.88 h respectively.

The distribution half-life ($t_{1/2\alpha}$) was short – 0.46 h (Table 2).

Table 2: Pharmacokinetic parameters of ciprofloxacin after single intramuscular application to pigs at a dose of 10 mg/kg body weight (Mean±SEM)

Parameter	Units	Compartmental analysis		Parameter	Units	Non-compartmental analysis	
		Mean	SEM			Mean	SEM
$t_{1/2\alpha}$	h	0.46	0.01	$t_{1/2\beta}$	h	4.61	0.16
$t_{1/2\beta}$	h	4.83	0.02	MRT	h	9.68	0.74
MRT	h	9.89	0.13	$AUC_{0\rightarrow 24\ h}$	μg.h/mL	14.23	2.08
$t_{1/2abs.}$	h	0.56	0.06	$AUC_{0\rightarrow\infty}$	μg.h/mL	16.84	1.74
$AUC_{0\rightarrow\infty}$	μg.h/mL	16.63	1.34	C_{max}	μg/mL	0.63	0.12
C_{max}	μg/mL	0.71	0.23	T_{max}	h	0.88	0.26
T_{max}	h	0.76	0.02	$AUMC_{0\rightarrow\infty}$	μg.h/mL	512.34	4.24
MAT	h	1.15	0.23	MAT	h	1.12	0.44
F	%	76.23	2.76	F	%	75.69	1.92
				r^2	-	0.991	0.05

$t_{1/2\alpha}$ – distribution half-life; $t_{1/2\beta}$ – elimination half-life; $t_{1/2abs}$ – absorption half-life; MRT – mean residence time; MAT – mean absorption time; $AUC_{0\rightarrow 24h}$ – area under the plasma concentration curve from hour 0 to hour 24; C_{max} – maximum plasma concentration; T_{max} – time to reach maximum plasma concentration; F – absolute bioavailability; r^2 – correlation coefficient.

It should be noted that biological half-life ($t_{1/2\beta}$) was insignificantly shorter than that after *i.v.* application – 4.83 h and 4.61 h, respectively (Table 2). An opposite tendency was exhibited by MRT, which was 9.89 h and 9.68 h determined by both pharmacokinetic models

Discussion

Data from the present pharmacokinetic experiment suggested that serum concentrations curves for both routes of administration of the tested fluoroquinolone fitted the two-compartmental model. They were comparable to previous investigations in other animal species – cats (Albarelos, 2004), broiler chickens (Atta and Sharif, 1997; Anadón *et al*., 2001), sheep (Javed *et al.*, 2009; Iqbal *et al*., 2012), goats (Iqbal *et al*., 2007; Raina *et al*., 2008; Javed *et al.*, 2009; Iqbal *et al*., 2011), calves (Mohan and Garg, 2003), cows and buffaloes (Javed *et al.*, 2009) and rabbits (Bashir *et al*., 2007; Bashir *et al*., 2008a; Bashir *et al*., 2008b; Parikh *et al*., 2008).

The present study in sexually intact clinically healthy pigs established rapid distribution of *i.v.* and *i.m.* injected ciprofloxacin followed by slower elimination, a trend, observed after application of other fluoroquinolones in pigs (enrofloxacin and pefloxacin) (Dimitrova *et al*., 2009.; Bimazubite *et al*., 2009; Dimitrova *et al*., 2012). A similar tendency was reported by other researchers in other species – broiler chickens (Anadon *et al*., 2001; Bashir *et al*., 2008a; Raina *et al*., 2008; Iqbal *et al*., 2011).

For both used routes of administration in pigs, ciprofloxacin was characterized with a relatively long biological half-life which after *i.v.* injection was 5.92±0.98 h (compartmental model) and 5.76±0.92 h (non-compartmental analysis), and after intramuscular application – 4.83±0.24 h and 4.61±0.16 h, respectively (Tables 1 and 2). The elimination half-life values ($t_{1/2\beta}$) after *i.v.* injection of the quinolone were similar to those reported in broiler chickens (Raina *et al*., 2007), but lower than those in chickens (Atta and Sharif, 1997; Anadón *et al*., 2001) and rabbits (Bashir *et al*., 2007), and higher than values in cats (Albarelos *et al*., 2004), sheep (Javed *et al*., 2009), goats (Raina *et al*., 2008; Javed *et al*., 2009), calves and buffalo calves (Saini and Srivastava, 2001; Mohan and Garg, 2003), buffaloes and cattle (Javed *et al*., 2009).

The V_c and V_{ss} values determined by the two pharmacokinetic models showed that ciprofloxacin penetrated well in all body tissues and was distributed within a large volume, similarly to what was reported by others (Anadón *et al*., 2001; Saini and Srivastava, 2001; Javed *et al*., 2009; Iqbal *et al*., 2011).

The area under the time concentration curve ($AUC_{0\rightarrow\infty}$) for intravenously administered ciprofloxacin in pigs was comparable to that in rabbits (Prikh *et al*., 2008), cats (Albarellos *et al*., 2004) and broiler chickens (Anadón *et al*., 2001).

We demonstrated that the studied gyrase inhibitor was absorbed well and rapidly in the muscles of the neck, as evidenced by values of pharmacokinetic parameters $t_{1/2abs.}$, MAT, C_{max} and T_{max} (Table 2) and HPLC-assayed serum concentrations, which were detected to be sufficiently enough high as early as the 10^{th} min in all pigs after intramuscular application of the fluoroquinolone – over 0.10 μg/ml, and persisted at that level until post application hour 10.

After intramuscular injection, the ciprofloxacin was rapidly absorbed and resulting maximum serum concentrations (C_{max}) were comparable or close to those reported in cats (Albarellos *et al*., 2004), but lower that those in buffaloes, cows and goats (Javed *et al*., 2009; Iqbal *et al*., 2007). The time for attaining maximum serum levels (T_{max}) was similar to values in those ruminant species – within 0.86 and 0.90 h.

In the present investigation, biological half-life values after *i.m.* application ($t_{1/2\beta}$) and mean residence times (MRT) were longer than values reported in buffaloes (Javed *et al*., 2009), cows (Javed *et al*., 2009), sheep (Javed *et al*., 2009) and goats (Javed *et al*., 2009; Iqbal *et al*., 2011). Probable reasons are differences related to the species, hormonal status of animals and the different dosage of the drug.

The absolute bioavailability (F) of ciprofloxacin for this non-venous route of application, determined according to the two pharmacokinetic models – compartmental and non-compartmental analysis (Table 2) was higher than values established in cats (Albarellos *et al*., 2004) but comparable to those observed by Dimitrova *et al*. (2009b) in sheep.

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