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Original article

Pretreatment with trikatu augments pharmacokinetic profile and bioavailability of orally administered levofloxacin in goat

Jatin H. Patel◆, Priti D. Vihol*, Kamlesh A. Sadariya*, Urvesh D. Patel**, Rasesh D. Varia, Shailesh K. Bhavsar***, Ashwin M. Thaker*** and Jitendra K. Raval***

Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari-396450, Gujarat, India

**Department of Veterinary Pathology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari-396450, Gujarat, India*

***Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Junagadh Agricultural University, Junagadh-362015, Gujarat, India*

****Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand-388 001, Gujarat, India*

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Abstract

Pharmacokinetics of levofloxacin in goats, following oral administration (4 mg/kg) was evaluated in trikatu pretreated goats. Reverse-phase High Performance Liquid Chromatography (HPLC) was applied for determination of levofloxacin concentration in plasma concentration. Maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2\beta}$), volume of distribution (Vd_{area}), total body clearance (Cl_B) and bioavailability were 0.60 ± 0.03 µg/ml, 0.95 ± 0.07 h, 1.91 ± 0.11 l/kg, 1.06 ± 0.06 l/h/kg and 21.49 %, respectively observed after oral administration of levofloxacin in goats. In trikatu pretreated goats, pharmacokinetic parameters, *viz*., maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2\beta}$), volume of distribution (Vd_{area}), total body clearance (Cl_B) and bioavailability were reported as 0.74 ± 0.03 µg/ml, 2.07 ± 0.15 h, 2.98 ± 0.26 l/kg, 1.02 ± 0.04 l/h/kg and 30.16 %, respectively. In conclusion, significant difference was observed in majority of pharmacokinetic data of levofloxacin in trikatu pretreated goats than those in normal goats. Trikatu pretreatment in goats significantly increased bioavailability of levofloxacin.

Keywords: Pharmacokinetics, oral, levofloxacin, trikatu, goat

1. Introduction

Levofloxacin is a third-generation fluoroquinolone with a wide spectrum of bactericidal activity (Martinez *et al*., 2006). The drug is active against Gram-negative, Gram-positive and anaerobic bacteria including *Pseudomonas* species (Davis and Bryson, 1994). Pharmacokinetic studies of levofloxacin have been reported, following intravenous administration in cats (Albarellos *et al*., 2005), cow calves (Dumka and Srivastava, 2007a,b), horses (Goudah *et al*., 2008), camels (Goudah, 2009), chickens (Varia *et al*., 2009; Patel *et al*., 2012), sheep (Goudah and Hasabelnaby, 2010; Patel *et al*., 2012ab) and goats (Goudah and Abo-El-Sooud, 2009) and various in pharmacokinetics of the drug in different species have been observed. In addition to this, pharmacokinetic studies of levofloxacin have also been reported, following subcutaneous administration in sheep (Patel *et al*., 2012a) and calves (Dumka and Srivastava, 2007a,b; Ram *et al*., 2010). Moreover, pharmacokinetic studies of enrofloxacin and pefloxacin were performed in small ruminant to explore any possibility for oral administration in small ruminants like sheep and goats and it was found that bioavailability was ranged between 10 to 35 % (Elmas *et al*., 2000; Malik *et al*., 2002). Pharmacokinetics of newer fluoroquinolone, marbofloxacin was also studied in chickens (Patel *et al.*, 2019) as well as safety of morbofloxacin was evaluated in normal and piperine pretreated rats (Chauhan *et al*., 2017).

