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Pharmacokinetics of ciprofloxacin in animals

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ABSTRACT

Ciprofloxacin is absorbed primarily from the duodenum and jejunum when administered orally to monogastric animals. Bioavailability from parenteral injection sites is nearly 100 percent for all fluoroquinolones in most cases. Enrofloxacin (Congener of ciprofloxacin) penetrates into milk to attain approximately twice the maximum concentration of ciprofloxacin at similar plasma concentrations, although the elimination of enrofloxacin from mild is approximately twice as fast as that of ciprofloxacin. The article highlights the proper dose, route of administration, pharmacokinetic parameters of animals as well as recommended dosages of ciprofloxacin in animals.

Keywords: Pharmacokinetics, Ciprofloxacin, Dose, Animals.

INTRODUCTION

General pharmacokinetic properties of fluoroquinolones in animals include variable but good oral absorption (except in ruminants and equines), complete parenteral absorption, good tissue distribution (volume of distribution of 2-4 1/kg), renal excretion by GFR (largely tubular secretion), hepatic metabolism via oxidation renal excretion by GFR (largely tubular secretion), hepatic metabolism via oxidation and glucuoronidation and elimination half lives of 2-4 hour in animals (Brown, 1996).

PHARMACOKINETICS OF CIPROFLOXACIN IN ANIMALS

Pharmacokinetics of ciprofloxacin has been extensively investigated in humans. The data on the pharmacokinetics of ciprofloxacin in animals are limited but expanding. The data on the pharmacokinetics of ciprofloxacin documented in various animal species is presented in Table 1.

Goats

Pharmacokinetics and urinary excretion of ciprofloxacin in goats following single dose intravenous administration (4 mg/kg of body weight). The respective values for elimination half life (t1/2β), apparent volume of distribution [Vd (area)] and total body clearance (Cl_B) were 1.83 hours, 2.27 l kg^{-1} and 13.45 ml min^{-1} kg^{-1}. They also found that more than 25 per cent of the administered goats.

Table 1: Pharmacokinetics of ciprofloxacin in domestic animals

Animal	Dose	Route of Administration	Pharmacokinetic parameters							
			T1/2 β (h)	Vd (area) L/Kg	$Cl_{(B)}$ Ml min-kg –l)	AUC (μg.h/ml)	C_{max}	T max	MRT (h)	F
1	2	3	4	5	6	7	8	9	10	11
Goats	4	IV	1.83	2.27	13.45	5.44	-	-	- -	
	5	IV	2.78 ± 0.08	2.14 ± 0.07	14.7 ± 0.43	-	-	-	- -	
		IM	-	-	-	-	1.92 ± 0.05	1	-	95.9
	Not available	IV	1.46 ± 0.29	3.31 ± 0.42	18.33 ± 0.00	-	-	-	-	-
		IM	2.5 ± 0.76	-	-	-	1.26 ± 0.25	0.20 ± 0.05	-	68.5
	2	3	4	5	6	7	8	9	**10**	11
		Intra mammary	4.50 ± 1.80	-	-	-	0.44 ± 0.16	1.49 ± 0.49	-	75.38
	10	IV	2.72 ± 1.04	3.37 ± 0.89	19.60 ± 90.06	10.32 ± 5.14	-	-	3.33 ± 1.43	
Sheep	7.5	IV	1.21 ±0.07	1.89 ± 0.15	18.0 ± 0.00	7.02 ± 0.53	-	-	1.46 0.06	-
		IM	3.08 ± 0.33	-	-	3.40 ± 0.54	0.69 ± 0.12	0.53 ± 0.11	4.62 ± 0.48	49.0
Cows	10	IV	2.16 ± 0.29	2.84 ± 0.23	15.10 ± 2.36	3.31 ±0.38	-	-	3.04 ± 0.20	-
Calves	2.8 ± 0.11	IV	2.44 ± 0.61	2.5 ± 0.20	12.1 ±2.0	3.93 ± 0.77	-	-	-	-
		PO	8.0 ± 1.4	-	-	2.1 ± 0.9	0.27 ± 0.13	3.0	-	53.14
	5	IV	3.24 ± 0.09	4.05 ± 0.17	14.29 ± 0.46	5.87 ± 0.22	-	-	4.01 ± 0.09	-
	4	IV	3.54 ± 0.37	3.92* ± 0.33	12.18 ± 1.43	5.86 ± 0.56	-	-	4.76 ± 0.49	-
1	2	3	4	5	6	7	8	9	10	11
Pigs	3.06 ± 0.46	IV	2.57 ± 0.29	3.83 ± 0.78	17.3 ± 3.7	2.88 ±0.52	-	- -		-
	3.3	PO	3.1	-	-	1.16	0.17	2	-	37.3
Horses	5	IV	2.63	3.45 ± 0.72	18.12 ± 3.99	4.83 ± 1.08	-	-	3.25 ± 0.65	-
		PO	-	-	-	0.28 ± 0.2	-	-	-	6.80 ± 5.3
Dogs	10.9 ± 1.4 every 12 h for 7 doses	PO Single Dose Multiple Dose	4.65 7.48	- -	- -	- -	0.93 1.18	1.18 1.7	- -	- -
1	23.2 ± 5.2 every 12 h for 7 doses	PO Single Dose Multiple Dose	3.95 4.48	-	-	-	2.33 5.68	1.85 1.38	- -	- -

