

Effect of Mastitis on Pharmacokinetics of Levofloxacin Following Single Dose Intravenous Administration in Goats

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Abstract

Disposition kinetics of levofloxacin was investigated after single dose intravenous administration at the dose of 10 mg/kg in six healthy and six mastitic Black Bengal lactating goats. Mastitis was induced in goats by coagulase positive *Staphylococcus aureus*. The maximum milk concentration was higher in mastitic goats ($17.01 \pm 0.67 \mu\text{g/ml}$) as compared to healthy ($14.75 \pm 0.95 \mu\text{g/ml}$). The therapeutic milk concentration in mastitic goats (0.10 ± 0.00 to $16.61 \pm 0.70 \mu\text{g/ml}$) was maintained for 48 h, which was significantly longer than healthy goats (36 h). The $t_{1/2\beta}$ in plasma (5.08 ± 0.18 h) and milk (7.28 ± 0.09 h) of mastitic goats were significantly longer than healthy goats (4.04 ± 0.24 and 4.16 ± 0.76 h). The total body clearance in plasma of healthy goats (5.64 ± 0.78 ml/kg/min) was almost similar to mastitic goats (5.82 ± 0.44 ml/kg/min). The $\text{AUC}_{\text{milk}}/\text{AUC}_{\text{plasma}}$ ratio (3.36) in mastitic goats indicated extensive penetration of levofloxacin from plasma to milk. The $t_{1/2\text{milk}}/t_{1/2\text{plasma}}$ ratio was 1.43. The AUC/MIC ratio in plasma and milk of mastitic goats were 296 and 1014 respectively. Based on the plasma kinetic parameters, it was concluded that levofloxacin may be used for treatment of mastitis in goats.

Keywords: Goats; Levofloxacin; Mastitis; Pharmacokinetics

Introduction

Levofloxacin (LVX), a third-generation fluoroquinolone and L-isomer of ofloxacin possess a broad-spectrum antimicrobial activity and active against most gram-positive, gram-negative and anaerobic bacteria [1-2]. It is also active against several species of Staphylococci, Streptococci including *Streptococcus pneumoniae*, Bacteroides, Clostridium, Haemophilus, Moraxella, Legionella, Mycoplasma and Chlamydia [3,4]. It acts by selective inhibition of bacterial enzymes DNA gyrase and Topoisomerase IV [5]. LVX is widely distributed throughout the body and penetrates well into most body fluids and its uptake by phagocytic cells makes it suitable for use against intracellular pathogens [3]. Levofloxacin concentrations in tissues and fluids are generally greater than those observed in plasma, but penetration into the cerebrospinal fluid is relatively poor [6]. LVX is excreted through urine as unchanged drug and less than 5% is metabolized in the liver to demethyl-levofloxacin and levofloxacin-N-oxide [7] and excreted in the urine of rats and humans [4]. Fluoroquinolones act by a concentration-dependent killing mechanism, whereby the optimal effect is attained by the administration of high doses over a short period of time [8].

Mastitis is an inflammatory condition of the mammary gland irrespective of causes and is a global problem in livestock [9]. It is characterized by physical, chemical and microbiological changes in milk and pathological changes in glandular tissues of mammary gland. The most frequent isolate of bacteria causing caprine mastitis is *Staphylococcus* spp [10-12].

It has also been evidenced that mastitis has an effect on the milk concentrations of antimicrobials in goats [9]. However, there is paucity of information on the pharmacokinetics of LVX and its diffusion into milk especially in mastitic goats. Most of the published papers about mastitis treatments report recommendations adapted from results obtained in cows. Inappropriate low doses of an antibiotic can lead to ineffective therapeutic blood or milk concentrations. In view of the marked variation in the kinetic variables of antimicrobials in diseased animals [13], the present study was undertaken to determine the pharmacokinetic study and milk penetration of LVX following single

intravenous (i.v.) administration in healthy and lactating mastitic goats for its clinical application.

