Effect of Febrile Condition and Ketoprofen Co-administration on Pharmacokinetics of Moxifloxacin Following Intravenous Administration in Sheep

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ABSTRACT

The present study was planned to determine the effect of intramuscularly administered ketoprofen (3 mg/kg) and lipopolysaccharide induced febrile condition on pharmacokinetics of moxifloxacin following intravenous administration (5 mg/kg) in sheep. Moxifloxacin was assayed in plasma by High Performance Liquid Chromatography. Following intravenous administration of moxifloxacin in normal sheep, apparent volume of distribution area (Vd_{area}), under plasma drug concentration-time curve ($AUC_{0-\infty}$), area under first moment curve (AUMC), elimination half-life ($t_{1/2\beta}$), total body clearance (Cl_B) and mean residence time (MRT) were 4.88 ± 0.20 L/kg, 8.38 ± 0.23 mg.h/mL, 49.52 ± 3.83 mg.h^2/mL, 5.70 ± 0.37 h, 0.60 ± 0.02 L/h/kg and 5.87 ± 0.32 h, respectively. Following intravenous administration of moxifloxacin in ketoprofen-treated sheep, a significant increase in mean value of $AUC_{(0-\infty)}$ and AUMC while significant decrease in mean value of $t_{½\beta}$, Vd_{area}, Vd_{ss}, Cl_B and MRT were observed in comparison to respective pharmacokinetic parameters of moxifloxacin in normal sheep. However, in febrile sheep, the $AUC_{(0-\infty)}$ and AUMC were significantly increased while Cl_B and Vd_{area} were significantly decreased as compared to normal sheep. Febrile condition and ketoprofen co-administration appears to alter the pharmacokinetics of moxifloxacin in sheep.

Keywords: Pharmacokinetics, moxifloxacin, ketoprofen, febrile condition, sheep.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently recommended with antibiotics for the treatment of various bacterial infections in animals. It is well documented that concurrently administered drugs as well as the disease state may alter the pharmacokinetics of one or both drugs (1). Fluoroquinolones are group of antimicrobials that have become widely used in veterinary medicine. Moxifloxacin is a novel fourth generation fluoroquinolone with a broad spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria, anaerobes and atypical organisms such as *Mycoplasma* and *Chlamydia* spp. (2). It has the highest potency against *Staphylococcus aureus* and *Staphylococcus epidermidis* compared to gatifloxacin, levofloxacin, ciprofloxacin and ofloxacin (3). The drug thus seems to be extremely useful in a variety of infections including those of urinary tract, respiratory tract, soft tissues, bones and joints of animals. Ketoprofen is a routinely used non-steroidal anti-inflammatory, analgesic and antipyretic agent in veterinary practice (4).

Pharmacokinetics of moxifloxacin has been studied in

calves (5), buffalo calves (6), lactating ewes (7), goats (8), camels (9), rats (10) and rabbits (11). The disposition kinetics of levofloxacin (12), gatifloxacin (13), danofloxacin (14), marbofloxacin (15) and enrofloxacin (16, 17) has been determined following intravenous administration in febrile goats. Despite the great potential for clinical use of moxifloxacin, the data on its pharmacokinetics in febrile condition and ketoprofen co-administration in sheep are not available. In view of this, the present study was undertaken to determine the effect of ketoprofen and febrile condition on pharmacokinetics of moxifloxacin in sheep.

MATERIALS AND METHODS

Experimental Animals

The study was conducted on six Patanwadi sheep of 2-3 years of age weighing between 25 and 30 kilograms. They were examined clinically and to be found healthy. The animals were housed in separate pens and provided with standard ration. Water was provided *ad libitum*. All necessary managerial procedures were adopted to keep the animals free from stress.

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC No. 2010/VPT/80) and constituted by Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (Reg. No. 486/01/A/CPCSEA).

Induction of febrile state

Febrile state in sheep was induced by injecting lipopolysaccharide (LPS) of *Escherichia coli* (055:B5) at the dose rate of 0.2 µg/kg body weight intravenously (13). This dose of LPS caused a rise in body temperature within 30 minutes and fever persisted for 12 h. The minimum rise in temperature (0.84 to 1.12˚C) after injection of LPS endotoxin was considered as the time of the drug administration (18). LPS was again injected at dose rate of 0.1 µg/kg body weight at 12 h and at dose rate of 0.05 µg/kg body weight after 24 h of first dose of LPS respectively to maintain the febrile state for up to 36 h.