	2.5	IV	3.0 ± 0.64	4.88 ± 0.68	19.03 ± 4.27	2.30 ± 0.84	-	-	4.45 ± 1.26	-
	2	3	4	5	6	7	8	9	10	11
	5.0	IV	2.16 ± 0.78	3.06 ± 0.75	17.72 ± 7.38	5.23 ±1.90	-	-	4.01 ± 0.41	-
	10.0	IV	2.55 ± 0.63	2.96 ± 0.43	14.14 ± 5.31	12.93 ± 4.66	-	-	4.43 ± 0.38	-
	10.0	PO	4.90 ± 063	-	-	12.67 ± 1.56	1.55 ±0.26	2.58 ±0.18	8.52 ± 1.09	-
	20.0	PO	5.28 ±0.57	-	-	28.42 ±4.76	3.08 ±0.37	3.00 ±0.46	9.48 ± 0.92	-
	40.0	PO	8.86 ±1.39	-	-	100.79 ± 22.52	7.18 ±1.34	4.18 ±1.21	14.90 ±2.37	-
1	5.0	IV	-	1.92 ±0.33	7.83 ±1.5	-	-	-	4.20 ±0.83	-
	2	3	4	5	6	7	8	9	10	11
Chicken	5.0	IV	9.01 ±0.32	2.02 ±0.20	1.54 ±0.06	-	-	-	24.55 ±1.10	-
		PO	-	-	-		4.67 ±0.13	0.71 ±0.06	31.53 ±1.43	70.09 ±4.00
	5.0	IV	2.25 ±0.54	1.83 ±0.19	12.45 ±3.28	7.45 ±1.63	-	-	2.76 ±0.64	-

