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Disposition Kinetics and Optimal Dosage of Ciprofloxacin in Healthy Domestic Ruminant Species

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Abstract

The purpose of this experimental study was to determine the disposition kinetics and optimal dosages of ciprofloxacin in healthy domestic ruminant species including adult female buffalo, cow, sheep and goat. The drug was given as a single intramuscular dose of 5 mg/kg. The plasma concentrations of the drug were determined with HPLC and pharmacokinetic variables were determined. The biological half-life ($t_{1/2}$ ß) was longer in cows (3.25 ± 0.46 h) followed by intermediate values in buffaloes (3.05 ± 0.20 h) and sheep (2.93 ± 0.45 h) and shorter in goats (2.62 ± 0.39 h). The volume of distribution (V_d) in buffaloes was 1.09 ± 0.06 l/kg, cows 1.24 ± 0.16 l/kg, sheep 2.89 ± 0.30 l/kg and goats 3.76 ± 0.92 l/kg. Total body clearance (Cl_B) expressed in l/h/kg was minimum in buffaloes 0.25 ± 0.02 followed by values in cows 0.31 ± 0.02 and sheep 0.75 ± 0.04 and maximum in goats 1.09 ± 0.11.

An optimal dosage regimen for 12-h interval consisted of 5.17, 5.62, 6.54 and 6.10 mg/kg body weight as priming and 4.84, 5.37, 6.26 and 5.91 mg/kg body weight as maintenance intramuscular dose in buffalo, cow, sheep and goat, respectively. The manufacturers of ciprofloxacin have claimed 5 mg/kg dose to be repeated after 24 h. However, the investigated dosage regimen may be repeated after 12 h to maintain MIC at the end of the dosage interval. Therefore, it is imperative that an optimal dosage regimen be based on the disposition kinetics data determined in the species and environment in which a drug is to be employed clinically.

Disposition kinetics, ciprofloxacin, domestic ruminants, dosage

Ciprofloxacin is an important member of the fluoroquinolone group of antibiotics. It is a broad-spectrum antibiotic used to combat various infectious diseases in animals and humans. Information regarding biodisposition of ciprofloxacin shows that it has not been studied in local ruminant species.

Most of the developing countries like Pakistan import raw or finished drugs for their human and veterinary health programmes. Drug developments supported by extensive preclinical and clinical investigations are carried out in the drug exporting countries. In most cases the genetic make up of humans and animals and environmental conditions are different amongst the drug importing and exporting countries. This difference manifests itself through an influence on biochemical and physiological indicators ultimately affecting the disposition kinetics and response to the drugs. Several studies have shown that the pharmacokinetic characteristics, optimal dosage, renal clearance and urinary excretion of the investigated drugs were different under indigenous conditions when compared with the values given in the literature or in the product inserts supplied by the manufacturers (Muhammad et al. 2003; Javed et al. 2003; Javed et al. 2005 ab; Javed et al. 2006; Iqbal et al. 2007).

In view of the above mentioned facts, the present project was planned to investigate disposition kinetics of ciprofloxacin in indigenous adult female buffaloes, cows, sheep and goats under local environmental conditions for suggesting optimal dosage regimen.

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Materials and Methods

Experimental animals

For the study of disposition kinetics of ciprofloxacin, 32 experiments were conducted, 8 each in Nili Ravi buffaloes (368 ± 44 kg), Sahiwal cows (280 ± 13 kg), Lohi sheep (40 ± 2 kg) and Teddy goats (35 ± 2 kg). All the ruminant animals were clinically healthy adult females maintained under similar environmental and managemental conditions at the Livestock Experimental Farm, Institute of Nutrition and Feed Technology, University of Agriculture, Faisalabad, Pakistan. They were stall-fed dry wheat straw and green fodder of the season and had free access to drinking water. Experiments were performed during the months of November and December. These experiments were conducted following approval of Directorates of Research, Advanced Studies and Animal Ethics Committee, University of Agriculture, Faisalabad, Pakistan.

Methodology

Each animal was weighed before the start of each experiment. The animals were restrained in standing position during the experimental procedures. One of the jugular veins was cannulated under strict aseptic conditions with plastic cannula No. 90 (Protex Ltd., England) for the collection of blood samples.