Drugs and Chemicals

Moxifloxacin technical grade pure powder was obtained from Ms. Zydus Research Centre, Gujarat, India. Orthophosphoric acid, acetonitrile, methanol and water of HPLC grade were purchased from Merck Limited, Mumbai, India. Lipopolysaccharide of *Escherichia coli* (055:B5) was purchased from Sigma Pvt. Ltd., Mumbai, India.

Experimental plan and drug administration

The study was conducted in a cross-over design with an interval of fifteen days between successive administrations of the drug. Six healthy sheep were employed to investigate the effect of intramuscularly administered ketoprofen (3 mg/kg) and LPS induced febrile condition on pharmacokinetics of moxifloxacin following intravenous administration (5 mg/kg) in sheep. Intramuscular (IM) injection was given into the deep gluteal muscle using 20G × 25mm needle and the intravenous (IV) injection of the drug was given through the jugular vein.

Collection of blood samples

Blood samples (2 mL) were collected from an IV catheter (Venflon, BD, Franklin Lakes, NJ, USA. 22G × 0.9 × 25 mm) fixed into the contralateral jugular vein. Following IV administration, blood samples were collected in sterile heparinized vials at 0 minutes (before drug administration), 2, 5, 10, 15, 30 and 45 minutes and at 1, 2, 4, 8, 12, 18, 24 and 36 h. Plasma was separated soon after collection by centrifugation at 3000 rpm for 10 minutes at 10˚C (Eppendorf 5804 R, Germany). Separated plasma samples were transferred to labeled cryovials and stored at -40˚C until assayed for moxifloxacin concentration.

Moxifloxacin assay

Moxifloxacin was assayed in plasma by adopting the procedure as reported by Sultana *et al.* (2010) with minor modifications (19). The high performance liquid chromatography (HPLC) apparatus of Laballiance (Pennsylvania, USA) comprising of 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 (PARTISIL 5 ODS-3 RAC-II column; 4.6 ´ 100 mm ID, Whatman, Kent, UK) at room temperature. The HPLC data integration was performed using software Clarity (Version 2.4.0.190, Dataapex, Petrzilkova, Czech Republic, Central Europe). The mobile phase consisted of a mixture of methanol and water (55:45 v/v), pH adjusted to 2.3 with ortho-phosphoric acid. The mobile phase was pumped into column at a flow rate of 0.7 ml/min at ambient temperature. The effluent was monitored at 296 nm

wavelength. The limit of detection was 0.05 mg/ml. The lower limit of quantitation was 0.1 mg/ml.

For extraction of moxifloxacin from plasma, 100 ml (0.1 mL) of plasma sample was taken in micro-centrifuge tube (2.0 mL capacity). Acetonitrile (200 ml) was added in order to precipitate plasma proteins. The mixture was vortexed for 1 minute and centrifuged at 10000 rpm for 5 minutes at 10°C. The supernatant was decanted in clean sterile microcentrifuge tubes and 20 ml supernatant was injected into the loop injector. A standard curve of moxifloxacin was prepared using drug-free sheep plasma. The assay was found to be sensitive, reproducible and its linearity was observed from 0.1 to 50 mg/mL with mean correlation coefficient (r^2) > 0.999. Non-compartmental pharmacokinetic analysis was performed using software PK solution (version 2.0, Summit Research Services, Colorado, USA) to calculate various pharmacokinetic parameters from plasma concentrations of moxifloxacin.

Statistical analysis

Moxifloxacin plasma concentrations and pharmacokinetic parameters of different treatment groups were compared by students' "t" test using SPSS software (version 12.0.1). Statistical differences were considered at p≤0.05 and p≤0.01. The pharmacokinetic parameters were expressed in terms of Mean ± Standard Error (S.E.).

