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Effect of Ketoprofen Co-administration and Febrile State on Pharmacokinetic of Cefepime in Goats

¹Hiren B. Patel, ¹Nimesh N. Patel, ¹Shital D. Patel, ¹Shilpesh Dewda, ²Jatin H. Patel, ²Shailesh K. Bhavsar and ¹Aswin M. Thaker

¹Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand 388 001, India

²Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari 396 450, India

Corresponding Author: Jatin H. Patel, Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari 396 450, India Tel: +91 2637 282771 Fax: +91 02637 283234

ABSTRACT

The pharmacokinetic of cefepime (20 mg kg⁻¹) was studied following intramuscular administration of cefepime alone, co-administered with ketoprofen (3 mg kg⁻¹) and under febrile state (*Escherichia coli* LPS induced) in goats. The concentration of cefepime in serum was detected by using High Performance Liquid Chromatography. Following single dose intravenous administration of cefepime, elimination half life (2.38±0.11 h), area under curve (133.77±3.49 µg h mL⁻¹), body clearance (2.38±0.05 L h⁻¹ kg⁻¹) and volume of distribution (0.5±0.03 L kg⁻¹) were determined. Following single dose intramuscular administration of cefepime alone, peak serum concentration (30.26±2.96 µg mL⁻¹) was obtained at 0.75 h. The absorption half life (t_{1/2Ka}), volume of distribution (Vd_{area}), total body clearance (Cl_T) and elimination half life (t_{1/2β}) of cefepime were 0.27±0.05 h, 1.05±0.09 L kg⁻¹, 2.38±0.2 L h⁻¹ kg⁻¹ and 5.13±0.27 h, respectively. No significant changes were reported in pharmacokinetic parameters following co-administration of cefepime with ketoprofen. While under febrile state, all pharmacokinetic parameter of cefepime remained non-significantly altered except elimination half life (6.64±0.33 h) and peak serum concentration (39.23±1.11 µg mL⁻¹). Cefepime pharmacokinetic data generated from the present study suggest that the drug can be administered intramuscularly (20 mg kg⁻¹) with ketoprofen and in febrile condition at 12 h interval to combat susceptible bacterial infections in goats.

Key words: Pharmacokinetic, cefepime, ketoprofen, fever, goat

INTRODUCTION

Antibacterial and NSAIDs are used most frequently in multiple drug prescriptions. It is well documented that concurrently administered drugs may alter pharmacokinetics of one or both drugs. Cefepime is a semi-synthetic broad spectrum fourth generation cephalosporin antibiotic with a modified zwitterionic structure that allows more favorable penetration into the bacterial cells, higher affinity for its molecular target (PBP3) and reduced susceptibility to β-lactamases (Del Rio *et al.*, 2008). Cefepime is unique because of its broad spectrum of activity that includes gram-positive cocci, enteric gram-negative bacilli and *Pseudomonas*. It has advantage of activity against some Extended-spectrum β-lactamase (ESBL)-producing strains of *Klebsiella* and *E. coli*

that have become resistant to many other β -lactam drugs and fluoroquinolones (Riviere and Papich, 2009). Ketoprofen is a routinely used as non-steroidal anti-inflammatory, analgesic and antipyretic agent in veterinary practice (Boothe, 2001). Pharmacokinetics of cefepime administered as single drug were investigated in healthy ewes and calves (Ismail, 2005a, b; Patel *et al.*, 2006a, b), buffalo calves (Joshi and Sharma, 2009), dogs (Stampley *et al.*, 1992), horses (Guglick *et al.*, 1998), neonatal foals (Gardner and Papich, 2001) and goats (Rule *et al.*, 2004; Patni *et al.*, 2008). However, there is no information available on the influence of co-administration of ketoprofen and febrile state on the pharmacokinetic of cefepime in goats. Looking to possibility for interaction of ketoprofen and to reveal pharmacokinetic of cefepime in goat under febrile state, the study was undertaken to determine effect ketoprofen and febrile condition on pharmacokinetics of cefepime in goat.

