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Disposition Kinetic of Levofloxacin in Experimentally Induced Febrile Model of Sheep

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ABSTRACT

The present study was planned to investigate pharmacokinetics of levofloxacin following a single dose (3 mg kg^{-1}) intravenous (i.v.) and subcutaneous (s.c.) administration in sheep with febrile condition. Plasma samples were collected after each treatment in crossover design and analyzed for drug concentration using High Performance Liquid Chromatography (HPLC). Following intravenous administration, the drug was rapidly and widely distributed in the body with distribution and elimination half-lives of 0.24±0.03 and 2.15±0.07 h, respectively. The high volume of distribution of the drug with total clearance of 0.42±0.03 L h^{-1} kg^{-1} was observed. The drug was rapidly absorbed from subcutaneous site of administration and maximum drug concentration (C_{max}) of 1.60±0.09 μg mL^{-1} was achieved at 1 h (T_{max}). The elimination half-life and total body clearance of the drug was comparative to those observed following intravenous injection. The bioavailability (F) of the drug following subcutaneous administration in febrile sheep was 89.20±3.84%. Pharmacokinetic characteristics and absence of adverse reactions in the present study revealed that levofloxacin may be a potentially useful drug to treat bacterial diseases in sheep having acute phase reaction.

Key words: Levofloxacin, disposition, bioavailability, febrile model, sheep

INTRODUCTION

Emergence of bacterial resistance is one of greatest threats for effective therapy with fluoroquinolone drugs as an effective antibiotic class (Bakken, 2004; Ayana and Surekha, 2008; Manikandan *et al*., 2011). Levofloxacin (LFX), a third-generation fluoroquinolone possess a wide spectrum of activity against both Gram-positive and Gram-negative bacteria (Swoboda *et al*., 2003; Martinez *et al*., 2006; Aigbekaen and Oshoma, 2010). The drug is found to be effective against *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus* species, *Pseudomonas* species, *Mycoplasma* and *Chlamydia* species (Davis and Bryson, 1994; Blondeau, 1999).

The drug distributes widely in body fluids and tissues of body systems including saliva and skin with enhancing activity to liver microsomal enzyme (Langtry and Lamb, 1998; Sheikh *et al*., 2010;

Dwivedi *et al.*, 2011). The residue of levofloxacin has been reported in organs sample from poultry (Naeem and Rafiq, 2006). Its pharmacokinetic properties have been evaluated in laboratory animal, human volunteers (Sheikh *et al.*, 2010; Iqbal *et al.*, 2000) and also in variety of domestic animal species including sheep (Albarellos *et al.*, 2005; Dumka and Srivastava, 2006, 2007a, b; Dumka, 2007; Dumka *et al.*, 2008; Goudah *et al.*, 2008; Goudah, 2009; Varia *et al.*, 2009; Goudah and Abo-El-Sooud, 2009; Goudah and Hasabelnaby, 2010; Patel *et al.*, 2012). However, the pharmacokinetic studies in animals with febrile condition have not been carried out. It is proved that drug disposition can be altered by the acute phase response induced by endotoxin or infectious diseases in laboratory and farm animals (Rao *et al.*, 2000; Waxman *et al.*, 2003; Ismail, 2006; Prasad *et al.*, 2006).

Febrile condition produced by administration of *Escherichia coli* endotoxin (lipopolysaccharide, LPS) in the animals is good model to study the drug disposition in the presence of acute phase response in the domestic animals. Although this model is not a standard substitute for bacterial infection, the utility of the model system is easy and it has relative similarity to systemic bacteremia (Post *et al.*, 2003). To the best of our knowledge, the pharmacokinetic behaviour of levofloxacin in febrile animal has not been studied elsewhere. Therefore, the present study was planned to evaluate the disposition kinetic of levofloxacin in febrile sheep following a single dose intravenous (i.v.) and subcutaneous (s.c.) administration at dose rate of 3 mg kg^{-1} b.wt.

MATERIALS AND METHODS

Experimental material and design: Six healthy 2-3 years old female Patanwadi sheep were procured from and maintained at the Instructional Farm, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand, India. All animals were kept in separate pen for constant observation for two weeks prior to commencement of the experiment and were clinically examined to exclude the possibility of any disease. The animals were provided standard ration and water *ad libitum*. The experimental protocol for conducting the study has been approved by the Ethics Committee of the college.

