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Plasma pharmacokinetics and dosage regimen of cefpirome sulfate in ewes

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ABSTRACT

Cefpirome is fourth- generation cephalosporin class of drug with a broad spectrum of activity against Gram-positive and Gram- negative organisms. A pharmacokinetic study of single dose intravenous (IV) and intramuscular (IM) administration of cefpirome sulfate (10 mg/kg body weight) was conducted using High Performance Liquid Chromatography (HPLC) and the pharmacokinetic parameters established were utilized to calculate optimal dosage regimens in ewes. Following IV administration of cefpirome in ewes the mean value of the elimination rate constant (β), elimination half life ($t_{½β}$), the area under the plasma drug concentration-time curve ($AUC_{0-\infty}$), the area under the first moment of the plasma drug concentration (AUMC), the mean residence time (MRT), the apparent volume of distribution (Vd_{area}) and total body clearance (Cl_B) were 0.43 ± 0.04 h^{-1}, 1.68 ± 0.21 h, 82.71 ± 3.76 μg.h/mL, 211.06 ± 23.99 μg.h^2/mL, 2.51 ± 0.19 h, 0.28 ± 0.03 L/kg and 0.11 ± 0.00 L/h/kg, respectively, while following IM administration of cefpirome the mean values were 0.33 ± 0.01 h^{-1}, 2.04 ± 0.06 h, 73.27 ± 4.04 μg.h/mL, 229.02 ± 20.32 μg.h^2/mL, 3.09 ± 0.12 h, 0.45 ± 0.03 L/kg and 0.14 ± 0.01 L/h/kg, respectively. The bioavailability following IM administration of cefpirome was 88.85 ± 4.07 %. Cefpirome concentration in plasma was maintained above the target MIC (≥0.25 μg/mL) for 12 h. The therapeutic dosage regimen calculated using the pharmacokinetic parameters generated by the intravenous route of drug administration indicated the most appropriate dose of cefpirome to maintain MIC at ≥ 0.25 μg/mL with a dosage interval of 12 h, would be 13.00 mg/kg body weight in ewes.

Key words: pharmacokinetics; dosage regimen; cefpirome sulfate; ewes

Introduction

Antimicrobials have been in use for several years for treating various disease conditions in animals and humans (GOULD, 2016). In clinical practice, cephalosporins are grouped into five "generations" based upon their chronological sequence of development, and successive generations of cephalosporins are characterised by increased stability to Gram-negative β- lactamases and

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increased activity against Gram-negative bacteria. Cefpirome is an injectable aminothiazolyl fourth-generation cephalosporin, with a broad spectrum of activity against Gram-negative and Gram-positive organisms (MUJEEB and JALIKAR, 2015). Cefpirome is a cephalosporin derivative with a 2,3-cyclopenteno-pyridine group instead of a 3'-acetoxy group found on the cefotaxime structure, and its chemical name is 3- [2,3- cyclopentento-1-pyridinium) methyl]-7-[2-methyoximino- 2- (2-aminothiazole-4- yl)- acetamido] ceph-3-em-4carboxylate (KOBAYASHI et al., 1986; TURLEY et al., 1988). It has low affinity for β- lactamase (KOBAYASHI et al., 1986) hence it is more resistant to inactivation by β- lactamase-producing bacteria. Cefpirome is zwitterionic compound, which facilitates rapid penetration through the outer membrane of Gram-negative bacteria (GARAU et al., 1997), which results in potent activity against many Gram-negative bacteria, including strains producing derepressed class I (AmpC) β- lactamase, which are resistant to most third- generation cephalosporins.

Among the third and fourth generation cephalosporin class of drugs, only cefovecin, cefquinome and ceftiofur are recommended for veterinary use, while other drugs are recommended in livestock and poultry for disease treatment purpose. Cefpirome was developed for treatment in bovine clinical mastitis as it is bactericidal, penetrates tissue well and is rapidly excreted in urine (BARRAGRY, 1994). Fourth generation cephalosporins, particularly cefepime and cefpirome, are the first line drugs for febrile neutropenia. Cefpirome is indicated for various infectious inflammatory diseases induced by sensitive bacteria such as sepsis/ bacteremia; complicated urinary tract infections, including pyelonephritis, pyelitis, urethritis and cystitis; respiratory infections, including pneumonia, lung abscess and pleural empyema; skin and soft tissue infections; wound infections; and infections with neutropenia.