A commercial injectable preparation of ciprofloxacin, CIPROCIN-100®, batch No. 539009 (Han Dong Corporation Ltd., Korea) was used in these studies. Each ml of the injection contained 100 mg of ciprofloxacin. A single dose of ciprofloxacin was injected intramuscularly in the neck region at the dose rate of 5 mg/kg body weight.

Blood samples were collected in heparinized plastic centrifuge tubes. Prior to drug administration, a control blood sample was collected in each experiment. Following drug administration, the blood samples were drawn at 15 and 30 min, then at half-hourly intervals until 3 h followed by the samples collected at 4, 6, 8 and 10 h post medication. Blood samples were centrifuged and plasma was separated and stored at -20 °C until analysis.

Analytical procedures

Ciprofloxacin concentration in plasma was determined by using HPLC (Soback et al. 1994).

Calculations

Disposition kinetics

Pharmacokinetic calculations were done after a two-compartment open model with the computer programme MW/PHARM, version 3.02, by F. Rombout, in cooperation with the University Centre for Pharmacy, Department of Pharmacology and Therapeutics, University of Gronigen & Medi/Ware, copyright 1987–1991.

Dosage regimen

Based on kinetic variables, optimal dosage regimens of ciprofloxacin were calculated in healthy adult female buffaloes, cows, sheep and goats according to the following formulae. Calculation of the maintenance dose (D) was based on the minimum effective concentration ($C°_p$ (min)) of the drug and was given by:

$D = C°_p$ (min). Vd (e^{kt}-1)

The priming dose was obtained by omitting "-1" from the above equation.

Statistical analysis

The mean values and standard error of mean (mean ± SEM) for each concentration and variable were calculated. Analysis of variance (ANOVA) was performed with species as treatments. When a significant F value was obtained, Duncan's Multiple Range Test (DMR) was used to determine which species was different from the other. Statistical analysis was carried out with PC-program MStat-C by Freed, R.D. and Eisensmith, S.P., Michigan State University, USA, and the figure was prepared using Microsoft Excel version 2003.

Results

Disposition kinetics

Mean values of plasma concentration at different time intervals in buffaloes, cows, sheep and goats are given in Fig 1. The statistical appraisal indicated that the buffaloes had the highest, cows and sheep intermediate and the goats showed the lowest plasma concentrations of intramuscularly injected ciprofloxacin. Mean ± SEM results of various disposition kinetic variables in 8 animals of each species along with the inter-species statistical comparison are shown in Table 1.

The mean ± SEM values of maximum concentration (C_{max}) were similar in buffaloes and cows ($P > 0.05$) but were significantly higher ($P < 0.05$) than in sheep and goats. The mean values for the absorption half-life ($t_{1/2}$abs) of ciprofloxacin were similar ($P > 0.05$) in four domestic ruminant species and the same was the case with distribution half-life ($t_{1/2}\ \alpha$). Zero time concentrations (A) of ciprofloxacin in the distribution phase were similar ($P > 0.05$) amongst buffaloes, sheep and goats and were ($P < 0.05$) lower than that in cows. The mean values for the zero time plasma concentration of the drug (B) in the elimination phase were

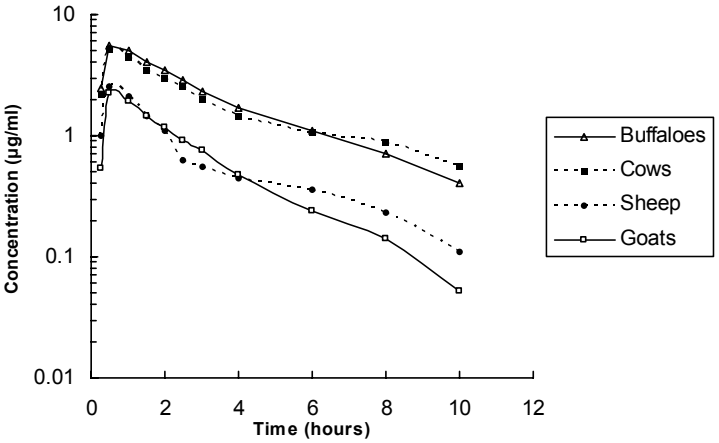

Fig. 1. Mean plasma concentrarion of ciprofloxacin on a semilogarithmic scale versus time after single intramuscular administration (5 mg/kg) in ruminants

