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Levofloxacin disposition and urinary excretion in febrile cross bred calves

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ABSTRACT

Disposition and urinary excretion of levofloxacin following a single intravenous administration of 4 mg/kg body mass were investigated in six febrile crossbred calves. The drug levels in plasma and urine were estimated by microbiological assay. Levofloxacin was rapidly distributed from the blood to the tissue compartment, as evidenced by the high values of the distribution coefficient (9.93 ± 0.73 h^{-1}). The high AUC (11.5 ± 0.95 μg/mL/h) indicated good antibacterial activity of levofloxacin in calves. The elimination half-life, volume of distribution and total body clearance were 2.22 ± 0.07 h, 1.18 ± 0.15 L/kg and 0.36 ± 0.03 L/kg/h, respectively. About 37.7 per cent of the administered dose of levofloxacin was eliminated in urine within 24 h. An appropriate intravenous dosage regimen for levofloxacin would be 5.0 mg/kg, repeated at 12 h intervals for the treatment of bacterial infections, manifested with fever in calves.

Key words: calves, disposition, excretion, febrile, levofloxacin

Introduction

Fever is one of the most common manifestations of all bacterial infections and is known to induce several biochemical and physiological alterations in cells (VANMIERT, 1987; LOHUIS et al., 1988). Febrile conditions have been reported to markedly alter the disposition of antibacterials in bovines (DUMKA et al., 2000; CHAUDHARY et al., 2002; DARDI et al., 2005). Levofloxacin possesses excellent activity against gram-positive, gram-negative and anaerobic bacteria (DAVIS and BRYSON, 1994; NORTH et al., 1998) and has pronounced bactericidal activity against resistant organisms, such as *Pseudomonas*, *Enterobacteriaceae* and *Klebsiella* (KLESEL et al., 1995). Levofloxacin has been found to be very effective in the treatment of infections of the upper and lower respiratory tract,

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genitourinary system, skin and soft tissue (DAVIS and BRYSON, 1994). About 80% of the administered dose of levofloxacin in man was found in urine as the unchanged drug and ≤5% as inactive metabolites (LANGTRY and LAMB, 1998). The disposition of levofloxacin has been investigated in man (CHULAVATNATOL et al., 1999), rabbits (DESTACHE et al., 2001), calves (DUMKA and SRIVASTAVA, 2006; DUMKA and SRIVASTAVA, 2007), rats (ITO et al., 1999) and guinea pigs (EDELSTEIN et al., 1996). However, information on the disposition of levofloxacin in cattle species under febrile conditions is completely lacking. In view of the paucity of pharmacokinetic data of levofloxacin in febrile conditions in cattle, the present study was undertaken to determine the disposition, urinary excretion and an appropriate dosage regimen of levofloxacin during *E. coli* endotoxin-induced fever, in cross bred calves following its single intravenous administration.

Materials and methods

Experimental animals and induction of fever. The experiments were performed on 6 healthy male cross bred calves (Holstein Friesian x Sahiwal) of 1-1.5 years with an average body mass of 87.8 ± 13.1 kg. The animals were dewormed and kept under observation for two weeks of acclimatization before the commencement of the experiment. During the experimental period, the animals were maintained on concentrate and free grazing. Water was provided *ad libitum*. The experimental protocol followed the ethical guidelines on the proper care and use of animals. Fever was induced by a single intravenous injection of freshly prepared 1% *E. coli* endotoxin solution in sterilized normal saline, at a dose rate of 1 μg/kg body mass. *E. coli* endotoxin (lipopolysaccharide, serotype 055:B5) was purchased commercially from Sigma Chemicals Co., USA. The rise in body temperature was monitored by frequent recording of rectal temperature.

Drug administration. After induction of fever, levofloxacin [Tavanic (0.5% Levofloxacin), Hoechst Marion Roussel Ltd., India] was administered at a dose rate of 4 mg/kg body mass into the left jugular vein. The dosage level of levofloxacin employed in the present study was comparable to the intravenous dose of the drug used by previous workers in rabbits (DESTACHE et al., 2001) and man (LANGTRY and LAMB, 1998) to study the pharmacokinetics of levofloxacin.