Hypersensitivity reactions and pain are the most common adverse effects associated with parenteral cephalosporin compounds (THOMPSON and JACOBS, 1993; BAUMGART and BALDO, 2002). The severe or irreversible adverse effects of cefpirome, which give rise to further complications, include thrombocytopenia, granulocytopenia, agranulocytosis, eosinophilia, elevated hepatic enzymes and superinfection, if given over longer periods. The blood cell count should therefore be monitored for courses of treatment lasting far more than ten days. Vomiting and diarrhoea may occur in monogastric animals.

Domestic sheep (*Ovis aries*) are small ruminants typically kept as livestock. It has been seen that wide varieties of bacterial diseases affect ewes. Fever is one of the most common manifestations in bacterial diseases produced by Gram positive organisms such as *Streptococcus pyogenes*, *Streptococcus pneumoniae, Staphylococcus aureus* and endotoxin of Gram negative organisms such as *Escherichia coli*. As a wide antibacterial spectrum, low toxicity and anti-staphylococcal activity are the main advantages of cefpirome, it is used to treat severe sepsis, febrile neutropenia, and other infections, which are difficult to treat with routine antibiotics (POIATA et al., 2007). However, it is used off-label in ewes and data on MRL (Maximum Residue Limit) and withdrawal period are not available for food producing animals in the public domain.

The pharmacokinetics of cefpirome have been studied in several animal species such as buffalo calves (RAJPUT et al., 2007a), cow calves (PATEL et al., 2013), goats (BAROT et al., 2013; SOLANKI et al., 2014), monkeys (KLESEL and SEEGER, 1983), dogs (KITA et al., 1992), rats (ISERT et al., 1992; MUJEEB and JALIKAR, 2015), rabbits (MRESTANI et al., 2003) and also in humans (MAAB et al., 1987; BADIAN et al., 1988; MEYER et al., 1992; SAUERMANN et al., 2005). Extrapolation of the pharmacokinetic data generated in one target animal species may not truly match with other target animal species. Therefore, for judicious use of antibiotics at rational dosages, pharmacokinetic investigations are necessary in ewes. There is no literature available on the pharmacokinetic behaviour of cefpirome in ewes, so the main goal of our study was to optimize and standardize the method for detection of cefpirome in the plasma of ewes by High Performance Liquid Chromatography (HPLC), and to calculate

therapeutic dosage regimens to maintain the plasma drug concentration above the targeted minimum inhibitory concentration (0.25 µg/mL) using kinetic parameters established after single dose intravenous (IV) and intramuscular (IM) administration of cefpirome sulfate (10 mg/kg body weight) in ewes.

Materials and methods

Project approval by Institutional Animal Ethics Committee (IAEC). The animal experimentation protocol of the present study was approved by the IAEC of the College of Veterinary Science and Animal Husbandry, Anand Agricultural University (AAU), Anand, Gujarat, India (Registration no. 486/G0/Re-s/Re-Bi-L/01/CPCSEA).

Experimental animals. The study was conducted in six Patanwadi ewes of 2-3 years of age, weighing between 30 and 35 kilograms. The animals were maintained at the Instructional Farm, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand. They were kept under constant observation for ten days prior to commencement of the experiment. The animals were then housed in separate pens and were provided with standard ration and water *ad libitum*.

Drugs, chemicals and reagents. Cefpirome sulfate technical grade powder was procured from Sigma-Aldrich Chemicals Pvt. Ltd., Bangalore, India, and was used for creating reference standards during the development and validation of the HPLC method. For dosing purposes, Cefpirome sulfate (Bacirom® 1000 mg injection) was obtained from Aristo Pharmaceuticals Pvt. Ltd., Ahmedabad, Gujarat. Perchloric acid (70-72%) and sodium acetate of analytical grade; while water, methanol, acetonitrile and acetic acid (glacial) of HPLC grade were purchased from Merck Life Science Pvt. Ltd., Mumbai, India.

