PLASMA DISPOSITION AND URINARY EXCRETION OF LEVOFLOXACIN FOLLOWING A SINGLE INTRAVENOUS ADMINISTRATION IN BUFFALO CALVES

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ABSTRACT

Disposition kinetics and urinary excretion of levofloxacin was investigated after a single intravenous dose of 3 $mg.kg^{-1}$ in male buffalo calves. The drug concentration was estimated in plasma and urine by microbiological assay using *E. coli* as the test organism. Disposition kinetic parameters were determined using a two-compartment open model and an appropriate dosage schedule was computed. Drug levels above MIC in plasma were detected up to 10 h. Levofloxacin was rapidly distributed from blood to the tissue compartment as evidenced by high values of the distribution rate constant (7.46 ± 0.28 h^{-1}) and the micro rate constant of transfer of drug from the central to the peripheral compartment (4.88 ± 0.21 h^{-1}). The elimination half-life, AUC and volume of distribution were 2.56 ± 0.09 h, 10.5 ± 0.11 $\mu g.h.ml^{-1}$ and 1.08 ± 0.05 $L.kg^{-1}$, respectively. Approximately 25% of the microbiological activity of the administered levofloxacin was recovered in the urine of calves within 24 h. On the basis of disposition kinetic parameters, an appropriate intravenous dosage regimen for levofloxacin in buffalo calves would be 3.0 $mg.kg^{-1}$ to be repeated at 12 h intervals. The observations on urinary excretion indicated that levofloxacin may be effective against urinary tract infections in buffalo species.

Keywords: buffalo calves, dosage, levofloxacin, disposition, urinary excretion

INTRODUCTION

Fluoroquinolone antibacterials are being increasingly employed in veterinary medicine for the treatment of mild to severe bacterial infections. Levofloxacin, a second generation fluoroquinolone, is very effective in the treatment of infections of upper and lower respiratory tract, genitourinary system, skin and soft tissue and possesses excellent activity against gram-positive, gram-negative and anaerobic bacteria. The pharmacokinetics of levofloxacin has been investigated in man (Chulavatnatol *et al*., 1999), rabbits (Destache *et al*., 2001) and calves (Dumka and Srivastava, 2007; Dumka *et al*., 2008). However, there is meager information available on the pharmacokinetics of levofloxacin in buffalo species barring two studies after extravascular administration (Ram *et al*., 2008, 2010).

In view of the marked species variation in the kinetic data of antimicrobial drugs, the present study was undertaken to determine the pharmacokinetics, urinary excretion and an appropriate dosage regimen of levofloxacin in buffalo calves following its single intravenous administration.

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MATERIALS AND METHODS

The study was conducted on six healthy male buffalo calves of non-descript breed, ranging between 1-1.5 years of age and weighing 82-148 kg. The animals were kept in an animal shed under standard conditions and had access to green fodder and water *ad libitum*. The experimental protocol followed ethical guidelines on the proper care and use of animals and was approved by the institutional animal ethics committee. Levofloxacin was administered at the dose of 3 $mg.kg^{-1}$ body weight into the left jugular vein.

For the disposition study, the animals were kept in metabolic stalls of standard size designed in such a way that whole amount of urine excreted naturally by the animals within a period is automatically collected without contamination or spillage in the 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, 10, 15, 30 minutes 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. Urine samples were also collected simultaneously from the same animals at time intervals of 2, 4, 6, 8, 10, 12, 16 and 24 h after administration of the drug. 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.

The concentration of levofloxacin in plasma and urine samples was estimated by a microbiological assay technique using *Escherichia coli* (ATCC 10536) as the test organism. This method estimated the level of drug and its active metabolites having antibacterial activity. The assay could detect a minimum of 0.1 $\mu g.ml^{-1}$ of levofloxacin (Figure 1). Disposition parameters were calculated manually by regression analysis.

RESULTS AND DISCUSSION

Evaluation of the results revealed that the disposition pattern of levofloxacin best fitted a two-compartment open model (Figure 1). Consistent to our findings, the disposition curve of levofloxacin in calves (Dumka and Srivastava, 2007) and other fluoroquinolones, danofloxacin in buffalo calves and ofloxacin in calves, followed a two-compartment open model after intravenous administration (Gaur *et al*., 2004; Gosal *et al*., 2008).