Blood and urine sampling. To conduct the disposition study, the animals were kept in metabolic stalls of standard size, designed in such a way that the entire quantity of urine excreted naturally by the animals within a certain period was automatically collected, without contamination or spillage, in containers placed beneath the stalls. Blood samples (5 mL) were withdrawn from the contralateral jugular vein into heparinized glass centrifuge tubes before and at 1, 2.5, 5, 7.5, 10, 15, 20, 30 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 h after administration of 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 on the day after collection. Urine samples were also collected simultaneously from the same animals at various predetermined time intervals of 2, 4, 6, 8, 10, 12, 16 and 24 h after administration of the drug. At the end of the given time interval, the volume of total urine voided and collected in the container, was measured for each animal and after filtration, 10 mL samples were taken for analysis.

Analytical procedure. The concentration of levofloxacin in plasma and urine samples was estimated by microbiological assay, using *Escherichia coli* (ATCC 10536) as the test organism. The test organism was cultured on antibiotic medium no. 1 at 37 ^{0}C for 24 h and a suspension was prepared in sterile normal saline. 20 mL of molten seed layer containing bacterial suspension was poured onto a Petri dish, with the help of a Cornwell Continuous Pipetting Device (Becton Dickinson, New Jersey, USA). Preliminary experiments were conducted to determine the actual amount of bacterial suspension to be used in the preparation of the seed layer. After solidification of the media, six wells were punched at equal distances with the help of a punching device. The samples were thawed at room temperature and suitably diluted with phosphate buffer. The alternate three wells were filled with one plasma or urine sample and the remaining three wells with a standard reference solution of levofloxacin (0.2 μg/mL). These assay plates were incubated at 34 ^{0}C for 7 h. At the end of incubation, the diameter of the zone of inhibition of each well was measured with a Fisher Lilly Antibiotic Zone Reader (Fisher Scientific Company, New Jersey, USA). For each sample, 9 replicates were analysed and correlated with the zone of inhibition of standard reference solution. The concentration of levofloxacin in the samples was calculated as μg/mL of plasma or urine. This method estimated the level of parent drug and its active metabolites having antibacterial activity. The assay could detect a minimum of 0.1 μg/mL of levofloxacin.

Calculation of disposition parameters. Various disposition parameters were calculated manually by the least-squares regression technique (GIBALDI and PERRIER, 1982). The mean pharmacokinetic variables were obtained by averaging the variables calculated for drug disposition after intravenous drug administration to each animal.

Results

After a single intravenous injection of *E. coli* endotoxin (1 μg.kg^{-1}), fever was induced within 60-90 min and persisted up to 12 h. During the experimental period, the body temperature of febrile animals ranged between 39.0 ± 0.11 ºC to 39.8 ± 0.05 ºC. The mean plasma concentrations of levofloxacin in febrile calves, as a function of time on a semilogarithmic scale, are presented in Fig. 1. At 1 min, the mean plasma drug concentration was 15.8 ± 0.55 μg/mL which rapidly declined to 5.61 ± 0.18 μg/mL at 10 min and then declined gradually to 0.16 ± 0.01 μg/mL at 12 h. Evaluation of the results revealed that the disposition pattern of levofloxacin was best fitted into a 2-compartment

open model, and it was adequately described by the bi-exponential equation: $C_p = Ae^{-\alpha t} + Be^{-\beta t}$, 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 distribution and elimination phases, respectively. α and β are the distribution and elimination rate constants, respectively.