Administration of cefpirome. Cefpirome sulfate was administered at the dose rate of 10 mg/kg of body weight. The solution of the cefpirome sulfate injection was prepared by dissolving Cefpirome sulfate 1000 mg injection (Bacirom) in sterile water to make a total volume of 10 mL, for both intravenous and intramuscular administration. Intravenous injection of the drug was through the jugular vein, while intramuscular injection was given in the gluteal muscle, using a 22G x 25mm needle.

Collection of blood samples. Blood samples (2 mL) were collected with the help of an intravenous catheter (Venflon, 22×0.9×25 mm) fixed into the contra lateral jugular vein and then transferred to clean sterilized heparinized vials. Blood samples were collected at time 0 (before drug administration), and at 0.033 (2 minutes), 0.083 (5 minutes), 0.166 (10 minutes), 0.25 (15 minutes), 0.5 (30 minutes), 0.75 (45 minutes), and 1, 2, 4, 8, 12, 18 and 24 hours after intravenous administration. Following intramuscular administration the blood samples were collected at time 0 (before drug administration), and at 0.083 (5 minutes), 0.166 (10 minutes), 0.25 (15 minutes), 0.5 (30 minutes), 0.75 (45 minutes), and 1, 2, 4, 8, 12, 18, 24, 36 and 48 hours.

Preparation of plasma samples. The plasma was separated immediately after blood collection using a centrifuge machine (Eppendorf 5804 R, Germany) at 2655 g for 10 minutes at 10°C. The separated plasma samples were transferred to labeled cryovials and stored at -60°C until assayed for cefpirome concentrations using HPLC. The drug quantitation was performed within 48 hours of sample collection.

Cefpirome assay.

Apparatus. Laballiance (USA) high performance liquid chromatography apparatus was used for the assay, comprising a quaternary gradient delivery pump (model AIS 2000) connected to an autosampler (model Sykam S 5200) and UV detector (model 500). Chromatographic separation was performed by reverse phase C_{18} column (Whatman, PARTISIL 5 ODS-3 RAC-II; 4.6 × 100 mm ID) at room temperature. The data integration was performed using Clarity software (Version 8.3.0).

Chromatographic conditions. The detection of cefpirome in different standard solutions and in plasma samples was carried out using the gradient mobile phase. The mobile phase consisted of water (solution A), acetonitrile (solution B), and buffer (solution C). The buffer was prepared by mixing sodium acetate and water to yield a strength of

0.2 M sodium acetate, with pH 5.2, adjusted using 0.2 M acetic acid (glacial). The mobile phase was filtered by 0.45 µm size filter (Ultipor N66 Nylone 6,6 membrane, PALL Pharmalab filtration Pvt. Ltd., Mumbai) and degassed by an ultrasonic sonicator. The ratio of solutions A, B and C of the mobile phase was programmed initially *i.e.* at 0 min (86:10:4), and at 4 min (76:20:4) and at 8 min (86:10:4). The mobile phase was pumped into the column with a flow rate of 1.0 mL/min at ambient temperature, and the effluent was monitored at 258 nm wavelength.

Extraction and sample preparation. In the present study, exactly 50 µL of plasma sample was placed into a 2 mL micro-centrifuge tube and then 100 µL of solution containing 0.8 M perchloric acid:methanol (50:50) was added to precipitate the plasma proteins. The mixture was vortexed for 1 minute and then centrifuged at 4116 g for 10 minutes at 10^0C. The clean supernatant was decanted into a clean sterile micro-centrifuge tube, and 20 µL of each sample was injected into the loop injector using the autosampler.

