

1-1-2010

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PRAWEZ, SHAHİD; RAINA, RAJİNDER; DIMITROVA, DIMITRITCHKA; PANKAJ, NRİP KİSHORE; AHANGER, AZAD AHMAD; and VERMA, PAWAN KUMAR (2010) "The pharmacokinetics of cefepime in goats following single-dose i.v. and i.m. administration," *Turkish Journal of Veterinary & Animal Sciences*: Vol. 34: No. 5, Article 2. <https://doi.org/10.3906/vet-0811-13>
Available at: <https://journals.tubitak.gov.tr/veterinary/vol34/iss5/2>

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The pharmacokinetics of cefepime in goats following single-dose i.v. and i.m. administration

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Received: 25.11.2008

Abstract: The pharmacokinetics of cefepime was studied in 5 goats following i.v. and i.m. administration of 10 mg/kg of body weight. Following i.v. administration, the cefepime plasma concentration-time curves were best fitted in a one-compartment open model. The elimination half-life ($t_{1/2\beta}$), area under curve ($AUC_{0-\infty}$), and total body clearance (Cl_B) were 1.86 ± 0.54 h, 181.58 ± 80.52 $\mu\text{g}\cdot\text{h}/\text{mL}$, and 1.10 ± 0.54 mL/min/kg, respectively. Following i.m. administration, pharmacokinetic parameters were analyzed using statistical moment theory (SMT). The drug was absorbed rapidly, with an absorption half-life ($t_{1/2\text{abs}}$) of 0.77 ± 0.34 h. The peak plasma concentration (C_{max}) of 49.32 ± 10.33 $\mu\text{g}/\text{mL}$ was attained after (T_{max}) 0.80 ± 0.11 h, with an elimination half-life ($t_{1/2\beta}$) of 1.65 ± 0.38 h. The systemic bioavailability (F) of cefepime in the goats after i.m. administration was $86.45 \pm 17.39\%$ and in vitro plasma protein binding was $7.45 \pm 4.46\%$. The dosage regime was estimated via the PK-PD relationship, considering the t_{MIC} value. The results suggest that cefepime was a potential bactericidal agent for more than 7 h by both administration routes, and that it might be very useful in the treatment of various infections in goats at 10 mg/kg of body weight administered i.v. or i.m. with 10 h as the dosage interval.

Key words: Pharmacokinetics, cefepime, i.v. and i.m. routes, goats

Introduction

Cefepime is a semi-synthetic, parenteral fourth-generation cephalosporin antibiotic with significant potential advantages over other broad-spectrum cephalosporins (1). It is non-susceptible to β -lactam

hydrolysis. Cefepime shows excellent activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus clocae*, *Staphylococcus aureus*, and *Streptococcus* spp., and is considered a broad spectrum antibiotic (2). The efficacy of

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cephalosporins is estimated via the PK-PD relationship to prevent the problem of bacterial resistance. When MIC remains 40%-60% above the inter-dose interval, better therapeutic results with low-level resistance have been observed (3).

The pharmacokinetic profile of cefepime has been studied in rats and monkeys (4), humans (5), horses (6), foals and dogs (7), cow calves (8), and buffalo calves (9). The objective of the present study was to explore further the therapeutic potential of cefepime in goats following i.v. and i.m. administration, and to estimate the dosage regimen in consideration of the PK-PD relationship.

Materials and methods

Drugs and experimental animals

Cefepime hydrochloride powder (Megapime[®], Alkem Ltd., Mumbai, India) was diluted with sterile distilled water to 10% immediately before administration. The experiment was conducted using healthy goats (n = 5) aged 1.5-3 years with a body weight between 30 and 47 kg. The animals were procured from the Department of Sheep Husbandry, Jammu (J & K, India). One month before the experiment all the animals were de-wormed with mebendazole and acclimatized to their new environment. Water was provided ad libitum.

Experimental design

A 2-way crossover design was applied with a washout period of 20 days between treatments. Cefepime was administered at 10 mg/kg of body weight i.v. for intravenous study. In the second part of experiment cefepime at 10 mg/kg of body weight was administered i.m. for intramuscular study. The i.v. injection was administered in the *v. jugularis* and the i.m. injection in the thigh muscle. Blood samples (4 mL) were collected into heparinized tubes from the contra-lateral *v. jugularis* prior to injection and at 0.08, 0.16, 0.33, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after administration. Plasma was separated after centrifugation at 1000'g for 15 min and stored at -20 °C until analysis.