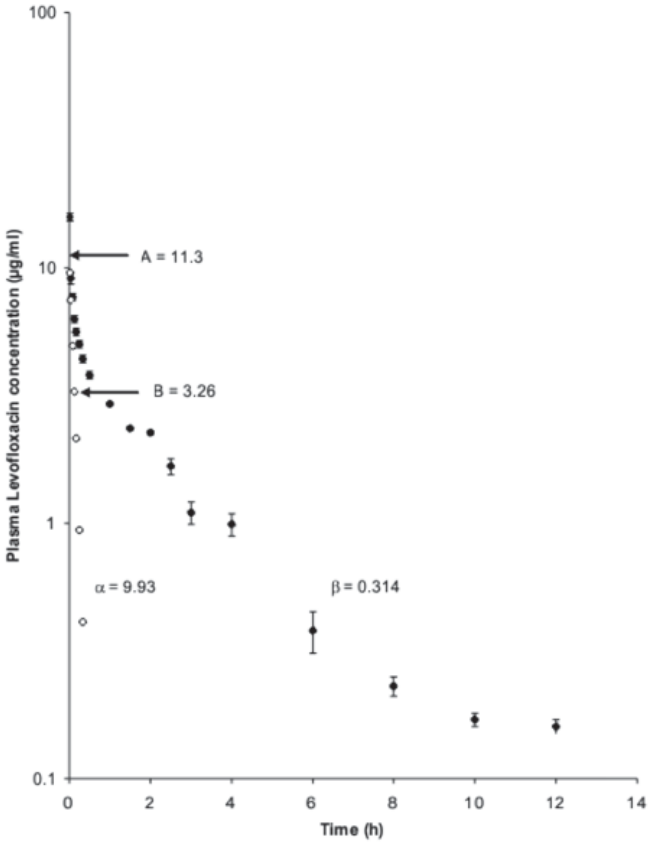

Fig. 1. Semilogarithmic plot of plasma concentration-time profile of levofloxacin following its single intravenous injection of 4 mg/kg body mass in febrile cross bred calves. Values are presented as mean ± SE of 6 animals. The data were analyzed according to the two-compartment open model. Distribution (α) and elimination (β) phases are represented by least square regression lines. The calculated points (o) of distribution phases were obtained by the feathering technique.

Various disposition parameters, describing the distribution and elimination pattern of levofloxacin in febrile calves, were calculated and presented in Table 1. The mean cumulative amount and per cent of total dose of levofloxacin excreted in urine at different time intervals, are shown in Table 2. Using convenient dosage interval and the values of β and Vd_{area} from Table 1, the priming (D) and maintenance (D') doses of levofloxacin were calculated from following equations:

$D = C_p(min) \propto Vd\ (e^{\beta\tau})$ $\quad D' = Cp\ (min) \propto Vd\ (e^{\beta\tau}-1)$

where, Cp (min) ∝ is the minimum therapeutic concentration of levofloxacin, Vd is the apparent volume of distribution, β is the elimination rate constant and τ is the dosing interval (BAGGOT, 1977).

Table 1. Disposition of levofloxacin in febrile calves (n = 6) following single intravenous dose of 4 mg/kg body mass

Parameter	Unit	Mean ± SE
Cp^0	mg/mL	14.6 ± 0.69
A	mg/mL	11.3 ± 0.44
B	mg/mL	3.26 ± 0.39
α	h^{-1}	9.93 ± 0.73
β	h^{-1}	0.314 ± 0.009
$t_{1/2\alpha}$	h	0.07 ± 0.01
$t_{1/2\beta}$	h	2.22 ± 0.07
K_{12}	h^{-1}	6.43 ± 0.49
K_{21}	h^{-1}	2.51 ± 0.32
AUC	mg/mL/h	11.5 ± 0.95
Vd_{area}	L/kg	1.18 ± 0.15
Cl_B	L/kg/h	0.36 ± 0.03
K_{el}	h^{-1}	1.30 ± 0.08
MRT	h	2.85 ± 0.03
td	h	11.8 ± 0.37
P/C	ratio	3.20 ± 0.41
Vc	L/kg	0.28 ± 0.01
AUC/MIC	ratio	114.5 ± 9.49