A number of scientific investigations have highlighted the importance and the contribution of many plants, *i.e.*, Asteraceae, Liliaceae, Apocynaceae, Solanaceae, Caesalpinaceae, Rutaceae, Piperaceae and Sapotaceae for treatment of chronic conditions (Nayanabhirama, 2016) and herbal formulation found to be helpful in decreasing side effects of the drug (Bhadarka *et al.*, 2018; Shaul *et al.*, 2018). Herbal active constituent like piperine is proved to be helpful in modulating the disposition of drug (bioavailability) upon pretreatment or concomitant administration. Effects of bioenhancers are studied along with the drug having less bioavailability (Singh *et al.*, 2009). Piperine (PIP), the major constituent obtained from the peppercorns of black pepper is used in anticonvulsant formulations in traditional Chinese medicine (Parveen *et al.*, 2016). The plasma concentration of sodium valproate was significantly increased (11-fold) when it

Author for correspondence: Dr. Jatin H. Patel
Assistant Professor, Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari-396450, Gujarat, India
E-mail: drjatinvet@yahoo.co.in
Tel.: +91-9428489543

was given along with piperine (Parveen *et al.,* 2016). Piperine (Piperaceae family) is content of trikatu formulation (*Piper nigrum* L., *Piper longum* L., *Zingiber officinale* Roscoe : 1:1:1) and known to have various effects, *viz*., enhance the permeation of drug through the epithelial barrier (Khajuria *et al.,* 1998), inhibit the expression and functional activity of metabolic enzymes and drug transporters and, thus it has capacity to improve bioavailability of different drugs ranging from 30-200% (Atal *et al*., 1985). In addition, levofloxacin was rapidly and almost completely absorbed after SC administration as shown in previous study (Patel *et al*., 2013). Looking to above facts, it was planned to determine the disposition kinetics and bioavailability of levofloxacin in goat, following oral administration alone and in trikatu pretreated goats.

2. Materials and Methods

2.1 Experimental animals

Six healthy female Surti non-lactating goats having body weight ranging from 30 to 35 kg were used in the experiment. The animals were obtained 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 and subjected to clinical examination 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 (IAEC/VPT/63/2009) for general procedure and use of animals for conducting the present study has been approved by the Institutional Animal Ethics Committee of College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand, Gujarat, India

2.2 Drug and chemical

Levofloxacin oral tablet (250 mg; Loxof®, Ranbaxy Laboratories Ltd., Himachal Pradesh) was procured from local pharmacy. Levofloxacin technical grade powder was procured from Moxy Laboratory Pvt. Ltd., Gujarat, India. Acetonitrile, triethylamine, perchloric acid (70%), ortho-phosphoric acid (min. 58%) (Analytical grade) and water of HPLC grade were purchased from Merck Limited, Mumbai. Tikatu was purchased from Dhanvantri Pharma Ltd., Anand, Gujarat, India.

2.3 Drug administration and sample collection

Levofloxacin was administered at a dose rate of 4 mg/kg of body weight orally and randomly in six goats. Levofloxacin tablet (250 mg) was dissolved in 25 ml sterile water and used for oral administration using a syringe. Animals were fasted for 24 h before the oral administration of the drug. Pulverized trikatu was suspended in water and piperine equivalent to 20 mg/kg body weight was given orally through esophageal tube for 7 days (pretreatment) before administration of levofloxacin.

Blood samples (2 ml) were collected through an intravenous catheter (Venflon, 22 × 0.9 × 25 mm) fixed in the jugular vein in test tubes (K_3 EDTA), prior to injection (0 h) and at 0.083, 0.166, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 12 and 18 h post-treatment after oral administration. Blood samples were subjected to centrifugation at 3000 g for 10 min and plasma samples were collected and preserved at – 20°C, and analyzed within 48 h for determination of levofloxacin concentration.

2.4 Analytical assay of levofloxacin

Levofloxacin concentration in plasma samples was determined by reverse-phase High Performance Liquid Chromatography (HPLC) after extraction, using a reported assay (Varia *et al.*, 2009) with minor modifications. The High Performance Liquid Chromatography (HPLC) apparatus (Laballiance, USA), comprised of quaternary gradient delivery pump (model AIS 2000), UV detector (model 500) and C18 column (Thermo ODS: 250 × 4.6 mm ID) were used. Pharmacokinetic data integration was done by software 'Clarity' (Version 2.4.0.190).