Abo el-Sooud (1998) studied pharmacokinetics of ciprofloxacin in lactating goats following intravenous and intramuscular administration (5mg/kg of body weight). After a single intravenous injection, the elimination half life (t1/2β), volume of distribution at steady state [Vd(ss)] and total body clearance (ClB) were 2.78 ± 0.08 hours, 2.14 ±0.07 l kg^{-1} and 14.7 ± 0.43 ml min^{-1} kg^{-1}, respectively. Following single dose intramuscular administration, ciprofloxacin after intramuscular administration was 95.9 ±6.4 per cent. The drug was detected in therapeutic concentrations for 10 hours in serum and milk and for 24 hours in urine. Following intramuscular injection at 5mg/kg of body weight for 5 consecutive days, ciprofloxacin showed a cumulative behaviors in serum, mild and urine of goats. Ciprofloxacin pharmacokinetics and its concentration in udder and milk of goats following intreavenous, intramuscular and intramammary administration. Following intravenous administration the respective values for elimination half life (t ½ β), apparent volume of distribution [Vd(area)] and total body clearance (ClB) were 1.46 ±0.29 hours, 3.31 ± 0.42 l kg-1 and 18.33 ml min-1kg-1. following intramuscular administration the respective values for elimination half life (t1/2β) and bioavailability were 2.51 ± 0.76 hours and 68.57 per cent. The peak plasma concentration (Cmax; 1.26± 0.25 μg ml-1) was observed at 0.20 ±0.02 hours. Following intramammary administration the respective values for elimination half life (t1/2β) and bioavailability were 4.50 ± 1.80 hour and 7.38 per cent. The peak plasma concentration (Cmax; 0.44 ± 0.16 μg ml^{-1}) was observed at 1.49 ± 0.49 hours. They also found that accumulation of ciprofloxacin occurs in milk following the drug administration by all the three routes. The concentration of the drug in milk was 2-5 times greater than in the plasma at 2,4,6 and 8 hours after administration of the drug. This indicates the possibility of using ciprofloxacin prenterally for the treatment of mastitis in animals. Racis Ovando *et al.* (2000) reported pharmacokinetics of ciprofloxacin in goats following single dose intravenous administration (10mg/kg of body weight). The respective man values of elimination half life (t 1/2β), volume of distribution at steady state [$Vd_{(ss)}$], total body clearance (ClB), area under curve

(AUC) and mean resident time (MRT) were 2.72 ±1.04 hours, 3.37±0.89 l kg^{-1}, 10.32±5.14 μg.h ml^{-1} and 3.33 ±1.43 hours. Based on the pharmacokinetic data they recommended an intravenous dose of 10 mg/kg of body weight, which should be repeated at twelve hour intervals in goat.

Sheep

Pharmacokinetics of ciprofloxacin after its single dose intravenous and intramuscular administration: (7.5 mg/dg of body weight) in sheep. Mean elimination half lives after intravenous and intramuscular administration were 1.2 ±0.07 and 3.08±0.33 hours, respectively. The absorption of intramuscularly administered ciprofloxacin was fast as the maximal plasma concentration (C_{max}: 0.69) 0.69 μg/ml) reached quickly (t_{max}:31.93 minutes). The bioavailability of intramuscularly administered drug was 49 per cent. They concluded that following intramuscular administration of ciprofloxacin at the dose rate of 7.5 mg/kg of body weight, the therapeutically effective serum drug concentration (≥ 0.12 μg ml^{-1}) against most common bacteria remains for a period for more than 8 hours. Mengozzi *et al.* (1996) studied pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin after intravenous and intramuscular administration (20.5 mg/kg of body weight) in sheep. Ciprofloxacin accounted for 35 and 55 per cent of the parent drug (enrofloxacin) plasma concentrations after intravenous and intramuscular administration, respectively. Peak ciprofloxacin plasma concentrations of 0.13 ± 0.02 and 0.14 ± 0.02 μg ml^{-1} were noted at 2.92 ± 0.42 hours after intravenous and at 5.00 ± 0.45 hour after intramuscular administration enrofloxacin. At 24 hours after intravenous administration of enrofloxacin, the mean plasma concentration of ciprofloxacin was similar to that of the parent drug. However, the plasma concentration of ciprofloxacin (0.05 ±0.01 μg ml^{-1}) was slightly higher than that of enrofloxacin (0.02 ±0.01 μg ml^{-1}) at 24 hours after intramuscular administration of enrofloxacin.