Cp^0 = plasma drug concentration at time zero after intravenous dose; α and A = distribution rate constant from central to peripheral compartment and the zero time intercept of distribution phase, respectively; B and β = zero time intercept of the elimination phase and elimination rate constant, respectively; $t_{1/2\alpha}$ = distribution half life; $t_{1/2\beta}$ = elimination half life; K_{12} and K_{21} are rate constants of drug transfer from central to peripheral and from peripheral to central compartment, respectively; K_{el} = rate constant for elimination of drug from central compartment; AUC = area under the plasma-concentration time curve; Vd_{area} = apparent volume of distribution; Cl_B = total body clearance of drug; MRT = mean residence time; td = total duration of pharmacological effect; P/C = ratio of drug present in peripheral to central compartment; Vc = volume of central compartment; MIC = minimum inhibitory concentration of levofloxacin.

Table 2. Urinary excretion of levofloxacin in febrile calves following single intravenous dose of 4 mg/kg body mass

Time interval (h)	Amount excreted (mg)	Per cent of total dose excreted	Time interval (h)	Cumulative amount excreted (mg)	Cumulative per cent of total dose excreted
0-2	40.8 ± 7.65	12.2 ± 1.69	0-2	40.8 ± 7.65	12.2 ± 1.69
2-4	51.4 ± 15.1	14.5 ± 3.19	0-4	70.0 ± 13.4	20.2 ± 2.90
4-6	25.4 ± 1.69	8.17 ± 1.54	0-6	95.4 ± 12.7	28.4 ± 3.33
6-8	18.5 ± 2.10	5.19 ± 0.93	0-8	110.9 ± 14.7	32.7 ± 3.23
8-10	5.60 ± 0.91	1.62 ± 0.35	0-10	115.5 ± 14.9	34.1 ± 3.23
10-12	4.46 ± 0.39	1.37 ± 0.18	0-12	120.0 ± 14.9	35.4 ± 3.23
12-16	4.26 ± 0.94	1.16 ± 0.26	0-16	123.5 ± 15.7	36.4 ± 3.30
16-24	4.23 ± 1.11	1.30 ± 0.33	0-24	127.8 ± 15.6	37.7 ± 3.31

The values given at different time intervals are mean ± SE of the results obtained from 6 animals

Discussion

In accordance with our findings, the disposition curve of levofloxacin and other fluoroquinolones, pefloxacin and enrofloxacin, after intravenous administration, have been reported to follow two-compartment open model in healthy and febrile calves (DUMKA et al., 2000; DUMKA and SRIVASTAVA, 2007; AHANGER and SRIVASTAVA, 2000; SRIVASTAVA et al., 2000). An average plasma concentration of 0.008-0.125 mg/mL 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* of human and animal models of infection (DRAGO et al., 2001; HO et al., 2004; GRIFFITH et al., 2006; DUGGIRALA et al., 2007). In this discussion, an average MIC_{90} of 0.1 mg/mL of levofloxacin has been taken into consideration. At 1 min of injection, the plasma level (15.8 ± 0.55 mg/mL) was approximately 158 fold higher than the MIC of levofloxacin and the drug was detected in plasma up to 12 h of administration. Levofloxacin was rapidly transferred from the central to peripheral compartment in febrile calves, as is evident from the high values of distribution rate constant (9.93 ± 0.73 h) and K_{12} (6.43 ± 0.49 h). Comparable values of distribution rate constant (12.2 h) and K_{12} (7.43 h) were reported after a single intravenous injection of levofloxacin in healthy calves (DUMKA and SRIVASTAVA, 2007). The high value of P/C ratio (3.2 ± 0.41) and apparent volume of distribution reflected that levofloxacin penetrated well into various body