Febrile model in sheep was induced by injecting lipopolysaccharide (LPS) of *Escherichia coli,* 055:B5 (Sigma Pvt. Ltd., Mumbai, India) at the dose rate of 0.2 μg mL^{-1} b.wt. intravenously (Verma and Roy, 2006). This dose of lipopolysaccharide caused increase in temperature within 30 min and fever persisted for 10-12 h. At least 1.5°F increase of temperature from normal temperature was taken as the time of the drug administration (Agarwal *et al.*, 2002). Taking into account the elimination half-life observed after intravenous administration of levofloxacin in healthy sheep and goat (Patel *et al.*, 2012; Goudah and Abo-El-Sooud, 2009), LPS was again injected at dose rate of 0.1 μg mL^{-1} b.wt. to maintain fever at least 1.5°F higher than normal temperature. Rectal temperature was increased at least 1.5 to 2.0°F within half an h of LPS injection.

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 intravenous and subcutaneous routes according to a crossover design. Levofloxacin (3 mg kg^{-1} b.wt.) was injected intravenously via left jugular vein and subcutaneously 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 intravenous catheter (Venflon, 22×0.9×25 mm) fixed into the right jugular vein into heparinized centrifuge tube. Following intravenous 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 subcutaneous 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 after collection by centrifugation at 3000 g for 10 min and transferred to labeled cryovials to store at -35°C until assay for levofloxacin concentration using High Performance Liquid Chromatography (HPLC) procedure which was done within 24-36 h.

Analytical method: Levofloxacin concentrations in the plasma samples were determined by high-performance liquid chromatography (Laballiance, USA) with UV detection (290 nm wavelength) according to the method described elsewhere (Varia *et al*., 2009). In short, perchloric acid (50 μL) was added in order to precipitate plasma proteins. Solution of pure enrofloxacin powder (40 μL microliter of 0.5 mg mL^{-1} concentration) was added as an Internal Standard (IS) in each sample. 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. 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 filter and pumped into column at a flow rate of 1.5 mL min^{-1} at ambient temperature. The HPLC data integration was performed using software Clarity (Version 2.4.0.190). 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. 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. 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 >80% 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.

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:

$$Cl_B = Dose*F/AUC;\ Vd_{area} = Dose*F/(AUC)(\beta)$$

where, for i.v., 100% bioavailability (F = 1) was considered and

$$Vd_{(ss)} = Dose*AUMC/(AUC)^2$$

The extent of absorption (F) following s.c. administration of the drug was calculated as:

$$(AUC_{s.c.}/AUC_{i.v.}) \times (Dose_{i.v.}/Dose_{s.c.}) \times 100$$

Student's t-test was used to test the pharmacokinetic parameters for significant difference between pharmacokinetic parameters in febrile and healthy sheep according to Snedecor and Cochran (1980).

Pharmacokinetic/pharmacodynamic integration: PK/PD indices like C_{max}/MIC and $AUC_{(0-\infty)}$/MIC for s.c. administration were calculated using the values of C_{max} and $AUC_{(0-\infty)}$. There is no published study stating MIC_{90} values of levofloxacin against ovine bacterial isolates. To cover most of the susceptible organisms, in this discussion, the MIC_{90} of 0.12 μg mL^{-1} of levofloxacin has been taken into consideration (Goudah and Hasabelnaby, 2010).

RESULTS

Plasma levofloxacin concentrations at different time intervals following intravenous and subcutaneous injection under febrile state in sheep is presented as semi logarithmic plot in Fig. 1. Following intravenous administration, the drug was distributed faster in febrile sheep. The mean values of apparent volume of distribution (Vd_{area}) and volume of distribution at steady-state (Vd_{ss}) were calculated to be 1.30±0.12 and 0.92±0.11 L kg^{-1}, respectively. The mean value of total body clearance (Cl_B) and elimination half-life ($t_{1/2\beta}$) were 0.42±0.03 L h^{-1} kg^{-1} and 2.15±0.07 h, respectively.

