

Single Dose Pharmacokinetics of Cefepime after Intravenous and Intramuscular Administration in Goats

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Abstract: Pharmacokinetics of cefepime was determined following single dose intravenous (IV) and intramuscular (IM) administration at the rate of 10 mg/kg body weight in a crossover design with an interval of 21 days between IV and IM injections. The experiment was done on 6 healthy young female Surati goats (4-6 months of age). All animals were randomly allocated to receive either IV or IM injection of the drug. Blood samples were collected at various time intervals. Cefepime concentration in serum was determined by high performance liquid chromatography (HPLC). The serum drug concentration-time profile was characteristic of a 2- and 1-compartment open model following IV and IM administration, respectively. Following single dose IV administration, the drug was rapidly distributed ($t_{1/2\alpha}$: 0.20 ± 0.02 h; $V_{d(\text{area})}$: 0.52 ± 0.04 l/kg) and slowly eliminated ($t_{1/2\beta}$: 2.71 ± 0.08 h) from the body. Following IM administration, the drug was rapidly absorbed ($t_{1/2ka}$: 0.16 ± 0.01 h) and slowly eliminated ($t_{1/2\beta}$: 4.89 ± 0.24 h) from body. The bioavailability of cefepime was $69 \pm 6.0\%$ following IM injection. Based on observed serum drug concentration, cefepime can be used intramuscularly at the dose rate of 10 mg/kg every 12 h in goats.

Key Words: Pharmacokinetics, cefepime, goats, intravenous, intramuscular

Introduction

Cefepime is a semisynthetic, parenteral fourth-generation cephalosporin antibiotic. It is stable to hydrolysis by common plasmid and chromosomally mediated β -lactamases. Cefepime shows broad spectrum of activity, which includes Gram-positive cocci, enteric Gram-negative bacilli, and *Pseudomonas aeruginosa*. It lacks activity against methicillin-resistant *Staphylococcus aureus*, enterococci, *Bacteroides fragilis*, and *Listeria monocytogenes* (1,2). It was found highly active against canine isolates of *Staphylococcus intermedius*, *Pseudomonas aeruginosa*, and *Escherichia coli* (3). Diseases like coliform septicaemia, pneumonia, colibacillosis, and meningitis are major causes of neonatal mortality in sheep and goats where cefepime may be highly effective in treating bacterial infections.

Pharmacokinetics of cefepime has been determined for rats and monkey (4), men (5), foals and dogs (6), horses (7), calves (8), and ewes (9). Despite the great

potential for clinical use of cefepime in veterinary medicine, the data on its pharmacokinetics in goats are limited. The present study was therefore planned to determine various pharmacokinetic parameters of cefepime following IV and IM injection in goats.

Material and Methods

Experimental Animals

The experiment was conducted on 6 healthy young (4-6 months of age) Surati female goats (*Capra hircus* L.), weighing 25-34 kg. The work was carried at the instructional farm of the College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand (India). The experimental protocol was approved by the institutional animal ethics committee. The animals were examined clinically to establish health status and to rule out the possibility of any diseases. Each animal was housed in a separate pen and provided standard ration. Water was provided ad libitum.

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Drugs and Chemicals

Pure cefepime standard powder was obtained from Aurobindo Pharma Ltd., Hyderabad, India. Cefepime hydrochloride (1.19 g) (Novapime, Lupin Ltd., Mumbai, India) equivalent to cefepime 1 g for injection was purchased from market. Sodium acetate, acetic acid, water, acetonitrile, methanol, and perchloric acid (70%) of HPLC grade were procured from Merck India Ltd., Mumbai.

Experimental Design

Study was conducted in a cross over design with an interval of 21 days between 2 successive injections. All goats were randomly allocated to receive either IV or IM injection. Cefepime hydrochloride (Novapime, Lupin Ltd, Mumbai, India) was diluted with sterile water to make concentration of 100 mg/ml and administered at a rate of 10 mg/kg body weight. IV injection of the drug was given in the left jugular vein, while IM injection was given in the gluteal muscles, using a 20 G × 25 mm sterile needle.

Blood samples (3-4 ml) were collected from IV catheter (Mediflon, 22 × 0.9 × 25 mm) fixed into the right jugular vein. The blood samples were drawn into clean sterilized test tubes. Blood samples were collected at 0 time (before drug administration), and at 0.033 (2 min), 0.083 (5 min), 0.166 (10 min), 0.25 (15 min), 0.5 (30 min), 1, 2, 4, 6, 8, 12, 18, and 24 h after IV administration. Following IM administration, the blood samples were collected at 0 time (before drug administration), and at 0.083 (5 min), 0.166 (10 min), 0.25 (15 min), 0.5 (30 min), 1, 2, 4, 6, 8, 12, 18, 24, and 36 h. The blood samples were allowed to clot and serum was harvested from all samples by centrifugation at 4192.5 g for 15 min. The serum samples were then stored at - 40 °C and analyzed within 24 h.

