Pharmacokinetics of Cefepime Following Intravenous and Intramuscular Administration in Sheep

P. N. PATEL, U. D. PATEL, SH. K. BHAVSAR and A. M. THAKER

Received February 10, 2009; Revised June 29, 2009; Accepted August 5, 2009

ABSTRACT
Pharmacokinetics of cefepime was studied following single dose intravenous and intramuscular administration at the dose of 20 mg/kg of body weight in sheep. Drug concentration in serum was determined using high performance liquid chromatography (HPLC). Following single dose intravenous administration, the drug was rapidly distributed \( t_{1/2\alpha} : 0.20 \pm 0.02 \) h and eliminated \( t_{1/2\beta} : 2.54 \pm 0.12 \) h from the body. The area under curve \( (\text{AUC}_{0-\infty}) \) was \( 135.50 \pm 5.63 \) \( \mu \)g h/mL. The drug was cleared at the rate of \( 2.48 \pm 0.09 \) mL/min/kg with mean residence time (MRT) of \( 2.84 \pm 0.13 \) h. Following IM administration, the drug was rapidly absorbed \( (C_{\text{max}}: 26.34 \pm 1.44 \mu \text{g/mL}; t_{\text{max}}: 0.75 \) h) and slowly eliminated \( (t_{1/2\beta}: 5.17 \pm 0.44 \) h) from body. The volume of distribution at steady state \( (V_{\text{dss}}) \), area under curve \( (\text{AUC}) \), total body clearance \( (C_{\text{lb}}) \) and mean residence time (MRT) were \( 1.11 \pm 0.10 \) L/kg, \( 140.90 \pm 8.67 \) \( \mu \)g h/mL, \( 0.15 \pm 0.01 \) mL/min/kg and \( 6.89 \pm 1.0 \) h, respectively. The bioavailability of cefepime following intramuscular administration was \( 103 \pm 8.0 \% \).

Keywords: Pharmacokinetics, Cefepime, Sheep, Intravenous, Intramuscular

Cefepime is an extended spectrum, semi-synthetic, parenteral fourth-generation cephalosporin antibiotic. It has excellent activity against gram-positive and gram-negative bacteria, except for Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, Clostridium difficile, Bacteroides spp. and some strains of Pseudomonas spp. [1, 2]. It has variable activity against anaerobic bacteria [3]. Cefepime was found highly active against canine isolates of Staphylococcus intermedius, Pseudomonas aeruginosa and Escherichia coli with MIC values of 0.03, 0.5, 1.0 \( \mu \)g/mL, respectively [4]. Pharmacokinetic profile of cefepime has been studied in monkey [5], cow calves [6-8], horses [9], foals and dogs [10], ewes [6] and goats [11-13]. Cefepime may be useful in cases of sub-clinical and clinical mastitis in sheep as it has been reported to be excreted in milk following intravenous and intramuscular administration in goats [12]. Findings from pharmacokinetic studies in animals encourage the use of cefepime to treat many types of bacterial infections in sheep. Therefore, the present study was planned to determine the pharmacokinetic parameters of cefepime following single dose intravenous and intramuscular administration in Patanwadi breed of sheep.

MATERIALS AND METHODS

Experimental Animals
The experiment was conducted on six healthy Patanwadi female sheep (4-5 years old), weighing 25-30 kg. The study was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals, Chennai (India). The animals were examined clinically to evaluate health status. Each animal was housed in a separate pen and provided standard ration. Water was provided ad libitum.

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 trichloroacetic acid of analytical or...
Cefepime Assay

Cefepime concentration in serum samples was determined by reverse-phase high performance liquid chromatography (HPLC) assay [10] with minor modification. The HPLC system (Laballiance, USA) comprised of gradient solvent delivery pump (model AIS 2000) and UV detector (model 500). Chromatographic separations were performed by using reverse phase C18 column (Thermo, 5 µ ODS; 250 × 4.6 mm ID) at room temperature. Data integration was performed using Clarity (Version 2.4.0.190). The mobile phase was a mixture of 0.2 M sodium acetate (3.2%), 0.2 M acetic acid (2.2%), acetonitrile (15.0%) and HPLC water (79.6%) with pH 5.1. Mobile phase was filtered through a 0.45 μ filter and pumped into column at a flow rate of 1.0 mL/min at ambient temperature. The elute was monitored at 257 nm wavelength. Serum samples were deproteinized by diluting 500 µl of serum with 500 µl of trichloroacetic acid (10%) and centrifuged at 5000 revolution per minute for 10 minutes. The clean supernatant was collected and an aliquot of 20 µl of the 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 200 µg/mL and processed as described above. Quantification was done by reference to the resultant calibration curves. The calibration curve was prepared daily and not accepted unless it had a R2 value ≥ 0.99. Recovery from serum was estimated by comparing the detector response of series of standards (0.1 to 200 µg/mL) extracted from serum with non extracted standards in mobile phase. Recovery of the drug from serum samples was estimated to be 88.3%. The lower limit of quantitation was 0.1 µg/mL. The assay was sensitive, reproducible and linearity was observed from 0.1 to 200 µg/mL. The retention time of cefepime was 4.0 minutes.

