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Effect of ketoprofen co-administration or febrile state on pharmacokinetic of cefepime in sheep

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

[1]*Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry Anand Agricultural University, Anand, India*

[2]*Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari, India*

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ABSTRACT

The pharmacokinetics of cefepime (20 mg/kg) were studied following intramuscular administration of cefepime alone, co-administered with ketoprofen (3 mg/kg) and in a febrile state (*Escherichia coli* LPS induced) in sheep. The concentration of cefepime in the serum was detected by High Performance Liquid Chromatography. Following single dose intravenous administration of cefepime, elimination half life (2.50 ± 0.05 h), the area under the curve (143.48± 7.36 µg.h/mL), body clearance (0.14 ± 0.01 L/h/kg) and volume of distribution (0.51 ± 0.03 L/kg) were determined. Following a single dose intramuscular administration of cefepime alone, peak serum concentration (28.76 ± 0.54 µg/mL) was obtained at 0.75 h. The absorption half life ($t_{1/2K\alpha}$), volume of distribution (Vd_{area}), total body clearance (Cl_B) and elimination half life ($t_{1/2\beta}$) of cefepime were 0.16 ± 0.01 h, 1.02 ± 0.08 L/kg, 0.13 ± 0.01 L/h/kg and 5.31 ± 0.23 h, respectively. Following co-administration of ketoprofen (30.74 ± 1.22 µg/mL) and in a febrile condition, a higher peak serum concentration of cefepime (39.68 ± 1.13 µg/mL) was observed at 0.75 h and 1 h, respectively. However, no significant changes were reported in other pharmacokinetic parameters following co-administration of cefepime with ketoprofen. In a febrile state, absorption half life, area under the curve and bioavailability were significantly increased while the volume of distribution and clearance of cefepime were significantly decreased following intramuscular administration. Cefepime pharmacokinetic data (20 mg/kg) generated from the present study suggest that the drug may be administered with ketoprofen, and in febrile conditions in sheep, the drug may be given intramuscularly at 24 h intervals to combat susceptible bacterial infections.

Key words: pharmacokinetic, cefepime, ketoprofen, fever, sheep

*Corresponding author:

Dr. Bhavsar, S. K. M.V.Sc., Ph.D Professor and Head, Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Navsari Agricultural University, Navsari 396 450, India, Phone: +91 2637 282 771; Fax: +91 02637 283 234; E-mail: skbhavsar@yahoo.com

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Introduction

Antibacterial and NSAIDs are used most frequently in multiple drug prescriptions. It is well documented that concurrently administered drugs may alter the pharmacokinetics of one or both drugs (HARDMAN and LIMBIRD, 2001). 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 can be used for infections that are resistant to third generation cephalosporins and for respiratory, urinary, intra-abdominal and cutaneous infections (RULE et al., 2004). Cefepime is considered a broad spectrum drug and shows excellent activity against *Escheria coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus* spp. (BARRADELL and BRYSON, 1994). Ketoprofen is routinely used as a non-steroidal anti-inflammatory, analgesic and antipyretic agent in veterinary practice (BOOTHE, 1995). The pharmacokinetics of cefepime administered as a single drug have been investigated in healthy ewes and calves (ISMAIL, 2005a and 2005b), 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).

However, there is no information available on the influence of co-administration of ketoprofen and a febrile state on the pharmacokinetics of cefepime in animals. Given the possibility of interaction of ketoprofen and to discover the pharmacokinetics of cefepime in sheep in a febrile state, this study was undertaken to determine the effect of ketoprofen and a febrile condition on the pharmacokinetics of cefepime in sheep.

Materials and methods

Experimental animals. The experiment was conducted on six healthy adult (3-4 years of age) Patanwadi sheep, weighing 25-30 kg. Each sheep was housed in a separate pen and provided with a standard ration and water *ad libitum*. The sheep were kept under constant observation for two weeks before the commencement of the experiment and subjected to clinical examination to exclude the possibility of disease. The experimental protocol was approved by the Institutional Animal Ethics Committee.

Drug and chemicals. 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 on the 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 an intramuscular injection of cefepime at a dose rate of

20 mg/kg. 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 (20 mg/kg) was administered in the left deep gluteal muscles, while ketoprofen was administrated deeply intramuscularly at a dose rate of 3 mg/kg in the contra-lateral 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 intramuscular administration of cefepime alone or in combination with ketoprofen. A febrile state was induced in the sheep by injecting lipopolysaccharide (LPS) of *Escherichia coli* at a dose rate of 0.2 µg/kg body weight intravenously (VERMA and ROY, 2006). LPS was again injected at a dose rate of 0.1 and 0.05 µg/kg at 12 h and 24 h from the first dose of LPS to maintain the febrile state up to 36 h. Sheep 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 1957 g for 15min. 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. High Performance Liquid Chromatography (HPLC) apparatus of Laballiance (USA) comprising a 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 the 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 minutes. An aliquot of supernatant was collected in a clean vial and 20 µL injected into a loop of the 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. The mobile phase was filtered by a 0.45µ filter and pumped into the column at a flow rate of 1.5mL/min at ambient temperature. The effluent was monitored at 257 nm wavelength.