Solution of pure enrofloxacin powder (40 ml of 0.5 µg/ml concentration) was utilized as an internal standard (IS). After addition of internal standard, each plasma sample (500 µl), was deproteinized by addition of perchloric acid (50 µl) and mixed on vortex for one minute. This was followed by centrifugation at 3000 g for 10 min. An aliquot of supernatant was collected in clean vial and 20 µl was injected into loop of HPLC system, using 50 µl glass syringe (Hamilton Bonaduz AG, Switzerland). 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 m size filter (Ultipor N_{66} Nylone 6, 6 membrane, PALL Pharma lab filtration Pvt., Ltd., Mumbai) and degassed by ultra-sonication. Thereafter, mobile phase was pumped into column at a flow rate of 1.5 ml/min at ambient temperature. The effluent was monitored at 290 nm wavelength.

Calibration curve was prepared daily for drug concentration ranging from 0.01 to 50 µg/ml. The assay was sensitive (LLOD: 0.01 µg/ml), reproducible and linearity was observed from 0.01 to 50 µg/ml (r^2 = 0.99). The lower limit of quantification of the drug with a coefficient of variation of less than 8.36% was 0.01 µg/ml. The mean extraction recovery from plasma was >82.81 ± 3.83% at the spiked concentrations between 0.01 and 50 µg/ml. Precision and accuracy were determined using quality control (QC) samples at concentrations of 0.05, 1, 2.5, 10 and 50 µg/ml (5 replicates each per day). The intraday and interday coefficients of variation for 5 QC samples were satisfactory with the relative deviations (RSD) of less than 9.77 %.

2.5 Calculation of pharmacokinetic parameters

Pharmacokinetic parameters were calculated as per standard methods (Baggot, 1977; Gibaldi and Perrier, 1982). Absorption rate constant (K_a) and elimination rate constant (β) were calculated by least square regression analysis method. Absorption half-life ($t_{½ka}$) and elimination half-life ($t_{½\beta}$) were calculated from $0.693/K_a$ and $0.693/\beta$, respectively. Maximum drug concentration in plasma (C_{max}) and time of maximum observed concentration in plasma (T_{max}) were obtained from actual plasma concentrations of rats. Area under curve ($AUC_{(0-\infty)}$) and area under the first moment of curve (AUMC) were calculated by linear trapezoidal rule. Apparent volume of distribution (Vd_{area}) was calculated from (Dose × F)/(β × AUC). The value of total body clearance ($Cl_{(B)}$) was obtained using formula $\beta \times Vd_{(area)}$. Mean residence time (MRT) was obtained by dividing the value of AUMC by AUC. The bioavailability (%) was calculated as ($AUC_{Oral} \times Dose_{IV}$) × 100/($AUC_{IV} \times Dose_{Oral}$). Where, AUC after intravenous administration of levofloxacin in goat has been referred from our previous published study (Patel *et al*., 2018).

2.6 Statistical analysis

Data of pharmacokinetic parameters of levofloxacin between both treatment groups were compared by students' 't' test.

3. Results

No local or systemic adverse reactions were observed in clinical examination of all animals after the single-dose of levofloxacin and multiple treatment of trikatu in the animals studied. The chromatogram of the levofloxacin in plasma sample collected from goat under study is shown in Figure 1. The mean plasma drug concentrations after oral administration of levofloxacin (4 mg/kg) are presented in Table 1. The mean plasma concentration vs. time profile and pharmacokinetic parameters of levofloxacin (4 mg/kg) following oral administration of levofloxacin alone and in trikatu pretreated goats are presented in Figure 2 and Table 2, respectively.