Materials and Methods

Twelve clinically healthy Black Bengal lactating goats (14-20 kg) of 2 to 2.5 years were used in this study. Levofloxacin (Loxof) infusion was injected i.v. @ 10 mg/kg body weight to each of six healthy and six mastitic goats. The blood samples were collected in heparinized test tubes from left jugular vein by venipuncture and milk samples were collected manually from both the quarters in sterile test tubes by hand milking at 0, 2.5, 5, 10, 15, 20, 30, 45 min and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 60 h following drug administration.

Mastitis was induced in each of six goats by coagulase positive *Staphylococcus aureus* by the method of Sar et al. [9] with slight modification. After six hours of induction, animals showed the symptoms of inflammation, fever (103°F to 104°F , persisted for 6 hours) and inappetance. The goats also showed partial agalactia and defecated semisolid faeces. Mastitis in goats was confirmed by standard tests (California mastitis test, Bromocresol Purple test, Somatic Cell Count, Catalase Test).

Quantitative estimation of LVX in plasma and milk were done by HPLC [14] with UV-VIS detector. The sensitivity of the method was $0.065 \mu\text{g/ml}$ and linearity was 0.999 in plasma and milk both. The mean percentage of inter- and intra-day coefficient of variation was 7.5% and 4.13% in plasma and 9.1% and 4.9% in milk respectively. The percentage

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of recovery of LVX from plasma and milk were 95.33% and 93.47% respectively.

The plasma protein binding of LVX was determined by the “equilibrium dialysis” technique [15,16]. Plasma standard solutions of LVX of 6.25, 12.5, 25 and 50 µg/ml were prepared. The concentrations of drug in plasma and buffer were read with the help of HPLC and plasma protein binding of drug was calculated by the formula given by Linkenheimer et al. [17].

$$\text{Plasma protein binding} = \frac{\text{Conc. of drug in plasma} - \text{Conc. of drug in buffer}}{\text{Conc. of drug in plasma}} \times 100\%$$

Statistical Analysis

Variability among the pharmacokinetic data of levofloxacin due to induced mastitis was assessed by t-test according to the method of Snedecor and Cochran [18].

Results

The semilogarithmic plot of comparative mean plasma and milk concentrations of LVX in healthy and mastitic goats are depicted in Figure 1 and 2 respectively. The therapeutic plasma concentration ($C_{p_{ther}}$) of LVX in healthy and mastitic goats was maintained for 24 h in mastitic as well as healthy goats. The maximum milk concentrations ($C_{m_{max}}$) of LVX in healthy and mastitic goats were 14.75 ± 0.95 and

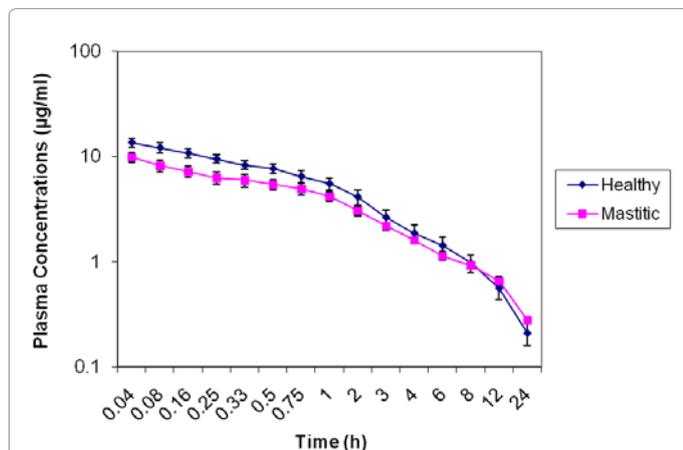


Figure 1: Semilogarithmic plot of comparative plasma concentrations (µg/ml) (Mean ± SE) of LVX in healthy and mastitic goats (n=6) after single i.v. dose (10 mg/kg) administration.

