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Pharmacokinetics and dosage regimen of levofloxacin in buffalo calves after single subcutaneous administration

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ABSTRACT

The present study was conducted on six male buffalo calves to investigate the pharmacokinetics of levofloxacin following a single subcutaneous administration at the dose rate of 3 $mg.kg^{-1}$ body weight. Appreciable plasma concentration of levofloxacin (0.28 ± 0.01 $\mu g.mL^{-1}$) was detected 2.5 min after injection and the peak plasma level of 2.94 ± 0.07 $\mu g.mL^{-1}$ was observed at 1 h. Drug levels of 0.28 ± 0.01 $\mu g.mL^{-1}$ in plasma were detected up to 12 h from administration. Rapid absorption of the drug was also evident by the high value of the absorption rate constant (2.53 ± 0.53 h^{-1}). The absolute bioavailability of levofloxacin after subcutaneous administration calculated on the basis of AUC (10.5 ± 0.11 $\mu g.mL^{-1}.h$) and Ke (0.272 ± 0.009 h^{-1}) after a single intravenous injection in buffalo calves was 44.3 ± 1.76 per cent. The high value of AUC (8.02 ± 0.2 $\mu g.mL^{-1}.h$) reflected major exposure in the buffalo calves. Extensive distribution of the drug into various body fluids and tissues was reflected by the high value of Vd_{area} (1.06 ± 0.04 $L.kg^{-1}$). The elimination half-life and MRT were 4.43 ± 0.1 h and 6.71 ± 0.17 h, respectively. On the basis of the pharmacokinetic parameters, the calculated subcutaneous dosage regimen for levofloxacin in buffalo calves was 4.6 $mg.kg^{-1}$ at 24 h intervals.

Key words: buffalo calves, dosage, levofloxacin, pharmacokinetics, subcutaneous

Introduction

Fluoroquinolone resistance relates directly to human and veterinary usage and emerging bacterial resistance poses the single greatest threat to the future survival of fluoroquinolone drugs as an antibiotic class (BAKKEN, 2004). Levofloxacin [(-) -9-Fluoro-3-methyl-10-(4-methyl-1-piprazinyl)-7-oxo-2, 3-dihydro-7H-pyrido [1, 2, 3-de] [1, 4]-benzoxazine-6-carboxylic acid], a second generation fluoroquinolone, possesses excellent activity against gram-positive, gram-negative and anaerobic bacteria (DAVIS

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and BRYSON, 1994; NORTH et al., 1998). As compared to other fluoroquinolones, ofloxacin and ciprofloxacin, it also has more pronounced bactericidal activity against organisms such as Pseudomonas, Enterobacteriaceae and Klebsiella (KLESEL et al., 1995). The drug distributes well to target body tissues and fluids in the respiratory tract, skin, urine and prostrate and its uptake by cells makes it suitable for use against intracellular pathogens (LANGTRY and LAMB, 1998). Levofloxacin is metabolized in the liver to demethyl-levofloxacin and levofloxacin-N-oxide and excreted in urine (LANGTRY and LAMB, 1998). The pharmacokinetics of levofloxacin have been investigated in man (CHULAVATNATOL et al., 1999), calves (DUMKA and SRIVASTAVA, 2006, 2007a, and 2007b; DUMKA, 2007; DUMKA et al., 2008) and guinea pigs (EDELSTEIN et al., 1996). However, there is only meager information available on the pharmacokinetics of levofloxacin in buffalo species, except one report after intramuscular administration of levofloxacin in buffalo calves (RAM et al., 2008). In view of the marked species variation in the pharmacokinetic data of antimicrobial drugs, the present study was undertaken to determine the pharmacokinetics and an appropriate dosage regimen of levofloxacin following its single subcutaneous administration in buffalo calves.