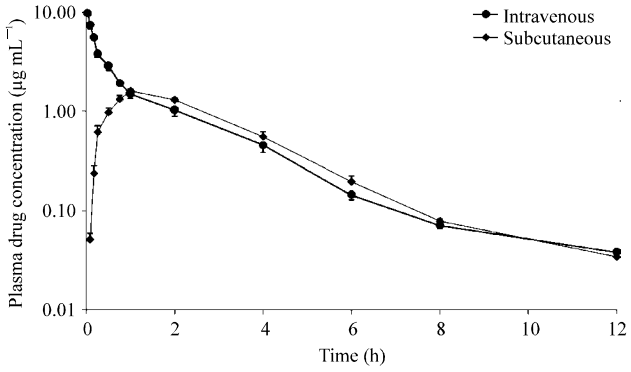

Fig. 1: Plasma concentration profile (Mean±SE) of levofloxacin following intravenous and subcutaneous administration at a dosage of 3 mg kg^{-1} b.wt. in febrile sheep (n = 6)

Table 1: Pharmacokinetic parameters (Mean±SE) of levofloxacin after intravenous and subcutaneous administration at a dosage of 3 mg kg^{-1} b.wt. in febrile sheep (n = 6)

Parameters	Unit	Intravenous	Subcutaneous
Cp^0	μg mL^{-1}	9.22±0.93	-
α	h^{-1}	3.22±0.47	-
K_a	h^{-1}	-	2.66±0.27
β	h^{-1}	0.32±0.01	0.36±0.01*
$t_{1/2\alpha}$	h	0.24±0.03	-
$t_{1/2Ka}$	h	-	0.28±0.03
$t_{1/2\beta}$	h	2.15±0.07	1.90±0.03**
$AUC_{0-\infty}$	μg h mL^{-1}	7.37±0.51**	6.59±0.37**
AUMC	μg h^2 mL^{-1}	14.49±1.24**	17.69±1.40**
Vd_{area}	L kg^{-1}	1.30±0.12	1.13±0.07**
Vd_{ss}	L kg^{-1}	0.92±0.11	-
K_{12}	h^{-1}	1.41±0.30	-
K_{21}	h^{-1}	0.81±0.10	-
Cl_B	L h^{-1} kg^{-1}	0.42±0.03*	0.47±0.04**
MRT	h	1.96±0.03	2.98±0.03*
C_{max}	μg mL^{-1}	-	1.60±0.09
T_{max}	h	-	1.00±0.00
F	%	-	89.20±3.84

*Significant at $p<0.05$, **Highly significant at $p<0.01$ when compared with respective values in healthy sheep (Patel *et al*., 2012). Abbreviations: C_{p0} : Concentration at time 0, α: Distribution rate constant, K_a: Absorption rate constant, β: Elimination rate constant, $t_{1/2\alpha}$: Half-life of distribution phases, $t_{1/2Ka}$: 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; K_{12} and K_{21}: First order rate constants for drug distribution from central and peripheral compartments; Cl_B: Total body clearance; MRT: Mean residence time; C_{max}: Maximum drug concentration; T_{max}: Time to time to peak plasma drug concentration; F: Bioavailability

Following subcutaneous administration of the drug, the drug was rapidly absorbed with absorption half-life of 0.28±0.03 h and well distributed in the body which as reflected by good apparent volume of distribution. The mean value of total body clearance (Cl_B) and elimination half-life ($t_{½\beta}$) of the drug were 0.47±0.04 L h^{-1} kg^{-1} and 1.90±0.03 h, respectively. The bioavailability (F) of the drug was found to be 89.20±3.84%. Various kinetic determinants that describe the absorption and elimination pattern of levofloxacin after intravenous and subcutaneous injection under febrile state were calculated and are presented in Table 1.