MATERIALS AND METHODS

Experimental animals: The experiment was conducted on six healthy adult (2-3 years of age) Surti goat, weighing 28-32 kg. Each animal was housed in a separate pen and provided standard ration with *ad libitum* water. Goats were kept under constant observation for two weeks before the commencement of the experiment and subjected to clinical examination to exclude the possibility of any diseases. The experimental protocol was approved by Institutional Animal Ethics Committee.

Drug and chemical: Cefepime technical grade powder was procured from Aurobindo Pharma, Hyderabad. Cefepime hydrochloride powder (1 g Biopime[®]; Biochem pharmaceutical Industries Ltd., Mumbai) and ketoprofen injection (Neoprofen[®]; RFCL Limited, Uttarakhand) were purchased from local market. Water, Acetonitrile, Acetic acid (HPLC grade), Sodium Acetate (AR grade), Perchloric acid were purchased from Merck India Ltd., Mumbai, India.

Drug administration and sample collection: All six animals were randomly allocated to receive either an intravenous or intramuscular injection of cefepime at the dose rate of 20 mg kg⁻¹. A washout period of 2 weeks was observed between treatments. An intravenous injection of cefepime was administered in the left jugular vein. Blood samples (5 mL) were collected through an intravenous catheter (Venflon, 22×0.9×25 mm) fixed in the contra lateral jugular vein in glass test tubes, prior to injection and at 2, 5, 10, 15, 30 min and 1, 2, 4, 8, 12, 18, 24 and 36 h after intravenous administration. The intramuscular injection of cefepime was administered in the left deep gluteal muscle, while ketoprofen was administered deep intramuscular at the dose rate of 3 mg kg⁻¹ in contralateral gluteal muscle. Blood samples (5 mL) were collected, before administration and at 5, 10, 15, 30 min and 1, 2, 4, 8, 12, 18, 24 and 36 h after concurrent intramuscular administration of cefepime and ketoprofen. Febrile state in goat was induced by injecting Lipopolysaccharide (LPS) of *Escherichia coli* (O55:B5) at the dose rate of 0.2 µg kg⁻¹ body weight intravenously (Verma and Roy, 2006). LPS was repeated at dose rate of 0.1 and 0.05 µg kg⁻¹ at 12 and 24 h, respectively to maintain the febrile state up to 36 h. Goats were monitored for any adverse reactions during the entire study period. Blood samples were allowed to clot and the serum was harvested by centrifugation at 3000 g for 10 min. The serum samples were stored at -40°C and analyzed within 24 h for determination of cefepime concentration.

Analytical assay of cefepime and pharmacokinetic analysis: Cefepime concentration in serum samples was determined by reverse-phase High Performance Liquid Chromatography

(HPLC) after extraction, using a reported assay (Gardner and Papich, 2001) with minor modifications. The High Performance Liquid Chromatography (HPLC) apparatus of Laballiance (USA) comprised of quaternary gradient delivery pump (model AIS 2000), UV detector (model 500) and C18 column (Thermo ODS: 250 x 4.6 mm ID) were used. Pharmacokinetic data integration was done by software "Clarity" (Version 2.4.0.190).

Serum (500 μL) was deproteinized by addition of perchloric acid (0.8 M) and vortexed for one minute. This was followed by centrifugation at 1957 g for 15 min. An aliquot of supernatant was collected in clean vial and 20 μL injected into loop of HPLC system. The mobile phase was a mixture of 0.2 M sodium acetate (3.2%), 0.2 M acetic acid (2.2%), acetonitrile (10.0%) and HPLC water (84.6%) having pH 5.1. 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 effluent was monitored at 257 nm wavelength.

Calibration curve was prepared daily for drug concentration ranging from 0.5 to 200 $\mu\text{g mL}^{-1}$. The assay was sensitive (LLOD: 0.5 $\mu\text{g mL}^{-1}$), reproducible and linearity was observed from 0.5 to 200 $\mu\text{g mL}^{-1}$ ($r^2 = 0.99$). Precision and accuracy were determined using Quality Control (QC) samples at concentrations 1, 5, 50 $\mu\text{g mL}^{-1}$ (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 4%. Various pharmacokinetic parameters were calculated from serum concentration of cefepime using software PK solution (version 2.0). The bioavailability (F) was calculated using following formula:

$$F \% = \frac{\text{AUC (IM)}}{\text{AUC (IV)}} \times \frac{\text{DOSE (IV)}}{\text{DOSE (IM)}}$$

Statistical analysis: Cefepime serum concentration and pharmacokinetic parameters of different treatment groups were compared by students' "t" test using SPSS software (version 12.0.1).