Materials and methods

Experimental animals and drug administration. Six healthy male buffalo calves of non-descript breed, ranging between 1-1.5 years of age and 82-128 kg body weight were used for the study. The animals were maintained on seasonal green fodder, wheat straw and water *ad libitum.* The average day temperature in the shed was about 25 ^{0}C during the experimental period. The experimental protocol followed the ethical guidelines on the proper care and use of animals. Levofloxacin [Tavanic (0.5% Levofloxacin), Hoechst Marion Roussel Ltd., India] was administered subcutaneously at the dose rate of 3 mg.kg^{-1} body weight into the neck region.

Collection of samples. Blood samples (5 mL) were withdrawn from the jugular vein into heparinized glass centrifuge tubes before and at 1, 2.5, 5, 10, 15, 30 min and 1, 2, 4, 6, 8, 10, 12, 16 and 24 h after administration of the drug. Plasma was separated by centrifugation at 1300 g for 15 min at room temperature and kept at -20 ^{0}C until analysis, which was usually done on the next day after collection.

Estimation of drug. The level of levofloxacin in the plasma samples was estimated by a microbiological assay technique (ARRET et al., 1971) using *Escherichia coli* [ATCC (American type culture collection) 10536] as the test organism. This method estimated the level of drug and its active metabolites with antibacterial activity. The assay could detect a minimum of 0.1 μg.mL^{-1} of levofloxacin. For each sample, 9 replicates were analysed and compared with the zone of inhibition of the reference solution of levofloxacin (0.3 μg.mL^{-1}). The level of levofloxacin in the samples was calculated as μg.mL^{-1} of plasma.

Pharmacokinetic variables and dosage regimen. The plasma concentration-time profile of levofloxacin after subcutaneous administration in each animal was used to establish various pharmacokinetic determinants and mean kinetic variables were obtained by averaging the variables calculated for individual animals. Absolute systemic bioavailability was calculated by using the values of AUC and β obtained after single intravenous administration of levofloxacin in the same animals used for subcutaneous study of levofloxacin at an interval of 30 days. Pharmacokinetic parameters were calculated manually by the computed least-squares linear regression technique (GIBALDI and PERRIER, 1982). The maintenance (D') dose of levofloxacin was calculated according to the equation: $D' = C_p(min)^{\propto}.Vd\ (e^{\beta\tau}-1)$, where, Cp (min) $^{\propto}$ is the minimum inhibitory concentration of levofloxacin, β is the elimination rate constant and τ is the dosing interval. The priming dose was obtained by omitting -1 from the above equation (BAGGOT, 1977).

Results

The plasma levels of levofloxacin at different time intervals following its single subcutaneous injection at the dose rate of 3 $mg.kg^{-1}$ body weight in buffalo calves are presented in Table 1. Subcutaneous injection resulted in an appreciable plasma concentration of drug (0.28 ± 0.01 $\mu g.mL^{-1}$) at 2.5 min and peak plasma level of 2.94 ± 0.07 $\mu g.mL^{-1}$ was attained 1 h post administration. The plasma levels then declined gradually to 0.28 ± 0.01 $\mu g.mL^{-1}$ at 12 h.

Table 1. Plasma levels of levofloxacin in buffalo calves (n = 6) following single subcutaneous administration of 3 $mg.kg^{-1}$ body weight

Time after levofloxacin administration	Animal number						Mean ± SE
	1	2	3	4	5	6	
2.5 min	0.30	0.28	0.25	0.27	0.29	0.28	0.28 ± 0.01
5 min	0.31	0.29	0.28	0.29	0.32	0.31	0.30 ± 0.01
10 min	0.57	0.60	0.56	0.55	0.57	0.60	0.57 ± 0.01
15 min	1.34	1.46	1.60	1.36	1.40	1.46	1.44 ± 0.04
30 min	2.01	2.05	2.30	2.14	2.10	1.96	2.10 ± 0.05
1 h	2.80	2.80	3.20	3.10	2.90	2.86	2.94 ± 0.07
2 h	2.40	2.00	2.25	2.40	2.30	1.96	2.22 ± 0.08
4 h	1.10	1.30	1.20	1.10	1.10	1.20	1.17 ± 0.03
6 h	0.92	0.86	0.84	0.86	0.88	0.86	0.87 ± 0.01
8 h	0.61	0.56	0.59	0.57	0.57	0.60	0.58 ± 0.01
10 h	0.56	0.46	0.44	0.41	0.35	0.57	0.46 ± 0.03
12 h	0.30	0.29	0.29	0.26	0.27	0.29	0.28 ± 0.01