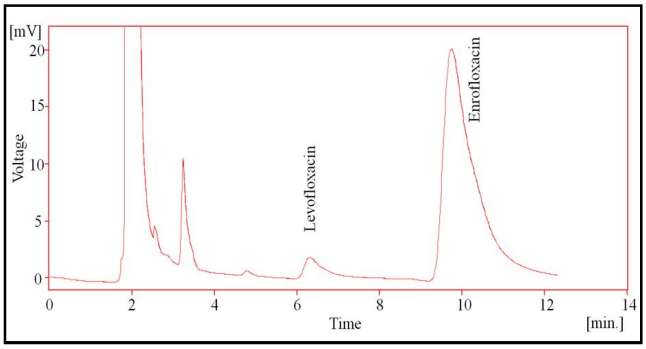

Figure 1: Representative chromatogram of levofloxacin in plasma after oral administration in goat (4 mg/kg) with enrofloxacin as IS.

Table 1: Plasma concentrations (µg/ml) of levofloxacin administered (4 mg/kg) in normal and trikatu pretreated goat following oral administration (n = 6)

Time after drug administration (h)	Plasma concentrations (µg/ml)	
	Levofloxacin alone	Levofloxacin in trikatu pretreated goat
0.5	0.07 ± 0.01	0.1 ± 0.01
0.75	0.14 ± 0.02	0.24 ± 0.01
1	0.26 ± 0.02	0.34 ± 0.02
2	0.42 ± 0.02	0.51 ± 0.03
4	0.60 ± 0.03	0.74 ± 0.03
6	0.32 ± 0.02	0.39 ± 0.02
8	0.07 ± 0.01	0.19 ± 0.02
12	ND	0.05 ± 0.01

ND: Not detected

Following oral administration of levofloxacin, peak plasma drug concentration (C_{max}) of 0.60 ± 0.03 µg/ml was observed at 4 h (T_{max}). Following oral administration of levofloxacin in trikatu pretreated goats, plasma drug concentrations were found significantly higher at 0.5, 0.75, 1, 2, 4, 6 and 8 h in trikatu pretreated goat in comparison to normal goats (Table 1).

The area under curve and area under first moment curve following oral administration in normal goats was calculated to be 2.86 ± 0.14 µg.h/ml and 11.62 ± 0.70 µg.h^2/ml, respectively. In trikatu pretreated goats, pharmacokinetic parameters like $t_{½\beta}$ (2.07 ± 0.15), C_{max} (0.74 ± 0.03 µg/ml), $AUC_{0-\infty}$ (4.15 ± 0.10 µg.h/ml), AUMC (20.53 ± 0.65 µg.h^2/ml), Vd_{area} (2.98 ± 0.26 l/kg), MRT (4.95 ± 0.15 h), MAT (2.41 ± 0.33 h) and bioavailability (30.16 ± 1.31 %) were significantly higher in comparison to normal goat.

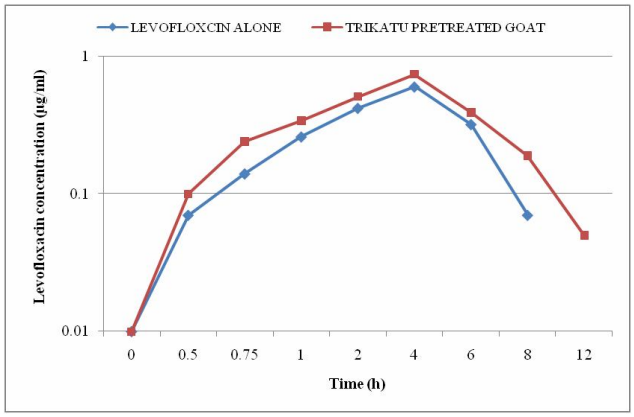

Figure 2: Plasma concentration vs. time profile of levofloxacin (4 mg/kg, orally) in normal and tirkatu pretreated goat (n = 6).