similar ($P > 0.05$) in cows and buffaloes but were higher ($P < 0.05$) than those in sheep and goats. The mean values for the absorption half-life ($t_{1/2}$abs) of ciprofloxacin were similar ($P > 0.05$) in the four domestic ruminant species and the same was the case with distribution half-life ($t_{1/2}$ α). The elimination half-life ($t_{1/2}$ ß) was also similar ($P > 0.05$) in the four species of ruminants. No interspecies differences ($P > 0.05$) were noted in the mean values of elimination rate constant (ß). The mean values for the volume of distribution (V_d) were similar ($P > 0.05$) in buffaloes and cows and were lower ($P < 0.05$) than those in sheep and goats. The mean ± SEM value of total body clearance (Cl_B) in buffaloes was similar to that of cows. However, these values were lower ($P < 0.05$) than that in sheep which was in turn lower

Table 1. Mean ± SEM values for the disposition kinetics of ciprofloxacin following intramuscular administration of 5 mg/kg body weight in each of the 8 adult female buffaloes, cows, sheep and goats

Variables	Units	Buffaloes (n = 8)	Cows (n = 8)	Sheep (n = 8)	Goats (n = 8)
C_{max}	(µg/ml)	4.89 ± 0.28A	4.35 ± 0.29A	1.97 ± 0.15B	1.77 ± 0.20B
t_{max}	(h)	0.87 ± 0.03	0.86 ± 0.04	0.88 ± 0.09	0.90 ± 0.04
K_{abs}	(h^{-1})	1.57 ± 0.08	1.27 ± 0.19	1.41 ± 0.22	1.38 ± 0.10
$t_{1/2abs}$	(h)	0.45 ± 0.03	0.73 ± 0.19	0.63 ± 0.16	0.52 ± 0.04
A	(µg/ml)	7.22 ± 0.91B	12.01 ± 2.64A	4.34 ± 0.73B	3.08 ± 0.40B
α	(h^{-1})	1.57 ± 0.08	1.94 ± 0.28	1.61 ± 0.18	1.38 ± 0.10
$t_{1/2}$α	(h)	0.45 ± 0.03	0.40 ± 0.04	0.46 ± 0.05	0.52 ± 0.04
B	(µg/ml)	3.56 ± 0.30A	2.97 ± 0.36A	1.13 ± 0.08B	1.07 ± 0.24B
β	(h^{-1})	0.23 ± 0.01	0.26 ± 0.05	0.26 ± 0.03	0.29 ± 0.03
$t_{1/2}$β	(h)	3.05 ± 0.20	3.25 ± 0.46	2.93 ± 0.45	2.62 ± 0.39
V_c	(l/kg)	0.49 ± 0.04C	0.40 ± 0.06C	1.01 ± 0.11B	1.33 ± 0.16A
V_d	(l/kg)	1.09 ± 0.06B	1.24 ± 0.16B	2.89 ± 0.30A	3.76 ± 0.92A
K_{el}	(h^{-1})	0.54 ± 0.04	0.85 ± 0.20	0.78 ± 0.11	0.74 ± 0.05
k_{12}	(h^{-1})	0.55 ± 0.04A	0.74 ± 0.10A	0.55 ± 0.09A	0.32 ± 0.05B
k_{21}	(h^{-1})	0.71 ± 0.08	0.61 ± 0.08	0.56 ± 0.05	0.62 ± 0.14
Cl_B	(l/h/kg)	0.25 ± 0.02C	0.31 ± 0.02C	0.75 ± 0.04B	1.09 ± 0.11A

Mean values followed by different letters in a row indicate significant difference ($P < 0.05$)

Table 2. Intramuscular dosage regimens of ciprofloxacin (mg/kg) for different dosing intervals in adult female buffaloes, cows, sheep and goats

