Indian Journal of Animal Sciences **93** (8): 770–776, August 2023/Article
https://doi.org/10.56093/ijans.v93i8.125060

Pharmacokinetics of cefpirome following intravenous and intramuscular administrations in healthy and febrile sheep (*Ovis aries*)

VAIDEHI N SARVAIYA[1]✉, KAMLESH A SADARIYA[1], SHAILESH K BHAVSAR[1], ASWIN M THAKER[1] and RAKESH J MODI[1]

Kamdhenu University, Anand, Gujarat 388 001 India

Received: 23 June 2022; Accepted: 27 July 2023

ABSTRACT

Cefpirome is fourth generation cephalosporin class of drug, which facilitates rapid penetration through the outer membrane of Gram-negative bacteria and results in potent activity against Gram-negative pathogens. As fever is one of the most common manifestations in bacterial diseases, the study was undertaken to investigate pharmacokinetics of single dose intravenous and intramuscular administrations of cefpirome (10 mg/kg of body weight) in healthy and lipopolysaccharide (LPS) induced febrile sheep as well as to perform PK-PD analysis using MIC values reported in previous studies and the pharmacokinetic parameters obtained in this study. Following intravenous and intramuscular administrations of cefpirome in healthy sheep, the plasma drug concentration was detected up to 12 h, while plasma drug concentration was detected up to 18 h following intravenous and intramuscular administrations in febrile sheep. Induction of febrile state significantly altered pharmacokinetic profile of cefpirome including significant increase in the mean values of $t_{½\beta}$, $AUC_{0-\infty}$ and MRT while significant decrease in the mean values of Vd_{area}, Vd_{ss} following intravenous administration, while significant decrease in the mean values of Vd_{area} and Cl_B, whereas significant increase in the mean values of $t_{½\beta}$, C_{max}, $AUC_{0-\infty}$ and MRT following intramuscular administration of cefpirome as compared to their respective mean values in healthy sheep. Based on pharmacokinetic-pharmacodynamic integration, an optimal intramuscular dosage regimen of 10 mg/kg once daily for cefpirome in febrile sheep was predicted for targeted average MIC of ≤ 0.25 µg/mL.

Keywords: Cefpirome sulfate, Febrile, Pharmacodynamic, Pharmacokinetic, Sheep

Antibiotic chemotherapy for most of the bacterial infections is highly effective if the causative agent is susceptible to the particular antibacterial drug (Balaban *et al.* 2019). The cephalosporin class is most widely prescribed antibacterial because of its broad spectrum of activity, low toxicity, ease of administration and favorable pharmacokinetic profile. Cephalosporins are bactericidal drugs and like other beta lactam antibiotics show time dependent killing dynamics (Rodriguez-Gascon *et al.* 2021).

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). Fourth generation cephalosporins are the first line drugs for febrile neutropenia (FN). Cefpirome is indicated for various infectious inflammatory diseases like sepsis/ bacteremia; complicated urinary tract infections, respiratory infections, soft tissue infections; wound infections and infections with neutropenia.

Present address: [1]College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Banaskantha, Gujarat. ✉Corresponding author email: vaidehisarvaiya@gmail.com

Fever with sepsis/ bacteremia has been defined as the oldest and most obscure syndromes in medicine (Corcione *et al.* 2021). Febrile condition produced by *Escherichia coli*-derived lipopolysaccharide (LPS) has been considered as the suitable model for septic shock in laboratory animals as well as in farm animals. Disposition kinetic studies following intravenous administration have been reported for cefpirome (10 mg/kg) in cross-bred calves (Rajput *et al.* 2011), for cefepime (10 mg/kg) (Joshi and Sharma 2009) and for ceftazidime (10 mg/kg) (Sharma and Ul Haq 2012) in febrile buffalo calves. While disposition kinetic study following intramuscular route of administration have been reported for cefepime (20 mg/kg) in febrile sheep (Patel *et al.* 2012a) and goat (Patel *et al.* 2012b) and for ceftiofur (2.2 mg/kg) in febrile calves (Altan *et al.* 2017). However, no literature is available for influence of fever on the pharmacokinetics of cefpirome in sheep.

