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Pharmacokinetics of Levofloxacin Following Intravenous and Subcutaneous Administration in Sheep

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ABSTRACT

The present study was conducted to investigate the disposition kinetics of levofloxacin following a single intravenous (i.v.) and subcutaneous (s.c.) injection at a dose rate of 3 mg kg^{-1} body weight (b.wt) in sheep due to unavailability of disposition data of the drug following s.c. administration in target species of animal. Plasma samples collected after treatments were analyzed for drug concentration using High performance liquid chromatography (HPLC). After i.v. administration, distribution of the drug was rapid ($t_{1/2(\alpha)}$: 0.25±0.01 h) and wide as reflected by the steady-state volume of distribution of 0.92±0.08 L kg^{-1}. Drug elimination was relatively faster with a total body clearance of 0.55±0.02 L/h/kg. The elimination half-life was 2.38±0.22 h. The rapid ($t_{1/2Ka}$: 0.24±0.04 h) and near to complete absorption (bioavailability: 91.12±3.71%) of the drug was observed from s.c injection site. The maximum plasma drug concentration of 1.56±0.09 μg mL^{-1} (C_{max}) was attained at 1 h (T_{max}). The drug was widely distributed as reflected by apparent volume of distribution ($Vd_{(area)}$: 1.43±0.05 L kg^{-1}). The drug was cleared at rate of 0.58±0.02 L/h/kg (Cl_B) from body and elimination half-life ($t_{1/2\beta}$) of the drug was 1.73±0.04 h. Pharmacokinetic parameters, absence of adverse reactions and values of efficacy predictors in the present study revealed that levofloxacin may be a potentially useful drug to treat bacterial diseases in sheep.

Key words: Pharmacokinetics, intravenous and subcutaneous administration, fluroquinolone, antibacterial drug, levofloxacin, sheep

INTRODUCTION

Fluroquinolones are now being used for treatment of various bacterial diseases in animals. An emergence of bacterial resistance against this class of drugs needs great efforts to evaluate the newer fluoroquinolones for therapy in human and veterinary medicine (Bakken, 2004; Manikandan *et al*., 2011). Levofloxacin is a third-generation fluoroquinolone with a wide spectrum of bactericidal activity (Davis and Bryson, 1994; Swoboda *et al*., 2003; Martinez *et al*., 2006). The drug is active against Gram-negative, Gram-positive and anaerobic bacteria including Pseudomonas species. It has enhanced activity against *Streptococcus pneumoniae,*

Staphylococcus aureus and *Enterococcus* species, besides having good activity against *Mycoplasma* and *Chlamydia* species (Davis and Bryson, 1994; Blondeau, 1999). Enterobacteriaceae including *E. sakazakii* (isolated from food products) is also found sensitive to levofloxacin (Aigbekaen and Oshoma, 2010). The drug distribution in body fluids and tissues of various body systems including saliva and skin which makes the drug to be effective against intracellular pathogens (Langtry and Lamb, 1998; Sheikh *et al*., 2010). Levofloxacin enhance hepatic enzyme activity (Dwivedi *et al*., 2011) and is metabolized at certain extent in the liver to demethyl-levofloxacin and levofloxacin-N-oxide and excreted in urine, mainly as active drug (Hurst *et al*., 2002). The levofloxacin has found at higher concentration in liver and kidney samples collected from poultry products (Naeem and Rafiq, 2006).

Drug disposition of levofloxacin has been clinically evaluated in laboratory animal and human volunteers (Sheikh *et al*., 2010; Iqbal *et al*., 2000). Looking to the emergence of bacterial resistance against various antibacterial drugs in animals, the evaluation of disposition of newer fluoroquinolone in small ruminants is needed. The potential value of levofloxacin in a variety of animals were pointed out by previous studies describing its pharmacokinetic profiles (Goudah and Abo-El-Sooud, 2009; Albarellos *et al*., 2005; Dumka and Srivastava, 2006, 2007a, b; Dumka, 2007; Ram *et al*., 2008; Goudah *et al*., 2008; Goudah, 2009; Goudah and Hasabelnaby, 2010). However, there is limited information available on the disposition of levofloxacin following subcutaneous administration in sheep. Therefore, the present study was planned to determine the disposition kinetics and bioavailability of levofloxacin in sheep following subcutaneous (s.c.) administration at rate of 3 mg kg^{-1} b.wt.