Cattle and Buffalo

Pharmacokinetics, renal clearance and metabolism of ciprofloxacin in calves and piglets following intervenous (2.80 ±0.11 mg/kg of body weight in calves and 3.06±0.46 mg/kg of body weight in pigs) and oral (2.80 ± 0.11 mg/kg of body weight in calves and 3.1 mg/kg of body weight in pigs) administration. They observed that following intravenous administration, the drug has short elimination half life of 2.5 hours in both species and it was rapidly and well distributed in the body having apparent volume of distribution [$V_{d(area)}$] of 2.50 ±0.20 l kg^{-1} in calves and 3.83 ± 0.73 l kg^{-1} in piglets. Ciprofloxacin was rapidly absorbed following oral administration with t_{max} of 2-3 hours in both species. The oral bioavailability of the drug was 53 ± 14 percent in calves and 37.3 percent in piglets. The renal clearance values of the free drug in piglets (20.2 ± 3.1 ml $min^{-1}kg^{-1}$) and calves 28.3 ±14.8 ml $min^{-1}kg^{-1}$) were at least ten times higher than creatinine clearance and indicated predominant tubular secretion. Renal clearance accounted for about 46 percent of the total drug elimination. They also detected small amounts of two metabolites of ciprofloxacin in urine of calves, but not in piglets. Pharmacokinetics of ciprofloxacin following intravenous administration (5mg/kg of body weight) in calves. Mean values of elimination half life ($t_{1/2\beta}$), apparent volume of distribution [Vd(area)], total body clearance Cl_B) were 3.24±0.09 hours, 4.05 ±0.17 l kg^{-1}, respectively. Based on the results obtained, they concluded that an intravenous loading dose of 6.8 mg/kg of body weight and a maintenance dose of 6.3 mg/kg of body weight repeated at twelve hour intervals would maintain the minimum therapeutic blood concentration of 0.12 μg ml^{-1}. Pharmacokinetics of ciprofloxacin in lactating cows following intravenous

administration (10 mg/kg of body weight). The respective mean values of elimination half life ($t_{1/2\beta}$), apparent volume of distribution [$V_{d(area)}$], volume of distribution at study state [$V_{d(ssa)}$] total body clearance (Cl_B), area under curve (AUC) and mean residence time (MRT) were 2.16±0.29 hours, 2.84±0.23 l $kg^{-1,}$ 2.75 ±0.22 l kg^{-1}, 15.10 ±2.36 ml min^{-1}) kg $^{-1}$ 3.31 ±0.38 μg.h ml^{-1}) and 3.04 ±0.20 hours. Based on the pharmacokinetic date they recommended an intravenous dose of 10 mg/kg of body weight every twelve hours for 3 to 5 days in cows. Pharmacokinetics of ciprofloxacin following intravenous administration (4mg/kg) of body weight) in buffalo calves. The respective mean values of elimination half life ($t_{1/2\beta}$), apparent volume of distribution [$V_{d(area)}$], volume of distribution at steady state [$V_{d(ss)}$] and total body clearance (ClB) were 3.54 ±0.37 hours, 3.61 ±0.39kg^{-1} , 3.92 ±0.33 l kg^{-1} and 12.18 ±1.43 ml min^{-1} kg^{-1}. Based on the results obtained, they recommended an intravenous loading dose of 4.80 mg/kg of body weight followed by maintenance dose of 4.20 mg/kg body weight repeated at twelve hour intervals to achieve and maintain the minimum therapeutic blood concentration of 0.12μg ml^{-1}. Pharmacokinetics of enrofloxacin after single intravenous, intramuscular and subcutaneous injections (5mg/kg of body weight) in lactating cows. They determined concentration of enrofloxacin and its metabolite ciproflaoxacin in serum and milk. They found that the mean elimination half lives of the antimicrobial activity in serum was 1.7, 5.9 and 5.6 hours after intravenous, intramuscular and subcutaneous administration, respectively. The half lives of enrofloxacin and its metabolite ciprofloxacin were approximately the same.

Pigs

Anadon *et al.* (1999) studied pharmacokinetics and tissue residues of enrofloxacin and ciprofloxacin in healthy pigs following intravenous and intramuscular administration of enrofloxacin (2.5 mg/kg of body weight). They found that after intramuscular administration, enrofloxacin was metabolized to ciprofloxacin and the metabolite concentration was 51.5 percent of the parent drug plasma concentration. Plasma concentration of ciprofloxacin peaked (0.71± 0.14μg ml $^{-1}$) at 1.75 ± 0.63 hours after intramuscular administration of enrofloxacin. The elimination half life of ciprofloxacin after intramuscular administration of enrofloxacin was 14.20 ± 1.40 hours. They also revealed mean concentrations of enrofloxacin and ciprofloxacin ranging from 0.029 to 0.079 μg g^{-1}in muscular, hepatic, renal and adipose tissues five days after the last injection (2.5mg/kg of body weight per day intramuscularly for three days). However, ciprofloxacin was not detected in any tissue ten days after the last injection.