The duration of time during which drug concentrations exceed the minimum inhibitory concentration (T>MIC) is the major determinant of the antibacterial activity of the cephalosporins (Craig 1998, Craig 2003). Therefore, for judicious uses of cefpirome at rational dosage, knowledge of pharmacokinetics is required in sheep. The present study was undertaken to evaluate pharmacokinetics of single dose

intravenous (IV) and intramuscular (IM) administrations of cefpirome (10 mg/kg) in healthy and lipopolysaccharide (LPS) induced febrile sheep.

MATERIALS AND METHODS

Experimental animals: The study was conducted in six healthy female Patanwadi sheep (*Ovis aries*) of 2-3 years of age weighing between 30 and 35 kg. The animals were maintained at Livestock Farm Complex, College of Veterinary Science and Animal Husbandry which is located at semi-arid type of climate region of Anand, Gujarat. The animals were then housed in separate pens and were provided standard ration and *ad lib.* water. The animal experimentation protocol of present study (No. 197/VPT/15) was approved by Institutional Animal Ethics Committee (IAEC) of College of Veterinary Science and Animal Husbandry, Anand, Gujarat, India.

Six sheep were randomly divided into two treatment groups to study pharmacokinetics of cefpirome (10 mg/kg) following IV and IM administrations in healthy sheep in phase 1, and to study pharmacokinetics of cefpirome (10 mg/kg) following IV and IM administrations in experimentally induced febrile condition in phase 2. Both phases of study were performed in cross over design with washout period of 15 days.

Induction of febrile state and administration of cefpirome in febrile sheep: To study the effect of fever on pharmacokinetics of cefpirome, febrile state in sheep was induced by injecting lipopolysaccharides (LPS) from *Escherichia coli* (055:B5) at the dose rate of 0.2 µg/kg body weight intravenously (Verma and Roy 2006). This dose of lipopolysaccharides increased the body temperature of sheep within 30 min and fever persisted for 12 h. At least 1.5 to 2.0°F increase in body temperature was taken in consideration for drug administration (Agrawal *et al.* 2002). Rectal temperature, respiratory rates and heart rates before and after administration of LPS in sheep under treatment of cefpirome were recorded. LPS was again injected at dose rate of 0.1 µg/kg body weight at 12 h and at dose rate of 0.05 µg/kg body weight after 24 h of first dose, respectively to maintain the febrile state up to 36 h. Cefpirome was administered at a dose rate of 10 mg/kg of body weight in febrile sheep *i.e.* after minimum rise of 1.5°F temperature, which occurred around 1 h after injection of LPS. Intravenous injection of the drug was given through jugular vein and intramuscular injection was given in deep gluteal muscle using 22G × 25 mm needle.

Collection of blood samples: In both phases of pharmacokinetic study, blood samples (2 mL) were collected with the help of 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 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), 0.75 (45 min), 1, 2, 4, 8, 12, 18 and 24 h respectively after intravenous administration; while following intramuscular 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), 0.75 (45 min), 1, 2, 4, 8, 12, 18, 24, 36 and 48 h, respectively.

The plasma was separated immediately after blood collection at 2655 g for 10 min at 10°C using centrifuge machine (Eppendorf 5804 R, Germany). The separated plasma samples were transferred to labeled cryovials and stored at –40°C until assayed for cefpirome concentrations using HPLC. The drug quantitation was done within 48 h of sample collection.

Cefpirome assay: Plasma concentration of cefpirome was quantified by high-performance liquid chromatography method. High-performance liquid chromatography apparatus of Lab alliance (USA) comprising quaternary gradient delivery pump (model AIS 2000) connected with auto-sampler (model Sykam S 5200) and UV detector (model 500) was used for assay. 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 software Clarity (Version 8.3.0).

Chromatographic conditions: Detection of cefpirome in different standard solutions and in plasma samples were carried out using gradient mobile phase consisting of water (solution A), acetonitrile (solution B) and buffer part (solution C). Buffer part was prepared by mixing sodium acetate and water to yield strength of 0.2 M sodium acetate having pH 5.2 adjusted using 0.2 M acetic acid (glacial). Mobile phase was filtered by 0.45 µm size filter and degassed by ultrasonic sonicator. Ratio of solution A, B and C of mobile phase initially *i.e*. at 0 min (86:10:4), at 4 min (76:20:4) and at 8 min (86:10:4) were programmed. The mobile phase was pumped into column with flow rate of 1.0 mL/min at an ambient temperature and effluent was monitored at 258 nm wavelength.