MATERIALS AND METHODS

Animals: Six healthy female Patanwadi non-lactating sheep, 2-3 years old ranging in body weight from 23.5 to 30.0 kg were used in the experiment. The animals were obtained from and maintained at the Instructional Farm, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand, India. They were kept under constant observation for two weeks prior to commencement of the experiment. During this period, they were subjected to clinical examination in order to exclude the possibility of any disease. The animals were then housed in separate pen and were provided standard ration. Water was provided *ad libitum*. The experimental protocol for general procedure and use of animals for conducting the present study has been approved by the Ethics Committee. The study was conducted during the period of June 2008 to July 2009.

Experimental design: All animals were randomly treated with levofloxacin (Tavanic®, 100 mL vial of solution of levofloxacin hemihydrate equivalent to 500 mg levofloxacin, Aventis Pharmaceutical Ltd, Bangalore) by the i.v. and s.c. routes according to a crossover design. The drug was administered i.v. via the left jugular vein at a dose rate of 3 mg kg^{-1} b.wt as a bolus. For the s.c. administration, the injection site was located at neck region. The washout period of 15 days was observed between two treatments to rule out possibility of drug residue. Blood samples (3 mL) were collected from i.v. catheter (Venflon, 22×0.9×25 mm) fixed into the right jugular vein into 10 mL heparinized centrifuge tube. Following i.v. administration of the drug, blood samples were collected at 0 (prior to treatment), 0.033, 0.083, 0.166, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24 and 36 h post-treatment. Whereas following s.c. administration of the drug, blood samples were collected at 0 (prior to treatment), 0.083, 0.166, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and

48 h post-treatment. Plasma was separated soon after collection by centrifugation at 3000 g for 15 min and transferred to labeled cryovials and stored at -35°C until assayed for levofloxacin concentration using High Performance Liquid Chromatography (HPLC) procedure which was usually done with in 24 to 36 h.

Levofloxacin assay: Levofloxacin concentrations in the plasma samples were determined by high-performance liquid chromatography (HPLC) with UV detection according to the methods described by Varia *et al.* (2009). Experimental and fortified plasma samples (0.5 mL) were taken in micro-centrifuge tube (1.5 mL capacity). Solution of pure enrofloxacin powder (40 μL of 0.5 mg mL^{-1} concentration) was added as an Internal Standard (IS) in each sample. Perchloric acid (50 μL) was added in order to precipitate plasma proteins. The mixture was vortexed for 1 min and centrifuged at 3000 g for 10 min. The supernatant was decanted in clean sterile micro-centrifuge tube and 20 μL supernatant was injected directly into the chromatographic system (Laballiance, USA) using 50 μL glass syringe (Hamilton Bonaduz AG, Switzerland). Chromatographic separation was performed by using reverse phase C_{18} column (Thermo, ODS; 250×4.6 mm ID) at room temperature. The HPLC data integration was performed using software Clarity (Version 2.4.0.190). The mobile phase consisted of a mixture of 1% triethylamine in water and acetonitrile (85:15 v/v) adjusted to pH 3.0 with ortho-phosphoric acid. Mobile phase was filtered by 0.45 μ size filter (Ultipor N_{66} Nylone 6,6 membrane, PALL Pharmalab filtration Pvt., Ltd., Mumbai) and degassed by ultra-sonication. The mobile phase was pumped by quaternary gradient delivery pump (Model: AIS 2000, Laballiance, USA) into column at a flow rate of 1.5 mL min^{-1} at ambient temperature. The effluent was monitored at 290 nm wavelength (UV detector model 500, Laballiance, USA). All chemicals used for assay were of analytical or HPLC grade purchased from Merck Limited, Mumbai, India.