Preparation of standard calibration curve. Accurately weighed 10.0 mg of pure cefpirome sulfate powder was dissolved in 10 mL of HPLC grade water to obtain a 1000 µg/mL concentration of cefpirome stock solution. Different standards with concentrations of 20, 10, 5, 2.5, 1, 0.5, 0.25 and 0.12 µg/mL were prepared in both HPLC water and drug free sheep plasma by diluting the stock solution.

Partial validation of assay. To fulfill the requirements of partial validation of this HPLC method for analysis of cefpirome, the major parameters calculated were: linearity, absolute recovery, accuracy, precision (intraday and interday), limit of detection (LOD), and limit of quantification (LOQ). The assay was sensitive, reproducible, and its linearity was observed in the range from 0.12 to 20.00 µg/mL. The calibration curve was found to be linear over this range, with a mean correlation coefficient (R^2) value of 0.9996. Absolute recovery was calculated by comparison of the areas of peak of cefpirome standards in the water and plasma, containing concentrations of 1, 5 and 20 µg/mL. Intraday and interday precision (n=3) was expressed in terms of C.V. % (Co-efficient of variance) and was calculated as Precision C.V. % = (standard deviation / mean of observed concentration) X 100. The highest intraday and interday C.V. % calculated was 10.653 % (at 1 µg/mL) and 9.475 % (at 1 µg/mL), respectively. The retention times of cefpirome ranged between 4.327 and 4.723 minutes, with a mean of 4.525 minutes. Limit of detection (LOD) and limit of quantification (LOQ) were calculated as 0.494 and 1.498 µg/mL, respectively, using the standard deviation of responses (Std. Dev.) and the slope value of the calibration curve (ICH, 2005).

Pharmacokinetic analysis. The plasma concentration-time curves of individual sheep were subjected to non-compartmental analysis using 'PK Solver 2.0' software for calculating the targeted pharmacokinetic (PK) parameters of cefpirome, and the values were presented as mean ± standard error (SE) using the data set of six ewes.

Dosage regimen. The minimum inhibitory concentration (MIC) for the majority of cefpirome sensitive bacteria is in the range of 0.12 to 2.0 µg/mL (CRAIG and ANDES, 2015). For intravenous dosage regimens the priming dose (D) and maintenance dose (D') of cefpirome, based on the desirable minimum plasma concentration, was calculated by the following equation:

$$D = C_P^{\alpha}(\min).V_d(e^{\beta\tau})$$
$$D' = C_P^{\alpha}(\min).V_d(e^{\beta\tau} - 1)$$

Where: C_P^{α} is the minimum inhibitory concentration, V_d is the volume of distribution at steady state, e represents the base of natural logarithm, β is overall elimination rate constant and τ (Tau) is the dosage interval (BAGGOT, 1977).

Results

The semilogarithmic plot of the plasma levels of cefpirome as a function of time after single dose (10 mg/kg body weight) intravenous and intramuscular administration in ewes is depicted in Fig. 1. Following intravenous administration of cefpirome, the mean peak plasma drug concentration of 54.12 ± 0.99 µg/mL was observed at 0.033 h, which rapidly declined to 16.32 ± 0.67 µg/mL at 1 h. Thereafter, the drug concentration in the plasma diminished gradually and was detectable

up to 12 h. A drug concentration of 0.35 ± 0.12 µg/mL was detected in the plasma at 12 h. Following intramuscular administration of the cefpirome, a drug concentration of 8.80 ± 0.36 µg/mL was observed at 0.083 h. The mean peak plasma drug concentration (C_{max}) of 21.91 ± 0.50 µg/mL was achieved at 0.5 h (T_{max}) and it declined rapidly to 6.09 ± 0.8 µg/mL at 4 h. The drug concentration of 0.44 ± 0.08 µg/mL in plasma was detected at 12 h. The drug was not detected in plasma samples collected after 12 h after intravenous and intramuscular administration of cefpirome in the ewes.