*Extraction and sample preparation: E*xactly 50 µL of plasma sample was taken into 2 mL Eppendorf® micro-centrifuge tube and then 100 µL of solution containing 0.8 M perchloric acid: methanol (50:50) were added to precipitate the plasma proteins. The mixture was vortexed for 1 min and then centrifuged at 4116 g for 10 min at 10ºC. The clean supernatant was decanted in clean sterile micro-centrifuge tube and 20 µL of each sample was injected into the injector using autosampler. The assay was sensitive, reproducible and its linearity was observed in the range from 0.12 to 20 µg/mL. The calibration curve was found to be linear over this range with a mean correlation coefficient (R^2) value of 0.9996. The retention time of cefpirome was 4.53 min.

Pharmacokinetic analysis: The plasma concentration-time curves of individual sheep were subjected to non-compartmental analysis for working out targeted pharmacokinetic (PK) parameters of cefpirome with the software 'PK Solver 2.0'.

Statistical analysis: The effects of febrile condition on rectal temperature, heart rate, respiratory rate, plasma

cefpirome concentrations and pharmacokinetic parameters in sheep were statistically compared with healthy sheep by 'paired sample t-test' using software IBM SPSS (version 20), where $p<0.05$ was considered as statistically 'significant' and $p<0.01$ was considered as statistically 'highly significant'.

Pharmacokinetic-Pharmacodynamic (PK-PD) relationship: The time for which plasma drug concentrations remain above or equal to minimal inhibitory concentration (MIC) value (T>MIC) was calculated using the formula (Turnidge 1998):

$$\%\,T > MIC = ln\,\frac{D}{Vd_{area} \times MIC} \times \frac{t_{½\beta}}{\ln(2)} \times \frac{100}{\tau}$$

where T > MIC, the time interval (in %) during which the plasma concentration is above or equal to the MIC values; ln, natural logarithm; D, proposed dose; $Vd_{area,}$ apparent volume of distribution; $t_{½\beta}$, elimination half-life and τ, dosing interval.

In the present study, the MIC values between 0.12-2 µg/mL were used to calculate %T > MIC which is based on MIC_{90} values reported by Craig and Andes (2015) for cefpirome against susceptible bacteria.

RESULTS AND DISCUSSION

Present study did not reveal any abnormalities following intravenous and intramuscular administrations of cefpirome in healthy and febrile sheep. No local or systemic signs of adverse reactions were seen. In this study, rectal temperature, heart rates and respiratory rates before and after administration of LPS in sheep under treatment of intravenous and intramuscular cefpirome administrations were examined and the results are shown in Table 1. There was significant increase in body temperature, heart rates and respiratory rates in febrile sheep. Along with these, decreased feed consumption, dullness, depression, dryness of mouth and decreased movements were also recorded after 2-3 h of intravenous administration of *E. coli* LPS in sheep.

Similar to the result of present study, increase in body temperature, cardiac and respiratory rates following intravenous inoculation of the *E.coli* suspension into the rabbits (Goudah *et al.* 2006) has been reported. Sharma and Ul Haq (2012) and Joshi and Sharma (2009) have also reported identical results to the present study, in which body temperature rises significantly after intravenous administration of *E. coli* lipopolysaccharide in buffalo calves.

Plasma drug concentration at 1 h after intravenous administration of a single dose of cefpirome in febrile sheep was significantly higher ($p<0.01$) as compared to plasma drug concentration found at 1 h in healthy sheep (Table 2) (Fig. 1). As compared to our findings, lower mean peak plasma concentration of cefpirome (46.50±0.40 µg/mL) was achieved at 1 min, which rapidly declined to 11.80±0.15 µg/mL at 45 min and the drug was detected in plasma up to 14 h in febrile cross-bred calves (Rajput *et al.* 2011). However, higher mean peak plasma concentration of ceftazidime (152.3±6.77 µg/mL) was achieved at 2.5 min which rapidly declined to a plasma concentration of 88.4±4.07 µg/mL at 15 min and was detected upto 14 h in febrile buffalo calves (Sharma and Ul Haq 2012).