Values are expressed as $\mu g.\ mL^{-1}$ of plasma

Table 2. Pharmacokinetic parameters of levofloxacin in buffalo calves (n = 6) following a single subcutaneous dose of 3 mg.kg^{-1} body weight

Parameter	Unit	Mean ± SE
A'	µg.mL^{-1}	0.94 ± 0.13
Ka	h^{-1}	2.53 ± 0.53
$t_{½Ka}$	h	0.34 ± 0.07
B	µg.mL^{-1}	1.33 ± 0.05
Ke	h^{-1}	0.16 ± 0.04
$t_{1/2Ke}$	h	4.43 ± 0.10
AUC	µg.mL^{-1}.h	8.02 ± 0.20
AUMC	µg. mL^{-1}.h^2	53.8 ± 1.61
$Vd_{(area)}$	L.kg^{-1}	1.06 ± 0.04
MRT	h	6.71 ± 0.17
td	h	21.4 ± 0.47
C_{max}	µg.mL^{-1}	2.94 ± 0.07
t_{max}	min	60.0 ± 0.0
F	%	44.3 ± 1.76

A′ and B = zero-time plasma drug concentration intercepts of the regression lines of absorption and elimination phases, respectively; Ka and Ke = absorption and elimination rate constants, respectively; $t_{½Ka}$ = absorption half-life; $t_{½Ke}$ = elimination half-life; AUC = area under the plasma concentration-time curve; AUMC = area under the first moment curve; Vd_{area} = apparent volume of distribution; MRT = mean residence time; td = duration of therapeutic effect; C_{max} and t_{max} = peak plasma drug concentration and time required to attain the peak concentration, respectively; F = overall systemic bioavailability.

Evaluation of the results revealed that the disposition pattern of levofloxacin best fitted the one-compartment open model and it was adequately described by the equation: $C_p = Be^{-\beta t} - A'e^{-Kat}$where, C_p is the plasma level of levofloxacin at time t and e represents the base of natural logarithm, A' and B are the extrapolated zero-time intercepts of the absorption and elimination phases, respectively, Ka and Ke are the absorption and elimination rate constants, respectively. Table 2 shows the pharmacokinetic parameters that describe the absorption and elimination pattern of levofloxacin in buffalo calves. Taking various dosage intervals, the different desired plasma concentrations ranging from 0.06 to 0.14 µg.mL^{-1} and using the values for Ke and Vd_{area} from Table 2, the required doses of levofloxacin were calculated and are presented in Table 3.

Table 3. Calculated subcutaneous dosage regimen of levofloxacin ($mg.kg^{-1}$) at various intervals for different MICs in buffalo calves

MIC ($\mu g.mL^{-1}$)	Dose	Dosage interval (h)			
		8	12	16	24
0.06	D	0.22	0.42	0.79	2.79
	D'	0.16	0.35	0.72	2.73
0.08	D	0.30	0.56	1.05	3.72
	D'	0.21	0.47	0.97	3.64
0.1	D	037	0.70	1.31	4.65
	D'	0.27	0.59	1.21	4.54
0.12	D	0.45	0.84	1.58	5.58
	D'	0.31	0.71	1.45	5.45
0.14	D	0.52	0.98	1.84	6.51
	D'	0.32	0.83	1.69	6.36