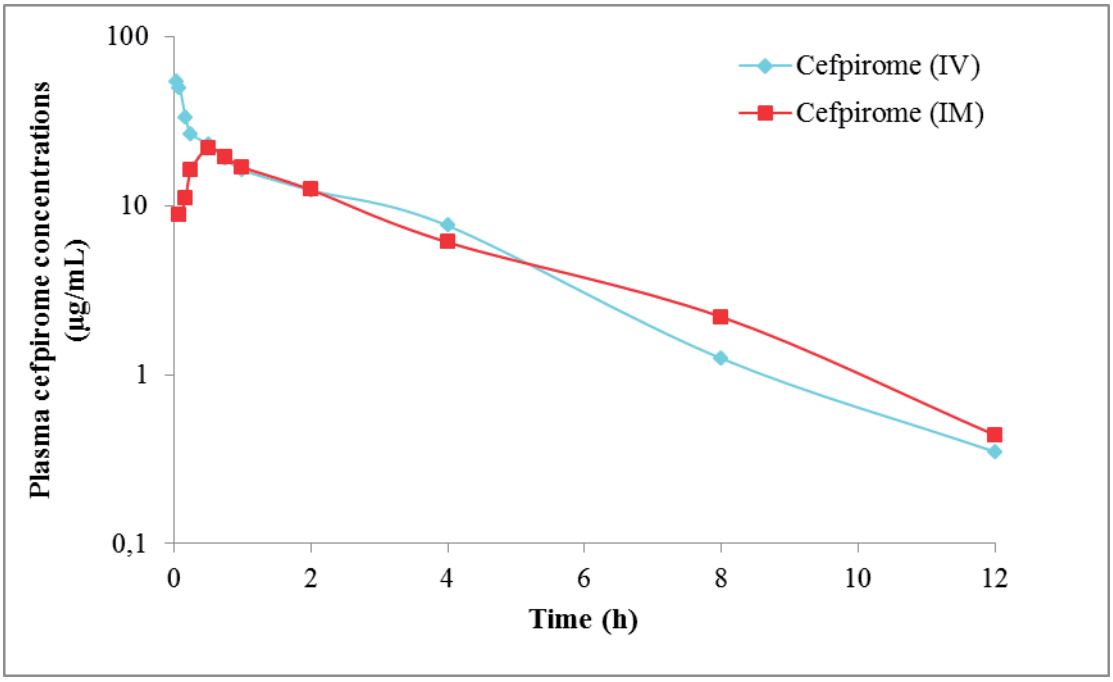

Fig. 1. Semilogarithmic plot of cefpirome concentration in plasma versus time following single dose intravenous and intramuscular administration at the dose rate of 10 mg/kg in ewes (Each point represents Mean ± SE of six animals)

In the present study, the plasma cefpirome concentrations measured at various time intervals following intravenous and intramuscular administrations in ewes were used to obtain pharmacokinetic (PK) parameters, which are summarized in Table 1. The cefpirome concentration in plasma was maintained above the target MIC (≥0.25 µg/mL) for 12 h. Therapeutic dosage regimens were calculated for maintenance of minimum concentrations of 0.12, 0.25, 0.5, 1 and 2 µg of cefpirome per mL of plasma at dosing intervals of 6, 8 and 12 h and are given in Table 2.

Discussion

In the present study, the elimination half-life ($t_{½β}$) of cefpirome following single dose intravenous administration at the dose rate of 10 mg/kg in ewes was 1.68 ± 0.21 h. However, higher values of half-life were observed for cefpirome in cow calves (2.41 ± 0.23 h) (PATEL et al., 2013), buffalo calves (2.14 ± 0.02 h) (RAJPUT et al., 2007b) and in goats [2.20 ± 0.03 h (SOLANKI et al., 2014) and 2.12 ± 0.14 h (BAROT et al., 2013)]. Moreover, a similar mean elimination half life of 1.69 ± 0.07 h for ceftriaxone (CORUM et al., 2018), and a higher

Table 1. Pharmacokinetic parameters of cefpirome after single dose intravenous and intramuscular administration (10 mg/kg) in ewes (Mean ± SE; n=6)