Species		Dosing interval (h)													
		12				18				24					
		C^0_p(min) or MIC (µg/ml)													
		0.02	0.05	0.1	0.2	0.3	0.02	0.05	0.1	0.2	0.3	0.02	0.05	0.1	0.2	0.3
Buffaloes	P	0.34	0.86	1.72	3.44	5.17	1.37	3.42	6.85	13.69	20.54	5.44	13.61	27.21	54.42	81.63
	M	0.32	0.81	1.61	3.23	4.84	1.35	3.37	6.74	13.47	20.21	5.42	13.55	27.10	54.20	81.30
Cows	P	0.56	1.40	2.81	5.62	8.42	2.67	6.68	13.36	26.73	40.09	12.72	31.80	63.59	127.19	190.78
	M	0.54	1.34	2.68	5.37	8.05	2.65	6.62	13.24	26.48	39.72	12.69	31.74	63.47	126.94	190.41
Sheep	P	1.31	3.27	6.54	13.09	19.63	6.23	15.57	31.15	62.29	93.44	29.64	74.11	148.22	296.43	444.65
	M	1.25	3.13	6.26	12.51	18.77	6.17	15.43	30.86	61.71	92.57	29.59	73.96	147.93	295.85	443.78
Goats	P	2.44	6.10	12.20	24.41	36.61	13.91	34.77	69.54	139.07	208.61	79.23	198.08	396.17	792.33	1188.50
	M	2.37	5.91	11.83	23.66	35.49	13.83	34.58	69.16	138.32	207.48	79.16	197.90	395.79	791.58	1187.37

P = Priming dose
M = Maintenance dose

($P < 0.05$) than the value in goats. The highest clearance value was recorded in goats, and the lowest one in the buffaloes.

Dosage regimen

Based on the kinetic variables, optimal intramuscular priming and maintenance doses of ciprofloxacin in mg/kg body weight for 12-, 18- and 24-h dosing intervals in each species of four adult female ruminants taking minimum inhibitory concentration (MIC) in blood as 0.02, 0.05, 0.1, 0.2 and 0.3 µg/ml are presented in Table 2.

Discussion

Disposition kinetics

Species difference amongst ruminants indicated that after a single intramuscular dose of 5 mg/kg, the highest plasma ciprofloxacin concentration was observed in buffaloes followed in a descending order by cows and sheep, and the lowest in goats (Fig. 1). Such differences in the plasma concentration amongst the animals of different species after an intramuscular injection of a similar dose of the same ciprofloxacin preparation are due to species-dependent variations in biodisposition of ciprofloxacin in these animals. However, in all ruminant species therapeutic concentrations of ciprofloxacin in plasma were maintained until 10 h after the drug administration.

In domestic ruminants of this study the $t_{1/2}$abs (0.45–0.73 h) and $t_{1/2}\ \alpha$ (0.40–0.52 h) do not correspond with 0.15–0.58 h $t_{1/2}$abs (Singh and Srivastava 2000; Al-Nazawi 2005; Rahal et al. 2006) and 0.19–0.37 h $t_{1/2}\ \alpha$ (Shem-Tov et al. 1998; García-Ovando et al. 2000; Saini and Srivastava 2001; Kumar et al. 2003; Aliabadi et al. 2003; Rahal et al. 2006). The values of C_{max} were higher in buffaloes and cows compared to sheep and goats, while t_{max} was almost the same in all four species with a minute difference. The absorption of a drug from the site of administration depends upon physicochemical characteristic and dosage form, while distribution varies with lipid solubility, plasma and tissue protein binding and rate and volume of blood flow to the organ. The C_{max} is dependent on both the extent and rate of drug absorption while t_{max} is closely related to the absorption rate.

Table 3. Reported values of some disposition kinetic indicators in domestic ruminant species