A calibration curve was prepared daily for drug concentrations ranging from 0.5 to 200 µg/mL. The assay was sensitive (LLOD: 0.5 µg/mL), reproducible and linearity was observed from 0.5 to 200 µg/mL (r^2 = 0.99). Precision and accuracy were determined using quality control (QC) samples at concentrations 1, 5, 50 µg/mL (5 replicates each per day). The intraday and inter-day coefficients of variation for 5 QC samples were satisfactory, with relative deviations (RSD) of less than 4%. Various pharmacokinetic

parameters were calculated from the serum concentration of cefepime using the software PK solution (version 2.0). The bioavailability (F) was calculated using the following formula:

$$F\% = \frac{AUC\ (i.m.)}{AUC\ (i.v.)} \times \frac{DOSE\ (i.v.)}{DOSE\ (i.m.)}$$

Statistical analysis. Cefepime serum concentration and pharmacokinetic parameters of different treatment groups were compared by the Student's *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 a febrile state in sheep is presented as a semi logarithmic plot in Fig. 1.

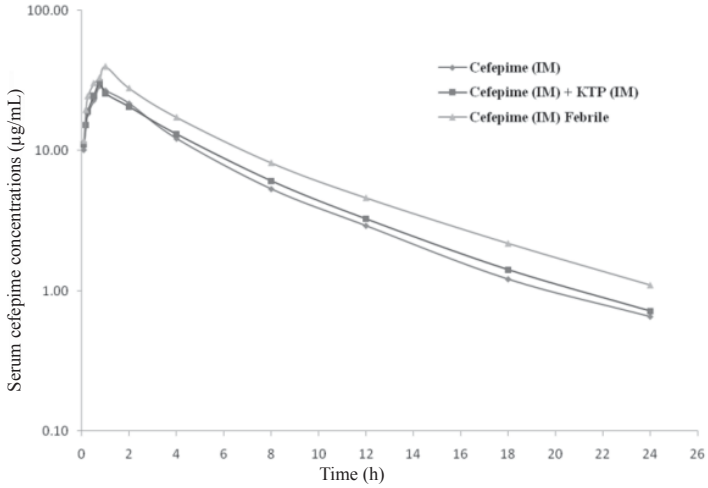

Fig. 1. Semilogarithmic plot of serum concentrations of cefepime after intramuscular administration (20 mg/kg) in healthy, ketoprofen- treated (3 mg/kg) and febrile sheep (LPS-induced). Each point represents a mean of six animals.

The serum concentration of cefepime at 2 min after intravenous administration was 126.09 ± 2.99 µg/mL, which rapidly declined to 28.71 ± 1.67 µg/mL at 1 h and was detected up to 12 hrs (1.24 ± 0.09 µg/mL). Following intramuscular injection of cefepime alone, the serum concentration of cefepime at 5 min was 10.09 ± 0.62 µg/mL, which gradually increased and reached the peak concentration (28.76 ± 0.54 µg/mL) at 45 min. The bioavailability of cefepime following intramuscular administration was

107.11 ± 4.66%. On concurrent administration of ketoprofen and cefepime, the initial serum concentration of cefepime at 5 min was 11.10 ± 1.33 µg/mL, which increased to attain the peak serum concentration (30.74 ± 1.22 µg/mL) at 45 min. The bioavailability of cefepime following intramuscular administration in ketoprofen treated sheep was 112.95 ± 7.53%. In a febrile condition, serum cefepime concentration following intramuscular injection was 11.73 ± 0.83 µg/mL at 5min, and attained peak concentration at 1 h (39.68 ± 1.13 µg/mL). The bioavailability of cefepime following intramuscular administration in a febrile condition in sheep was 148.20 ± 11.64%. Drug levels above the minimum inhibitory concentration (MIC) were detected in serum up to 18 h following a single dose intramuscular administration of cefepime alone and co-administrated with ketoprofen, while in the febrile state it was maintained up to 24 h in sheep. Various kinetic determinants that describe the absorption and elimination pattern of cefepime after intravenous injection and intramuscular administration, either used alone or in combination with ketoprofen and in a febrile state were calculated and are presented in Table 1. Following intramuscular administration of cefepime (20 mg/kg) in sheep either alone, co-administered with ketoprofen (3 mg/kg) or under a febrile condition, no adverse effects or toxic manifestations were observed.