The disposition parameters of levofloxacin in buffalo calves are presented in Table 1. Levofloxacin was rapidly transferred from the central to the peripheral compartment in buffalo calves, as is evident from the short $t_{1/2\alpha}$ and high value of K_{12}. In support of the present findings, a short $t_{1/2\alpha}$ of 0.059 h and high value of K_{12} (7.43 h^{-1}) has been reported after intravenous administration of levofloxacin in calves (Dumka and Srivastava, 2007). The high value of P/C ratio (4.58 ± 0.2) and apparent volume of distribution further suggested extensive drug distribution. High values of P/C ratio have also been reported for gatifloxacin (10.1) and danofloxacin (3.06) in buffalo calves and ofloxacin in calves (4.12) following their intravenous administration (Gaur *et al*., 2004; Gosal *et al*., 2008; Raipuria *et al*., 2007). The large Vd_{area} established in this study (1.08 ± 0.05 $L.kg^{-1}$) is in agreement with the finding in cross bred calves (1.38 $L.kg^{-1}$) and man (0.94 $L.kg^{-1}$) following intravenous injection of levofloxacin (Langtry and Lamb 1998; Dumka *et al*., 2008). Further, large volume of distribution of another fluoroquinolone used in veterinary medicine, danofloxacin was reported to be 1.42 $L.kg^{-1}$ in goats and 4.35 $L.kg^{-1}$

Table 1. Disposition parameters of levofloxacin in buffalo calves following a single intravenous administration (n=6).

Parameter	Unit	Mean ± SE
Cp^0	$\mu g.ml^{-1}$	15.9 ±0.44
A	$\mu g.ml^{-1}$	13.5 ± 0.39
B	$\mu g.ml^{-1}$	2.29 ± 0.09
α	h^{-1}	7.46 ± 0.28
β	h	0.272 ± 0.009
$t_{1/2\alpha}$	h	0.093 ± 0.003
$t_{1/2\beta}$	h	2.56 ± 0.09
K_{12}	h^{-1}	4.88 ± 0.21
K_{21}	h^{-1}	1.35 ± 0.07
AUC	$\mu g.h.ml^{-1}$	10.5 ± 0.11
Vd_{area}	$L.kg^{-1}$	1.08 ± 0.05
Cl_B	$ml.kg^{-1}h^{-1}$	286.6 ± 2.74
K_{el}	h^{-1}	1.51 ± 0.03
MRT	h	3.07 ± 0.09
td	h	12.6 ± 0.41
P/C	ratio	4.58 ± 0.2

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

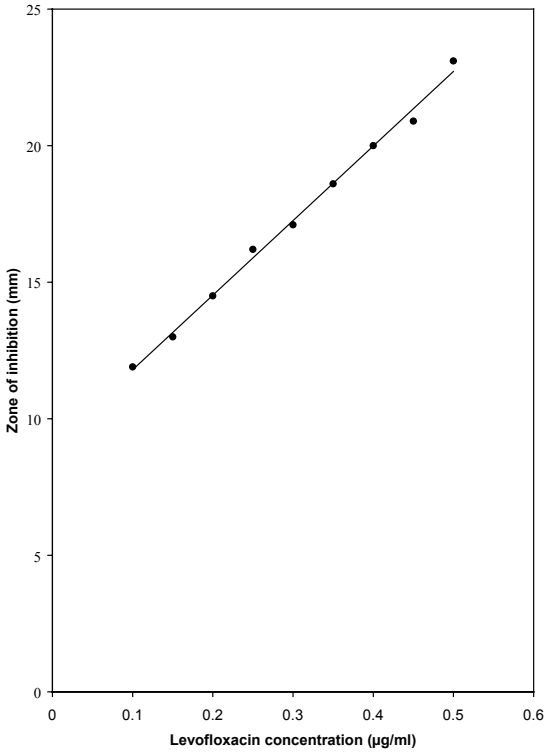

Figure 1. Standard curve of levofloxacin in plasma of buffalo calves. Each point represents the mean of the results from 14 assays.

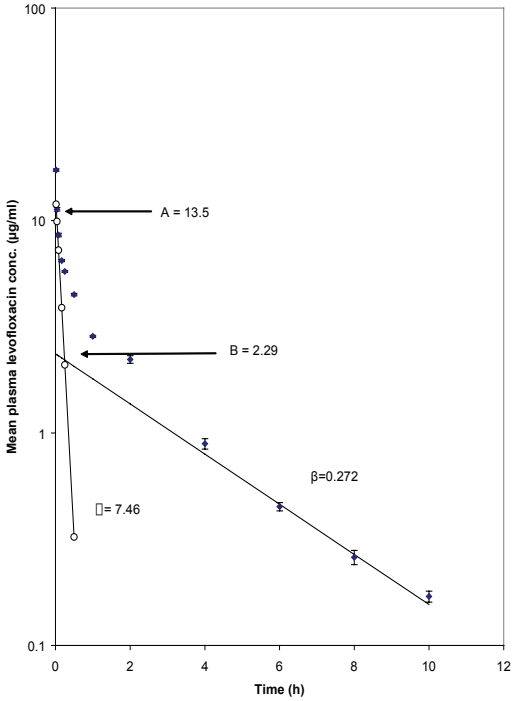

Figure 2. Semilogarithmic plot of plasma concentration-time profile of levofloxacin following its single intravenous injection of 3 $mg.kg^{-1}$ body weight in buffalo calves.