Species	Description	Fluoroquinolone	Dose (mg/kg)	Route	$t_{1/2}\beta$ (h)	V_d (l/kg)	Cl_B (l/h/kg)	Reference
Buffalo	Bulls	Enrofloxacin	5	IM	1.97	0.61	0.21	Verma et al. 1999
	Calves	Ciprofloxacin	5	IV	3.88	3.97	0.71	Saini and Srivastava 2001
	Calves	Enrofloxacin	4	IV	2.92	5.33	1.94	Kumar et al. 2003
	Calves	Enrofloxacin	4	IV	2.9	6.9	1.67	Sharma et al. 2003
	Calves	Gatifloxacin	4	IM	7.45	3.2	0.30	Raipuria et al. 2006
	Calves	Danofloxacin	1.25	IV	4.99	4.11	0.67	Sappal et al. 2006
Cow		Ciprofloxacin	-	-	2.4	2.5	0.73	Nouws et al. 1988
	New-born calves	Enrofloxacin	5	IM	6.6	1.8	0.19	Kaartinen et al. 1997
	One week old calves	Enrofloxacin	6	IM	4.9	2.3	0.39	Kaartinen et al. 1997
		Danofloxacin	1.25	IV	0.91	2.04	1.55	Shem-Tov et al. 1998
	Calves	Ciprofloxacin	5	IM	10.3	34.3	2.42	Singh and Srivastava 2000
	Cross-bred calves	Pefloxacin	5	IV	2.21	1.44	0.45	Srivastava et al. 2000
	Calves	Marbofloxacin	2	IV	4.23	1.28	0.21	Aliabadi and Lees 2002
	Calves	Levofloxacin	4	IM	3.67	1.02	0.20	Dumka and Srivastava 2006
Sheep		Enrofloxacin	-	-	3.7	3.0	0.73	Mengozzi et al. 1996
		Ciprofloxacin	-	-	1.2	1.9	1.08	Munoz et al. 1996
		Danofloxacin	1.25	IV	3.39	3.37	0.71	Aliabadi et al. 2003
		Enrofloxacin	5	IV	3.3	2.91	0.61	Haritova et al. 2003
		Enrofloxacin	5	IV	2.6	2.97	0.86	Rahal et al. 2006
		Enrofloxacin	5	SC	5.77*	2.97	0.36	Rahal et al. 2006
Goat		Enrofloxacin	5	Oral	9.26	3.27	0.24	Elmas et al. 2000
		Ciprofloxacin	10	IV	2.72	3.37	1.18	Garcia Ovando et al. 2000
		Danofloxacin	1.25	IV	1.35	1.41	0.59	Atef et al. 2001
		Difloxacin	5	IV	6.3	1.1	0.13	Atef et al. 2002
		Pefloxacin	10	IV	1.6	5.14	3.60	Abd El-Aty and Goudah 2002
		Pefloxacin	10	IV	1.12	1.08	0.82	Malik et al. 2002
		Enrofloxacin	5	IM	1.39	1.52	0.80	Rao et al. 2002
		Marbofloxacin	2	IV	7.32	1.19	0.24	Waxman et al. 2003
		Ofloxacin	5	IV	15.58	2.85	0.14	Baruah et al. 2004
		Marbofloxacin	2	IV	7.18	1.31	0.23	Waxman et al. 2004
		Enrofloxacin	5	IV	4.7	3.8	0.57	Al-Nawazi 2005
		Enrofloxacin	5	IM	4.4	3.8	0.60*	Al-Nawazi 2005
		Danofloxacin	1.25	IV	4.54	2.64	0.58	Ismail 2006

IV = Intravenous IM = Intramuscular SC = Subcutaneous * = Calculated from data

The values of $t_{1/2}\beta$, V_d and Cl_B in indigenous adult female buffaloes, cows, sheep and goats are comparable to or lower/higher than the most reported literature values in their foreign counterparts (Table 3). The primary mechanism of renal excretion for ciprofloxacin and all other fluoroquinolones is mainly by glomerular filtration (Bregante et al. 1999). Iqbal (2008) reported lower GFR in indigenous domestic ruminants as compared to their foreign counterparts; in female buffaloes 0.72 ml/min.kg, in cow 0.36 ml/min.kg, in sheep 1.33 ml/min.kg and in goats 1.87 ml/min.kg. In the present study, the longer values for elimination half-life in cows, followed by intermediate values in buffaloes and sheep, and shorter values in goats correspond to the above mentioned lower values of GFR in cow, intermediate in buffaloes and sheep and higher GFR in goats. It reflects that the higher the GFR, the lower is the half-life value. The lower GFR in indigenous domestic ruminant species seems to be responsible for longer half-life. Higher than unity values of V_d in

buffaloes, cows, sheep and goats indicate extensive tissue localization of ciprofloxacin in these species. The values for the volume of distribution in buffaloes, cows and sheep are lower, whereas in goats they are higher than most values of ciprofloxacin and other fluoroquinolones given for their foreign counterparts in literature (Table 3). In the present study, total body clearance has been determined in buffaloes, cows, sheep and goats as 4.17 ± 0.33, 5.17± 0.33, 12.5 ± 0.67, 18.2 ± 1.83 ml/min/kg respectively. In another study, the respective GFR values in these animals have been reported as 0.72 ± 0.15, 0.36 ± 0.09, 1.33 ± 0.35 and 1.87 ± 0.39 ml/min/kg (Iqbal 2008). Ciprofloxacin like other fluoroquinolones was expected to be excreted mainly through filtration (Bregante et al. 1999). In the present study, 6 to 14 times higher body clearance values than those of GFR values indicate an involvement of active tubular secretion and/or extra renal elimination of the drug in the ruminant species.

