The Pharma Innovation Journal 2019; 8(6): 729-733

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(6): 729-733
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www.thepharmajournal.com
Received: 07-04-2019
Accepted: 09-05-2019

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Pharmacokinetics of levofloxacin after oral administration in normal and ketoprofen-treated sheep

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Abstract
The pharmacokinetics of levofloxacin was evaluated in female sheep following its single oral administration (3 mg kg^{-1}) alone and on concomitant intramuscular (i.m.) administration of ketoprofen (3 mg kg^{-1}). Levofloxacin concentration was determined using the High Performance Liquid Chromatography. Following oral administration of the drug, mean absorption rate constant (K_a) and mean elimination rate constant (β) were 1.21 ± 0.19 and 0.13 ± 0.01 h^{-1}, respectively. The absorption ($t_{½Ka}$) and elimination half-life ($t_{½β}$) were 0.75 ± 0.23 and 5.25 ± 0.21 h, respectively. The mean apparent volume of distribution ($Vd_{(area)}$), area under plasma drug concentration-time curve ($AUC_{(0-\infty)}$) and area under first moment curve (AUMC) were 4.35 ± 0.29 L/kg, 2.78 ± 0.21 µg.h/mL and 22.54 ± 1.14 µg.h^2/mL, respectively. The mean value of total body clearance (Cl_B) of the drug was 0.55 ± 0.01 L/h/kg with mean residence time (MRT) of 8.18 ± 0.28 h. The calculated mean value of mean absorption time (MAT) was 6.45 ± 0.26 h. The levofloxacin concentrations from 8 to 24 hrs were significantly higher when ketoprofen was administered along with levofloxacin. However, pharmacokinetic parameters of orally administered levofloxacin were not significantly affected by concomitant administration of ketoprofen in sheep. Oral administration of levofloxacin at 3 mg/kg in sheep resulted in lower concentrations overall thus the drug may be efficacious against bacteria with lower MIC value (0.03 µg/mL).

Keywords: Pharmacokinetics, levofloxacin, ketoprofen, oral administration, sheep

Introduction
Antibacterial drugs are employed for the treatment of bacterial diseases in animals. Tetracyclines, cephalosporins, quinolones are important groups of drugs which are used for the treatment of mixed infection in animals. Pharmacological aspects of cephalosporins are studied in animals particularly pharmacokinetic profiles are extensively evaluated (Tiwari *et al*., 2009, Patel *et al*., 2006[ab]; Patani *et al*., 2006; Gohil *et al*., 2009; Maradiya *et al*., 2010; Patel *et al*. 2010; Swati *et al*., 2010) [33, 30, 26, 21, 10, 17, 31, 36] and many of them are now used in animals. However, due to constrain of bacterial resistance, the newer generation of cephalosporines are kept for limited uses in animals. Newer generation fluoroquinolones are extensively evaluated for having good pharmacokinetics in animals and birds (Patel *et al*., 2011; Modi *et al*., 2012) [25, 18]. Amongst them, levofloxacin is newer generation fluoroquinolone which is active against Gram-positive aerobic organisms, Gram-negative bacteria and anaerobes (Davis and Bryson, 1994; Klesel *et al.*, 1995) [4, 15]. The potential value of levofloxacin was described by previous studies on its pharmacokinetic profiles in various species of domestic animals and birds (Gonzaalez *et al.*, 2001; Albarellos *et al.*, 2005; Patel *et al*., 2012[abc]; Varia *et al*., 2009; Varia *et al*., 2012; Patel *et al*., 2013[a]) [11, 1, 23, 28, 29, 38, 37]. Many studies have been done to evaluate pharmacokinetic profile of levofloxacin following intravenous, intramuscular or subcutaneous administration in animals. Safety profile of levofloxacin has also been studied in sheep and poultry (Patel *et al*., 2009; Patel *et al*., 2013[ab]) [24, 22, 27].

In addition, concomitant use of NSAIDs may invariably affect disposition of the quinolones (Shiba *et al.*, 1992) [34] with enhancement of the convulsant activity of quinolone. The alteration in disposition of levofloxacin on concomitant administration of paracetamol and meloxicam in calves have been reported previously (Dumka *et al*., 2007[ab], Dumka, 2007) [6, 7, 5]. Ketoprofen (KTP), an aryl propionic acid derivative, non-selective COX inhibitor NSAID which is useful as anti-inflammatory, analgesic and antipyretic drug for the treatment of inflammatory conditions including rheumatoid arthritis and osteoarthritis in animals (Green, 2001, Owens *et al.* 1995[ab]) [13, 19, 20].