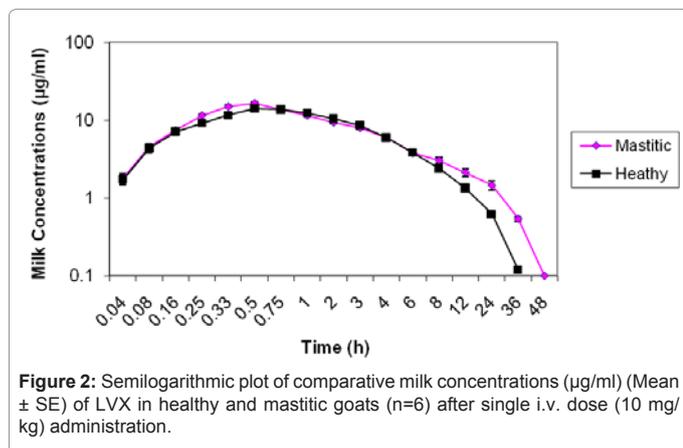


Figure 2: Semilogarithmic plot of comparative milk concentrations (µg/ml) (Mean ± SE) of LVX in healthy and mastitic goats (n=6) after single i.v. dose (10 mg/kg) administration.

Kinetic parameters	Healthy	Mastitic	P value
C^0p (µg/ml)	15.51 ± 1.41	12.48 ± 1.36	0.11 ^{NS}
$t_{1/2\beta}$ (h)	4.04 ± 0.24	5.08 ± 0.18	0.01*
Vd_{area} (L/kg)	1.89 ± 0.18	2.56 ± 0.21	0.05 ^{NS}
AUC(mg/L.h)	33.68 ± 5.11	29.62 ± 2.18	0.52 ^{NS}
MRT(h)	5.61 ± 0.49	7.77 ± 0.28	0.01**
Cl_B (ml/kg/min)	5.64 ± 0.78	5.82 ± 0.44	0.86 ^{NS}
K_{12} (h ⁻¹)	2.44 ± 0.70	6.24 ± 1.35	0.05*
K_{21} (h ⁻¹)	2.83 ± 0.97	3.59 ± 0.59	0.55 ^{NS}
K_z (h ⁻¹)	0.37 ± 0.05	0.39 ± 0.04	0.76 ^{NS}
T/P ratio	1.05 ± 0.17	1.77 ± 0.28	0.07 ^{NS}

NS = Non significant; *P < 0.05; **P < 0.01.

C^0p (µg/ml) = Zer-time plasma concentration; $t_{1/2\alpha}$ (h) = Distribution plasma half-life; $t_{1/2\beta}$ (h) = Elimination plasma half-life; Vd_{area} = Volume of distribution based on area under curve; AUC = Area under curve; Cl_B = Total body clearance rate; K_{12} = Rate constant for transfer of drug from central to peripheral compartment, K_{21} = Rate constant for transfer of drug from peripheral to central compartment, K_z = elimination from central compartment, MRT = Mean residence time; T/P ratio = Tissue to plasma ratio.

Table 1: Kinetic profile (Mean ± SE) of LVX (10 mg/kg, i.v.) in Plasma of healthy and mastitic goats.

Kinetic parameters	Healthy	Mastitic	P value
$C_{m_{max}}$ (µg/ml)	14.75 ± 0.95	17.01 ± 0.67	0.11 ^{NS}
$t_{1/2\beta}$ (h)	4.61 ± 0.76	7.28 ± 0.09	0.00**
Vd_{area} (L/kg)	0.95 ± 0.05	1.05 ± 0.05	0.23 ^{NS}
AUC(mg/L.h)	82.18 ± 2.78	101.49 ± 6.23	0.03*
MRT	7.10 ± 0.20	10.63 ± 0.30	0.00**
Cl_{BM} (ml/kg/min)	2.04 ± 0.07	1.67 ± 0.09	0.01*
T_{max} (h)	0.58 ± 0.05	0.47 ± 0.03	0.09 ^{NS}

NS = Non significant; *P < 0.05; **P < 0.01.