RESULTS

Serum cefepime concentrations at different time intervals following intramuscular injection alone or co-administered intramuscularly with ketoprofen and under febrile state in goats is presented as semi logarithmic plot in Fig. 1.

The serum concentration of cefepime at 2 min after intravenous administration was $138.56 \pm 6.3 \mu\text{g mL}^{-1}$ which rapidly declined to $32.02 \pm 2.49 \mu\text{g mL}^{-1}$ at 1 h and detected upto 12 h ($0.99 \pm 0.18 \mu\text{g mL}^{-1}$). Following intramuscular injection of cefepime alone, the serum concentration of cefepime at 5 min was $9.52 \pm 1.33 \mu\text{g mL}^{-1}$ which gradually increased and reached to the peak concentration ($30.26 \pm 2.96 \mu\text{g mL}^{-1}$) at 45 min. On concurrent intramuscular administration of ketoprofen and cefepime, the initial serum concentration of cefepime at 5 min was $8.77 \pm 0.92 \mu\text{g mL}^{-1}$ which increased to attain the peak serum concentration ($30.17 \pm 1.64 \mu\text{g mL}^{-1}$) at 45 min. In febrile condition, serum cefepime concentration following intramuscular injection was $11.93 \pm 1.45 \mu\text{g mL}^{-1}$ at 5 min which attained peak concentration at 1 h ($39.22 \pm 1.11 \mu\text{g mL}^{-1}$). For cefepime the minimum inhibitory concentration against majority of Gram-negative and Gram-positive pathogens has been reported to be 0.25-2.0 $\mu\text{g mL}^{-1}$ for most of pathogens (Washington *et al.*, 1993; Lozniewski *et al.*, 2001). The drug levels above the Minimum Inhibitory Concentration (MIC) were detected in serum up to 18 h following single dose intramuscular administration of cefepime alone, co-administrated with ketoprofen and in febrile state. Various kinetic determinants that describe the absorption and elimination pattern of cefepime after

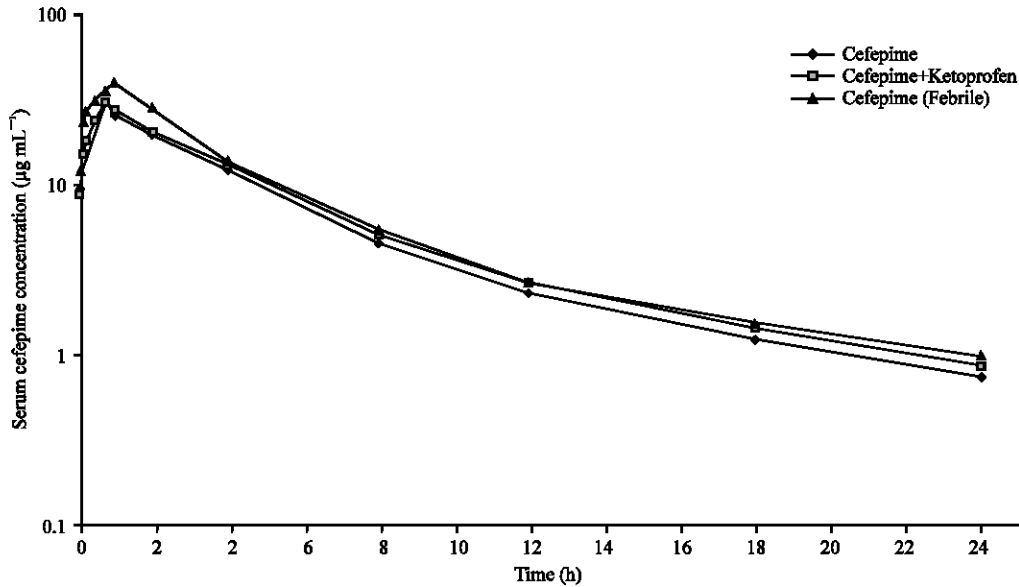


Fig. 1: Semilogarithmic plot of Cefepime serum concentrations after intramuscular administration of cefepime alone (20 mg kg^{-1}), Ketoprofen-treated (3 mg kg^{-1}) and febrile goats. Each point represents mean of six animals