A pharmacokinetic profile of ketoprofen has been evaluated in animals (Landoni *et al*., 1999; Ratndeep Singh *et al*., 2014) [16, 32].

Data on pharmacokinetics of levofloxacin in small ruminants like sheep following oral administration are not available. The pharmacokinetic interaction of levofloxacin along with ketoprofen administration has not been studied in sheep. Thus, present study was carried out to evaluate the pharmacokinetics of levofloxacin following oral administration in sheep with possible pharmacokinetic interaction with ketoprofen.

Material and Methods

Experimental animals

The experiment was conducted on six healthy female Patanwadi non-lactating sheep of 2-3 years old age ranging in body weight from 23.5 to 30.0 kg obtained from and maintained at the Instructional Farm, College of Veterinary Science and Animal Husbandry, AAU, Anand, India. Constant observation for two weeks prior to commencement of the experiment was followed with clinical examination in order to exclude the possibility of any disease. The experimental protocol of the present study has been approved by the Animal Ethics Committee.

Drug administration and sampling

Levofloxacin oral tablet were procured from local pharmacy. Levofloxacin tablet (250 mg) was dissolved in 25 mL sterile water and used for oral administration using a syringe without the needle. Animals were fasted for 24 h before the oral administration of the drug. Ketoprofen was administered at the dose rate of 3 mg/kg of body weight intramuscularly in deep gluteal muscle. The washout period of 15 days was observed between two treatments of levofloxacin alone and levofloxacin with ketoprofen 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 heparinized centrifuge tube. Following oral 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 ºC until assayed for levofloxacin concentration using high performance liquid chromatography (HPLC) procedure which was usually done within 24 to 36 h.

Levofloxacin assay

The high performance liquid chromatography apparatus of Laballiance (USA) comprising quaternary gradient delivery pump (model AIS 2000) and UV detector (model 500) was used for assay. 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). Levofloxacin concentrations in the plasma samples were determined by HPLC with UV detection according to the method described by Patel *et al*. (2012[b]) [28].

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were calculated using standard methods as described by Gibaldi and Perrier, (1982). Student's t-test was used to test the pharmacokinetic parameters for significant difference between pharmacokinetic parameters in ketoprofen treated and normal sheep according to Snedecor and Cochran (1980) [35].

PK/PD integration

Efficacy predictors like C_{max}/MIC_{90} and $AUC_{(0-\infty)}/MIC_{90}$ for concentration dependent antibiotic levofloxacin were calculated using the values of peak plasma drug concentration (C_{max}) and area under the curve ($AUC_{(0-\infty)}$) after oral administration. MIC_{90} data of levofloxacin against ovine bacterial isolates have not been reported earlier. Thus, 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} of levofloxacin has been taken into consideration as described by Goudah and Hasabelnaby (2010) [12].

Result and Discussion

Following oral administration of the levofloxacin, the drug concentration of 0.026 ± 0.005 µg/mL was observed at 0.5 h. The mean peak plasma drug concentration of 0.779 ± 0.028 µg/mL was achieved at 4 h which declined rapidly to 0.147 ± 0.005 µg/mL at 12 h. The drug concentration of 0.018 ± 0.001 µg/mL in plasma was detected at 24 h. The drug was not detected in plasma samples collected after 24 h post oral administration of levofloxacin in sheep. Following oral administration of the levofloxacin along with ketoprofen, the levofloxacin concentration of 0.028 ± 0.003 µg/mL was observed at 0.5 h. The mean peak plasma drug concentration of 0.768 ± 0.030 µg/mL was achieved at 4 h which declined rapidly to 0.125 ± 0.012 µg/mL at 12 h. The drug concentration of 0.030 ± 0.003 µg/mL in plasma was detected at 24 h. The drug was not detected in plasma samples collected after 24 h post oral administration of levofloxacin with ketoprofen in sheep. The drug concentration-time profile of levofloxacin in normal and ketoprofen-treated sheep is tabulated in Table 1 and graphically depicted in Figure 1. Pharmacokinetic parameters of levofloxacin following oral administration in normal and ketoprofen-treated sheep are as per Table 2.