Pharmacokinetic Parameters	Unit	Intravenous	Intramuscular
Cp^0	µg/mL	57.91 ± 1.99	-
β	h^{-1}	0.43 ± 0.04	0.33 ± 0.01
$t_{½\beta}$	h	1.68 ± 0.21	2.04 ± 0.06
C_{max}	µg/mL	-	21.91 ± 0.50
T_{max}	h	-	0.50 ± 0.00
$AUC_{0-\infty}$	µg.h/mL	82.71 ± 3.76	73.27 ± 4.04
AUMC	$\mu g.h^2/mL$	211.06 ± 23.99	229.02 ± 20.32
MRT	h	2.51 ± 0.19	3.09 ± 0.12
Vd_{area}	L/kg	0.28 ± 0.03	0.45 ± 0.03
Vd_{ss}	L/kg	0.30 ± 0.01	-
Cl_B	L/h/kg	0.11 ± 0.00	0.14 ± 0.01
F	%	-	88.85 ± 4.07

Cp^0-Initial plasma drug concentration after IV administration, β-Elimination rate constant, $t_{½\beta}$-Elimination half-life, C_{max}-Peak plasma concentration, T_{max}-Time at which C_{max} was observed, $AUC_{0-\infty}$-Area under plasma drug concentration-time curve, AUMC-Area under first moment of the plasma drug concentration, MRT-Mean Residence Time, Vd_{area}-Apparent volume of distribution, Vd_{ss}-Volume of distribution at steady state, Cl_B-Total body clearance, F-Bioavailability.

Table 2. Proposed intravenous dosage regimens of cefpirome for ewes

MIC µg/mL	Dose (mg/kg) and dosing intervals (h)					
	6 h		8 h		12 h	
	D	D'	D	D'	D	D'
0.12	0.47	0.43	1.12	1.08	6.26	6.23
0.25	0.98	0.91	2.33	2.26	13.06	12.98
0.5	1.97	1.82	4.67	4.52	26.12	25.97
1	3.95	3.65	9.35	9.05	52.24	51.94
2	7.91	7.31	18.71	18.11	104.48	103.88

MIC-Minimum Inhibitory Concentration, D-Priming dose, D'-Maintenance dose.

mean elimination half life of 2.54 ± 0.12 h for cefepime (PATEL et al., 2010) were also reported in sheep. The elimination half-life of cefpirome following single dose intramuscular administration at the dose rate of 10 mg/kg in ewes was 2.04 ± 0.06 h, which is similar to the reported values of half-life for cefpirome in cross bred calves (2.06 ± 0.02 h) (RAJPUT et al*.,* 2012) and goats (2.09 ± 0.08 h) (BAROT et al., 2013). However, higher half-life values were also reported for cefpirome in cow calves (3.61 ± 0.12 h) (PATEL et al*.,* 2013), buffalo calves (2.39 ± 0.05 h) (RAJPUT et al., 2007a) and goats (3.58 ± 0.02 h) (SOLANKI et al., 2014), while lower values of half-life for cefpirome have been reported in dogs (1.12 ± 0.17 h) (ISERT et al*.,* 1992) and rats (0.40 ± 0.06 h) (ISERT et al., 1992). In addition, TOHAMY (2011) and PATEL et al. (2010) reported a higher mean elimination half life of 2.41 ± 0.19 h for cefquinome and 5.17 ± 0.44 h for cefepime, respectively, in sheep. The values of half-life observed by both routes of drug administrations in the present study indicate that cefpirome has fairly rapid elimination from the body.

The mean apparent volume of distribution (Vd_{area}) and mean volume of distribution at steady state (Vd_{ss}) calculated following single dose intravenous administration of cefpirome (10 mg/kg) in ewes were 0.28 ± 0.03 L/kg and 0.30 ± 0.01 L/kg, respectively. The values of Vd_{area} and