Table 1. Pharmacokinetic parameters of cefepime following a single dose intravenous injection (20 mg/kg body weight) and intramuscular administration (20 mg/kg body weight) alone, simultaneously with ketoprofen (3 mg/kg body weight) and in a febrile condition in sheep (Mean ± SE, n = 6)

Parameter	Unit	Cefepime (i.v.) (20 mg/kg)	Cefepime (i.m.) (20 mg/kg)	Cefepime (i.m.) (20 mg/kg) and Ketoprofen (IM) (3 mg/kg)	Cefepime (i.m.) (20 mg/kg) in Febrile State
K_a	/h	-	4.64 ± 0.56	3.15 ± 0.11	3.06 ± 0.34
B	/h	30.440 ± 1.96	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01
$t_{1/2k\alpha}$	h	-	0.16 ± 0.01	0.22 ± 0.01*	0.24 ± 0.02*
$t_{1/2\beta}$	h	2.50 ± 0.05	5.31 ± 0.23	5.22 ± 0.20	5.50 ± 0.25
C_{max}	µg/mL	-	28.76 ± 0.54	30.74 ± 1.22*	39.68 ± 1.13**
T_{max}	h	-	0.75 ± 0.00	0.75 ± 0.00	1.00 ± 0.0
$AUC_{0-\infty}$	µg.h/mL	143.48± 7.36	153.63 ± 10.16	162.37 ± 14.47	221.67 ± 15.42*
AUMC	µg.h^2/mL	397.77 ± 27.42	921.31 ± 84.21	1013.18 ± 116.63	1464.11 ± 185.12
Vd_{area}	L/kg	0.51 ± 0.03	1.02 ± 0.08	0.97 ± 0.1	0.73 ± 0.04*
Cl_B	L/h/kg	0.14 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.09 ± 0.01*
MRT	h	2.76 ± 0.05	5.95 ± 0.18	6.17 ± 0.19	6.48 ± 0.38
F	%	-	107.11 ± 4.66	112.95 ± 7.53	148.20 ± 11.64

*Significant at P<0.05, **Significant at P<0.01 when compared with respective values of cefepime alone (IM) treated sheep. K_a: Absorption rate constant, B: Zero-time intercept of elimination phase, $t_{1/2k\alpha}$: Absorption half life, $t_{1/2\beta}$: Elimination half life, C_{max}: Maximum drug concentration, T_{max}: Time of maximum observed concentration in serum, $AUC_{0-\alpha}$: Area under the curve, AUMC: Area under first moment of curve, Vd_{area}: Apparent volume of distribution, Cl_B: Total body clearance, MRT: Mean residence time , F: Bioavailabilty.

Discussion

A concentration of 0.004 - 1.0 μg/mL of plasma has been reported as the MIC for cephalosporins with various pathogens (HARDMAN and LIMBIRD, 2001). Peak serum cefepime concentration (C_{max}) observed in ketoprofen co-administrated and febrile sheep was significantly higher than peak concentrations observed in sheep treated with cefepime alone. A similar significant increase in peak plasma levels of ceftizoxime following concomitant intramuscular administration of paracetamol with ceftizoxime has been observed in cross-bred calves (SINGH et al., 2008). A significant increase in peak serum concentrations of cefazolin at 1, 2, 4 and 6 hours after intramuscular administration of phenylbutazone was also reported in rabbits (CARBON et al., 1981). Enhanced concentrations of cefotiam, cefmenoxime and ceftriaxone were observed following concomitant administration of diclofenac sodium in rabbits (JOLY et al., 1988). Similarly in a febrile state a significant increase has been reported in peak serum concentrations following intramuscular administration of cefepime in rabbits (GOUDAH et al., 2006). However, a decrease in maximum drug concentration has been reported following intramuscular administration of cefazolin in febrile goats (ROY et al., 1994).

Following intramuscular administration of cefepime with ketoprofen in sheep, a significant increase in absorption half life was observed. However none of the other pharmacokinetic parameters were significantly altered in comparison to sheep administered cefepime alone. Cefmenoxime's pharmacokinetic parameters remained unchanged following concurrent administration of diclofenac sodium with cefmenoxime in rabbits (JOLY et al., 1988), which supports the results of our study. Similarly no significant alterations in elimination rate constants and elimination half life were observed following coadministration of phenylbutazone and cefazolin in rabbits (CARBON et al., 1981). However, a significant increase in the area under the curve, and concentration and elimination half life have been reported following concomitant administration of paracetamol with ceftizoxime in crossbred calves (SINGH et al., 2008). A significantly longer elimination half-life of cefazolin was also reported following co-administration with phenylbutazone in rabbits (CARBON et al., 1981).