fluids and tissues. The value of Vd_{area} established in the present study (1.18 ± 0.15 L/kg) is in agreement with the findings of LANGTRY and LAMB (1998) and DUMKA and SRIVASTAVA (2006), who reported the volume of distribution of levofloxacin to be 0.94 L/kg in man and 1.02 L/kg in calves, respectively. However, the volume of distribution of another fluoroquinolone used in veterinary medicine, enrofloxacin, was 0.4 L/kg after intravenous administration in calves (AHANGER et al., 2003). Consistent with the high AUC (11.5 ± 0.95 mg/mL/h) in the present finding, high values for AUC of levofloxacin have been reported in man (55.3 mg/mL/h), rabbits (29.7 mg/mL/h) and calves (12.7 mg/mL/h) (LANGTRY and LAMB, 1998; DESTACHE et al., 2001; DUMKA and SRIVASTAVA, 2007). High values of AUC have also been reported after intravenous administration of other fluoroquinolones used in veterinary medicine: marbofloxacin (7.7 mg/mL/h) in cattle and enrofloxacin (17.8 mg/mL/h) in calves (AHANGER et al., 2003; THOMAS et al., 1994). The total body clearance of levofloxacin in the present study was 0.36 ± 0.03 L/kg/h. This finding is in agreement with the values of Cl_B reported for levofloxacin (0.32 L/kg/h) and enrofloxacin (0.28 L/kg/h) in healthy calves and marbofloxacin (0.3 L/kg/h) in cattle after intravenous administration (DUMKA and SRIVASTAVA, 2007; AHANGER et al., 2003; THOMAS et al., 1994). The elimination half-life of levofloxacin in febrile calves calculated in this study (2.22 ± 0.07 h) was shorter than 5.7 h for marbofloxacin in cattle (THOMAS et al., 1994) but longer than the $t_{½\,\beta}$ of 1.61h for levofloxacin and 0.95 h for enrofloxacin in healthy calves (DUMKA and SRIVASTAVA, 2007; AHANGER et al., 2003) indicating rapid elimination of the drug during fever in calves.

The amount of levofloxacin-equivalent inhibitory units excreted in the urine of febrile calves was very high (4.23 ± 1.11 mg), even 24 h after administration. Approximately 37.7 per cent of the microbiological activity of the administered drug was recovered in the urine of calves within 24 h, which was greater than the 27.3 % urinary recovery of levofloxacin after intravenous administration in healthy calves (DUMKA and SRIVASTAVA, 2007). These findings suggest that levofloxacin may be an appropriate drug for treating urinary tract infections in cattle.

The objective of the pharmacokinetic study was to determine an appropriate intravenous dosage regimen of levofloxacin during fever in calves. On the basis of the present study, the loading and maintenance doses of levofloxacin, at a dosage interval of 12 h, were calculated to be 4.92 and 4.8 mg/kg, respectively, or under field conditions, for most bacteria sensitive to levofloxacin, the most appropriate dosage regimen for levofloxacin, would be 5 mg/kg at 12 h intervals for the treatment of bacterial infections manifested with fever in calves. This dosage was higher than the intravenous dose of 3 mg/kg at 12 h intervals suggested for levofloxacin in healthy calves (DUMKA and SRIVASTAVA, 2007).

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SAŽETAK

Istražena je raspodjela levofloksacina i njegovo izlučivanje mokraćom nakon jednokratne intravenske primjene u dozi od 4 mg/kg tjelesne mase u šestero febrilne križane teladi. Razine lijeka u plazmi i mokraći bile su procijenjene na osnovi mikrobiološkog postupka. Levofloksacin se brzo proširio iz krvi u tkiva što je vidljivo po visokim vrijednostima koeficijenta raspodjele (9,93 ± 0,73 h). Visoki AUC (površina ispod krivulje) (11,5

± 0,95 μg/mL/sat) upućuje na dobro antibakterijsko djelovanje levofloksacina u teladi. Poluvrijeme eliminacije iznosilo je 2,22 ± 0,07 sati, volumen raspodjele 1,18 ± 0,15 L/kg, a ukupni klirens 0,36 ± 0,03 L/kg/sat. Oko 37,7% primijenjene doze levofloksacina bilo je tijekom 24 sata izlučeno putem mokraće. Kod bakterijskih zaraza što se očituju vrućicom levofloksacin treba primijeniti u dozi od 5,0 mg/kg u razmaku od 12 sati.

Ključne riječi: telad, raspodjela, vrućica, levofloksacin