Table 1: Cefepime pharmacokinetic parameters following intravenous and intramuscular administration of cefepime alone (20 mg kg^{-1}) and in ketoprofen treated (3 mg kg^{-1}) and febrile goats (Mean \pm SE, n = 6)

Pharmacokinetic parameter	Unit	Cefepime (IV)	Cefepime (IM)	Cefepime (IM) and ketoprofen (IM)	Cefepime (IM) and febrile state
K_a	/h	-	3.00 ± 0.48	4.03 ± 0.33	2.57 ± 0.25
β	/h	28.34 ± 1.35	0.14 ± 0.01	0.13 ± 0.00	$0.11\pm 0.01^*$
$t_{1/2k_a}$	h	-	0.27 ± 0.05	0.18 ± 0.02	0.28 ± 0.30
$t_{1/2\beta}$	h	2.38 ± 0.11	5.13 ± 0.27	5.32 ± 0.32	$6.64\pm 0.33^*$
C_{max}	$\mu\text{g mL}^{-1}$	-	30.26 ± 2.96	30.17 ± 1.64	$39.23\pm 1.11^*$
T_{max}	h	-	0.75 ± 0.00	0.75 ± 0.00	1.00 ± 0.00
AUC_{0-8}	$\mu\text{g h mL}^{-1}$	133.77 ± 3.49	139.08 ± 10.28	149.75 ± 13.1	179.18 ± 11.05
AUMC	$\mu\text{g h}^2 \text{ mL}^{-1}$	343.66 ± 15.37	880.54 ± 121.27	999.19 ± 92.37	1181.15 ± 138.71
$V_{d_{area}}$	L kg^{-1}	0.5 ± 0.03	1.05 ± 0.09	1.03 ± 0.11	1.03 ± 0.04
Cl_B	$\text{L h}^{-1} \text{ kg}^{-1}$	2.38 ± 0.05	2.38 ± 0.20	2.23 ± 0.22	1.80 ± 0.11
MRT	h	2.5 ± 0.14	5.97 ± 0.53	6.70 ± 0.15	6.16 ± 0.29
F	%	-	104.90 ± 9.53	111.06 ± 8.67	126.50 ± 6.31

*Significant at $p < 0.05$ when compared with respective values of cefepime alone (Intramuscular) treated goats. K_a : Absorption rate constant, B: Zero-time intercept of elimination phase, $t_{1/2k_a}$: Absorption half life, $t_{1/2\beta}$: Elimination half life, C_{max} : Maximum drug concentration, T_{max} : Time of maximum observed concentration in serum, AUC_{0-8} : Area under curve, AUMC: Area under first moment of curve, $V_{d_{area}}$: Apparent volume of distribution, Cl_B : Total body clearance, MRT: Mean residence time, F: Bioavailability

intravenous injection and intramuscular administration either used alone or in combination with ketoprofen and under febrile state were calculated and are presented in Table 1.

DISCUSSION

Following intramuscular administration cefepime (20 mg kg^{-1}) in goat either alone, co-administered with ketoprofen (3 mg kg^{-1}) no adverse effects or toxic manifestations were