$C_{m_{max}}$ = maximum milk concentration; $t_{1/2\beta M}$ = elimination half-life in milk; Vd_{areaM} = volume of distribution based on area under curve in milk; AUC = area under the curve; MRT = Mean residence time; Cl_{BM} = total clearance in milk and T_{maxM} = time to peak concentration in milk

Table 2: Kinetic profile (Mean ± SE) of LVX (10 mg/kg, i.v.) in milk of healthy and mastitic goats.

17.01 ± 0.67 µg/ml respectively and was attained in 0.58 ± 0.05 h, and 0.47 ± 0.03 h respectively. The therapeutic milk concentration ($C_{m_{ther}}$) was maintained for 48 h in mastitic and 36 h in healthy goats. The mean (± SE) values of plasma and milk pharmacokinetic parameters of levofloxacin after single dose i.v. administration in healthy and mastitic goats are shown in Table 1 and 2. The zero-time plasma concentration (C^0p) in healthy and mastitic goats were 15.51 ± 1.41 µg/ml and 12.48 ± 1.36 µg/ml respectively. The elimination half-life ($t_{1/2\beta}$) in mastitic goats (5.08 ± 0.18 h) was significantly ($p < 0.05$) higher to that in healthy goats (4.04 ± 0.24 h). The total body clearance (Cl_B) in mastitic and healthy goats were 5.82 ± 0.44 ml/kg/min and 5.64 ± 0.78 ml/kg/min respectively. Apparent volume of distribution (Vd_{area}) in mastitic and healthy goats were 2.56 ± 0.21 L/kg and 1.89 ± 0.18 L/kg respectively. The rate of transfer of drug from central to peripheral compartment (K_{12}) in mastitic goats (6.24 ± 1.35 h⁻¹) was significantly ($p < 0.05$) higher than healthy (2.44 ± 0.70 h⁻¹). The plasma protein binding of levofloxacin was found to be 27.46 ± 4.48 %.

The milk half-life ($t_{1/2\beta M}$) in mastitic goats (7.28 ± 0.09 h) was significantly ($p < 0.01$) higher than healthy (4.61 ± 0.76 h). The total body clearance in milk (Cl_{BM}) of mastitic goats (1.67 ± 0.09 ml/kg/min) was significantly ($p < 0.05$) lower than healthy goats (2.04 ± 0.07 ml/kg/min). The AUC/MIC ratio of milk in healthy and mastitic goats were 296 and 1014 respectively.

Discussion

The semilogarithmic plot of plasma-level time profile of LVX after single dose i.v. administration in healthy and mastitic goats evidenced two compartment open model in all animals.

Disease conditions may influence the pharmacokinetics and pharmacodynamics of various antibiotics, including aminoglycosides and cephalosporins [19]. Fluoroquinolones are concentration-dependent antibacterials [8] and they must reach minimal inhibitory concentration ($\leq 0.1\mu\text{g/ml}$) in order to be effective. The Cm_{max} in case of mastitic goats ($17.01 \pm 0.67\mu\text{g/ml}$) was slightly higher than healthy goats ($14.75 \pm 0.95\mu\text{g/ml}$). The value was greater than those reported for pefloxacin in lactating goats [20] and danofloxacin in ewes [21].

Weak organic acids having high pKa value tend to diffuse more rapidly into the milk than acids with low pKa values [22]. It is obvious from the above findings that in the present experiment, LVX (pKa_1 -6.8 and pKa_2 -8.2) diffused passively from blood (pH 7.4) to milk (pH 8.6) in mastitic goats and could cross the plasma-milk barrier at an increased rate. The concentrations of LVX in milk of mastitic goats were higher as compared to milk of healthy goats, which may be due to increased permeability and intercellular spaces of mammary epithelial cells due to the release of several chemical mediators during inflammation [23] along with damage of mammary epithelium and break down of blood-milk barrier [24]. This finding is strengthened by a study on disposition kinetics of orbifloxacin in clinically normal lactating goats after i.v., s.c. and i.m. administration showed that orbifloxacin penetrated from blood into the milk and attained high concentrations in milk as compared to blood [25].