Vd_{ss} of cefpirome found in ewes are in agreement with the values of Vd_{area} and Vd_{ss} reported in cow calves (Vd_{ss}: 0.33 ± 0.01 L/kg) (PATEL et al., 2013) and goats (Vd_{ss}: 0.35 ± 0.01 L/kg) (BAROT et al., 2013). However, higher values of Vd_{area} and Vd_{ss} have been reported in buffalo calves (Vd_{area}: 0.42 ± 0.005 L/kg and Vd_{ss}: 0.40 ± 0.004 L/kg) (RAJPUT et al., 2007b) and goats (Vd_{ss}: 0.40 ± 0.01 L/kg) (SOLANKI et al., 2014). ISMAIL (2005) reported a similar value of Vd_{ss} (0.32 ± 0.01 L/kg) for cefepime, while CORUM et al. (2018) reported a higher value of Vd_{area} (0.92 ± 0.13 L/kg) for ceftriaxone and Vd_{ss} (0.42 ± 0.02 L/kg) for cefepime (PATEL et al., 2010) in sheep. The mean Vd_{area} calculated following single dose intramuscular administration of cefpirome (10 mg/kg) in ewes was 0.45 ± 0.03 L/kg in the present study. The Vd_{area} of cefpirome found in ewes is similar to the value of Vd_{area} reported in buffalo calves (0.42 ± 0.01 L/kg) (RAJPUT et al., 2007a). While, higher values have been reported in cow calves (0.81 ± 0.07 L/kg) (PATEL et al., 2013) and dogs (6.3 ± 1.90 L/kg) (ISERT et al., 1992) for cefpirome. A higher value of Vd_{area} (1.11 ± 0.1 L/kg) has been also reported for cefepime in sheep (PATEL et al., 2010). The lower value of Vd_{area} by both routes of drug administration in the present study indicates the poorer distribution of the drug in body tissues and fluids, as seen with other cephalosporin class drugs.

The total body clearance of cefpirome in ewes following single dose intravenous administration was calculated to be 0.11 ± 0.00 L/h/kg, which is similar to the value obtained in buffalo calves (0.14 ± 0.002 L/h/kg) (RAJPUT et al., 2007b). In contrast to the present study, CORUM et al. (2018) and PATEL et al. (2010) reported higher value of total body clearance *i.e.* 0.38 ± 0.05 L/h/kg for ceftriaxone and 2.48 ± 0.09 L/h/kg for cefepime, respectively, in sheep. The total body clearance of cefpirome in ewes following single dose intramuscular administration was calculated to be 0.14 ± 0.01 L/h/kg in the present study, which is similar to the clearance of cefpirome in buffalo calves (0.12 ± 0.003 L/h/kg) (RAJPUT et al., 2007a) and cefepime in sheep (0.15 ± 0.01 L/h/kg) (PATEL et al., 2010). Cefpirome is mainly excreted by the kidneys by means of glomerular filtration (CRAIG and SUH, 1991). The slow clearance rate of cefpirome from the body of sheep in the present study might be due to lower glomerular filtration and tubular secretion of the drug.

The MRTs calculated following single dose intravenous and intramuscular administrations of cefpirome in the present study were 2.51 ± 0.19 h and 3.09 ± 0.12 h, respectively, in ewes. The values obtained following IV administration was comparable with the value of MRT in goats (2.60 ± 0.03 h) (SOLANKI et al., 2014), while higher values were reported in buffalo calves (2.89 ± 0.01 h) (RAJPUT et al., 2007b) and goats (2.72 ± 0.11 h) (BAROT et al., 2013), and a lower value was reported in cow calves (2.14 ± 0.06 h) (PATEL et al., 2013). PATEL et al. (2010) reported a higher mean value of MRT (2.84 ± 0.13 h), while ISMAIL (2005) reported a lower value (2.28 ± 0.09 h) for cefepime following intravenous administration. Following intramuscular administration of cefquinome and cefepime, higher values of MRT *i.e.* 5.132 ± 0.370 h (TOHAMY, 2011) and 6.89 ± 1.0 h (PATEL et al., 2010), respectively, were observed in sheep. The value of MRT in the present study indicates that cefpirome remains for a relatively longer duration in the body due to its lower elimination rate.