Following intramuscular administration of cefpirome in febrile sheep, the peak plasma concentration (C_{max}) observed at 0.5 h (T_{max}) was significantly higher ($p<0.01$) than healthy sheep (Table 2) (Fig. 1). Patel *et al.* (2012a) and Patel *et al.* (2012b) have reported relatively higher mean peak plasma concentrations at 1 h (T_{max}) for cefepime (C_{max}) i.e. 39.68±1.13 µg/mL (febrile sheep) and 39.23±1.11 µg/mL (febrile goat), respectively.

The elimination half-life ($t_{½\beta}$) of cefpirome following intravenous administration in febrile sheep was

Table 1. Rectal temperature, heart rate and respiratory rate after IV administration of *E. coli* lipopolysaccharide in sheep treated with IV and IM cefpirome (Mean±SE, n=6)

Time (h)	Rectal temperature (°F)		Heart rate/min		Respiratory rate/min	
	IV	IM	IV	IM	IV	IM
0 (Control)	100.8±0.78	100.8±0.36	68.1±0.47	69.0±0.57	26.1±0.30	26.0±0.36
0.5	101.4±0.63	101.2±0.42	70.1±0.60*	72.1±0.47**	26.5±0.42	30.5±0.42**
1	102.6±0.47	102.4±0.24*	71.5±0.42**	71.8±0.79**	27.6±0.42*	31.0±0.57**
2	102.0±0.40	102.3±0.38*	71.8±0.47**	73.0±0.57**	27.5±0.42*	32.0±0.68**
3	102.8±0.32	102.0±0.46	71.6±0.84*	74.5±0.42**	29.8±0.47**	32.5±0.76**
4	102.6±0.39	102.2±0.48	73.8±0.60**	73.1±0.47**	31.0±0.57**	31.3±0.55**
5	102.1±0.44	102.6±0.42*	73.3±0.66**	72.8±0.60**	32.0±0.57**	30.6±0.61**
6	102.9±0.33	102.4±0.27*	75.1±0.47**	73.1±0.30**	32.3±0.42**	32.0±0.57**
8	102.1±0.38	103.0±0.23**	73.0±0.57**	72.0±0.57*	31.5±0.42**	33.0±0.57**
12	103.0±0.37**	103.2±0.49**	71.3±0.49**	72.3±0.71*	29.5±0.42**	31.5±0.76**
18	102.0±0.29	101.7±0.26*	70.0±0.57*	73.5±0.42**	27.3±0.42	30.8±0.60**
24	101.4±0.39	102.5±0.56	72.5±0.42**	72.6±0.42*	29.5±0.56**	32.8±0.60**
30	102.3±0.44**	101.7±0.41	71.5±0.42*	71.3±0.49**	29.1±0.54**	31.1±0.70**
36	101.5 ±0.37	101.4±0.47	71.1±0.60*	72.8±0.60**	31.0±0.73**	30.8±0.60**

Mean values bearing * and ** superscripts within column differ significantly from control value when compared using paired sample t-test at significance level of $P<0.05$ and $P<0.01$, respectively.

Table 2. Comparison of plasma concentrations (µg/mL) of cefpirome after IV and IM administration (10 mg/kg) in healthy and febrile sheep (n=6)

Time of drug administration (h)	Intravenous (IV)		Intramuscular (IM)	
	Healthy	Febrile	Healthy	Febrile
0.033	54.12±0.99	63.37±0.34**	-	-
0.083	49.92±1.45	57.81±0.52**	8.80±0.36	13.63±0.48**
0.166	33.62±0.65	48.33±0.57**	11.00±0.71	16.87±0.64**
0.25	26.74±0.76	44.28±0.85**	16.43±0.61	24.49±0.24**
0.5	23.16±0.98	39.12±0.75**	21.91±0.50	29.86±0.56**
0.75	19.09±0.50	32.89±0.55**	19.47±0.69	28.55±0.57**
1	16.32±0.67	26.58±0.64**	16.96±0.46	25.55±0.41*
2	12.37±0.57	20.45±0.52**	12.45±0.55	22.95±0.62**
4	7.63±0.61	16.09±0.75**	6.09±0.80	15.48±0.42**
8	1.25±0.40	9.20±0.46**	2.20±0.46	9.00±0.72**
12	0.35±0.12	2.95±0.63**	0.44±0.08	3.89±0.82*
18	ND	0.83±0.16	ND	0.67±0.08
24	ND	ND	ND	ND

