IJPT
1735-2657/06/52-127-130
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 5:127-130, 2006

RESEARCH ARTICLE

Pharmacokinetics and Dosage Regimen of Cefepime following Single Dose Intravenous Administration in Calves

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Received May 11, 2006; Revised October 5, 2006; Accepted November 7, 2006

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

Pharmacokinetics of cefepime was studied after single dose intravenous administration at the dose rate of 5 mg/kg body weight in calves. Blood samples were collected from the jugular vein at predetermined time intervals before and after drug administration. Serum was harvested and analysed for cefepime concentration by reverse-phase high performance liquid chromatography. Following intravenous administration, the mean serum cefepime level of 44.93 ± 5.47 μg/mL was observed at 0.033 h (2 minutes). The therapeutically effective concentration of cefepime (≥ 1.00 μg/mL) was maintained in serum up to 12 h. The distribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) were 0.09 ± 0.01 h and 3.70 ± 0.16 h, respectively. The mean values of apparent volume of distribution [$V_{d(area)}$] and volume of distribution of drug at steady-state ($V_{d\ (ss)}$) were calculated to be 0.57 ± 0.03 and 0.43 ± 0.03 L/kg, respectively. The mean value of total body clearance (Cl_B) was 1.81 ± 0.16 mL/min/kg. The average values for area under serum drug concentration-time curve (AUC) and area under first moment of curve (AUMC) were 47.73 ± 4.05 μg h/mL and 190.3 ± 19.9 μg h^2/mL. The average value of mean residence time (MRT) was 3.95 ± 0.11 h. A satisfactory intravenous dosage regimen would be 4.20 mg/kg body weight as priming dose followed by 3.78 mg/kg repeated at 12 h intervals.

Keywords: *Cefepime, Calves, Pharmacokinetics, Intravenous*

Cefepime, a semi-synthetic, parenteral fourth-generation cephalosporin antibiotic, has a broad spectrum of activity against a wide range of Gram-positive and Gram–negative bacteria. Cefepime exhibits increased stability against hydrolysis by class 1 chromosomally mediated β- lactamases. Cefepime shows excellent activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus cloacae*, *Staphylococcus aureus* and *Estreptococcus* spp. [1] but lacks activity against methicillin-resistant Staphylococci and Enterococci. It has variable activity against anaerobic bacteria [18].

Cefepime is well tolerated and effective against infections of soft tissues, the abdominal cavity, urinary tract, lower respiratory tract and provides efficacious antibacterial prophylaxis for biliary tract and prostate surgery [10, 11]. Cefepime pharmacokinetics have previously been studied in adult horses [5], neonatal foals and dogs [3, 15], goats [13] and cow calves [6]. Cefepime is a highly effective antibiotic against Gram-negative bacteria including those resistant to third generation cephalosporins [12, 14, 16]. Diseases like coliform septicaemia, pneumonia, colibacillosis and meningitis are major causes of neonatal calf mortality where it can be used for treatment. Therefore, the present study was planned to determine various pharmacokinetic parameters of cefepime and to predict its dosage regimen following single dose intravenous administration in cow calves.

MATERIALS AND METHODS

Experimental Animals

The experiment was conducted on six healthy young (4-6 months of age) Holstein-Friesian (H.F.) calves (*Bos taurus* L.), weighing 57-80 kg. The animals were examined clinically to evaluate health status and to rule out the possibility of any diseases. Each calf was housed in a separate pen and provided standard ration. Water was provided *ad libitum.*

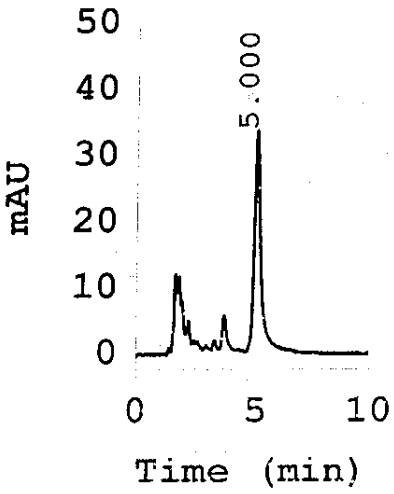

Fig 1.Typical Chromatogram of calf serum containing cefepime. Plasma concentrations versus time data of cefepime obtained during study were utilized for calculating different pharmacokinetic parameters using "method of least square" and "method of residual yields" as described by Gibaldi and Perrier [4]. The dosage regimen of cefepime was also determined based on the kinetic data. The priming (D) and maintenance (D') doses were calculated using equations:

$$D=Cp\ (min)^{\alpha} \cdot Vd\ e^{\beta\tau}\ ,\ D' = Cp\ (min)^{\alpha}\ Vd\ (e^{\beta\tau} - 1)$$