observed. In endotoxin induced febrile condition symptoms viz., increased respiration and pulse rate, decrease in feed intake, dryness of mouth and muzzle and incoordination in movements were observed. Peak serum cefepime concentration (C_{max}) observed in ketoprofen co-administrated goats was not altered significantly as compared to goats given cefepime alone. In contrast, variations in pharmacokinetics of different cephalosporins have been observed following concurrent administration with NSAIDs. Significant increase in peak plasma levels of ceftizoxime was observed in cross-bred calves following concomitant intramuscular administration of paracetamol with ceftizoxime (Singh *et al.*, 2008). Peak serum concentration of cefazolin was significantly increased at 1, 2, 4 and 6 h after intramuscular administration of phenylbutazone with cefazolin in rabbits (Carbon *et al.*, 1981). Enhanced concentrations of cefotiam, cefmenoxime and ceftriaxone following concomitant administration of diclofenac sodium in rabbits have also been observed (Joly *et al.*, 1998). In febrile goats, significantly higher cefepime peak concentration was observed as compared to non-febrile goats. This observation was supported by significant increase in cefepime peak concentration following intramuscular administration of cefepime in febrile rabbits (Goudah *et al.*, 2006). However, concurrent administration of diltiazem with ibuprofen and caffeine with gliclazide have no effect on plasma concentration of diltiazem in rabbits and caffeine in rats, respectively (Bari *et al.*, 2000; Mohiuddin *et al.*, 2009).

Following intramuscular administration of cefepime with ketoprofen in goats no pharmacokinetic parameters were altered significantly in comparison to cefepime alone administrated goats. Cefmenoxime pharmacokinetics parameters remained unchanged following concurrent administration of diclofenac sodium with cefmenoxime in rabbits (Joly *et al.*, 1998) which supports results of our study. However, significant decrease in body clearance, volume of distribution, elimination half life and absorption half life were found after concurrent intramuscular administration of ceftriaxone with acetaminophen in febrile goats (Jimoh *et al.*, 2011). Moreover, alteration in pharmacokinetics following concomitant administration of several drugs was also found (Ansari *et al.*, 2003; Singh *et al.*, 2008; Salam *et al.*, 2009; Carbon *et al.*, 1981).

Following intramuscular administration of cefepime in goats having febrile state, elimination half life was significantly increased compared to non-febrile cefepime treated goats. Apparent decrease in body clearance with no change in the volume of distribution of drug in febrile goats might have lead to increase in elimination of half life of cefepime as compared to non febrile goats. Moreover, bioavailability was also found to be greater than 100% which may be due sequestration of cefepime at injection site. Whereas values of volume of distribution, area under curve, area under first moment of curve and mean residence time were not significantly altered following intramuscular administration of cefepime in febrile compared to non febrile goats. The findings indicate that administration of lipopolysaccharide modulates the elimination of the drug which could be due to organ (renal and hepatic) modifications caused by the toxin. Endotoxin induces toxic and adverse effects on the kidneys, including direct vascular damage to the endothelium and platelet aggregation in renal glomerular capillaries. It also produces some functional changes including decrease in the renal blood flow and glomerular filtration rate and changes in the intra-renal hemodynamics (Jernigan *et al.*, 1988; Hasegawa *et al.*, 1999). 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 cefepime. Following intramuscular administration of cefazolin in febrile goats, along with elimination half life, volume of distribution was significant increased while significant decrease in the value of area

under curve was reported (Roy *et al.*, 1994). Similarly significant increase in area under first moment of curve, area under curve, mean residence time and significant shorter elimination half life following intramuscular administration of cefepime in febrile rabbits were reported by Goudah *et al.* (2006). In other study significant decrease in body clearance, volume of distribution, elimination half life and absorption half life after single intramuscular administration of ceftriaxone were found in febrile goats (Jimoh *et al.*, 2011). Whereas significant higher body clearance and significant lower volume of distribution were reported after single intravenous administration of ceftriaxone in febrile buffalo calves (Dardi *et al.*, 2005). No significant alterations in elimination half life and body clearance were found after single intravenous administration of cefepime (10 mg kg⁻¹) in febrile buffalo calves (Joshi and Sharma, 2009). Variation in pharmacokinetic parameters of cefepime and other cephalosporins when given with NSAIDs and in febrile condition were observed in number of experiments by coworkers that may be due to differences in chemistry of drugs and species difference.

Cefepime can successfully co-administrated with Ketoprofen for combating inflammatory conditions without alteration of dosage regimen of cefepime. Moreover integrating the pooled cefepime pharmacokinetic data generated from the present study with the MIC range for most of the gram-positive and gram-negative microorganisms, a cefepime intramuscular dose of 20 mg kg⁻¹ repeated at 12 h interval is sufficient to maintain serum concentration above the MIC.

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