Table 2: Pharmacokinetic parameters (Mean ± SE) of levofloxacin (at a dose rate of 4 mg/kg of body weight) in normal and tirkatu pretreated goat after oral administration (n = 6)

Pharmacokinetic parameter	Unit	Levofloxacin	Trikatu pretreatment + levofloxacin
K_a	h^{-1}	0.92 ± 0.04	0.88 ± 0.13
β	h^{-1}	0.75 ± 0.07	0.34 ± 0.02**
$t_{½Ka}$	h	0.76 ± 0.03	0.88 ± 0.13
$t_{½\beta}$	h	0.95 ± 0.07	2.07 ± 0.15**
C_{max}	µg/ml	0.60 ± 0.03	0.74 ± 0.03**
T_{max}	h	4.00 ± 0.00	4.00 ± 0.00
$AUC_{0-\infty}$	µg.h/ml	2.86 ± 0.14	4.15 ± 0.10**
AUMC	µg.h^2/ml	11.62 ± 0.70	20.53 ± 0.65**
Vd_{area}	l/kg	1.91 ± 0.11	2.98 ± 0.26**
Cl_B	l/h/kg	1.06 ± 0.06	1.02 ± 0.04
MRT	h	4.05 ± 0.09	4.95 ± 0.15**
MAT	h	1.51 ± 0.23	2.41 ± 0.33**
F	%	21.49 ± 1.60	30.16 ± 1.31**

* Significant with $p < 0.05$; ** Significant with $p < 0.01$; Ka, absorption rate constant; β, elimination rate constant; $t_{1/2k(a)}$, absorption half-life; $t_{1/2\beta}$, elimination half-life; C_{max}, maximum drug concentration; T_{max}, time to peak plasma drug concentration; $AUC_{(0-\infty)}$, area under the curve from zero to infinity; AUMC, area under first of moment curve; Vd_{area}, apparent volume of distribution; Cl_B, total body clearance; MRT, mean residence time; F, bioavailability.

4. Discussion

Following oral administration of levofloxacin, peak plasma drug concentration (C_{max}) was found in proximate to C_{max} of enrofloxacin (0.25 ± 0.03 µg/ml) observed following oral administration in goats (Elmas *et al.*, 2000). However, higher value of C_{max} of pefloxacin

(2.22 ± 0.48 µg/ml) was reported following oral administration in goats (Malik *et al.*, 2002). Time at which maximum plasma concentration observed in present study was 4 h and similar observations were reported with oral enrofloxacin in goats with t_{max}: 5.20 ± 1.20 h (Elmas *et al*., 2000), 5.5 h in sheep (Berminghan, 2002) and 4.0 h in *Nemorhaebus goral* (Rae Gandolf *et al*., 2006). Time at which maximum plasma concentration of marbofloxacin after oral administration in buffalo calves was observed 0.5 to 6.0 h (Baroni *et. al*., 2007) which shows wide variation in t_{max} of fluoroquinolones in ruminants may be due to complex ecosystem of rumen. Values of AUC following oral administration of enrofloxacin (4.92 ± 0.52 µg.h/ml) and pefloxacin (10.48 ± 1.31 µg.h/ml) in goats (Elmas *et al*., 2000; Malik *et al*., 2002) were reported higher than the AUC found in present study. Elimination half-life of levofloxacin reported in goats (0.95 ± 0.07 h) was observed lower than elimination half-life of enrofloxacin (9.26 ± 0.65 h) and pefloxacin (2.91 ± 0.50 h), following oral administration (Elmas *et al*., 2000; Malik *et al*., 2002). The mean apparent volume of distribution (Vd_{area}) after oral administration of levofloxacin was found lower (1.91 ± 0.11 l/kg) in goats in comparison to pefloxacin (3.63 ± 0.89 l/kg) in goats (Malik *et al*., 2002). The total body clearance of levofloxacin observed in the present study in goats was found higher to the clearance of enrofloxacin (0.24 ± 0.01 l/h/kg) and pefloxacin in goats (0.82 ± 0.08 l/h/kg), following its oral administration (Elmas *et al*., 2000; Malik *et al*., 2002).