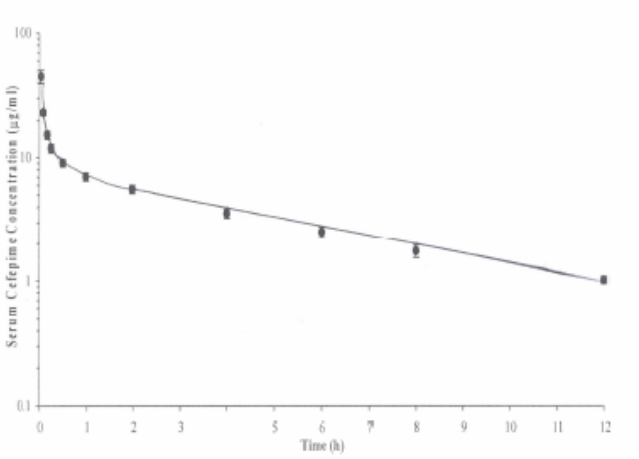

Fig 2. Semilogarithmic plot of cefepime concentration in serum versus time following single dose intravenous administration at the dose rate of 5 mg/kg of body weight calves. Each point represents mean ± S.E of six calves.

Drugs and Chemicals

Pure cefepime powder was obtained from Aurobindo Pharma Ltd., Hyderabad, India. Cefepime hydrochloride (Novapime, Lupin Ltd., Mumbai, India) equivalent to 1 g cefepime. was purchased from pharmacy. Water, sodium acetate, acetic acid, acetonitrile and perchloric acid (70%) of HPLC grade were procured from Merck India Ltd., Mumbai.

Experimental Design

All six animals were randomly allocated to receive intravenous injection of cefepime. Cefepime hydrochloride (Novapime, Lupin Ltd, Mumbai, India) was diluted with sterile water to make concentration of 100 mg/mL and administered at a dose rate of 5 mg/kg body weight. Intravenous injection of the drug was given through left jugular vein, using a 20 G × 25 mm needle. Blood samples (4-5 mL) were collected from the right jugular vein through a fixed catheter prior to injection and at 2, 5, 10, 15, 30 min and 1, 2, 4, 6, 8, 12, 18 and 24, h following intravenous administration of cefepime. Calves were observed for any adverse reactions during the study after administration of drug.

Blood samples were allowed to clot and the serum was harvested by centrifugation at 5000 revolution per min for 15 min. The serum samples were stored at – 40 °C until drug analysis was performed.

Cefepime Assay

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 some modifications.

The HPLC system (Knauer, Germany) comprised of isocratic solvent delivery pump (model K 501) and UV detector (model K 2501). Chromatographic separations were performed by using reverse phase C18 column (Zorbax, ODS; 25 cm × 46 mm ID) at room temperature. 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 %), acetronitrile (10.0 %) and HPLC water (84.6 %) with pH 5.1. Mobile phase was filtered through a 0.45 µ filter and pumped into column at a flow rate of 1.5 mL/min at ambient temperature. The eluate 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 5000 revolution per minute for 10 minutes. The clean supernant was collected and an aliquot of 20 µl of this supernant 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 were prepared daily and not accepted unless it had a R^2 value > 0.99. The lower limit of quantitation was 0.5 µg/mL. The assay was sensitive, reproducible and linearity was observed from 0.5 to 100 µg/mL. The typical chromatogram of cefepime in calf serum is shown in Fig 1. The retention time of cefepime was 5.0 minutes.

RESULTS

The comparative disposition of cefepime following single dose intravenous administration in cow calves was plotted on semi logarithmic scale (Fig 2). Various pharmacokinetic parameters calculated from serum con-

Table 1.Pharmacokinetic parameters of cefepime in calves after a single intravenous administration (5 mg/kg of body weight)

Kinetic Parameters[a]	Unit	Determinants (Mean ± S.E., n = 6)
$t_{1/2\alpha}$	h	0.09 ± 0.01
$t_{1/2\beta}$	h	3.7 ± 0.16
AUC	μg h/mL	47.73 ± 4.05
AUMC	μg h^2/mL	190.3 ± 19.9
$Vd_{(area)}$	L/kg	0.57 ± 0.03
$Vd_{(ss)}$	L/kg	0.43 ± 0.03
K_{12} / K_{21}	ratio	3.84 ± 0.65
Cl (B)	mL/min/kg	1.81 ± 0.16
MRT	h	3.95± 0.11

[a] Kinetic parameters as described by Gibaldi and Perrier (1982), $t_{1/2\alpha}$: half-life of distribution phases; $t_{1/2\beta}$: elimination half life; AUC: total area under serum drug concentration-time curve; AUMC: area under first moment of curve; $Vd_{(area)}$: apparent volume of distribution; $Vd_{(ss)}$: 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;

centration of cefepime after its single dose intravenous administrations are summarized in Table 1. Various intravenous dosage regimens were computed and are presented in Table 2.