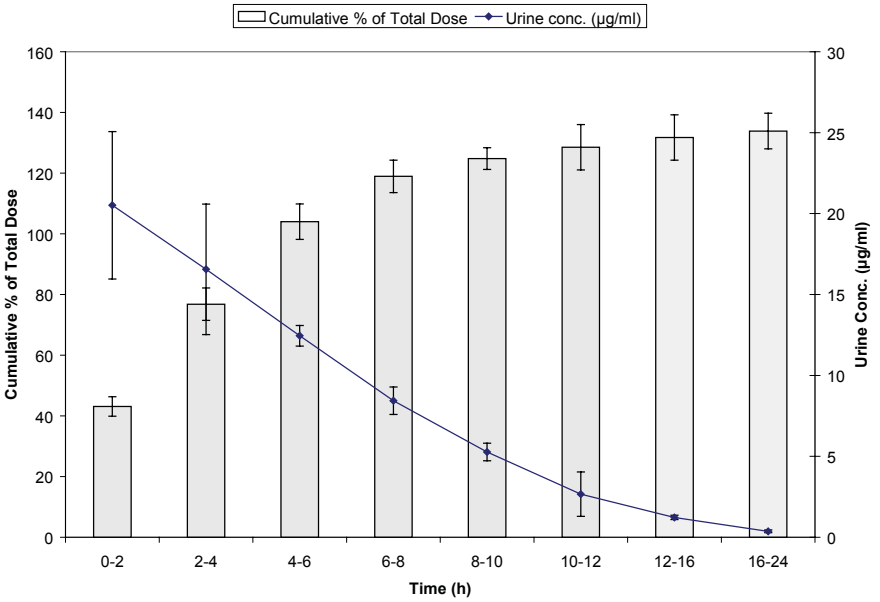

Figure 3. Urinary recovery of levofloxacin in buffalo calves following its single intravenous dose of 3 mg.kg^{-1} body weight.

in buffalo calves after intravenous administration (Atef *et al*., 2001; Sappal *et al*., 2009). The high value of AUC (10.5 ± 0.11 µg.h^{-1}ml) was in agreement with the AUC of levofloxacin reported in man (55.3 µg.h^{-1}ml), rabbits (29.7±6.3 µg.h^{-1}ml) and calves (12.7 µg.h^{-1}ml) [2, 4, 5]. High values of AUC after iv administration have also been reported for other fluoroquinolones as 26.55 µg.h^{-1}ml for ofloxacin in calves (Gaur *et al*. 2004), 17.1 µg.h^{-1}ml for gatifloxacin in buffalo calves (Raipuria *et al*., 2007) and 29.6 µg.h^{-1}ml for danofloxacin in goats (Atef *et al*., 2001).

The total body clearance of levofloxacin in the present study was 286.6 ± 2.74 ml.kg^{-1}h^{-1}. This finding is in agreement with the values of Cl_B reported for levofloxacin (317.2 ml.kg^{-1}h^{-1}) and ofloxacin (189.9 ml.kg^{-1}h^{-1}) after iv administration in calves (Gaur *et al*., 2004; Dumka and Srivastava, 2007). The elimination half-life of levofloxacin in buffalo calves calculated in this study (2.56 ± 0.09 h) was longer than its corresponding value of 1.61 h in cross bred calves (Dumka and Srivastava, 2007); however, it was shorter than the $t_{1/2\beta}$ of 10.4 h reported for gatifloxacin in buffalo calves (Raipuria *et al*., 2007), 4.01 h, 4.24 h and 5.37 h for danofloxain in goats, buffalo calves and camels, respectively (Atef *et al*., 2001; Aliabadi *et al*., 2003; Sappal *et al*., 2009) and 26.27 h for ofloxacin in calves (Gaur *et al*., 2004).

The concentration of levofloxacin-equivalent inhibitory units in the urine of buffalo calves was very high in this study. High urinary concentrations of danofloxacin (2.37 µg.ml^{-1}) and gatifloxacin (2.6 µg.ml^{-1}) have also been reported 24 h post intravenous dosing in buffalo calves (Raipuria *et al*., 2007; Sappal *et al*., 2009). Approximately 25% of the microbiological activity of the administered levofloxacin was recovered in the urine of buffalo calves within 24 h. This finding was less than the urinary recovery of 38.4% of the total dose of levofloxacin in cross bred calves (Dumka *et al*., 2008) but more than 19.7% of

gatifloxacin (Raipuria *et al*., 2007) and 4.53% of danofloxacin (Gosal *et al*., 2008) in buffalo calves within the first 24 h of intravenous administration.

The results indicated that levofloxacin may be effective against urinary tract infections in buffalo species. Under field conditions, for most bacteria sensitive to levofloxacin, an appropriate intravenous dosage regimen for levofloxacin, would be 3 $mg.kg^{-1}$ repeated at 12 h intervals for the treatment of infections caused by levofloxacin susceptible bacteria in buffalo calves (Table 2).

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