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Pharmacokinetics of Cefpirome Following Intravenous and Intramuscular Administration in Cow Calves

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ABSTRACT

Background: Cefpirome is a broad-spectrum semi synthetic β-lactamase resistant fourth generation cephalosporin. Looking to potential for clinical use, pharmacokinetics of cefpirome following intravenous and intramuscular administration (10 mg kg^{-1}) in cow calves was determined. **Methods:** Cefpirome concentration in plasma samples was determined by reverse-phase high performance liquid chromatography with mobile phase. The mobile phase was a mixture of 0.2 M sodium acetate (3.5%), acetronitrile (17.5%) and HPLC water (79%) with a pH of 5.1. Mobile phase was filtered by 0.45 μ filters and pumped into column at a flow rate of 1.0 mL min^{-1} at ambient temperature. The effluent was monitored at 258 nm wavelength. **Results:** Following intravenous administration of the cefpirome in goats, volume of distribution at steady-state (Vd_{ss}), elimination half-life ($t_{1/2\beta}$) and total body clearance (Cl_B) were reported 0.33±0.01 L kg^{-1}, 2.41±0.23 h and 2.36±0.18 mL min^{-1} kg^{-1}, respectively. Following intramuscular administration of the drug, peak plasma concentration (C_{max}), elimination half-life ($t_{½\beta}$), apparent volume of distribution (Vd_{area}), total body clearance (Cl_B), bioavailability (F) were 13.27±0.19 μg mL^{-1}, 3.61±0.12 h, 0.81±0.007 L kg^{-1}, 2.83±0.08 mL min^{-1} kg^{-1} and 61±1%, respectively. **Conclusion:** Pharmacokinetic – pharmacodynamics integration indicates cefpirome can be useful in cow calves at dose rate of 10 mg kg^{-1} and repeated at interval of 12 h by intramuscular route.

Key words: Cefpirome, pharmacokinetics, intravenous, intramuscular, cow calves

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INTRODUCTION

Cefpirome is a broad-spectrum semi synthetic β-lactamase resistant fourth generation cephalosporin used in severely ill patients in the intensive care, oncology and transplantation units[1]. It has increased affinity for PBPs[2], reduce susceptibility to extended-spectrum β-lactamase and have ability to interfere with PBPs mediated cell wall synthesis ultimately leads to cell lysis[3]. It has potent bactericidal activity against a broad range of gram-negative and gram-positive organisms, including *Pseudomonas aeruginosa* and methicillin susceptible Staphylococcus spp., *Haemophillus influenzae* type B and many members of the Enterobacteriaceae family[4]. The disposition kinetics of cefpirome have been investigated in rabbits, dogs, mice, rat and monkey[5], buffalo calves[6,7] and goats[8]. However, there is no information available on the pharmacokinetic of cefpirome in cow calves following intravenous and intramuscular routes of administration. Looking to potential for clinical use and possibility for species difference, the study was undertaken on pharmacokinetics of cefpirome following intravenous and intramuscular administration in cow calves.

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MATERIALS AND METHODS

Experimental animals: The experiment was conducted on six healthy crossbred (Kankrej X H.F), weighing 65-105 kg. Each animal was housed in a separate pen and provided standard ration with *ad libitum* water. Cow calves were kept under constant observation for two weeks before the commencement of the experiment and subjected to clinical examination to exclude possibility of any diseases. The experimental protocol was approved by Institutional Animal Ethics Committee.

Drug and chemical: Cefpirome technical grade powder was procured from Orchid Pharma Ltd., Chennai. Cefpirome sulpahte powder (1 g Ceforth®;

Biochem pharmaceutical Industries Ltd., Mumbai) was purchased from local pharmacy. Water, acetonitrile, acetic acid (HPLC grade), sodium acetate and perchloric acid (AR grade) were purchased from S.D. Fine Chem Ltd., Merck India Ltd. and Sisco Research Laboratories Pvt. Limited, Mumbai, India.