DISCUSSION

Pharmacokinetic studies of cefepime following intravenous and/or intramuscular administration have been reported in cow calves [6], foals and dogs [3, 15], horses [5] and goats [13]. Following intravenous administration of cefepime at the dose of 5 mg/kg, no adverse reactions were observed in calves in the present study; however some adverse effects have been reported in dogs [3, 15], foals [3], and horses [5].

Following intravenous administration, cefepime serum concentration versus time data can be best fitted to a two-compartment open model, which was similar to the disposition characteristics of cefepime observed in human [9], and other animal species [3, 5, 6]. In the present study, the peak and minimal detectable levels of 44.93 ± 5.47 and 1.01 ± 0.07 μg/mL of cefepime were measured at 0.033 and 12 h, respectively. The Therapeutic concentration of cefepime ≥ 1.0 μg/mL [2, 7, 8, 17] was maintained in serum up to 12 h.

The drug was rapidly distributed with a short distribution half-life ($t_{1/2\alpha}$) of 0.09 ± 0.01 h, this value was shorter than values of 0.20 ± 0.02 h in cow calves [6], 0.36 ± 0.18 h in horses [5], 0.39 ± 0.21 h in dogs [3] and 0.30 ± 0.16 h in foals [3]. The rapid distribution was further supported by high value of K_{12}/K_{21} (3.84 ± 0.65). The elimination half-life ($t_{1/2\beta}$) in this study (3.70 ± 0.16 h) was longer than the values of 2.38 ± 0.16 h and 2.1 ± 1.25 h in cow calves [6] and horses [5], respectively. In contrast the drug was rapidly eliminated in foals ($t_{1/2\,\beta}$: 1.65 ± 0.10 h) and dogs ($t_{1/2\,\beta}$: 1.09 ± 0.27 h) [3]. Low value of elimination rate constant (β: 0.19 ± 0.01 h^{-1}) observed in present study was comparable to the value of 0.29 ± 0.02 h^{-1} in cow calves [6] while lower than 0.36± 0.18 h^{-1} in horses [5], 0.42 ± 0.03 h^{-1} in foals 0.79 ± 0.08 h^{-1} in dogs [3] indicated that the elimination of cefepime is slower in horses, foals and dogs.

The value of mean residence time (3.95 ± 0.11 h) was almost similar to that of 3.38 ± 0.26 h reported in cow calves [6], but longer than the values of 2.03 ± 1.07, 2.16 ± 0.13 and 1.05 ± 0.14 h reported in horses [5], foals and dogs [3], respectively.

The area under curve (AUC) was calculated to be 47.73 ± 4.05 μg h/mL which was much lower than the values of 94.5 ± 7.6, 114.8 ± 36.62 and 182.47 ± 59.7 μg h/mL reported in cow calves [6], dogs and foals [3], respectively. The volume of distribution at steady state (Vd_{ss}: 0.43 ± 0.03 L/Kg) was higher than the values of 0.21 ± 0.01 L/kg in cow calves [6], 0.14 ± 0.04 L/kg in dogs and 0.18 ± 0.05 L/kg in foals [3] indicating good extravascular distribution in cow calves.

Total body clearance (Cl_B) in present study (1.81 ± 0.16 mL/min/kg) was comparable to value of 2.16 ± 0.66 mL/min/kg reported in dogs [3] but was slightly higher than 1.1 ± 0.08, 1.33 ± 0.33, and 1.18 ± 0.18 mL/min/kg reported in cow calves [6], foals [3], and horses [5], respectively.

The important objective of the present study was to compute a satisfactory dosage regimen of cefepime in cow calves. Thus appropriate dosage regimen of cefepime on the basis of pharmacokinetic data was calculated for calves. For cefepime the minimum inhibitory concentration against majority of Gram-negative and Gram-positive pathogens has been reported to be ≤ 1.0 μg/mL [2, 7, 8, 17]. A satisfactory intravenous dosage regimen would be 4.20 mg/kg body weight as priming dose followed by maintenance doses of 3.78 mg/kg

Table 2.Intravenous dosage regimens of cefepime for calves

MIC (μg/mL)	Dose (mg/kg) and Dosing intervals (h)					
	6 h		8 h		12 h	
	D	D'	D	D'	D	D'
0.05	0.07	0.04	0.098	0.077	0.21	0.189
0.10	0.10	0.09	0.20	0.154	0.42	0.38
0.50	0.67	0.46	0.98	0.77	2.10	1.89
1.00	1.35	0.92	1.97	1.54	4.20	3.78
2.00	2.69	1.83	3.93	3.07	8.40	11.07
5.00	6.72	4.57	9.83	7.68	21.10	18.88

body weight per 12 h to maintain the therapeutic drug concentration (≥ 0.1 μg/mL).

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