Calibration curves for levofloxacin in the range 0.01 to 50 μg mL^{-1} (5 concentrations) were prepared with the use of drug-free plasma of non-treated sheep. Pooled plasma samples were taken throughout the procedure and calibration curves were prepared using prepared standard in mobile phase or plasma by plotting the ratio (areas of peak of drug: Areas of peak of IS) at the ordinate and the drug concentration at abscissa. Linear regression analysis was used to determine correlation coefficients of calibration curves. The extraction efficiency of the drug under study was measured by comparison of the ratio of area (drug: IS) from the spiked plasma samples, with ratio of area resulting from direct injections of the standards in mobile phase. The inter-assay precision of the extraction and chromatography procedures was evaluated by processing replicate aliquots of plasma samples (quintuplicate determinations) containing known amounts of the drug on different days. The analytical method used to extract and quantify the plasma concentration of levofloxacin by chromatographic analysis using the UV detector was validated as follows: The regression lines between ratio of area (levofloxacin: Internal standard) and drug concentrations showed correlation coefficients >0.998. The mean extraction recovery from plasma was >82.81±3.83% at the spiked concentrations between 0.01 and 50 μg mL^{-1}. The inter-assay and intra-assay precision showed coefficients of variation <9.77 and 8.88%, respectively. The limit of drug quantification was established by injection of plasma blanks and measurement of baseline noise at the retention time of the levofloxacin peak. The mean baseline noise at the levofloxacin retention time plus six standard deviations was defined as the theoretical quantification limit; it was found to be 0.01 μg mL^{-1}.

Pharmacokinetic analysis: The plasma concentrations vs. time curves obtained after treatment in each individual animal were semi-logarithmically fitted with PK Solutions software program (Version 2.0, Summit research services, USA). The peak concentration (C_{max}) and time to peak concentration (T_{max}) were taken directly from the curve. A non-compartmental model (moment analysis) was used to determine the area under the concentration-time curve (AUC) and the area under the first moment curve (AUMC), using the linear trapezoidal rule with extrapolation of infinity. The mean residence time (MRT) was calculated as AUMC/AUC where AUC is as defined previously and AUMC is the area under the first moment curve (Gibaldi and Perrier, 1982). The distribution and elimination half-lives were calculated as ln 2 divided by the distribution and elimination rate constants, respectively. The estimated plasma concentration of the drug at zero time ($C_{p(0)}$) after its i.v. administration was the sum of the extrapolated zero-time concentrations of the coefficient A and B. Total body clearance (Cl_B), apparent volume of distribution (Vd_{area}) and volume of distribution at steady state were calculated using following formulas: Cl_B = Dose*F/AUC; Vd_{area} = Dose*F/(AUC)(β) where for i.v., 100% bioavailability (F = 1) was considered and $Vd_{(ss)}$= Dose*AUMC/$(AUC)^2$. The absolute bioavailability (F) following s.c. administration of the drug was calculated as:

$$(AUC_{s.c.}/ AUC_{i.v.})\times(Dose_{i.v.}/Dose_{s.c.})\times100$$

All data were expressed as Mean±S.E, The mean and S.E. were calculated and the graph was prepared in Microsoft Excel.

PK/PD integration: The peak plasma drug concentration (C_{max}) and area under the curve ($AUC_{(0-\infty)}$) were applied in the calculation of the predictors of efficacy for concentration dependent antibiotics: C_{max}/MIC and $AUC_{(0-\infty)}$/MIC for s.c. administration route. There are no published studies about MIC_{90} data of levofloxacin against ovine bacterial isolates. To cover most of the susceptible organisms like *Klebsiella* spp., *Shigella* spp. *Salmonella* spp., *Proteus* spp. and *Acinetobacter* spp. in this discussion, the MIC_{90} of 0.12 μg mL^{-1} (Marshall and Jones, 1993) of levofloxacin has been taken into consideration as described by Goudah and Hasabelnaby (2010).