It has been reported that fluoroquinolones are taken up by phagocytes that carry drug at the site of infection and also engulf the infective organisms [26-29]. The cellular uptake and accumulation of levofloxacin is of major importance from therapeutic point of view against intracellular pathogens [3], especially in this case, where acute mastitis is caused by *S. aureus*. This helps in attainment of a sufficient concentration of active drug at the site of infection i.e. mammary gland and plays a crucial role in the killing of the pathogen.

The $t_{1/2\beta}$ of LVX in plasma was significantly ($p < 0.01$) longer in case of mastitic goats ($5.08 \pm 0.18\text{ h}$) as compared to healthy ($4.04 \pm 0.24\text{ h}$). The elimination half-life of LVX was observed to be longer in CSF (3.8 to 5.6 h) of subjects suffering with pneumococcal meningitis as compared to blood (2.7 to 3.2 h) [30]. The K_{12}/K_{21} ratio of LVX obtained in this study was 0.93 in healthy goats while 1.69 in mastitic goats that indicated a faster drug transfer from central to peripheral compartment than from peripheral to central compartment. The T/P ratio in mastitic goats (1.77 ± 0.28) was found to be higher as compared to healthy goats (1.05 ± 0.17). The in-vitro plasma protein binding of LVX calculated in the present experiment ranged between $22.99 \pm 0.82\%$ to $34.79 \pm 1.07\%$. It is in agreement with the value of 24 to 38% [6].

The $t_{1/2\beta}$ of milk ($t_{1/2\beta\text{M}}$) was significantly ($p < 0.01$) longer in case of mastitic goats ($7.28 \pm 0.09\text{ h}$) as compared to healthy ($4.61 \pm 0.76\text{ h}$). This indicates greater persistence of the drug at the site of inflammation and is in consonance with a report of Wise et al. [31] where gatifloxacin showed a mean plasma elimination half-life of 6.8 h and that in inflammatory fluid, 7.2 h.

The $t_{1/2\text{milk}}/t_{1/2\text{plasma}}$ ratio (1.43) in this experiment also indicated persistence of drug in mastitic milk for longer period than in plasma. In contrast to this, ibafloxacin penetrated poorly from blood into the milk after i.v. administration in goats and was detectable in milk only till 6 h

and persisted for shorter time in milk than in plasma ($t_{1/2\text{milk}}/t_{1/2\text{plasma}} < 1$) [32]. For effective systemic treatment of mastitis, drug should penetrate extensively from the blood into the milk.

The AUC in mastitic goat plasma ($29.62 \pm 2.18\text{ mg/l.h}$) and milk ($101.49 \pm 6.23\text{ mg/l.h}$) in the present study was higher than the AUC (7.66 mg/l.h) of LVX in calves [33], reflected coverage of a vast body area by the drug.

Fluoroquinolones possess low MIC values against many gram-negative and gram-positive microorganisms [34]. In a study of LVX in cross bred calves after i.m. administration the MIC_{90} of LVX was considered to be $0.1\mu\text{g/ml}$, to cover most of the susceptible microorganisms [33]. So, here we considered the same value.

AUC/MIC and $\text{Cp}_{\text{max}}/\text{MIC}$ can be used to predict the efficacy of different agents against different pathogens and to define pharmacodynamics break point [35]. In this experiment, it was found that the $\text{AUC}_{\text{milk}}/\text{AUC}_{\text{plasma}}$ ratio in mastitic goats was 3.43. The AUC/MIC ratio of LVX in plasma and milk of mastitic goats were 296 and 1014 respectively, which indicates that LVX was effective against *S. aureus* as well as shows less chances of emergence of resistance. In addition the milk kinetics also point out its better clinical utility in the treatment of mastitis in goats.

On the basis of the results obtained in this study, it was concluded that levofloxacin may be effectively used in the treatment of mastitis in goats caused by *S. aureus*.

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