Following intramuscular administration in a febrile condition in sheep, absorption half life, area under the curve and bioavailability were significantly increased, while volume of distribution and body clearance were found to be significantly decreased compared to non-febrile cefepime treated sheep. The lower volume of distribution in febrile sheep was also reflected in the significantly higher peak concentration. Moreover, bioavailability was also found to be greater than 100% which may be due to sequestration of cefepime at the injection site. However, values of elimination half life, 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 sheep. 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 widely eliminated by the renal route, including cefepime. In comparison to this experiment, varied results were found, such as a significant increase in the area under the first moment of the curve, the area under the curve, mean residence time and significant shorter elimination half life following intramuscular administration of cefepime in febrile rabbits (GOUDAH et al., 2006). In another study, significantly lower body clearance and higher volumes of distribution after a single intravenous administration of cefepime (10 mg/kg) were found in febrile cross-bred calves (PAWAR and SHARMA, 2008). A significant increase in elimination half life and volume of distribution, and a significant decrease in the value of the area under the curve following intramuscular administration of cefazolin in febrile goats were also reported (ROY et al., 1994). However significant higher body clearance and significant lower volume of distribution were reported after a 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 a single intravenous administration of cefepime (10 mg/kg) in febrile buffalo calves (JOSHI and SHARMA, 2009). Variations in the pharmacokinetics of cefepime and other cephalosporins when given with NSAIDs and in a febrile condition have been observed in many experiments that may be due to differences in the chemistry of drugs and species difference.

It may be concluded that Ketoprofen may be successfully co-administrated with cefepime for combating inflammatory conditions without alterations of the dosage regimen of cefepime. In febrile conditions the cefepime concentrations was maintained above MIC for a longer period (24 h), hence favoring the use of cefepime in infectious diseases of sheep.

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PATEL, N. N., H. B. PATEL, S. D. PATEL, J. H. PATEL, S. K. BHAVSAR, A. M. THAKER: Učinak ketoprofena ili vrućice na farmakokinetiku cefepima u ovaca. Vet. arhiv 82, 473-481, 2012.

SAŽETAK

Istražena je farmakokinetika cefepima (20 mg/kg) nakon njegove intramuskularne primjene s ketoprofenom (3 mg/kg) u tijeku vrućice u ovaca izazvane lipopolisaharidima bakterije *Escherichia coli*. Koncentracija cefepima u serumu bila je određivana tekućinskom kromatografijom. Nakon jednokratne intravenske primjene poluživot njegova izlučivanja iznosio je 2,50 ± 0,05 h, površina ispod koncentracijske krivulje bila je 143,48 ± 7,36 µg.h/mL, ukupni tjelesni klirens iznosio je 0,14 ± 0,01 L/h/kg, a volumen raspodjele 0,51 ± 0,03 L/kg. Nakon jednokratne intramuskularne primjene samo cefepima vršna koncentracija u serumu iznosila je 28,76 ± 0,54 µg/mL nakon 0,75 h. Poluživot apsorpcije ($t_{1/2K\alpha}$) iznosio je 0,16 ± 0,01 h, volumen raspodjele (Vd_{area}) 1,02 ± 0,08 L/kg, ukupni klirens iz organizma (Cl_B) 0,13 ± 0,01 L/h/kg te poluživot izlučivanja ($t_{1/2\beta}$) 5,31 ± 0,23 h. Nakon istodobne primjene ketoprofena (30,74 ± 1,22 µg/mL) u uvjetima izazvane vrućice ustanovljena je veća vršna koncentracija cefepima (39,68 ± 1,13 mg/mL) u razdoblju od 0,75 h odnosno 1 sata. Vrijednosti ostalih farmakokinetičkih pokazatelja nisu se značajno promijenile poslije istodobne primjene cefepima s ketoprofenom. Poluživot apsorpcije, površina ispod koncentracijske krivulje i biološka raspoloživost bili su značajno povišeni, dok su volumen raspodjele i klirens cefepima bili značajno sniženi nakon intramuskularne primjene u febrilnih životinja. Farmakokinetičke značajke cefepima (20 mg/kg) proizašle iz ovog istraživanja upućuju na zaključak da se on u ovaca može primijeniti s ketoprofenom i u febrilnim stanjima. Može se primijeniti intramuskularno u razmaku od 24 sata za liječenje bolesti uzrokovanih bakterijama osjetljivima na cefepim.

Ključne riječi: farmakokinetika, cefepim, ketoprofen, vrućica, ovca