Drug administration and sample collection: All six animals were randomly allocated to receive either an intravenous or intramuscular injection of Cefpirome at the dose rate of 10 mg kg^{-1}. A washout period of two weeks was observed between treatments. An intravenous injection of Cefpirome was administered in the left jugular vein. Blood samples (3 mL) were collected through an intravenous catheter (Venflon, 22×0.9×25 mm) fixed in the contra lateral jugular vein in glass test tubes, prior to injection and at 2, 5, 10, 15, 30 min and 1, 2, 4, 8, 12 and 18 h after intravenous administration. Following intramuscular injection of Cefpirome in the left deep gluteal muscle, blood samples (3 mL) were collected before administration and at 5, 10, 15, 30 min and 1, 2, 4, 8, 12, 18 and 24 h. Cow calves were monitored for any adverse reactions during the entire study period. Blood samples were centrifuged at 4116 g for 10 min at 4°C and plasma was transferred to cryo-vials (2 mL) and, stored at -20°C. Samples were analyzed within 48 h to quantify cefpirome concentration using high performance liquid chromatography.

Analytical assay of cefpirome and pharmacokinetic analysis: Cefpirome concentration in plasma samples was determined by reverse-phase High Performance Liquid Chromatography (HPLC) after extraction, using reported assays[8,9] with minor modifications. The High Performance Liquid Chromatography (HPLC) apparatus of Adept Cecil comprised of binary gradient delivery pump (model 4901), UV detector (model 4902) and reverse phase C18 column (4.6×100 mm ID). Pharmacokinetic data integration was performed using software "Power Stream" (Version 4.2). Plasma (500 μL) was deproteinized by addition of perchloric acid (0.8 M) and methanol (50:50) and vortexed for one minute. This was followed by centrifugation at 4116 g for 10 min. An aliquot of supernatant was collected in clean auto sampler vial. The mobile phase was a mixture of 0.2 M sodium acetate (3.5%), acetronitrile (17.5%) and HPLC water (79%). 0.2M acetic acid was used to adjust pH of 5.1. Mobile phase was filtered by 0.45 μ filters and pumped into column at a flow rate of 1.0 mL min^{-1} at ambient temperature. The effluent was monitored at 258 nm wavelength.

Calibration curve was prepared daily for drug concentration ranging from 0.8-200 μg mL^{-1}. The assay was sensitive (LLOD: 0.8 μg mL^{-1}) and reproducible and linearity was observed from 0.8-200 μg mL^{-1} (r^2 = 0.99). Precision and accuracy were determined using Quality Control (QC) samples at concentrations 1.6, 50, 200 μg mL^{-1} (5 replicates each day). Intraday and interday co-efficients of variability for five QC samples were satisfactory with the relative deviations (RSD) of less than 6.54%. An absolute recovery of cefpirome was measured up to 96.30%. Various pharmacokinetic parameters were calculated from serum concentration of cefpirome using software PK solution (version 2.0). The bioavailability (F) was calculated using following equation:

$$F(\%) = \frac{AUC\ (IM)}{AUC\ (IV)} \times \frac{DOSE\ (IV)}{DOSE\ (IM)}$$

Determination of minimal inhibitory concentrations of levofloxacin: Minimal inhibitory concentrations were determined against different organism *Streptococcus pyogenes* (ATCC:8668), *Staphylococcus aureus* (ATCC:25923), *Escherichia coli* (ATCC:25922), *Salmonella typhimurium* (ATCC:23564), *Pseudomonas aeruginosa* (ATCC:27853), *Proteus mirabilis* (NCIM:2241) and *Bacillus subtilis* (ATCC:9372). Which were procured form National Collection of Industrial Microorganism (NCIM), National Chemical Laboratory, Pune. The MIC of cefpirome was determined by micro broth dilution method in triplicates[10].

Statistical analysis: Cefpirome serum concentration and pharmacokinetic parameters of different treatment groups were compared by students' "t" test using SPSS software (version 12.0.1).

RESULTS

Following single dose intravenous and intramuscular administration of cefpirome in the cow calves, adverse reactions were not observed. Pharmacokinetic parameters (Mean±SE) calculated for both route of drug administration have been depicted in Table 1.

Following intravenous administration of cefpirome, therapeutic concentration of cefpirome = 0.5 μg mL^{-1} was maintained in plasma from upto 8 h. Following intramuscular administration of the cefpirome, mean peak plasma drug concentration (C_{max}) of 13.27±0.19 μg mL^{-1} was achieved at 0.75 h (T_{max}) which declined rapidly to 8.27±0.14 μg mL^{-1} at 2 h. The drug concentration of 1.06±0.05 μg mL^{-1} in plasma was detected at 12 h and thereafter drug was not detected in plasma samples collected beyond 12 h post intramuscular administration in cow calves.