Horses

Pharmacokinetics of ciprofloxacin in ponies following intravenous and oral administration (5 mg/kg of body weight). Following intravenous administration the mean values of elimination half life ($t_{1/2}\beta$) total body clearance (Cl_B) and volume of distribution at steady state [$Vd_{(ss)}$] were 2.63 hours, 18.12 ml min^{-1} kg^{-1} and 3.451kg^{-1}, respectively. The mean oral ciprofloxacin bioavailability in ponies was 6.8 per cent. They also determined ciprofloxacin concentration in various body fluids and tissues at 1, 2 and 4 hours after intravenous administration. Ciprofloxacin concentrations in muscle, spleen, kidney, liver and lung were consistently higher than plasma concentration. The tissues or plasma concentration roughly declined with time and remained more than 0.12 μg g^{-1} or ml^{-1} at all times. The highest ciprofloxacin concentration occurred in urine (12.74 to 36.28 μg ml^{-1}). Ciprofloxacin concentrations in cerebrospinal fluid (CSF), joint fluid and aqueous humor were consistently lower than plasma concentration. From the pharmacokinetic data and reported minimum

inhibitory concentrations for gram-negative bacteria they concluded that intravenous administration of ciprofloxacin at dose rate of 5.32 mg/kg of body weight repeated at twelve hour intervals would be appropriate for use in equines. Pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin in horses after single dose intravenous and intramuscular administration (5 mg/kg of body weight) of enrofloxacin. They found that enrofloxacin was rapidly metabolized to ciprofloxacin. The ciprofloxacin concentration in serum reached 20-35 per cent of that of the parent drug. Ciprofloxacin and enrofloxacin disappeared from the blood circulation with elimination half lives of 5.1 hours and 4.4 hours, respectively.

Dogs

Abaida *et al.* (1994) studied pharmacokinetics of ciprofloxacin following intravenous administration (2.5, 5 and 10 mg/kg of body weight in dogs. They found variable elimination half lives, plasma clearance rates and volume of distribution at three doses. The respective values were 3.0 ± 0.64 hours, 19.03 ±4.23 ml min^{-1} kg^{-1} and 4.88 ± 0.68 $1kg^{-1}$ for 2.5 mg/kg of body weight, 2.16 ± 0.78 hours, 17.72 ml min^{-1} kg^{-1} and 3.06 ± 0.75 $1kg^{-1}$ for 5 mg/kg of body weight and 2.55 ± 0.62 hours, 14.14 ml min^{-1} kg^{-1} min^{-1} kg^{-1} and 2.96 ± 0.43 $1kg^{-1}$ for 10 mg/kg of body weight.

Abaida *et al.* (1995) studied pharmacokinetics of ciprofloxacin after oral administration (10, 20, and 40 mg/kg of body weight) in dogs. The peak plasma concentrations of 1.55 ± 0.26, 3.08 ± 0.37 and 7.18 ± 1.34 μg ml^{-1} were observed at 2.58 ± 0.18, 3.00 ± 0.46 and 4.18 ± 1.21 hours after oral administration of the drug given at the rate of 10, 20 and 40 mg/kg of body weight, respectively. The respective elimination half lives ($t_{½}$ β) were 4.90 ±0.63, 5.28 ±0.57 and 8.86 ± 1.39 hours.

Cester and Toutain (1997) studied transformation of enrofloxacin to ciprofloxacin and disposition of enrofloxacin and ciprofloxacin following intravenous and oral administration (5 mg/kg of body weight) in dogs. Following intravenous administration of ciprofloxacin, the respective values for plasma clearance (Cl_B), volume of distribution at steady state [$V_{d\ (ss)}$] and mean residence time (MRT) were 7.83 ± 1.50 ml min^{-1} kg^{-1}, 1.92 ± 0.33 $1kg^{-1}$ and 4.20 ±0.82 hours. The mean residence time values were 4.89 ± 1.25 hours for enrofloxacin and 8.66±1.76 hour for ciprofloxacin, after oral administration of enrofloxacin. They concluded that enrofloxacin was largely metabolized to ciprofloxacin. The fractions of the administered enrofloxacin dose metabolized to ciprofloxacin were similar after intravenous (40.44±10.88 percent) and oral (40.17±8.33 percent) administrations.