D = priming dose, D' = maintenance dose

Discussion

The rapid appearance of levofloxacin in plasma following its subcutaneous administration in buffalo calves suggested that the drug rapidly entered systemic circulation. The high value of the absorption rate constant further confirmed the rapid absorption of levofloxacin. Rapid absorption has also been reported after intramuscular injection of levofloxacin in buffalo calves (RAM et al., 2008), and cross bred calves (DUMKA and SRIVASTAVA, 2006) and marbofloxacin (SCHNEIDER et al., 2004; SHEMTOV et al., 1997) in cattle and following extravascular administration of gatifloxacin in buffalo calves (RAIPURIA et al., 2006, 2007). An average plasma concentration of 0.008-0.125 $\mu g.mL^{-1}$ has been reported to be the minimum inhibitory concentration (MIC) of levofloxacin against most gram-positive, gram-negative and atypical bacteria including *Staphylococcus aureus, Staphylococcus epidermidis*, *Streptococcus* spp., *Corynebacterium* spp., *Bacillus* spp., *Pseudomonas aeruginosa, Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis, Proteus vulgaris*, *Providencia rettgeri*, *Enterococcus faecalis*, and *Haemophilus influenzae* in humans and animal models of infection (DRAGO et al., 2001; HO et al., 2004; GRIFFITH et al., 2006; DUGGIRALA et al., 2007). Keeping in mind the synergistic effect of the body immune system and other *in vivo* factors, and to cover most of the susceptible organisms, in this discussion, the MIC_{90} of 0.1 $\mu g.mL^{-1}$ of levofloxacin has been taken into consideration. Drug levels of 0.28 ± 0.01 $\mu g.mL^{-1}$ in the plasma were detected up to 12 h after administration. Similar to the present findings, peak plasma concentrations of 2.8-3.07 $\mu g.mL^{-1}$ after extravascular administration in cross bred calves (DUMKA and SRIVASTAVA, 2006, and 2007b), 2.95 $\mu g.mL^{-1}$ after intramuscular dosing in

buffalo calves (RAM et al., 2008) and 3.4 μg.mL^{-1} after single intraperitoneal injection in pneumonic guinea pigs (EDELSTEIN et al., 1996) have been reported for levofloxacin. However, a lower C_{max} of 0.23 μg.mL^{-1} was attained after subcutaneous administration of danofloxacin in calves (McKELLAR et al., 1999).

The apparent volume of distribution of 1.06 ± 0.04 L.kg^{-1} in the present study indicated good penetration of levofloxacin into various body fluids and tissues after subcutaneous injection. Large volumes of distribution for levofloxacin in calves (1.02 L.kg^{-1}), gatifloxacin in buffalo calves (3.2 L.kg^{-1}) and danofloxacin in goats (1.42 L.kg^{-1}) have also been reported (ATEF et al., 2001; DUMKA and SRIVASTAVA, 2006; RAIPURIA et al., 2007). The high value of AUC (8.02 ± 0.2 μg.mL^{-1}.h) obtained in the present study reflected the large extent of absorption. These observations are in accordance with the similar values of AUC for levofloxacin in calves (7.66 μg.mL^{-1}.h) and buffalo calves (8.81 μg.mL^{-1}.h), marbofloxacin in cows (7.648 μg.mL^{-1}.h) and gatifloxacin in buffalo calves (10.8 μg.mL^{-1}.h) after intramuscular injection (SCHNEIDER et al., 2004; DUMKA and SRIVASTAVA, 2006; RAIPURIA et al., 2006; RAM et al., 2008).

The elimination half-life (4.43 ± 0.1 h) in the present study was comparable to the $t_{½\beta}$ of 4.41 h for danofloxacin in goats (ALIABADI and LEES, 2001), however it was lower than the $t_{½\beta}$ of 7.06 h for gatifloxacin in buffalo calves following subcutaneous administration (RAIPURIA et al., 2007) and greater than the corresponding values of 3.67 h for levofloxacin (DUMKA and SRIVASTAVA, 2006), 2.53 h for marbofloxacin (SCHNEIDER et al., 2004) and 2.4 h for norfloxacin (GIPS and SOBACK, 1996) in cattle observed after intramuscular administration.