* in row denotes significant ($p<0.05$) variation; and ** in row denotes highly significant variation ($p<0.01$) in febrile sheep when compared using paired sample t-test to respective mean values of healthy sheep in same route of administration. ND, Not detected.

significantly ($p<0.05$) higher as compared to healthy sheep (Table 3). However, lower value of $t_{½\beta}$ (1.90±0.03 h) for cefpirome has been reported in febrile cross-bred calves (Rajput *et al.* 2011) and higher values have been reported for ceftazidime (3.73±0.42 h) and cefepime (3.00±0.18 h) in febrile buffalo calves (Joshi and Sharma 2009, Sharma and Ul Haq 2012). The elimination half-life of cefpirome following single dose intramuscular administration in febrile sheep was significantly ($p<0.01$) higher as compared to healthy sheep in present study. Similarly, significant ($p<0.05$) increase for cefepime (5.13±0.27 h) in febrile goat (6.64±0.33 h) (Patel *et al.* 2012b) and non-significant increase for cefepime (5.31±0.23 h) in febrile sheep (5.50±0.25 h) (Patel *et al.* 2012a) had been reported.

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 in febrile sheep were significantly lower as compared to healthy sheep (Table 3). The values obtained for cefpirome in present study were in agreement with values determined for ceftazidime (Vd_{area}: 0.26±0.05 L/kg and Vd_{ss}: 0.20±0.02 L/kg) (Sharma and Ul Haq 2012), while lower values were reported for cefpirome (Vd_{area}: 0.75±0.02 L/kg and Vd_{ss}: 0.68±0.02 L/kg) (Rajput *et al.* 2011) in febrile cross-bred calves and for cefepime (Vd_{area}: 0.42±0.02 L/kg and Vd_{ss}: 0.48±0.02 L/kg)

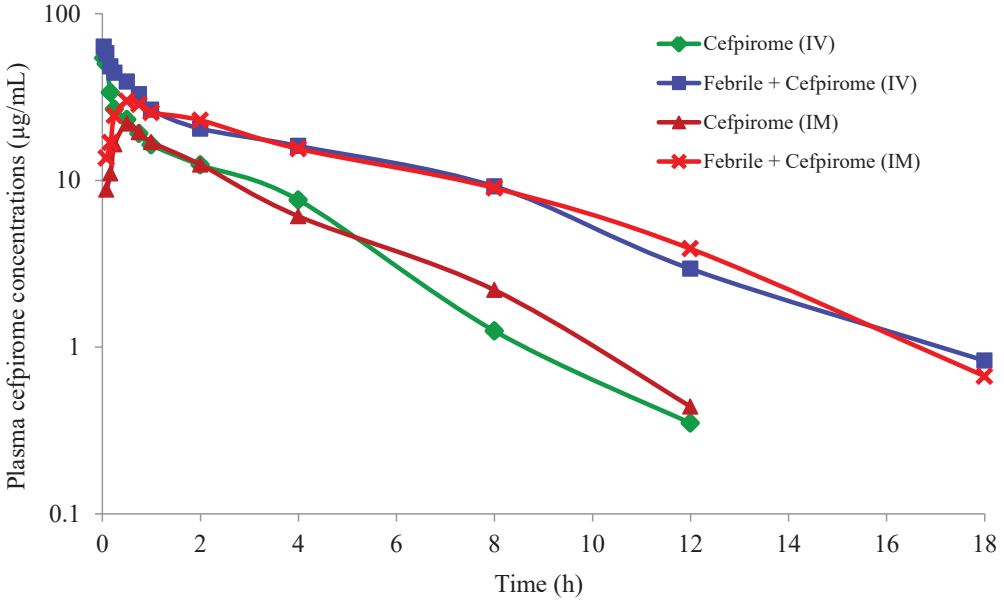

Fig. 1. Semilogarithmic plot of cefpirome concentration in plasma versus time following intravenous and intramuscular administrations (10 mg/kg) in healthy and febrile sheep (Each point represents mean of six animals).