Following intravenous administration of the drug in cow calves, distribution half-life ($t_{1/2\alpha}$) ranged between 0.46 and 0.64 h with a mean of 0.53±0.03 h. The mean values of volume of distribution at steady-state (Vdss) were calculated to be 0.30±0.01 L kg^{-1}. The elimination

Table1: Pharmacokinetic parameters of cefpirome (10 mg kg^{-1}) following intravenous and intramuscular administration in cow calves (Mean±SE, n = 6)

Pharmacokinetic parameters	Intravenous	Intramuscular
K_a (h^{-1})	-	4.38±0.37
β (h^{-1})	0.30±0.03	0.19±0.01
$t_{½Ka}$ (h)	-	0.16±0.01
$t_{½\alpha}$ (h)	0.53±0.03	-
$t_{½\beta}$ (h)	2.41±0.23	3.61±0.12
C_{max} (μg mL^{-1})	-	13.27±0.19
T_{max} (h)	-	0.75±0.00
$AUC_{(0-\infty)}$ (μg.h mL^{-1})	96.69±1.05	58.96±0.71
Vd_{ss} (L kg^{-1})	0.30±0.01	-
Vd_{area} (L kg^{-1})	-	0.81±0.07
$Cl_{(B)}$ (mL min^{-1} kg^{-1})	2.36±0.18	2.83±0.08
MRT (h)	2.14±0.06	4.88±0.13
F (%)	-	61.00±1.00

K_a: Absorption rate constant, β: Elimination rate constant, $t_{1/2\alpha}$: Half-life of distribution phases, $t_{1/2\beta}$: Elimination half life, $t_{1/2k(a)}$: Absorption half-life, $AUC_{(0-\infty)}$: Total area under plasma drug concentration-time curve, V_{darea}: Volume of distribution based on area, V_{dss}: Volume of distribution at steady state, Cl_B: Total body clearance, MRT: Mean residence time, C_{max}: Maximum drug concentration, T_{max}: Time of maximum concentration observed in plasma and F: Bioavailability

half-life ($t_{1/2\beta}$) ranged from 1.62 to 3.12 h with a mean of 2.41±0.23 h. Total body clearance (Cl_B) of the drug was 2.36±0.18 mL min^{-1} kg^{-1} with Mean Residence Time (MRT) of 2.14±0.06 h. Following intramuscular administration of the drug, absorption ($t_{½Ka}$) and elimination half-life (t½β) were 0.16±0.01 and 3.61±0.12 h, respectively. The mean apparent volume of distribution (Vd_{area}), total body clearance (Cl_B) and Mean Residence Time (MRT) were 0.81±0.07 L kg^{-1}, 2.83±0.08 mL min^{-1} kg^{-1} and 4.88±0.13 h, respectively. The bioavailability (F) of the drug following intramuscular administration ranged from 59-64% with an average of 61±1%.

The minimal inhibitory concentration of cefpirome were 0.13, 0.25, 0.5, 0.5, 1, 2 and 8 μg mL^{-1} for *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Proteus mirabilis*, respectively.

DISCUSSION

Following single dose intravenous administration, elimination half life ($t_{1/2\beta}$: 2.41±0.23 h) of cefpirome observed in cow calves is in agreement to the elimination half life of 2.14±0.02 h and 2.12±0.14 h reported in buffalo calves and goats[6,8]. However, shorter elimination half life of 0.19 h in mouse, 1.05 h in dogs, 1.17 h in monkeys and 1.48 h in rabbits[5], have been reported.