RESULTS

All animals remained in good health throughout the acclimatization and study period. Plasma moxifloxacin concentrations at different time intervals following IV injection alone, co-administered intramuscularly with ketoprofen and under a febrile state in sheep are presented as a semi logarithmic plot in Figure 1.

The intravenous administration of a single dose of moxifloxacin alone in sheep resulted in plasma concentrations of 8.48 ± 0.21 mg/mL at 2 minutes, which declined rapidly to 1.20 ± 0.03 mg/mL at 1 h and the drug concentration of 0.17 ± 0.01 mg/mL was detected up to 12 h. Plasma drug concentrations were significantly higher (p≤ 0.01) in ketoprofen-treated sheep as compared to normal sheep. A plasma drug concentration of 16.47 ± 0.71 mg/mL observed at 2 minutes in febrile sheep which declined to 2.09 ± 0.06 mg/mL at 1 h and was significantly higher (p≤ 0.01) as compared to plasma drug concentration found at 1 h in normal sheep. Plasma drug concentrations observed were significantly higher (p≤ 0.01) from 2 minutes to 18 h in febrile than normal sheep. Comparison of pharmacokinetic parameters (mean ± SE) of moxifloxacin after IV administration (5 mg/kg) in normal, ketoprofen-treated (3 mg/kg) and febrile sheep are depicted in Table 1.

Following IV administration of moxifloxacin in ketopro-

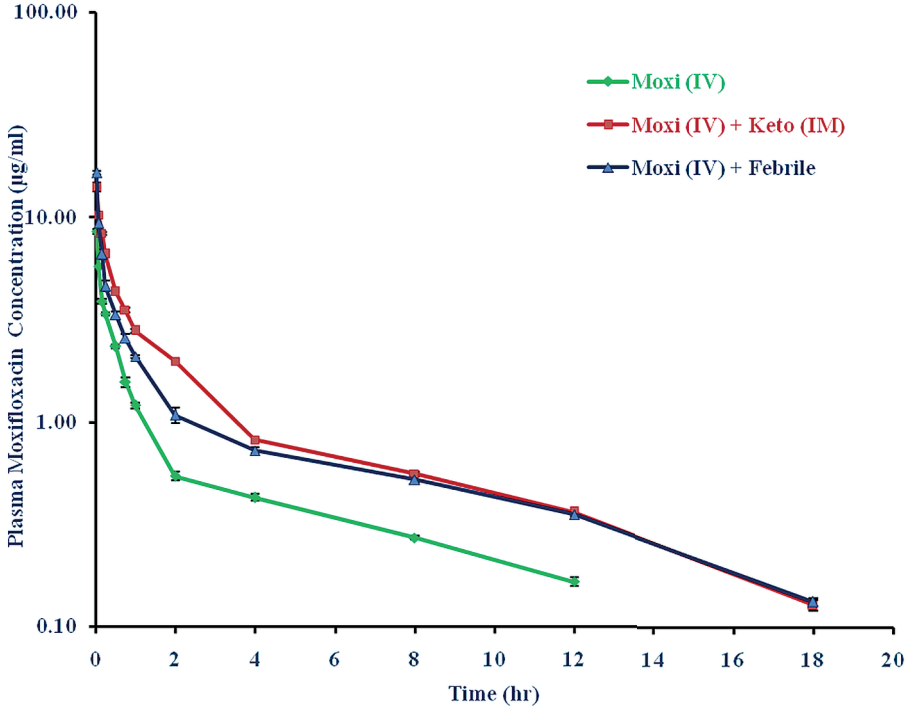

Figure 1: Semilogarithmic plot of moxifloxacin concentration in plasma versus time following intravenous administration (5 mg/kg) in normal, ketoprofen treated (3 mg/kg) and febrile sheep. Each point represents mean and standard error of six animals.

Table 1: Comparison of pharmacokinetic parameters (mean ± SE) of moxifloxacin after intravenous administration (5 mg/kg) in normal, ketoprofen-treated (3 mg/kg) and febrile sheep (n=6).