Cefepime HPLC Assay

Cefepime concentration in serum samples was determined by reverse-phase high performance liquid chromatography (HPLC) after extraction, using a reported assay with some modifications (6). The HPLC system (Knauer, Germany) comprised of isocratic solvent delivery pump (model K 501) and UV detector (model K 2501). Chromatographic separations were performed using reverse phase C18 column (Zorbax, ODS; 25 cm × 46 mm ID) at room temperature. The data integration was performed using Eurochrome software (Version 2000). 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 a 0.45 μ filter and pumped into column at a flow rate of 1.5 ml/min at ambient temperature. The effluent was monitored at 257 nm wavelength.

Serum samples were deproteinized by diluting 500 μl of serum with 500 μl of 0.8 M perchloric acid and centrifuged at 4192.5 g for 10 min. The clean supernatant was collected and an aliquot of 20 μl of this supernatant was injected into the loop of HPLC system through manual injector. Calibration curve was prepared by adding known amount of cefepime to blank unfortified serum for the expected range of concentrations from 0.1 to 100 μg/ml. Quantification was done by reference to the resultant calibration curve. The calibration curve was prepared daily and not accepted unless it had a R² value > 0.99. The lower limit of quantitation (LLOQ) was 0.5 μg/ml. The assay was sensitive and reproducible, and linearity was observed from 0.5 to 100 μg/ml with a mean correlation coefficient of 0.9985. Precision and accuracy were determined with quality control (QC) samples at concentrations of 0.5, 10, and 100 μg/ml (5 replicates, each, per day). The intraday and interday coefficients of variation for 5 QC samples were satisfactory, with relative standard deviations (RSD) less than 8.55%. Intraday and interday variations were under acceptable limits. The retention time of cefepime was 5.0 min.

Data Analysis

The intravenous serum drug concentration versus time data plot followed 2-compartment open model, whereas intramuscular disposition followed 1-compartment open model. Serum drug concentrations versus time data were best fitted to compartment models using Pharmkit software (Version 2.0). Pharmacokinetic parameters were calculated using the following formulas (10-12):

$$t_{1/2\beta} = \frac{0.693}{\beta}$$

AUC (0 - ∞) and AUMC were calculated by Trapezoidal rule.

$$Vd_{(area)} = \frac{Dose}{\beta \times AUC} \text{ (For Intravenous Injection)}$$

$$V_{d(\text{area})} = \frac{\text{Dose} \times F}{\beta \times \text{AUC}} \quad (\text{For Intramuscular Injection})$$

$$V_{d(\text{ss})} = \frac{\text{Dose} \times \text{AUMC}}{(\text{AUC})^2}$$

$$\text{Cl}_B = \beta \times V_{d(\text{area})} \times 1000$$

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}$$

$$F = \frac{\text{Dose (I.V.)} \times \text{AUC (I.M.)}}{\text{Dose (I.M.)} \times \text{AUC (I.V.)}} \times 100$$

(For Intramuscular Injection)

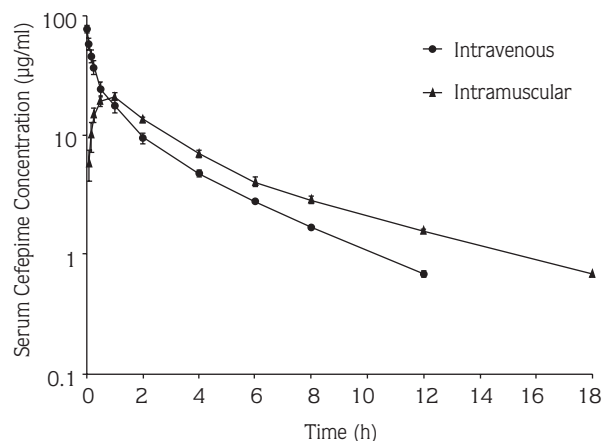


Figure. Semilogarithmic plot of serum cefepime concentrations versus time following single dose IV and IM administrations at the rate of 10 mg/kg of body weight in goats. Each point represents the Mean \pm S.E. of 6 animals.