Table 3. Comparison of pharmacokinetic parameters (Mean±SE) of cefpirome after IV and IM administration (10 mg/kg) in healthy and febrile sheep (n=6)

Pharmacokinetic parameter	Unit	Intravenous (IV)		Intramuscular (IM)	
		Healthy	Febrile	Healthy	Febrile
Cp^0	µg/mL	57.91±1.99	67.35±0.88*	-	-
β	h^{-1}	0.43±0.04	0.26±0.04*	0.33±0.01	0.23±0.01**
$t_{½β}$	h	1.68±0.21	2.81±0.32*	2.04±0.06	3.02±0.21**
C_{max}	µg/mL	-	-	21.91±0.50	29.86±0.56**
T_{max}	h	-	-	0.50±0.00	0.50±0.00
$AUC_{0-\infty}$	µg.h/mL	82.71±3.76	190.40±2.67**	73.27±4.04	178.50±6.24**
AUMC	$\mu g.h^2/mL$	211.06±23.99	886.77±41.30**	229.02±20.32	905.88±58.87**
MRT	h	2.51±0.19	4.64±0.17**	3.09±0.12	5.04±0.15**
Vd_{area}	L/kg	0.28±0.03	0.20±0.02*	0.45±0.03	0.25±0.02**
Vd_{ss}	L/kg	0.30±0.01	0.23±0.00**	-	-
Cl_B	L/h/kg	0.11±0.00	0.05±0.00**	0.14±0.01	0.05±0.00**
F	%	-	-	88.85±4.07	93.74±2.86

* in row denotes significant ($p<0.05$) variation; and ** in row denotes highly significant variation ($p<0.01$) in febrile sheep when compared using paired sample t-test to respective mean values of healthy sheep in same route of administration. Cp^0, Initial plasma drug concentration after IV administration; β, Elimination rate constant; $t_{½β}$, 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.

(Joshi and Sharma 2009) in febrile buffalo calves. The mean Vd_{area} calculated following single dose intramuscular administration of cefpirome was significantly ($p<0.01$) lower as compared to healthy sheep (Table 3). Similar to this finding, significant difference ($p<0.05$) was observed for cefepime (1.02±0.08 L/kg) in febrile sheep (0.73±0.04 L/kg) (Patel *et al.* 2012a) and non significant difference for cefepime (1.05±0.09 L/kg) in febrile goat (1.03±0.04 L/kg) (Patel *et al.* 2012b).

The AUC following intravenous administration of cefpirome in febrile sheep was significantly ($p<0.01$) higher as compared to value reported for healthy sheep (Table 3). Lower values have been reported for cefpirome (36.6±0.82 µg·h/mL) in febrile cross-bred calves (Rajput *et al.* 2011) and for cefepime (101.0±7.65 µg·h/mL) in febrile buffalo calves (Joshi and Sharma 2009), while higher value has been reported for ceftazidime (217.3±23.4 µg·h/mL) (Sharma and Ul Haq 2012) in febrile buffalo valves. Following intramuscular administration of cefpirome, the value of AUC in febrile sheep was significantly ($p<0.01$) higher as compared to healthy sheep (Table 3). Similar to this finding, significant ($p<0.05$) increase in the mean values of AUC for cefepime (153.63±10.16 µg·h/mL) in febrile sheep (221.67±15.42 µg·h/mL) (Patel *et al.* 2012a) and for desfuroyl ceftiofur after ceftiofur sodium injection (153±26 µg·h/mL) in febrile calves (223±41 µg·h/mL) (Altan *et al.* 2017), while non-significant increase for cefepime (139.08±10.28 µg·h/mL) in febrile goat (179.18±11.05 µg·h/mL) (Patel *et al.* 2012b) have been reported.