The mean residence time calculated following single dose intravenous administration was 2.14±0.06 h in cow calves, which is in agreement with reported values of 2.89±0.01 and 2.72±0.11 h in buffalo calves and goats[6,8]. However, it was observed that, cefpirome principally eliminated by the kidney and 80-90% of the administered drug was recovered as unchanged form in the urine[11]. Body clearance (2.36±0.18 mL min^{-1} kg^{-1}) of cefpirome in cow calves following intravenous route of administration in present study found to be higher than clearance values of 2.00±0.05 mL min^{-1} kg^{-1} in buffalo calves[6], 2.13±0.05 mL min^{-1} kg^{-1} in goats[8] and 3.2 mL min^{-1} kg^{-1} in dogs[8] reported following intravenous administration of cefpirome. The low value of mean volume of distribution at steady state (Vd_{ss}: 0.33±0.01 L kg^{-1}) in cow calves following cefpirome intravenous administration indicated the limited distribution of drug into various body fluids and tissues. Similar low value of Vd_{ss} (0.40±0.004 and 0.35±0.01 L kg^{-1}) have been reported in buffalo calves and goats[6,8]. In addition to this limited distribution of other cephalosporins like cefepime was also reported in goat and sheep[12,13,14,15].

Following intramuscular administration of cefpirome in cow calves, the peak plasma concentration (C_{max}) of 13.27±0.19 μg mL^{-1} was observed at 0.75 h (T_{max}). Similarly C_{max} of 9.04±0.5 μg mL^{-1} at 0.5 h in buffalo calves[6], 11.7 μg mL^{-1} at 0.42 h in monkeys, 9.2 μg mL^{-1} at 0.48 h in rats and 15.4 μg mL^{-1} at 0.70 h in dogs[5] and 10.97±0.34 μg mL^{-1} in goats [8]have been reported. Elimination half-life ($t_{½\beta}$:3.61±0.12 h) obtained in present study is higher than reported elimination half-life of 2.09±0.08 h in goats[8], 2.39±0.05 h in buffalo calves[7], 1.38 h in dogs and 1.23 h in monkeys[5]. Clearance (2.83±0.08 mL min^{-1} kg^{-1}) of the drug observed following intramuscular administration is similar to that reported in goat (2.88±0.10 mL min^{-1} kg^{-1})[8]. Moreover, value of mean apparent volume of distribution (Vd_{area}: 0.812±0.007 L kg^{-1}) indicated good distribution of drugs in body tissues following intramuscular administration of cefpirome in cow calvess. Value of Vd_{area} for cow calves in present study is higher than reported values of 0.42±0.01 L kg^{-1} in buffalo calves[11] and 0.52±0.02 L kg^{-1} in goats[8]. Systemic bioavailability (61±1%) following intramuscular administration of cefpirome in cow calves is higher than 35.3±3.1% reported in buffalo calves[7] and in less than that reported in goats (75±4%)[8]. High systemic bioavailability and maintenance of therapeutic concentration up to 12 h following intramuscular injection suggests that cefpirome is suitable for intramuscular administration for the treatment for systemic bacterial infections in cow calves.

For β-lactam antibiotics, time for which serum drug concentration exceeds the MIC (T>MIC) of pathogens is considered as primary determinant of antibacterial efficacy[16]. In addition to this, for β-lactam antibiotics maximum killing was seen when the time above MIC is at least 70% of the dosing interval[17]. Minimum inhibitory concentration obtain for cefpirome sensitive bacteria like *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Bacillus subtilis*, range from 0.1 to 0.5 μg mL^{-1} and similar finding were also reported buy other authors[18,19]. Integrating the cefpirome pharmacokinetic data and the MIC values a cefpirome, an intravenously or

intramuscular dose of 10mg kg^{-1} repeated at 12 h interval is sufficient to maintain plasma concentration of the drug above the MIC. However, for *Pseudomonas aeruginosa* (whose MIC value is 2 μg mL^{-1}), a cefpirome dose of 10 mg kg^{-1} is sufficient to maintain plasma concentration of the drug above the MIC when it is administered intravenously or intramuscularly at 8 h interval.

CONCLUSIONS

Pharmacokinetic-pharmacodynamics integration indicates cefpirome can be useful in cow calves at dose rate of 10 mg kg^{-1} and repeated at interval of 12 h by intramuscular route.