Pharmacokinetic parameter	Unit	Sheep		
		Normal/Healthy	Ketoprofen-treated	Febrile
Cp^0	µg/mL	7.00 ± 0.23	9.43 ± 0.78*	18.41 ± 1.54**
α	h^{-1}	0.22 ± 0.03	0.29 ± 0.04	3.00 ± 0.43**
β	h^{-1}	0.12 ± 0.01	0.17 ± 0.01*	0.12 ± 0.01
$t_{½\alpha}$	h	3.55 ± 0.56z	2.63 ± 0.42	0.25 ± 0.03**
$t_{½\beta}$	h	5.70 ± 0.37	4.08 ± 0.25*	5.70 ± 0.16
$AUC_{(0-\infty)}$	µg.h/mL	8.38 ± 0.23	17.55 ± 0.25**	14.88 ± 0.39**
AUMC	$\mu g.h^2/mL$	49.52 ± 3.83	84.14 ± 1.96**	88.82 ± 4.38**
Vd_{area}	L/kg	4.88 ± 0.20	1.67 ± 0.09**	2.76 ± 0.04**
Vd_{ss}	L/kg	3.49 ± 0.11	1.37 ± 0.02**	2.00 ± 0.03**
Cl_B	L/h/kg	0.60 ± 0.02	0.29 ± 0.01**	0.34 ± 0.01**
MRT	h	5.87 ± 0.32	4.79 ± 0.07*	5.95 ± 0.15

* Significant at P<0.05, ** significant at P<0.01 when compared with respective values of normal sheep. Cp^0: Concentration at time 0; α: Exponential coefficient of distribution; β: Exponential coefficient of elimination; $t_{½\alpha}$: Distribution half life, $t_{½\beta}$: Elimination half life, $AUC_{(0-\infty)}$: Area under the curve, AUMC: Area under first 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.

fen-treated sheep, a significant increase in the mean value of various pharmacokinetic parameters such as Cp^0 ($p \leq 0.05$), β ($p \leq 0.05$), $AUC_{(0-\infty)}$ ($p \leq 0.01$) and AUMC ($p \leq 0.01$) along with significant decrease in mean values of $t_{½\beta}$ ($p \leq 0.05$), Vd_{area} ($p \leq 0.01$), Vd_{ss} ($p \leq 0.01$), Cl_B ($p \leq 0.01$) and MRT ($p \leq 0.05$) were observed as compared to respective pharmacokinetic parameters of moxifloxacin in normal sheep. Following IV administration of moxifloxacin in febrile sheep, significant increases ($p \leq 0.01$) in mean values of Cp^0, α, $AUC_{(0-\infty)}$ and AUMC, whereas significant decreases ($p \leq 0.01$) in mean value of $t_{½\alpha}$, Vd_{area}, Vd_{ss} and Cl_B were observed as compared to respective pharmacokinetic parameters of moxifloxacin in normal sheep.

DISCUSSION

The pharmacokinetics of moxifloxacin (5 mg/kg) was studied following IV administration of moxifloxacin alone, co-administered with ketoprofen (3 mg/kg) and in a febrile state. Following IV administration of moxifloxacin in ketoprofen-treated and febrile sheep, the peak plasma levels of drug were higher ($p < 0.05$) than normal sheep (8.48 ± 0.21 µg/mL). The plasma moxifloxacin concentration was detected for up to 12 hrs in the moxifloxacin treated group, whereas in ketoprofen treated and febrile group it was detected up to 18 hrs. The LPS induced febrile state produced a significant increase in the plasma levels of moxifloxacin following IV administration in sheep. Similarly, significant increases in plasma levels of enrofloxacin (16), marbofloxacin (15) and danofloxacin (14) following IV administration has been observed in febrile goats.

In the present study, significant increases in mean values of Cp^0, β, $AUC_{(0-\infty)}$ and AUMC, whereas significant decrease in mean values of $t_{½\beta}$, Vd_{area}, Vd_{ss}, Cl_B and MRT were observed in ketoprofen-treated sheep as compared to respective pharmacokinetic parameters of moxifloxacin in normal sheep. Similarly, co-administration of paracetamol (50 mg/kg, IM) or meloxicam (0.5 mg/kg, SC) altered the pharmacokinetics of levofloxacin (4 mg/kg, IV) in crossbred calves (20, 21). The values of $AUC_{(0-\infty)}$ of levofloxacin (12.7 ± 0.12 µg.h/mL) following co-administration with paracetamol was higher as compared to levofloxacin alone (7.66 µg.h/mL) treated calves. Similar to finding as presented in this study, $t_{½\beta}$ of levofloxacin (1.38 h) following co-administration with paracetamol was shorter than levofloxacin alone (3.67 h) in treated calves (20, 22). A significant increase in $t_{½\beta}$ and a significant decrease in the C_{max} of enrofloxacin were found following co-administration with flunixin meglumine compared to enrofloxacin alone treated dogs (23). Concomitant IM administration of meloxicam (0.5 mg/kg) altered the disposition of moxifloxacin (5 mg/kg) in female rats (10).