Among the various pharmacokinetic parameters, bioavailability plays an important role in the therapeutic efficacy of a drug. On the basis of AUC and β after single intravenous (10.5 ± 0.11 μg.mL^{-1}.h and 0.272 ± 0.009 h^{-1}, respectively) and subcutaneous administration (Table 2) in buffalo calves, the absolute systemic bioavailability of levofloxacin was calculated to be 44.3 ± 1.76 per cent. This finding was less than the systemic bioavailability of levofloxacin (56.6%), norfloxacin (73%) and danofloxacin (91%) in cattle (APLEY and UPSON, 1993; GIPS and SOBACK, 1996; DUMKA and SRIVASTAVA, 2006) and levofloxacin (68.1%) and gatifloxacin (79.7% and 89.1%) in buffalo calves (RAIPURIA et al., 2006, and 2007; RAM et al., 2008) reported after their extravascular administration.

On the basis of the present study, the priming and maintenance doses of levofloxacin, at a convenient dosage interval of 24 h, were calculated to be 4.65 and 4.54 mg.kg^{-1}, respectively, or under field conditions, for most bacteria sensitive to levofloxacin, the subcutaneous dosage regimen for levofloxacin, would be 4.6 mg. kg^{-1} at 24 h intervals for bacterial infections in buffalo calves. This dosage was less than the intramuscular dose of 1.7 mg.kg^{-1} at 12 h intervals suggested for levofloxacin in buffalo calves, considered on the basis of a similar dosing interval (RAM et al., 2008). Lack of local reaction or any

other adverse effect, rapid absorption, moderate bioavailability and the large volume of distribution of levofloxacin observed in the present study revealed that levofloxacin may be effectively employed by the subcutaneous route in the treatment of bacterial infections in buffalo calves. However, in order to establish the dosage of levofloxacin in buffalo calves, further studies are required.

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SAŽETAK

Farmakokinetika levofloksacina nakon njegove jednokratne supkutane primjene u dozi od 3 $mg.kg^{-1}$ tjelesne mase određivana je na šest muške bivolje teladi. Mjerljiva koncentracija levofloksacina u plazmi (0,28 ± 0,01 $\mu g.mL^{-1}$) bila je ustanovljena 2,5 minute nakon primjene, a vršna razina od 2,94 ± 0,07 $\mu g.mL^{-1}$ ustanovljena je jedan sat nakon primjene. Razina lijeka od 0,28 ± 0,01 $\mu g.mL^{-1}$ bila je u plazmi dokazana do 12 sati nakon primjene. Brza apsorpcija lijeka očitovala se u visokoj vrijednosti stupnja apsorpcije (2,53 ± 0,53 h^{-1}). Apsolutna biološka raspoloživost levofloksacina nakon supkutane primjene izračunana na osnovi AUC (10,5 ± 0,11 $\mu g.mL^{-1}.h$) i Ke (0,272 ± 0,009 h^{-1}) nakon jednokratne intravenske primjene iznosila je 44,3 ± 1,76%. Visoka vrijednost AUC (8,02 ± 0,2 $\mu g.mL^{-1}.h$) bila je posljedica velike količine primijenjenoga lijeka. Široka raspodjela lijeka u različitim tjelesnim tekućinama i tkivima očitovala se velikom vrijednošću Vd_{area} (1,06 ± 0,04 $L.kg^{-1}$). Poluživot ~~izlučivanja lijeka iznosio je 4,43 ± 0,1 h, a MRT 6,71 ± 0,17 h. Na osnovi farmakokinetičkih pokazatelja,~~ izračunana supkutana doza levofloksanica u bivolje teladi iznosila je 4,6 $mg.kg^{-1}$ u razmacima od 24 sata.

Ključne riječi: bivol, telad, levofloksacin, doziranje, farmakokinetika