The bioavailability (F) of the levofloxacin ranged from 19 to 25 % with an average of 21.49 ± 1.60 %. However, higher bioavailability of pefloxacin was reported in goats (42.42 ± 5.83 %) and enrofloxacin in cow calves (66.0 ± 7.0 %) (Malik *et al*., 2002; Sharma and Varshney, 2009). Following oral administration, levofloxacin is poorly bioavailable with low distribution and high clearance rate. In support, it was reported that about 80 % of an orally administered dose of levofloxacin in human was found in the urine as unchanged and ≤ 5 % as inactive metabolites (Fish and Chow, 1997).

In general, fluoroquinolones are well absorbed following oral administration, with bioavailability for most agents in excess of 85 per cent in human but less bioavailability in ruminants. Serum drug levels achieved with the other fluoroquinolones (levofloxacin, moxifloxacin, and ofloxacin), after oral administration are comparable to concentrations achieved with intravenous (IV) dosing. This allows for early transition from IV to oral therapy and potential reduction of treatment costs (Walker, 1999). Levofloxacin is widely distributed throughout the body with satisfactory tissue concentrations. The drug is mainly excreted through renal route of drug excretion (Patel *et al.*, 2012a). Absorption of levofloxacin following oral administration in poultry was satisfactory but anatomical and physiological factors in ruminant creates barrier for absorption of the drug from rumen in animals (Varia *et al.*, 2009; Patel *et al.*, 2012). Levofloxacin, levo isomer of ofloxacin (Wimer *et al.*, 1998), shows its pharmacological activities by altering DNA of bacteria causes death by decreasing or blocking the activity of gyrase and topoisomerase. Like many other antimicrobial drugs, levofloxacin's antimicrobial activity is concentration dependent. The bactericidal activity increases as the increase in the concentration of the drug at the site of infection.

Plasma drug concentrations were observed significantly higher in trikatu pretreated goats in present study and similar results were observed in Gaddi goats, following oral administration of pefloxacin (Dama *et al*., 2008). In rabbits also, significant higher level of peak plasma concentration of norfloxacin in piperine treated group (17.78 ± 0.32 µg/ml) than norfloxacin alone group (7.07 ± 0.26 µg/ml) at 2 h was observed (Janakiraman and Manavalan, 2008). In this context, piperine is content of trikatu formulation (*P. nigrum*, *P. longum*, *Z. officinale*: 1:1:1) and known to enhance the permeation of drug through the epithelial barrier (Khajuria *et al.*, 1998) and inhibit the expression and functional activity of metabolic enzymes and drug transporters and, thus it has capacity to improve bioavailability of different drugs ranging from 30-200% (Atal *et al*., 1985). The piperine has reduced the rate of drug elimination and significantly increased the elimination half-life. Significant increased AUC value of levofloxacin in trikatu pretreated animals indicates increase in efficacy of the drug against susceptible bacteria which may have higher MIC values. P-glycoprotein (P-gp) is a protein encoded by multidrug resistance gene (MDR1). It belongs to ATP-binding cassette transporter superfamily (ABC). P-gp is localized in the cell-membrane and plays an important role in the transmembrane efflux of variety substances including drugs and toxins. The inhibition of P-gp by piperine in the study may be the reason for reduction in excretion of the drug (Kim *et al.*, 2018), which led to high concentration of the drug in piperine pretreated animals.

4. Conclusion

Looking to pharmacokinetic parameters of levofloxacin in goats, drug is poorly bioavailable after oral administration due to higher clearance rate and lower elimination half life. In trikatu pretreated goats, maximum plasma concentration was significantly improved by 23 per cent. Most pharmacokinetic parameters, following oral administration of levofloxacin were significantly higher in trikatu pretreated goats than those observed in normal goats. Trikatu treatment statistically increases bioavailability of levofloxacin which may be due to known herbal bioenhancer piperine present in the triherb mixture used in the study but, practically it seems to be increased only 9 percent.

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Conflict of interest

The authors declare that no conflict of interest exists in the course of conducting this research. All authors had final decision regarding the manuscript and the decision to submit the findings for publication.

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