Similarly, it has been reported that concomitant intravenous use of naproxen or diclofenac (20 mg/kg) significantly altered the pharmacokinetics of tetracycline (5 mg/kg) as compared to tetracycline alone treated rats (24). In contrast, it has been described that diclofenac sodium (1 mg/kg, I/M) did not alter significantly the pharmacokinetic profiles of enrofloxacin in calves (5 mg/kg, I/V) and in buffalo calves (4 mg/kg, I/V) (25, 26).

Following IV administration of moxifloxacin in febrile sheep, the AUC (14.88 ± 0.39 mg.h/mL) and AUMC (88.82 ± 4.38 mg.h^2/mL) were significantly higher as compared to normal sheep. Significant decreases in Vd_{area} (2.76 ± 0.04 L/kg), Vd_{ss} (2.00 ± 0.03 L/kg), Cl_B (0.34 ± 0.01 L/h/kg) and $t_{1/2\alpha}$ (0.25 ± 0.03 h) of the drug were observed in febrile compared to normal sheep. In the present study, Vd_{area} was significantly decreased from 4.88 ± 0.20 L/kg to 2.76 ± 0.04 L/kg in febrile compared to normal sheep.

The acute phase response induced by fever includes synthesis of acute phase hepatic proteins, including a_1-acid glycoprotein, which binds some drugs and which may produce a decrease in their volume of distribution. However, it should be noted that this contributes only a minor degree to the decline of moxifloxacin volume of distribution because of its low degree of protein binding (27).

After administration of the lipopolysaccharide, the slower elimination of the drug may be the result of renal and/or hepatic modifications caused by the toxin. Endotoxin can possibly impair the excretion process of organic anions in the liver at the stage of transport from intracellular storage to bile via the canalicular membrane (28). Furthermore, it is possible that a decrease in the 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. Moreover, it has been reported that endotoxin produces an increase in tubular reabsorption and a decrease in tubular secretion of some drugs including moxifloxacin (28, 29).

Findings of the present study agree with previous findings of significant increase in AUC (2.368 ± 0.18 to 4.26 ± 0.4 mg.h/mL), AUMC (9.93 ± 0.65 to 33.2 ± 1.9 mg.h^2/mL) and MRT (4.196 ± 0.3 to 8.3 ± 0.6 h) and decrease in Cl_B (0.58 ± 0.031 to 0.31 ± 0.02 L/h/kg) following IV administration of danofloxacin in febrile compared to normal goats (14). Approximating our findings, there was highly significant increase in absorption half life, α, β, $AUC_{(0-\infty)}$ and C_{max} whereas there was significant decrease in $t_{1/2\alpha}$ and $t_{1/2\beta}$ in febrile rabbits as compared to normal rabbits following oral administration of ciprofloxacin (30). Similarly, a significant rise in AUMC and a significant reduction in b, $t_{1/2\beta}$ and Vd_{area} were reported in experimentally induced febrile state as compared to normal rabbits (31). Additionally, the findings have been well supported by observing similar alterations in pharmacokinetics following IV administration of enrofloxacin (16), marbofloxacin (15) and gatifloxacin (13) in febrile goats, levofloxacin in febrile calves and febrile sheep (32, 33).

In conclusion, co-administration of ketoprofen and LPS induced febrile conditions causing alterations in pharmacokinetics of moxifloxacin in sheep. It would be prudent to raise the awareness regarding pharmacokinetics in febrile animals and the potential drug-to-drug interaction between moxifloxacin and ketoprofen.

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