The systemic bioavailability of cefpirome (88.85 ± 4.07 %) following intramuscular administration in ewes indicates adequate absorption of the drug. Similarly, good bioavailability has been reported in rats (88 %) at the dose rate of 40 mg/kg (ISERT et al., 1992), while comparatively lower bioavailability was reported in cow calves (61.00 ± 1.00 %) (PATEL et al., 2013), buffalo calves (35.3 ± 3.10 %) (RAJPUT et al., 2007a) and goats (72.0 ± 1.00 %) (SOLANKI et al., 2014). Similar to the present study, ISMAIL (2005) reported good bioavailability (86.8 ± 7.5 %), while PATEL et al. (2010) reported an even higher value of bioavailability (103.0 ± 8.0 %) following intramuscular administration of cefepime in sheep. The bioavailability obtained after intramuscular administration of the drug in ewes was almost comparable with administration of the drug by intravenous route, which is due to the adequate absorption of the drug in the body. Variations observed in plasma concentrations and

pharmacokinetic parameters are also attributable to species variation, along with differences in dose, drug administration method, dosage form, time of blood collection and assay methodology.

Conclusions

The optimal intravenous dosage regimen calculated using the pharmacokinetic parameters generated in the present study indicated that the most appropriate priming and maintenance doses of cefpirome to maintain MIC of ≥ 0.25 µg/mL with a dosage interval of 12 h, would be 13.00 mg/kg body weight in ewes.

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SARVAIYA, V. N., K. A. SADARIYA, S. BHAVSAR, A. M. THAKER: Farmakokinetika u plazmi i režim doziranja cefpirom-sulfata u ovaca. Vet. arhiv 92, 411-420, 2022

SAŽETAK

Cefpirom je cefalosporin četvrte generacije lijekova sa širokim spektrom djelovanja protiv gram-pozitivnih i gram-negativnih mikroorganizama. Istraživanje farmakokinetike pojedinačne doze cefpirom-sulfata, primijenjene intravenski (iv.) i intramuskularno (im.) (10 mg/kg tjelesne mase), provedeno je tekućinskom kromatografijom visoke djelotvornosti (HPLC) te su utvrđeni pokazatelji za optimalan režim doziranja u ovaca. Nakon intravenske primjene cefpiroma u ovaca prosječna vrijednost konstante brzine eliminacije (β) bila je 0,43 ± 0,04 h^{-1}, poluvijek eliminacije ($t_{½β}$) 1,68 ± 0,21 h, područje ispod krivulje odnosa koncentracije u plazmi i vremena ($AUC_{0-\infty}$) 82,71 ± 3,76 μg.h/mL, područje ispod krivulje prvog momenta koncentracije u plazmi (AUMC) 211,06 ± 23,99 μg.h^2/mL. Nadalje, srednja vrijednost vremena zadržavanja (MRT) bila je 2,51 ± 0,19 h, prividni volumen distribucije (Vd_{area}) 0,28 ± 0,03 L/kg i ukupni tjelesni klirens (Cl_B) 0,11 ± 0,00 L/h/kg. Srednje vrijednosti tijekom intramuskularne primjene cefpiroma za prethodno navedene parametre bile 0,33 ± 0,01 h^{-1}, 2,04 ± 0,06 h, 73,27 ± 4,04 μg.h/mL, 229,02 ± 20,32 μg.h^2/mL, 3,09 ± 0,12 h, 0,45 ± 0,03 L/kg i 0,14 ± 0,01 L/h/kg. Bioraspoloživost nakon intramuskularne primjene cefpiroma bila je 88,85 ± 4,07 %. Koncentracija cefpiroma u plazmi održavana je iznad ciljne vrijednosti MIK-a (≥ 0,25 μg/mL) tijekom 12 sati. Terapijski režim doziranja izračunat na temelju farmakokinetičkih pokazatelja dobivenih intravenskom primjenom lijeka upućuje na optimalnu dozu cefpiroma kojom se može održati MIK pri vrijednosti ≥ 0,25 μg/mL s intervalom doziranja od 12 sati, a ta bi doza u ovaca bila 13,00 mg/kg tjelesne mase.

Ključne riječi: farmakokinetika; režim doziranja; cefpirom-sulfat; ovce