RESULTS

No local or systemic adverse reactions were observed in clinical examination of all animals after the single-dose i.v. and s.c. administration of levofloxacin in the animals studied. The mean plasma concentration-time profile of levofloxacin following single i.v. and s.c. administration at 3 mg kg^{-1} b.wt is presented graphically in Fig. 1. Pharmacokinetic parameters (Mean±SE) estimated after each route of drug administrations are depicted in Table 1.

Following i.v. administration, the apparent volume of distribution (Vd_{area}), volume of distribution at steady state (Vd_{ss}), area under curve ($AUC_{(0-\infty)}$), elimination half-life ($t_{1/2\beta}$) and total body clearance (Cl_B) were 1.95±0.16, 0.92±0.08 L kg^{-1}, 5.47±0.21 μg h mL^{-1}, 2.38±0.22 h and 0.55±0.02 L/h/kg, respectively. The drug was absorbed rapidly after s.c. administration and the maximum plasma concentration of 1.56±0.09 μg mL^{-1} (C_{max}) was attained at 1.00 h (T_{max}) after injection. The apparent volume of distribution (Vd_{area}), area under curve ($AUC_{(0-\infty)}$), elimination half-lives ($t_{1/2\beta}$) and total body clearance $(Cl)_B$ were 1.43±0.05 L kg^{-1}, 4.74±0.14 μg h mL^{-1}, 1.73±0.04 h and 0.58±0.02 L/h/kg, respectively. The bioavailability (F) of the drug following s.c. administration was 91.12±3.71%.

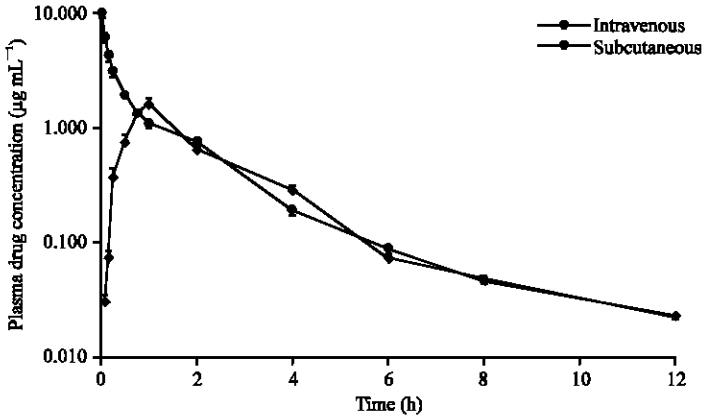

Fig. 1: Mean±SE plasma concentration profile of levofloxacin following intravenous and subcutaneous administration at a dose rate of 3 mg kg^{-1} of bwt in sheep (n = 6)

Table 1: Pharmacokinetic parameters (Mean±SE) of levofloxacin after intravenous and subcutaneous administration at a dose rate of 3 mg kg^{-1} of bwt in sheep (n = 6)

Parameters	Unit	Intravenous	Subcutaneous
$C_{p(0)}$	µg mL^{-1}	7.06±0.76	-
$t_{1/2\alpha}$	h	0.25±0.01	-
$t_{1/2Ka}$	h	-	0.24±0.04
$t_{1/2\beta}$	h	2.38±0.22	1.73±0.04
$AUC_{(0-\infty)}$	µg h mL^{-1}	5.47±0.21	4.74±0.14
AUMC	µg h^2 mL^{-1}	9.00±0.50	12.66±0.38
Vd_{area}	L kg^{-1}	1.95±0.16	1.43±0.05
Vd_{ss}	L kg^{-1}	0.92±0.08	-
Cl_B	L/h/kg	0.55±0.02	0.58±0.02
MRT	h	1.73±0.11	2.67±0.04
C_{max}	µg mL^{-1}	-	1.56±0.09
T_{max}	h	-	1.00±0.00
F	%	-	91.12±3.71