Chickens

Atta and Sharif (1997) reported pharmacokinetics of ciprofloxacin following intravenous and oral administration (5 mg/kg of body weight) in broiler chickens. The respective values of elimination half life (t 1/2β), apparent volume of distribution [$V_{d(area)}$], volume of distribution at steady state [$V_{d(ss)}$], total body clearance Cl_B), and mean residence time (MRT) were 9.01 ±0.32 hours, 2.02±0.2 l kg^{-1} 1.54±0.16 ml min^{-1} kg^{-1} and 24.55±2.7 hours after single dose intravenous administration. Following single dose oral administration the peak plasma concentration (C_{max}; 4.67±0.33 μg ml^{-1}) was achieved at 0.71±0.06 hours (42.5±8.14 minutes). The oral bioavailability of the drug was 70.09 ± 0.06 hours (42.5 ± 8.14 minutes). The oral bioavailability of the drug was 70.09 ± 9.8 percent. Based on the pharmacokinetic data and reported minimum inhibitory concentrations for avian pathogenic microorganisms they recommended an oral dosage of 5 mg/kg of body weight per day.

Anadon *et al.* (1995) studied pharmacokinetics and residues of enrofloxacin following single dose intravenous and oral administration (10 mg /kg of body weight

per day four days) of enrofloxacin in chickens. They found that enrofloxacin was extensively metabolized to ciprofloxacin. The tissue ciprofloxacin concentrations were equivalent or higher than those of the parent compound. They also found that enrofloxacin and its metabolite ciprofloxacin were eliminated more slowly from tissues than from plasma. The mean muscle, liver and kidney concentrations of ciprofloxacin (0.020-0.075 μg/g) persisted on day twelve after multiple oral dosing of enrofloxacin in chickens.

Pharmacokinetics of enrofloxacin and its metabolite ciprofloxacin following intravenous and oral administration in healthy broiler chickens. They found that the metabolite appeared slowly in the plasma and was distributed widely in the body, indication that ciprofloxcin is an important factor responsible for efficacy of enrofloxacin.

Recommended dosages of ciprofloxacin in animals

The recommended dosages of ciprofloxacin in animals are summarized in Table 2.

Table 2: Recommended dosages of ciprofloxacin in animals.

Animal	*Route of administration*	*Dosages*
Goats	Intravenous	10.0 mg/kg every 12 hours
Cows	Intravenous	10 mg/kg every 12 hours
		3.06 mg/kg every 8 hours.
		Priming dose: 6.8 mg/kg Maintenance dose: 6.3 mg/kg every 12 hours
Buffalos Calves	Intravenous	Priming dose: 4.80 mg/kg. Maintenance dose: 4.20 mg/kg every 12 hours
Pigs	Intravenous	2.80 mg/kg every 8 hours
Horses	Intravenous	5.32 mg/kg every 12 hours
Dogs and cats	Oral	5-8 mg/kg every 12 hours for urinary tract infections.
		10-15 mg/kg every 12 hours for soft tissue and bone infections.
	Oral or slow intravenous	10-15 mg/kg every 12 hours.
Chicken	Oral	5mg/kg every 24 hours.

CONCLUSION

Fluoroquinolones offer the advantage of oral administration (except in ruminant and horses), high potency against many gram-negative aerobes with moderate activity against gram-k positive aerobes, wide spreads distribution throughout the body including adequate penetration into the postate and cerebrospinal fluid and low host toxicity, in humans, the fluoroquinolones are used for the treatment of variety of severe infections that are either located in tissues inaccessible to other antibacterial agents or caused by bacterial pathogens resistant to other antimicrobial agents.

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