Following oral administration of levofloxacin in normal sheep, peak plasma drug concentration (C_{max}) observed at 4 h (T_{max}) is found to be lower than C_{max} of 4.38 ± 1.52 µg/mL at 1.18 h following oral administration (10 mg/kg) in cats (Albarellos *et al.*, 2005) [1]. It indicates slower and poor absorption of the drug following oral administration in sheep compared to cats. However, C_{max} of norfloxacin (1.28 ± 0.26 µg/mL) was also observed at 10.20 ± 3.98 h following oral administration (60 mg/kg) in sheep (Gonzaalez *et al.*, 2001) [11]. Significant higher ($p<0.05$) plasma drug concentrations were also obtained in ketoprofen-treated sheep (8 to 24 h) compared to respective values in normal sheep. The last observed drug concentrations in both ketoprofen-treated sheep were significantly higher than the respective value in normal sheep.

Following single dose oral administration of levofloxacin in normal sheep, the absorption rate constant (Ka) and half-life ($t_{1/2ka}$), were found to be 1.21 ± 0.19 h^{-1}, and 0.75 ± 0.23 h, respectively. The respective values for levofloxacin in ketoprofen-treated sheep were not significantly altered ($p>0.05$). Absorption half-life of 1.08 ± 0.05 h has been observed after oral administration of levofloxacin in chicken (Patel *et al*., 2012[a]) [23]. The volume of distribution (Vd_{area}) of the drug in ketoprofen-treated sheep was found to be similar

to that of normal sheep. As fluoroquinolones have high lipid solubility and low plasma protein binding they are widely distributed in body and the same has been observed in the present study. In most species, the distribution volume of levofloxacin and other fluoroquinolones is greater than that for most β-lactam antibiotics and aminoglycosides, and probably represents intracellular sequestration of the drug in various tissues (Brown, 1996) [2]. The values of AUC, AUMC, MRT and Cl_B of levofloxacin following oral administration were not significantly altered by administration of ketoprofen in sheep.

Following oral administration of levofloxacin relatively longer elimination half-life of 8.37 ± 3.47 h in cats (Albarellos *et al.*, 2005) [1], 3.62 ± 0.12h in chickens (Patel *et al*, 2012[a]) [23], 5.65 ± 0.14 h in mice (Ender *et al.*, 2003) [8], 7.1 h (Chien *et al.*, 1997) [3] and 4.23 ± 0.87 h (Hilte *et al.*, 2000) [14] in human have also been reported. Elimination half-life ($t_{1/2\beta}$) of the drug following oral administration is higher than $t_{1/2\beta}$ after intravenous administration (Patel *et al*, 2012[c]) [29]; this means drug is likely to act longer time after oral administration. Half-life depends on urinary pH of animal, and so may be different in various species. It also depends on volume of distribution and clearance of the drug and in the present study, clearance was found lower. So, half-life was found to be high, as it is inversely proportional to clearance.

The bioavailability of levofloxacin after oral administration in normal and ketoprofen-treated sheep was found to be similar. Higher bioavailability of levofloxacin following oral administration has been reported in cats (71.20 ± 22.99 %) and chickens (71.61 ± 1.38 %) (Albarellos *et al.*, 2005; Patel *et al*, 2012[a]) [1, 23]**.** Levofloxacin is rapidly absorbed from the gastrointestinal tract with absolute bioavailability after oral administration in humans. Administration of levofloxacin with food slows its absorption, prolongs peak serum concentrations by 1 h, and decreases the peak serum concentration by 14% (Fish and Chow, 1997) [9]. Moderate to low bioavailability in the present study indicates moderate absorption of levofloxacin via gastrointestinal tract after oral administration in normal and ketoprofen-treated sheep. Moreover, therapeutically effective concentration produced and maintained for up to 24 hours suggest that oral administration of levofloxacin may be conventional for the treatment of systemic bacterial infections in sheep. However, bacteria with lower MIC values can be effectively eradicated with levofloxacin administration by oral route in sheep.

Table 1: Comparison of plasma concentrations (µg/mL) of levofloxacin after oral administration (3 mg/kg) in normal and ketoprofen-treated (3 mg/kg) sheep

Time after drug administration (h)	(Normal)	(Ketoprofen-treated)
0.5	0.026 ± 0.005	0.028 ± 0.003
0.75	0.044 ± 0.006	0.051 ± 0.007
1	0.091 ± 0.002	0.145 ± 0.011*
2	0.291 ± 0.028	0.256 ± 0.003
4	0.779 ± 0.028	0.768 ± 0.030
6	0.291 ± 0.016	0.306 ± 0.036
8	0.147 ± 0.005	0.207 ± 0.020*
12	0.072 ± 0.004	0.125 ± 0.012**
18	0.033 ± 0.001	0.050 ± 0.005**
24	0.018 ± 0.001	0.030 ± 0.003**
36	ND	ND

ND: Not Detected; *Significant at $p<0.05$, **Highly significant at $p<0.01$ when compared with respective values of normal sheep.