$C_{p(0)}$: Concentration at time 0; $t_{1/2\alpha}$: Half-life of distribution phases; $t_{1/2k(a)}$: Absorption half-life; $t_{1/2\beta}$ elimination half-life; $AUC_{(0-\infty)}$: Area under the curve from zero to infinity; AUMC: Area under first of moment curve; Vd_{area}: Apparent volume of distribution; Vd_{ss}: Volume of distribution at steady state; Cl_B: Total body clearance; MRT: Mean residence time; C_{max}: Maximum drug concentration; T_{max} :Time to peak plasma drug concentration; F: Bioavailability

DISCUSSION

In the present study, plasma concentration-time profile of the drug following i.v. administration in sheep showed a rapid initial distributive phase, followed by relatively slower elimination phase with an estimated elimination half-life ($t_{1/2\beta}$) of 2.38±0.22 h which was proximate to that of danofloxacin, enrofloxacin, ciprofloxacin and moxifloxacin in sheep (McKellar *et al.*, 1998; Haritova *et al.*, 2003; Patel *et al.*, 2004; Rahal *et al.*, 2006, 2007; Escudero *et al.*, 2007; Goudah, 2008). The half-life of the drug has also been reported to be 3.29±0.23 h in sheep (Goudah and Hasabelnaby, 2010). The drug exhibits a relatively high volume of distribution suggesting an extensive tissue distribution in sheep as observed in goats (1.89±0.18 L kg^{-1}) by Ram *et al.* (2008). The Vd_{ss} for levofloxacin in sheep was also relatively high which is proximate to the Vd_{ss} reported in sheep (0.86±0.23 L kg^{-1}) and goats (0.73±0.22 L kg^{-1})

(Goudah and Abo-El-Sooud, 2009; Goudah and Hasabelnaby, 2010). The extensive penetration of the drug owing to its lipid solubility and low plasma protein binding. The plasma protein binding of levofloxacin in sheep has been reported to be 23.74% (Goudah and Hasabelnaby, 2010). Plasma protein binding of levofloxacin may exhibits positive correlation between drug concentration and plasma protein level (Sheikh *et al*., 2001). The variation in renal elimination has been found across fluroquinolones. Levofloxacin is eliminated primarily by the kidney, with the renal clearance exceeding creatinine clearance by approximately 60% (Martinez *et al*., 2006) suggesting the involvement of both glomerular filtration and tubular secretion (Okazaki *et al*., 1991). The total body clearance of the drug from body of sheep was parallel to the clearance of other fluoroquinolones like danofloxacin (0.63±0.04 and 0.79±0.15 L/h/kg), enrofloxacin (0.86±0.10 L/h/kg) and ciprofloxacin (0.65±0.10 L/h/kg) in sheep (McKellar *et al*., 1998; Patel *et al*., 2004; Rahal *et al*., 2006; Escudero *et al*., 2007). Faster clearance of levofloxacin in sheep may be due to low protein binding, excretion as unchanged form and minimal tubular reabsorption of the drug (Fish and Chow, 1997). Alteration in urine output may significantly affect the clearance of levofloxacin (Waheed *et al*., 2002).