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REFERENCES

1. Wiseman, L.R. and H.M. Lamb, 1997. Cefpirome. A review of its antibacterial activity, pharmacokinetic properties and clinical efficacy in the treatment of severe nosocomial infections and febrile neutropenia. Drugs, 54: 117-140.
2. Pucci, M.J., J. Boice-Sowek, R.E. Kessler and T.J. Dougherty, 1991. Comparison of cefepime, cefpirome and cefaclidine binding affinities for penicillin-binding proteins in *Escherichia coli* K-12 and *Pseudomonas aeruginosa* SC 8329. Antimicrob. Agents Chemother., 35: 2312-2317.
3. Nikaido, W., W. Liu and Y. Rosenberg, 1990. Outer membrane permeability and beta-lactamase stability of dipolar ionic cephalosporins containing methoxyimino substituents. Antimicrob. Agents Chemother., 34: 337-342.
4. Bertram, M.A., D.A. Bruckner and L.S. Young, 1984. *In vitro* activity of HR 810, a new cephalosporin. Antimicrob. Agents Chemother., 26: 277-279.
5. Klesel, N. and K. Seeger, 1983. Pharmacokinetic properties of the new cephalosporin antibiotic HR 810 in animals. Infection, 11 : 318-321.
6. Rajput, N., V.K. Dumka and H.S. Sandhu, 2007. Disposition kinetics and urinary excretion of cefpirome after intravenous injection in buffalo calves. J. Vet. Sci., 8: 21-25.
7. Rajput, N., V.K. Dumka and H.S. Sandhu, 2007. Pharmacokinetics of cefpirome in buffalo calves (*Bubalus bubalis*) following single intramuscular administration. Iranian J. Vet. Res., 8: 212-217.
8. Barot, D.K., S.K. Bhavsar, K.A. Sadariya, H.H. Soni and R.J. Patel, 2013. Pharmacokinetics of cefpirome following intravenous and intramuscular administration in goats. Israel. J. Vet. Med., 68: 106-110.
9. Nahata, M.C., 1991. Determination of cefpirome in human plasma by high-performance liquid chromatography. J. Liquid Chromatogr., 14: 193-200.
10. Wiegand, I., K. Hilpert and R.E.W. Hancock, 2008. Agar and broth dilution methods to determine the Minimal Inhibitory Concentration (MIC) of antimicrobial substances. Nat. Protocol., 3: 163-175.
11. Isert, D., N. Klesel, M. Limbert, A. Markus, G. Seibert and E. Schrinner, 1992. Pharmacokinetics of cefpirome administered intravenously or intramuscularly to rats and dogs. J. Antimicrob. Chemother., 29: 31-37.
12. Patani, K., U.D. Patel, S.K. Bhavsar, A.M. Thaker and J. Sarvaiya, 2008. Single dose pharmacokinetics of cefepime after intravenous and intramuscular administration in goats. Turk. J. Vet. Anim. Sci., 32: 159-162.
13. Patel, P.N., U.D. Patel, S.K. Bhavsar and A.M. Thaker, 2010. Pharmacokinetics of cefepime following intravenous and intramuscular administration in sheep. Iranian J. Pharmacol. Ther., 9: 7-10.
14. Patel, H.B., N.N. Patel, S.D. Patel, S. Dewda, J.H. Patel, S.K. Bhavsar and A.M. Thaker, 2012. Effect of ketoprofen co-administration and febrile state on pharmacokinetic of cefepime in goats. Asian J. Anim. Vet. Adv., 7: 46-53.
15. Patel, N.N., H.B. Patel, S.D. Patel, J.H. Patel, S.K. Bhavsar and A.M. Thaker, 2012. Effect of ketoprofen co-administration or febrile state on pharmacokinetic of cefepime in sheep. Vet. Arch, 82: 473-481.
16. Craig, W.A., 1995. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn. Microbiol. Infect. Dis., 22: 89-96.
17. Hyatt, J.M., P.S. Mckinnon, G.S. Zimmer and J.J. Schentag, 1995. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Clin. Pharmacokinetics, 28: 143-160.
18. Limbert, M., D. Isert, N. Klesel, A. Markus, K. Seeger, G. Seibert and E. Schrinner, 1991. Antibacterial activities *in vitro* and *in vivo* and pharmacokinetics of cefquinome (HR 111V), a new broad-spectrum cephalosporin. Antimicrob. Agents Chemoiher., 35: 14-19.
19. Sultana, N. and M.S. Arayne, 2007. *In vitro* activity of cefadroxil, cephalexin, cefatrizine and cefpirome in presence of essential and trace elements. Pak. J. Pharm. Sci., 20: 305-310.