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RESEARCH ARTICLE

Effect of Ketoprofen Co-administration on Pharmacokinetic of Cefepime in Cow Calves

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ABSTRACT

The pharmacokinetic of cefepime (5 mg/kg) was studied following intramuscular administration of cefepime alone and co-administered with ketoprofen (3 mg/kg) in cow calves. The concentration of cefepime in serum was detected by using High Performance Liquid Chromatography. Following single dose intravenous administration of cefepime, elimination half life (3.90±0.08 h), area under curve (48.68±2.53 µg.h/mL), body clearance (1.74±0.09 L/h/kg) and volume of distribution (0.52±0.03 L/kg) were determined. Following single dose intramuscular administration of cefepime alone, peak serum concentration (8.93±0.32 µg/mL) was obtained at 45 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 0.17±0.01 h, 0.79±0.05 L/kg, 1.76±0.10 L/h/kg and 5.15±0.09 h, respectively. No significant changes were reported in pharmacokinetic parameters following co-administration of cefepime with ketoprofen. Integration of pharmacokinetic data generated from the present study and minimum inhibitory concentration suggest that the cefepime can be administered intramuscularly (5 mg/kg) with ketoprofen at 12 h interval to combat susceptible bacterial infections in cow calves.

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INTRODUCTION

It is well documented that concurrently administered drugs may alter pharmacokinetics of one or both drugs and in therapeutics antibacterial and NSAIDs are used most frequently in multiple drug prescriptions. 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 spp. 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 (Lees, 2009). Pharmacokinetics of cefepime administered as single drug were investigated in healthy ewes and calves (Ismail, 2005[ab]; Patel *et al*., 2006[ab]), buffalo calves (Joshi and Sharma, 2009), dogs (Stampley *et al*., 1992), horses (Guglick *et al*., 1998), neonatal foals (Gardner and Papich, 2001) and goats (Patni *et al*., 2008, Patel *et al*., 2012). However, there is no information available on the influence of ketoprofen on the pharmacokinetic of cefepime in cow calves. Looking to possibility for interaction of ketoprofen with cefepime in cow calves, the study was undertaken to determine effect ketoprofen on pharmacokinetics of cefepime in cow calves.

MATERIALS AND METHODS

Experimental Animals

The experiment was conducted on six healthy female cow calves (6-12 months of age), weighing 100-150 kg. Each animal was housed in a separate pen and provided

standard ration with *ad libitum* water. Cow calves 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 (1g 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 5 mg/kg. A washout period of 2 weeks was maintained 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 administrated deep intramuscular at the dose rate of 3 mg/kg 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. Cow calves 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 3000g for 10min. The serum samples were stored at -40 ^{o}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 minutes. 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 0.45µ filter and pumped into column at a flow rate of 1.5mL/min at ambient temperature. The effluent was monitored at 257 nm wavelength.

Calibration curve was prepared daily for drug concentration ranging from 0.5 to 100 µg/mL. The assay was sensitive (LLOD: 0.5 µg/mL), reproducible and linearity was observed from 0.5 to 100 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 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:

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

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

Following intravenous administration of cefepime, the mean peak serum drug concentration of 39.04 ± 5.46 µg/mL was observed at 0.0333 h, which rapidly declined to 7.04 ± 0.28 µg/mL at 1 h and detectable up to 12 h (1.01 ± 0.05 µg/ml). Following intramuscular injection of cefepime alone, the serum concentration of cefepime at 5 min was 2.65 ± 0.26 µg/mL, which gradually increased and reached to the peak concentration (8.91 ± 0.43 µg/mL) at 45 min and detected upto 18 h (0.60 ± 0.03). On concurrent intramuscular administration of ketoprofen and cefepime, the initial serum concentration of cefepime at 5 min was 2.57 ± 0.08 µg/mL, which increased to attain the peak serum concentration (8.98 ± 0.35 µg/mL) at 45 min and detected upto 18 h (0.72 ± 0.02 µg/mL). 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 were calculated and are presented in Table 1. Serum cefepime concentrations at different time intervals following intramuscular injection alone and co-administered intramuscularly with ketoprofen in cow calves is presented as semi logarithmic plot in Figure 1.

DISCUSSION

Following intramuscular administration cefepime (5 mg/kg) in cow calves either alone or co-administered with ketoprofen (3 mg/kg) no adverse effects or toxic manifestations were observed. In the present study, peak serum cefepime concentration (Cmax) of 8.98 ± 0.35 µg/ml observed at 45 min in ketoprofen-pretreated cow

Table 1: Cefepime pharmacokinetic parameters following intravenous and intramuscular administration of cefepime alone (5mg/kg) and in ketoprofen treated (3 mg/kg) cow calves. (Mean ± SE, n=6).