Cefepime analysis

Plasma cefepime concentrations were measured using the agar-plate diffusion method (10,11) with the

test microorganism *Escherichia coli* MTCC 443 and assay media No. 1 (HiMedia, Mumbai, India). Cefepime standard solution was prepared in antibiotic-free goat's plasma at concentrations ranging from 0.2 to 50 µg/mL and a standard curve was obtained with the correlation coefficient $r > 0.98$. The minimal quantification level of the assay method was 0.2 µg/mL. Intra-assay precision was determined by measuring 6 replicates of representative standard concentrations prepared in plasma. The coefficient of variation was <5.54% and <9.66% for the intra-assay and inter-assay, respectively.

Pharmacokinetics analysis

Pharmacokinetic analysis of the data was performed by compartmental and non-compartmental methods using the TopFit v.2.0 pharmacokinetic computer program (12). The best fit was determined according to the Akaike Information Criterion (AIC) (13). A non-compartmental analysis based on statistical moment theory was also carried out (14). The area under the concentration-time curve ($AUC_{0 \rightarrow \infty}$, $AUC_{0 \rightarrow 12h}$) was calculated via the trapezoidal method (15). The peak plasma concentration (C_{max}) and the time to reach maximum concentration (T_{max}) were obtained from the plasma concentration-time curve of each animal. The absolute bioavailability after i.m. administration was calculated using the equation $F = (AUC_{i.m.}/AUC_{i.v.}) \times 100$.

Plasma protein binding

In vitro plasma protein binding of cefepime was determined according to the method described by Craig and Suh (16), using pooled plasma from the goats and phosphate buffer (pH 7.9 ± 0.1). The percentage of the protein-bound fraction was calculated using the following equation: protein binding % = (zone of inhibition in buffer - zone of inhibition in plasma/zone of inhibition in buffer) × 100.

Results

The drug concentration vs. time curves after i.v. injection was best fitted in a one-compartment open model. Following i.m. administration, plasma concentration data were analyzed using the non-compartmental method based on statistical moment theory.

The Table summarizes the pharmacokinetic parameters for cefepime following i.v. and i.m. administration. The drug was detected in goat plasma up to 12 h following i.v. and i.m. administration (Figure). The last detectable limit of the drug in plasma at 12 h for i.v. and i.m. routes of administration was $0.33 \pm 0.10 \mu\text{g/mL}$ and $0.34 \pm 0.17 \mu\text{g/mL}$, respectively. Plasma protein binding varied from 3.09% to 13.82%, with a mean \pm SD value of $7.45 \pm 4.46\%$. Plasma protein binding was independent of cefepime concentrations.

Discussion

Following i.v. administration of cefepime in the present study, the elimination half-life was lower than that in buffalo calves ($t_{1/2\beta} = 2.67$ h) (9), higher than that in dogs ($t_{1/2\beta} = 1.09$ h) (7), and similar to that in ewes ($t_{1/2\beta} = 1.76$ h) (17). Mean residence time (MRT) after i.v. and i.m. administration was shorter than that in rabbits (MRT = 3.65 h) (18) and calves (MRT =

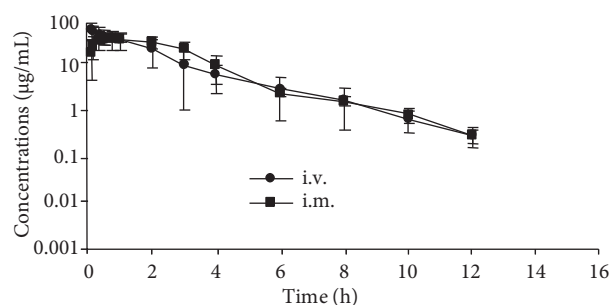


Figure. Plasma concentrations (mean \pm SD) of cefepime in goats following single i.v. and i.m. administration at 10 mg/kg body weight (n = 5).