DISCUSSION

In the present study, plasma concentration-time profile of the drug following intravenous administration in febrile sheep showed a rapid initial distributive phase, followed by relatively slower elimination phase with elimination half-life which was proximate to half-life (2.30±0.22 and 3.29±0.23 h) of the levofloxacin reported in healthy sheep (Goudah and Hasabelnaby, 2010; Patel *et al*., 2012). The plasma drug concentration during the time from initial (2 min) to 15 min following the intravenous administration of levofloxacin in febrile sheep was not significantly altered compared to the values observed in experiment conducted in healthy sheep (Patel *et al*., 2012). However, the plasma drug concentrations at 30 min to 12 h were significantly higher compared to the values observed in healthy sheep (Patel *et al*., 2012). The drug exhibits a relatively high volume of distribution (Vd_{ss}: 0.92±0.11 L kg^{-1}) suggesting an extensive tissue distribution in sheep as observed in healthy sheep (Goudah and Hasabelnaby, 2010; Patel *et al*., 2012). The

extensive penetration of the drug into various body fluids and tissues owing to its lipid solubility and low plasma protein binding (23.74%) as seen with other members of fluoroquinolones (Goudah and Hasabelnaby, 2010). Plasma protein binding of the drug may exhibit positive correlation between drug concentration and plasma protein level (Sheikh *et al*., 2001). The higher values of AUC, AUMC and lower value of body clearance in febrile sheep indicates that wide distribution and slower clearance of the drug in febrile sheep was in accordance to those observed in healthy sheep (Patel *et al*., 2012).

Following subcutaneous administration in febrile sheep, the shorter absorption half-life leads to rapid appearance of the drug into systemic circulation similar to observation found in healthy sheep (Goudah and Hasabelnaby, 2010; Patel *et al*., 2012). The mean apparent volume of distribution is found similar to that reported in healthy sheep (Patel *et al*., 2012) and it clearly indicates good penetration of levofloxacin in febrile similar to that in healthy animal. Moreover, significant lower ($p<0.01$) Vd_{area} of the drug in febrile sheep was observed in comparison to healthy sheep (Patel *et al*., 2012). In febrile condition, α_1-acid glycoprotein binds with some drugs and can produce a decrease in its volume of distribution. Significant decrease in total body clearance of the drug was also observed after intravenous and subcutaneous administration of levofloxacin in febrile sheep compared to healthy sheep (Patel *et al*., 2012). Alteration in total body clearance directly affected the mean residence time which was reflected through significant increase in mean residence time following subcutaneous injection compared to healthy sheep (Patel *et al*., 2012). The elimination half-life was also significantly increased in febrile sheep compared to healthy sheep following subcutaneous administration (Patel *et al*., 2012). The findings are indicative modification of renal physiology caused by the toxin following administration of lipopolysaccharide (Hasegawa *et al*., 1999; Jernigan *et al*., 1988). Moreover, levofloxacin is primarily eliminated by kidney with involvement of both glomerular filtration and tubular secretion (Martinez *et al*., 2006; Okazaki *et al*., 1991). It has been observed that alteration in urine output may significantly affect the clearance of the drug (Waheed *et al*., 2002). So it is probable that the decrease in glomerular filtration rate induced by endotoxin plays an important role in the decrease of body clearance of drugs which are widely eliminated by the renal route, including levofloxacin (Martinez *et al*., 2006; Okazaki *et al*., 1991).

The systemic bioavailability following subcutaneous administration of the drug was similar to that observed in healthy sheep (Goudah and Hasabelnaby, 2010; Patel *et al*., 2012). Nearly complete absorption has also been reported for levofloxacin in camels (93.95±8.38%), stallions (91.76±12.68%) and goats (84.91±7.52%) after extravascular injection (Goudah *et al*., 2008; Goudah and Abo-El-Sooud, 2009; Goudah, 2009).

For a concentration-dependent drug, such as levofloxacin, successful treatment and lower incidence of the development of resistance usually associated with high ratio of AUC/MIC_{90} and C_{max}/MIC_{90} (Dudley, 1991; Lode *et al*., 1998; Walker, 2000). The MIC of levofloxacin has not yet been determined for ovine bacterial isolates. 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 the data, dose rate of 3 mg kg^{-1} of levofloxacin after subcutaneous administration in sheep would result in AUC/MIC_{90} ratio of 54.92. Most important surrogate marker C_{max}/MIC_{90} was 13.33 which exceeds the recommended ratio. To prevent the emergence of bacterial resistance, control use of the newer antibacterial drug is necessary (Moniri and Dastehgoli, 2007).

CONCLUSION

Levofloxacin could have success against susceptible pathogens in sheep after parenteral administration in the presence of acute phase response for clinical treatment of various pulmonary as well as urinary infections in sheep, when approved drug fails.

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