Following s.c. administration, the peak plasma level (C_{max}) of levofloxacin attained at 1 h in the present study. However, higher C_{max} of 2.80±0.30 μg mL^{-1} at 0.75 h in cross-bred calves (Dumka and Srivastava, 2007b) and 2.94±0.07 μg mL^{-1} at 1 h in buffalo calves (Ram *et al*., 2007) was attained after single s.c. injection of levofloxacin. The difference in C_{max} might be due to the difference in dose of the drug. However, C_{max} of levofloxacin in sheep observed in the present study was higher than C_{max} of danofloxacin, enrofloxacin, difloxacin, ciprofloxacin and moxifloxacin reported following their s.c. administration in sheep (Rahal *et al*., 2006; Marin *et al*., 2007; Rahal *et al*., 2007; Escudero *et al*., 2007; Carceles *et al*., 2009). The elimination half-life ($t_{1/2\beta}$) of the drug was found lower than that of 3.0±0.2 h reported in cow calves (Dumka and Srivastava, 2007b). The findings indicate that levofloxacin is rapidly absorbed and eliminated form the body of sheep as compared to cow calves following s.c. administration. The elimination half-life of the drug was similar to that of ciprofloxacin (1.38±0.39 h) reported after s.c. administration in sheep (Rahal *et al*., 2007), however, it was lower than that recorded for danofloxacin (3.07±0.79 h), enrofloxacin (7.12±1.18 h), difloxacin (12.02±2.8) and moxifloxacin (7.42) in sheep (Rahal *et al*., 2006; Escudero *et al*., 2007; Marin *et al*., 2007; Carceles *et al*., 2009).

The absolute systemic bioavailability of the drug in sheep after s.c. administration was nearly complete (91.12±3.71%). This value indicates the excellent absorption of the drug from the injection site and the absorption process was rapid with absorption half-life ($t_{1/2k(a)}$) of 0.24±0.04 h which was supported by similar absorption half-life of 0.31±0.05 h in cow calves (Dumka and Srivastava, 2007b). The bioavailability of the drug in present study was found higher than that reported in cow calves (41.90±3.20%) and buffalo calves (44.3±1.76%) following s.c. administration of the drug (Dumka and Srivastava, 2007b; Ram *et al*., 2007). Good absorption after extravascular injection has also been reported for levofloxacin in other species of animals. Similarly, high bioavailability of other fluoroquinolones (difloxacin: 82.35±25.65%; danofloxacin: 93.6±13.7%; moxifloxacin: 102.20±23.76%) have also been observed following s.c. administration in sheep (Escudero *et al*., 2007; Marin *et al*., 2007; Goudah, 2008). The high systemic bioavailability of levofloxacin (91.35%) in sheep after IM administration has been reported which indicates excellent absorption of the drug from injection site (Goudah and Hasabelnaby, 2010).

For a concentration-dependent drug, such as levofloxacin, successful treatment usually correlates with PK-PD indices like AUC/MIC_{90} and C_{max}/MIC_{90} and a high ratio of the C_{max}/MIC_{90} has

also been associated with a lower incidence of the development of resistance (Lode *et al*., 1998). For effective eradication of bacteria and good clinical outcome an AUC/MIC_{90} ratio of >30 for Gram-positive and >100 for Gram-negative organisms has been suggested for levofloxacin (Nightingale *et al*., 2000). A C_{max}/MIC_{90} of 8-10 would be associated with better clinical results (Dudley, 1991). High C_{max}/MIC_{90} ratio has been associated with a lower incidence resistance development (Walker, 2000). The MIC of levofloxacin has not yet been determined for bacteria isolated from sheep. To cover most of the susceptible organisms, in this discussion, the MIC_{90} of 0.12 μg mL^{-1} of levofloxacin have been taken into consideration (Goudah and Hasabelnaby, 2010). Based on this data, a dose rate of 3 mg kg^{-1} levofloxacin s.c. in sheep would resulted in AUC/MIC_{90} ratio of 47.40. However, most important surrogate marker C_{max}/MIC_{90} was 13 which exceeds the recommended ratio. However, controlled use of newer antimicrobial drug in animals is necessary to prevent emergence of cross-resistance with human enteric pathogens (Moniri and Dastehgoli, 2007).

CONCLUSION

Base on results of the present experiment with lack of local reactions/adverse effects and pharmacokinetic characteristics of levofloxacin following i.v. and s.c. administration may be a indication of a new insight into the strategy for clinical use of the drug for pulmonary as well as urinary infections in sheep. Levofloxacin can be injected intravenously or subcutaneously for the treatment of systemic bacterial infections in sheep against susceptible bacteria having MIC≤0.12 μg mL^{-1}.

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