3.38 h, MRT = 3.95 h) (8,19), and longer than that in ewes (MRT = 2.28 h) (17). The Cl_B (1.10 ± 0.54 mL/min/kg) value following i.v. administration was lower than that in dogs ($Cl_B = 2.20$ mL/min/kg) (7) and similar to that in calves ($Cl_B = 1.10$ mL/min/kg) (8). The $t_{1/2\beta}$, MRT, and $AUC_{0 \rightarrow \infty}$ values for the 2 routes (i.v. and i.m.) were similar (Table).

Table. Pharmacokinetic parameters (n = 5) of cefepime following single i.v. and i.m. injection in goats at 10 mg/kg of body weight (mean \pm SD).

Pharmacokinetic parameters	Units	Compartmental analysis	Non-compartmental analysis
		<i>intravenous</i>	<i>intramuscular</i>
$t_{1/2\beta}$	h	1.86 ± 0.54	1.65 ± 0.38
MRT	h	2.70 ± 0.80	2.39 ± 0.30
$AUC_{0 \rightarrow 12h}$	$\mu\text{g.h/mL}$	173.97 ± 75.66	156.11 ± 0.04
$AUC_{0 \rightarrow \infty}$	$\mu\text{g.h/mL}$	181.58 ± 80.52	156.98 ± 44.50
Vc	L/kg	0.14 ± 0.07	-
Cl_B	mL/min/kg	1.10 ± 0.54	-
$t_{1/2abs.}$	h	-	0.77 ± 0.34
C_{max}	$\mu\text{g/mL}$	-	49.32 ± 10.33
T_{max}	h	-	0.80 ± 0.11
F	%	-	86.45 ± 17.39

$t_{1/2\beta}$ -elimination half-life, MRT-mean residence time,

$t_{1/2abs.}$ -absorption half-life,

$AUC_{0 \rightarrow 12}$ -area under the plasma concentration vs. time curve from 0 to 12 h,

$AUC_{0 \rightarrow \infty}$ -area under the plasma concentration vs. time curve from 0 to ∞ ,

Vc-apparent volume of central compartment, Cl_B -total body clearance,

C_{max} -peak drug concentration,

T_{max} -time to reach peak concentration,

F-Bioavailability.

Following i.m. injection of cefepime, C_{max} was $49.32 \pm 10.33 \mu\text{g/mL}$ at 0.80 h, which is in agreement with that reported by Joshi and Sharma (9) in buffalo calves. The drug was absorbed rapidly from thigh muscles ($t_{1/2abs} = 0.77 \pm 0.34$ h). The $t_{1/2\beta}$ and MRT values in the present study following i.m. administration were lower than those reported in calves ($t_{1/2\beta} = 3.03$ h, MRT = 4.72 h) (8).

The absolute bioavailability (F) observed in the present study indicates that there was very good absorption of the drug from the i.m. injection site (F = 86.45%). This value is similar to that reported in ewes (F = 86.8%) (17) and lower than that in calves (F = 95.7%) (8). A primary determinant of antibacterial activity for β -lactam antibiotics is $t_{>MIC}$ (20,21). The time above MIC was estimated from the plasma concentration versus time curve (Figure) and was expressed as a percentage of the inter-dose interval. A $t_{>MIC}$ of 35%-40% and an inter-dose interval of 60%-70% for cephalosporin have been established as optimal for bacteriostatic and bactericidal effect,

respectively (22,23). For cefepime the MIC against the majority of gram-positive and gram-negative pathogens has been reported to be $\leq 1 \mu\text{g/mL}$ (24,25). The MIC for both routes of administration in the present study was 2.5-fold greater than the 70% of dosage interval (7 h). This supports the fact that cefepime is a potential bactericidal agent for more than 7 h following i.v. and i.m. administration. This finding is in agreement with that reported by Ismail (17) in ewes. The findings of the present study indicate that cefepime might be very useful in the treatment of various infections in goats at the dose rate of 10 mg/kg of body weight and 10 h as the dosage interval when administered by i.v. or i.m. routes. In the present study cefepime was selected as a drug for the following reasons: i) to overwhelm resistant organisms, ii) to treat mixed-type infections, iii) to treat infections in tissues in which the reach of conventional cephalosporins is restricted, and iv) to obtain basic data concerning the drug's dosage regimen in goats.

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