Results

Comparative disposition of cefepime following single dose IV and IM administration in goats is shown in the Figure as a semilogarithmic plot. Pharmacokinetic parameters are presented in the Table. Following single dose IV administration, distribution half-life, elimination half-life, apparent volume of distribution, area under serum drug concentration-time curve, and total body clearance were 0.20 ± 0.02 h, 2.71 ± 0.08 h, 0.52 ± 0.04 l/kg, 78.38 ± 7.05 $\mu\text{g} \cdot \text{h ml}^{-1}$ and 2.19 ± 0.15 ml/min/kg, respectively. Following IM administration, peak serum drug concentration, elimination half-life, area

under the serum concentration-time curve, total body clearance, and systemic bioavailability were 15.75 ± 2.39 $\mu\text{g/ml}$, 4.89 ± 0.24 h, 93.12 ± 10.14 $\mu\text{g} \cdot \text{h ml}^{-1}$, 1.27 ± 0.08 ml/min/kg, and $69 \pm 6.0\%$, respectively.

Discussion

Following IV and IM administration, cefepime serum concentration versus time data can be best fitted to a 2-compartment and a 1-compartment open model,

Table. Pharmacokinetic parameters of cefepime in goats after single dose IV and IM administration (10 mg/kg of body weight).

Pharmacokinetic Parameters	Unit	IV (Mean \pm S.E., n = 6)	IM (Mean \pm S.E., n = 6)
$t_{1/2\alpha}$	h	0.20 ± 0.02	-
$t_{1/2\beta}$	h	2.71 ± 0.08	4.89 ± 0.24
$t_{1/2k(a)}$	h	-	0.16 ± 0.01
AUC _(0-∞)	$\mu\text{g} \cdot \text{h/ml}$	78.38 ± 7.05	93.12 ± 10.14
AUMC	$\mu\text{g} \cdot \text{h}^2/\text{ml}$	203.80 ± 10.05	492.30 ± 49.52
$V_{d(\text{area})}$	L/kg	0.52 ± 0.04	-
$V_{d(\text{ss})}$	L/kg	0.35 ± 0.03	-
K_{12} / K_{21}	ratio	2.34 ± 0.33	-
Cl _(B)	ml/min/kg	2.19 ± 0.15	1.27 ± 0.08
MRT	h	2.64 ± 0.09	4.89 ± 0.57
F	%	-	69 ± 6
C_{max}	$\mu\text{g/ml}$	-	15.75 ± 2.39
T_{max}	h	-	0.50

$t_{1/2\alpha}$: half-life of distribution phases; $t_{1/2\beta}$: elimination half life; $t_{1/2k(a)}$: absorption half-life; AUC_(0-∞): total area under plasma drug concentration-time curve; AUMC: area under first of moment curve; $V_{d(\text{area})}$: volume of distribution based on area; $V_{d(\text{ss})}$: volume of distribution at steady state; K_{12} : rate of transfer of drug from central to peripheral compartment; K_{21} : rate of transfer of drug from peripheral to central compartment; Cl_(B): total body clearance; MRT: mean residence time; F: bioavailability; C_{max} : maximum drug concentration; T_{max} : time of maximum concentration observed in serum.

respectively, which was supported by disposition characteristics of cefepime reported in men (5) and animals (6-8). The elimination half-life (2.71 ± 0.08 h) determined in the present study is longer than that reported in ewes (1.76 ± 0.07 h) (9) but shorter than that determined in foals (1.65 ± 0.10 h) and dogs (1.09 ± 0.27 h) (6). Clearance of cefepime observed in the present study is in agreement with that reported in ewes (9). In contrast, slower clearance of the drug has been reported in horses (6,7) and calves (8). The drug is widely distributed in the body as determined by apparent volume of distribution observed in the present study. This is in line with that reported in ewes (9). Higher ratio of K_{12} / K_{21} observed in the present study also suggests faster and wider distribution of drug into the tissues of goats.

Following IM administration, peak serum cefepime concentration (21.10 ± 1.85 $\mu\text{g/ml}$) was achieved at 1 h (t_{max}), which is lower than the peak cefepime concentration (31.9 ± 1.5 $\mu\text{g/ml}$) observed in ewes (9). The peak serum cefepime concentration observed in calves (8) is in line with that observed in goats. Elimination half-life following IM injection of the drug in the present study is longer than that reported in goats (9) and calves (8). The systemic bioavailability of cefepime following IM injection is less than that reported in ewes ($86.8 \pm 7.5\%$) (9) and calves ($95.7 \pm 7.44\%$) (8). Based on the observed serum drug concentration following IM administration of the drug in the present study, therapeutic concentration is maintained for up to 12 h, therefore IM injection of cefepime at the rate of 10 mg/kg may be used as a therapeutic dose in goats.

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