The total body clearance of cefpirome in febrile sheep following single dose intravenous administration was significantly ($p<0.01$) lower as compared to healthy sheep (Table 3). As compared to this finding, higher clearance rate (0.27±0.006 L/h/kg) was observed for cefpirome in febrile cross-bred calves (Rajput *et al.* 2011). The total body clearance of cefpirome in febrile sheep following single dose intramuscular administration was significantly ($p<0.01$) lower as compared to healthy sheep in this study. This finding is in agreement with the findings of Patel *et al.* (2012a) and Patel *et al.* (2012b), who reported significant ($p<0.05$) decrease in clearance rate for cefepime (0.13±0.01 L/h/kg) in febrile sheep (0.09±0.01 L/h/kg) and non-significant decrease for cefepime (2.38±0.20 L/h/kg) in febrile goat (1.80±0.11 L/h/kg), respectively.

Endotoxin of Gram-negative bacteria i.e. *E. coli* with their pyrogenic component lypopolysaccharide, is the most potent exogenous pyrogen. Endotoxin produces a dose related increase in body temperature. Febrile response is mediated by cytokines (particularly interleukin 6) in response to exogenous pyrogen (toxin). Acute phase response is the term used for hematological, endocrinological and metabolic changes that follow the onset of fever in response to infection, which are beneficial to the host (Holgersson *et al.* 2022). This response stimulates liver to produce various acute phase proteins (APPs) so there is increased synthesis and release of C-reactive protein (CRP) and α_1 acid glycoprotein into circulation in large amounts by hepatocytes. CRP plays a role in complement activation and increasing platelet aggregation (El-Radhi 2019). There are chances that drug may bind to APPs during febrile state. Smith *et al.* (2010) reported that there is change in plasma protein binding efficiency of drug during infection. Along with this, Strenkoski and Nix (1993) reported that cefpirome has low plasma protein binding capacity (~10%). These two factors might be ultimately responsible for significant decrease in the value of Vd_{area} of the drug in present study. Higher value of AUC in present study

Table 4. Calculated %T > MIC values for cefpirome following single intramuscular administration in healthy and febrile sheep at the dose of 10 mg/kg

Target MIC (µg/mL)	Cefpirome (IM)	Febrile + Cefpirome (IM)
	12 hourly dosing interval	24 hour dosing interval
0.12	128.05	105.45
0.25	110.05	92.13
0.5	93.05	79.55
1	76.05	66.96
2	59.05	54.38

indicates impaired tissue penetration of drug and large volume of plasma is covered by administered drug. The mean value of bioavailability was also increased in febrile group, which indicates extensive absorption of drug from site of drug administration along with significant increase in the value of AUC in febrile sheep as compared to healthy.

It is reported that output of anti-diuretic hormone (ADH), aldosterone and renal function are affected during higher body temperature in experimental animals, which ultimately decrease the kidney function (Mustafa *et al.* 2007). Addition to this, decrease in renal perfusion rate and endotoxin affected glomerular filtration rate may affects clearance of drug. So it is evidenced in the present study by significant decrease in the total body clearance of drug which is responsible for higher elimination half life in febrile sheep.

Cefpirome for bacteria with MIC value of ≤ 0.25 µg/mL maintained T > MIC values of 110.05% after single IM administration with 12 h of dosing interval and 92.13% after IM administration in febrile sheep with 24 h of dosing interval (Table 4). Studies recommend T > MIC values of 50% – 70% for cephalosporin (Connors *et al.* 2013). Optimal intramuscular dosage regimen of cefpirome would be 10 mg/kg body weight at 12 h of dosing interval based on observed plasma drug concentration as well as PK-PD integration and at 24 h of dosing interval in febrile sheep based on PK-PD integration for targeted average MIC of ≤0.25 µg/mL. Based on pharmacokinetic-pharmacodynamic relationship, it could be concluded that it would be highly efficacious to use cefpirome in sheep against susceptible bacterial infections.

ACKNOWLEDGEMENTS

This manuscript is a part of the Ph.D. thesis of the first author. The authors wish to acknowledge their gratitude to the Dean/Principal, College of Veterinary Science and Animal Husbandry, Anand, Gujarat, India for the financial support to carry out the research work.

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