Pharmacokinetic Parameter	Unit	Cefepime (IV)	Cefepime (IM)	Cefepime (IM) and Ketoprofen (IM)
K_a	/h	-	4.05 ± 0.22	3.99 ± 0.26
β	/h	0.18 ± 0.00	0.13 ± 0.00	0.13 ± 0.00
$t_{1/2k\alpha}$	h	-	0.17 ± 0.01	0.18 ± 0.01
$t_{1/2\beta}$	h	3.90 ± 0.08	5.15 ± 0.09	5.36 ± 0.19
C_{max}	µg/mL	-	8.93 ± 0.32	9.44 ± 0.52
T_{max}	h	-	0.75 ± 0.00	0.75 ± 0.00
$AUC_{0-\infty}$	µg.h/mL	48.68 ± 2.53	48.43 ± 3.35	50.68 ± 5.94
AUMC	µg.h^2/mL	243.07 ± 15.85	338.77 ± 23.35	367.26 ± 36.00
Vd_{area}	L/kg	-	0.79 ± 0.05	0.79 ± 0.06
Vd_{ss}	L/kg	0.52 ± 0.03	-	-
Cl_B	L/h/kg	1.74 ± 0.09	1.76 ± 0.10	1.67 ± 0.09
MRT	H	4.98 ± 0.12	7.00 ± 0.10	7.30 ± 0.15
F	%	-	100 ± 6.00	104 ± 2.34

All the values do not differ significantly ($p<0.05$) when compared with respective values of cefepime alone (Intramuscular) treated cow calves.

K_a: Absorption rate constant, B: Zero-time intercept of elimination phase, $t_{1/2ka}$: 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 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.

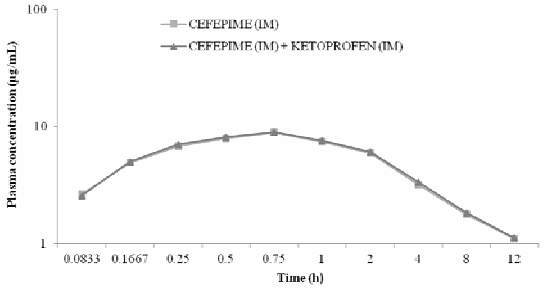

Fig. 1: Semilogarithmic plot of cefepime serum concentrations after intramuscular administration of cefepime alone (5 mg/kg) and in ketoprofen-treated (3 mg/kg) cow calves. Each point represents mean of six animals.

calves was not significantly altered than Cmax (8.91 ± 0.43 µg/ml) observed in cow calves given cefepime alone. However, serum cefepime concentration (Cmax) at 18 h observed in ketoprofen co-administrated cow calves was altered significantly as compared to cow calves given cefepime alone. Similarly, variations in pharmacokinetics of different cephalosporins have been observed following concurrent administration with NSAIDs i.e. 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 hour 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*., 1988). However, no significant alteration was found following intramuscular administration of cefepime in goats (Patel *et al*., 2012).

Following intramuscular administration of cefepime with ketoprofen in cow calves no pharmacokinetic parameters were altered significantly in comparison to cefepime alone administrated cow calves. Similarly, no significant alteration was found in pharmacokinetic parameters following intramuscular administration of cefepime in goats (Patel *et al*., 2012). However, significant increase in area under concentration-time curve (AUC : 39.2 ± 2.09 vs 74.1 ± 2.01 µg.h/ml) and $t_{1/2\beta}$ (1.44 ± 0.12 vs 4.08 ± 0.54 h) has been reported following concomitant intramuscular administration of paracetamol with ceftizoxime in cross-bred calves (Singh *et al*., 2008). Significant increase in elimination half life of cefazolin was also reported following co-administration with phenylbutazone in rabbits (Carbon *et al*., 1981). Significant increase in AUC of ceftriaxone (326.0 ± 91.4 vs 555.0 ± 124.0), cefotiam (17.5 ± 4.4 vs 32.9 ± 17.9) and elimination half life of ceftriaxone (2.8 ± 0.5 vs 3.45 ± 0.4 h) and significant decrease in clearance of cefotiam (23.7 ± 6 to 17 ± 5 ml/min) has been reported in rabbits (Joly *et al*., 1988).

For β-lactam antibiotics, many authors have advocated the time for which serum drug concentration exceeds the MIC (T>MIC) of pathogens as a primary determinant of antibacterial efficacy (Craig, 1995). For these drugs, maximum killing was seen when the time above MIC was at least 70 per cent of the dosing interval (Hyatt *et al*., 1995). Minimum inhibitory concentration for a majority of cefepime sensitive bacteria is in the range of 0.01 to 4.0 µg/ml. MIC_{90} range for gram-positive bacteria like *Streptococcus spp.* ranges between 0.03-0.07 with mean of 0.05 µg/ml and for most of the gram-negative bacteria (*Escherichia coli, Citrobacter, Klebsiella, Shigella, Proteus, Neisseria, Morganella, Haemophilus* and variety of Enterobacter spp.) ranges between 0.04-0.2 µg/ml (Khan *et al.*, 1984; Vuye and Pijck, 1985 and Cynamon *et al.*, 1987). Integrating the pooled cefepime pharmacokinetic data generated from the present study with the MIC_{90} range for most of the gram-positive and gram-negative microorganisms, a cefepime dose of 5 mg/kg will be sufficient to maintain serum concentration of the drug above the MIC_{90} when it is administered intravenously and intramuscularly at 12 h interval.

Conclusion

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 intravenous or intramuscular dose of 5 mg/kg repeated at 12 h interval is sufficient to maintain serum concentration above the MIC_{90}.

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