Dosage regimen

For the majority of organisms that are susceptible to ciprofloxacin, the reported MIC values are 0.02–0.3 µg/ml plasma levels that may be accepted as optimal MIC (Alestig 1990; Vance-Bryan et al. 1990; Giguère et al. 1996; Kaartinen et al. 1997; Saini and Srivastava 2001). During the course of therapy, plasma level of an antibiotic should not fall below a minimum inhibitory concentration at the end of a certain dosing interval. The dose recommended by the manufacturer of the pharmaceutical preparation of ciprofloxacin (5 mg/kg/24 h) used in the present investigations failed to maintain the therapeutic concentrations for 24 h in buffaloes, cows, sheep and goats. García-Ovando et al. (2000) reported a 10 mg/kg intravenous dose of ciprofloxacin repeated after 12 h in goats. Intramuscular doses of 5 mg/kg body weight after 12 h have been reported in cross-bred cow calves (Singh and Srivastava 2000).

Based on the 0.02–0.3 µg/ml MIC plasma level of ciprofloxacin, the disposition kinetics data of the present study demonstrate that the optimal dosage regimen for a 12-h dosing interval in adult female buffaloes, cows, sheep and goats should be:

1. In buffaloes, a priming dose of 5.17 mg/kg body weight and maintenance dose of 4.84 mg/kg.
2. In cows, priming and maintenance doses of 5.62 mg/kg body weight and 5.37 mg/kg, respectively.
3. In sheep, a priming dose of 6.54 mg/kg body weight and maintenance 6.26 mg/kg.
4. In goats, a priming dose of 6.10 mg/kg body weight and maintenance dose of 5.91 mg/kg.

It depicts that an optimal dosage regimen should be based on the disposition kinetics data determined in the species and the environment in which a drug is to be employed clinically.

Optimální dávkování ciprofloxacinu a jeho kinetika u zdravých domácích přežvýkavců

Cílem této experimentální studie bylo určit kinetické dispozice a optimální dávkování ciprofloxacinu u zdravých jedinců domácích přežvýkavců zahrnujících dospělé samice buvola, skotu, ovce a kozy. Látka byla podána v jednorázové intramuskulární injekci v dávce 5 mg/kg. Plazmatické koncentrace ciprofloxacinu byly stanoveny pomocí HPLC a vykazovaly druhově závislé farmakokinetické odlišnosti. Poločas rozpadu ($t_{1/2}$ ß) ciprofloxacinu byl nejdelší u krav (3.25 ± 0.46 h), středních hodnot dosahoval u samice buvola (3.05 ± 0.20 h) a u ovce (2.93 ± 0.45 h) a nejkratší byl u kozy (2.62 ± 0.39 h).

Distribuční objem (V_d) dosahoval u samice buvola hodnoty 1.09 ± 0.06 l/kg, u krávy 1.24 ± 0.16 l/kg, u ovce 2.89 ± 0.30 l/kg a u kozy 3.76 ± 0.92 l/kg. Celková tělesná clearance (Cl_B) vyjádřená v l/h/kg byla nejnižší u samice buvola (0.25 ± 0.02), dále následovaly hod-

noty 0.31 ± 0.02 zjištěné u krávy a 0.75 ± 0.04 u ovce, a maximální clearance 1.09 ± 0.11 byla naměřena u kozy.

Optimální dávkovací schéma pro 12- h interval u zvířat v tomto pořadí: samice buvola, kráva, ovce a koza, se skládalo z počátečních dávek 5.17, 5.62, 6.54 a 6.10 mg/kg tělesné hmotnosti a udržovacích dávek 4.84, 5.37, 6.26 a 5.91 mg/kg tělesné hmotnosti podávaných intramuskulárně. Komerčními výrobci je uváděno, že optimální dávka ciprofloxacinu 5 mg/kg má být opakována v intervalu 24 hod. Nicméně námi vyšetřované dávkovací schéma potvrzovalo vhodnost opakování ve 12-h intervalech tak, aby byla udržena MIC na konci dávkovacího intervalu. Výsledkem je tedy zjištění, že dávkovací schéma by mělo být založeno na farmakokinetice daného léčiva, která se liší jak druhově tak i v závislosti na prostředí, ve kterém je dané léčivo klinicky používáno.

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