Pharmacokinetic Analysis

Following intravenous administration of the drug, the drug concentration-time data were best fitted to two compartment open model, where as drug concentration-time data following intramuscular administration were analyzed by non-compartment technique. Following formulas were used to calculate various pharmacokinetic parameters [14-16].

\[
\begin{align*}
\alpha & \quad \text{Half-life} \\
\beta & \quad \text{Half-life} \\
AUC & \quad \text{Area under the serum drug concentration – time curve} \\
\text{MRT} & \quad \text{Mean residence time} \\
F & \quad \text{Fraction of drug absorbed after non-vascular administration} \\
\end{align*}
\]

RESULTS

Semilogarithmic plot of cefepime concentrations in serum versus time following single dose intravenous and intramuscular administrations (20 mg/kg) in sheep is shown in Fig 1. Cefepime pharmacokinetic parameters following intravenous and intramuscular administration in sheep are shown in Table 1. Following...
intravenous administration, the drug could not be detected in serum samples collected beyond 12 h. The distribution ($t_{1/2a}$) and elimination ($t_{1/2b}$) half-lives of cefepime were 0.20 ± 0.02 h and 2.54 ± 0.12 h, respectively. The values of volume of distribution at steady state ($V_{dss}$), area under curve (AUC), and total body clearance ($Cl_{ss}$) were 0.42 ± 0.02 L/kg, 135.50 ± 5.63 μg h/L, and 2.48 ± 0.09 mL/min/kg respectively. Following single dose intramuscular administration of cefepime in sheep, the peak serum cefepime concentration of 21.1 ± 1.85 μg/mL was observed at 0.75 h. The elimination ($t_{1/2b}$) half-life of cefepime was 5.17 ± 0.44 h. The average respective values for volume of distribution by area method ($Vd_A$), area under curve (AUC), and total body clearance ($Cl_{B}$) were 1.11 ± 0.1 L/kg, 140.90 ± 8.67 μg h/L, and 0.15 ± 0.01 mL/min/kg. The systemic bioavailability (F) of the drug was calculated to be 103.0 ± 8.0% per cent in sheep following intramuscular administration.

**DISCUSSION**

Following intravenous administration, the drug gets rapidly eliminated as evidenced by short half-life and faster clearance. Similar observations have been reported in goats [10] and calves [17]. More rapid elimination of cefepime has been found in foals ($t_{1/2b}$: 1.09 ± 0.27 h) [10]. The drug has moderate distribution in the body of sheep. This is in agreement with the $Vd_A$ of 0.35 ± 0.03, 0.32 ± 0.01 and 0.43 ± 0.03 L/kg reported in goats [11] ewes [6] and calves [7], respectively.

Following single dose intramuscular administration of cefepime, the peak and minimum serum cefepime concentration observed in sheep is in agreement with the peak serum cefepime concentrations of 21.1 ± 1.85 and 22.6 μg/mL reported in goats [11,13]. However, lower peak serum concentration was observed in horses, cow calves and dogs [4, 8, 9], while higher peak plasma concentration of cefepime (31.9 ± 1.5 μg/mL at 1.1 ± 0.2 h) has been reported in ewes [6]. The elimination half-life ($t_{1/2b}$) following intramuscular administration of cefepime in sheep is in line with that of 4.89 ± 0.24 h reported in goats [11] but longer than that of 3.02 ± 0.18 h reported in calves [3]. Longer half-life indicates that the drug is continuously absorbed during the elimination phase in sheep following intramuscular administration. The total body clearance of cefepime in sheep is slower than observed in goats [11] and cow calves [8]. Following intramuscular injection of cefepime in sheep, the drug gets extensively distributed. However, moderate distribution of the drug has been reported in goats (0.60 ± 0.06) [11]. The drug was completely absorbed from site of injection following intramuscular administration in sheep as evidence by cent percent bioavailability. Similarly higher systemic bioavailability of 111.0 ± 22.0 and 98.0 ± 3.0 was reported in horses [9] and cow calves [8]. However, lower systemic bioavailability of 69.0 ± 6.0 was reported in goats [11].

The pharmacokinetic profile of cefepime in sheep following intravenous and intramuscular administration indicates that it may be therapeutically useful against susceptible micro-organisms involved in most common infections in sheep. The high bioavailability of cefepime and maintenance of therapeutic concentration for a long time following intramuscular injection suggests that cefepime is suitable for intravenous and intramuscular administration (20 mg/kg repeated at 18 h interval) for the treatment for systemic bacterial infections in sheep.

**REFERENCES**

4. Giamarellou H, Sahin A, Chryssoli Z. Comparative in vitro evaluation of BMY-28142, a new broad spectrum cephalosporin,


CURRENT AUTHOR ADDRESSES

P. N. Patel, Department of Pharmacology, College of Veterinary Science, Anand Agricultural University, Anand 388001, India.

U. D. Patel, Department of Pharmacology, College of Veterinary Science, Anand Agricultural University, Anand 388001, India.

SH. K. Bhavsar, Department of Pharmacology, College of Veterinary Science, Anand Agricultural University, Anand 388001, India.

A. M. Thaker, Department of Pharmacology, College of Veterinary Science, Anand Agricultural University, Anand 388001, India.