Table 2: Pharmacokinetic parameters (Mean ± S.E.) of levofloxacin after oral administration (3 mg/kg) in normal and ketoprofen-treated (3 mg/kg) sheep

Pharmacokinetic parameter	Unit	(Normal)	(KTP-treated)
A'	µg/mL	0.67 ± 0.14	1.08 ± 0.23
B	µg/mL	0.41 ± 0.05	0.50 ± 0.03
K_a	h^{-1}	1.21 ± 0.19	1.32 ± 0.26
β	h^{-1}	0.13 ± 0.01	0.14 ± 0.003
$t_{½Ka}$	h	0.75 ± 0.23	0.61 ± 0.14
$t_{½\beta}$	h	5.25 ± 0.21	4.82 ± 0.11
C_{max}	µg/mL	0.78 ± 0.03	0.77 ± 0.03
T_{max}	h	4.00 ± 0.00	4.00 ± 0.00
$AUC_{(0-\infty)}$	µg.h/mL	2.78 ± 0.21	2.79 ± 0.11
AUMC	$\mu g.h^2/mL$	22.54 ± 1.14	22.92 ± 0.71
$Vd_{(area)}$	L/kg	4.35 ± 0.29	3.99 ± 0.19
$Cl_{(B)}$	L/h/kg	0.55 ± 0.01	0.57 ± 0.01
MRT	h	8.18 ± 0.28	7.57 ± 0.46
MAT	h	6.45 ± 0.26	5.90 ± 0.44
F	%	52.48 ± 2.52	52.97 ± 1.88

*Significant at $p<0.05$, compared with respective values of normal sheep.

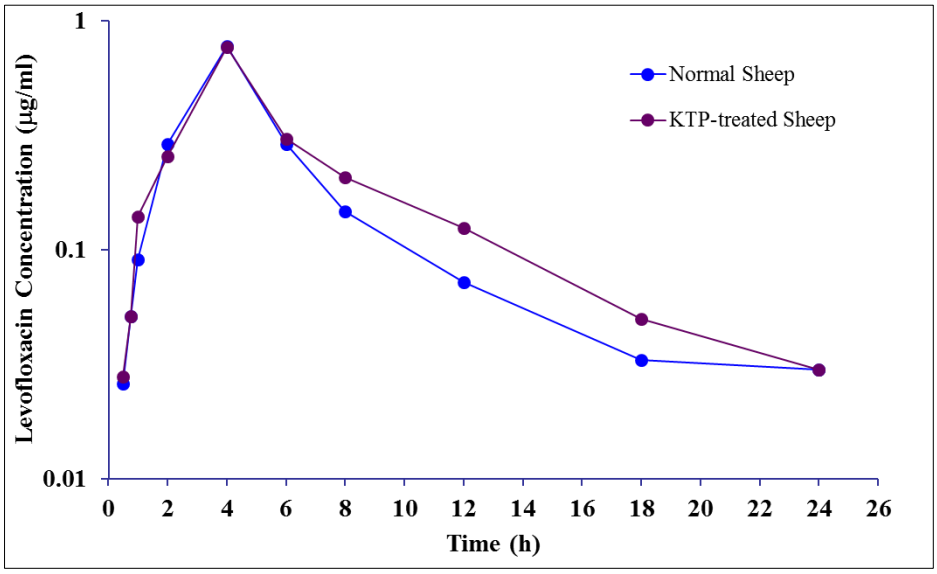

Fig 1: Comparison of plasma concentrations (µg/mL) of levofloxacin after oral administration (3 mg/kg) in normal and ketoprofen-treated (3 mg/kg) sheep

Conclusion

Pharmacokinetic profiles of levofloxacin in normal sheep were found moderate as compared to pharmacokinetic profiles of the drug following parental route of administration. Ketoprofen administration did not affect the oral pharmacokinetic profile of levofloxacin in sheep. After oral administration, PK/PD efficacy predictors indicated that oral administration of levofloxacin (3 mg/kg) in normal and ketoprofen-treated sheep would be efficacious against bacteria with low MIC of 0.03 µg/mL only or higher dose may be needed to overcome lesser extent of absorption following oral administration in sheep.

Acknowledgement

We are thankful to Principal and Dean, Veterinary College, Anand Agricultural University for providing the facility to conduct this study. We are also thankful to Dr. K.N. Wadhwani, for providing the facility.

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