

Pharmacokinetics and Dosage Regimen of Cefpirome in Febrile Cross-Bred Calves

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ABSTRACT

The pharmacokinetics of cefpirome after a single intravenous injection of 10 mg.kg⁻¹ was studied in febrile cross-bred calves. *E. coli* endotoxin was administered intravenously to induce fever in calves. Blood samples were collected at different time intervals and cefpirome levels were estimated by using microbiological assay technique. Based on the plasma drug levels, the pharmacokinetic parameters were determined. Maximum concentration of cefpirome was attained at 1 min and the drug was detected above MIC in plasma up to 12 h after its administration. The values of $t_{1/2\alpha}$, $V_{d\text{area}}$ and AUC were 0.06 ± 0.003 h, 0.75 ± 0.02 L.kg⁻¹ and 36.6 ± 0.82 $\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$. The high values of $t_{1/2\beta}$ (1.90 ± 0.03 h) and Cl_B (0.27 ± 0.006 L.kg^{-1}\cdot\text{h}^{-1}) reflected rapid elimination and body clearance of the drug in febrile calves. The study suggested that cefpirome was rapidly distributed and rapidly eliminated in febrile crossbred calves.}

Keywords: Cefpirome, Calves, Dosage, Fever, Pharmacokinetics

Cephalosporins are being increasingly used in veterinary and medical practices for the treatment of clinical infections caused by gram-positive and gram-negative microorganisms [1,2]. Cefpirome, a fourth generation cephalosporin, has been recently introduced for the treatment of serious and resistant infections including septicemia and lower respiratory tract infections. It has several advantages over earlier generation cephalosporins and is highly stable to hydrolysis by β -lactamases. It has potent bactericidal activity against a broad range of gram-negative and gram-positive organisms including *Pseudomonas aeruginosa* [3] and methicillin-susceptible *Staphylococcus* spp. It is also highly active against *Haemophilus influenzae* type B and many members of the family *Enterobacteriaceae* [4].

For the judicious use of an antibiotic in rational dosage, the pharmacokinetic investigations are essential. Pharmacokinetics of cefpirome has been studied in several species of animals like rabbits [5], rats [6], dogs [7], monkeys [8] buffalo calves [9,10] and humans [11]. Endotoxin produces many patho-physiological changes that generally alter the pharmacokinetics of antibiotics and ultimately the effectiveness of drug during bacterial infections. Fever is known to influence the pharmacokinetics of several antimicrobials [12]. Since fever is one of the most common manifestations in bacterial diseases, the study on influence of fever on the

pharmacokinetics of antibiotics has become essential. However, only meager information is available on the influence of fever on the pharmacokinetics of cephalosporins [13]. The present paper describes the pharmacokinetics of cefpirome during *E. coli* endotoxin-induced fever in cross-bred calves.

MATERIALS AND METHODS

The study was performed in five male cross-bred calves of 6 months to 1 year age and weighing between 80-120 kg. The animals were kept under uniform conditions and provided green fodder of the season and wheat straw. Water was provided *ad libitum*. Fever was induced following intravenous administration of *E. coli* endotoxin (Sigma Chemicals Co. USA) at the dose rate of 1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{b.wt}$. Rise in body temperature was monitored by frequent recording of rectal temperatures. Cefpirome was administered as a single intravenous injection into the jugular vein at the dose rate of 10 mg.kg⁻¹ body weight. The experimental protocol followed ethical guidelines on the proper care and use of animals and was approved by the institutional animal ethics committee of Punjab Agricultural University, Ludhiana, India vide approval number 392-94 dated 4.4.05 IAEC, PAU (Reg. No. 497/01/a/CPCSEA).

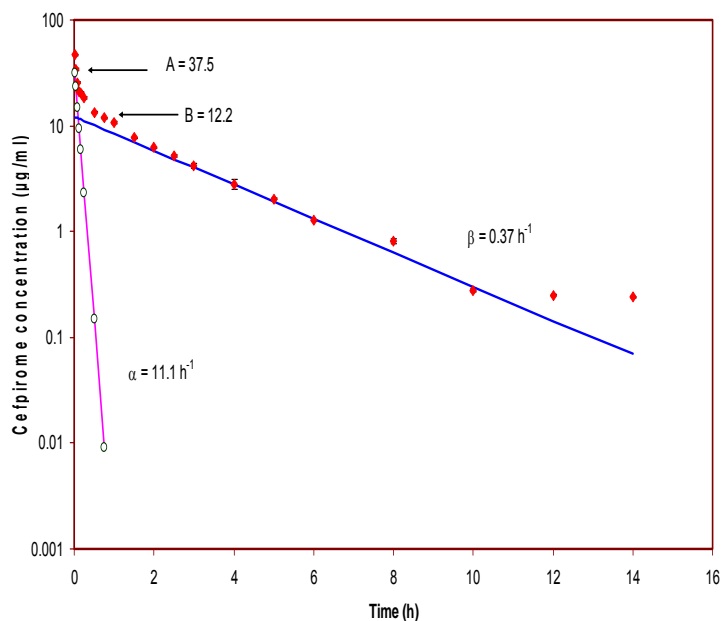


Fig. 1. Semilogarithmic plot of plasma concentration-time profile of cefpirome in febrile (*E. coli* endotoxin $1 \mu\text{g}\cdot\text{kg}^{-1}$, iv) cross-calves following a single intravenous dose of $10 \text{ mg}\cdot\text{kg}^{-1}$ body weight. Values given are mean \pm SE of 5 animals. Data was analyzed by the two-compartment open model. The distribution (α) and elimination (β) phases are represented by least square regression lines. The calculated points (o) of the distribution phase were obtained by the feathering technique.

Blood samples (5 ml) were withdrawn from contralateral jugular vein into heparinized glass centrifuge tubes at 1, 2.5, 5, 7.5, 10, 15, 30, 45 min and

1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 24 h after cefpirome administration. Plasma was separated by centrifugation at 3000 rpm for 15 min at room

temperature and kept at -20°C until analysis, which usually took place on the day after collection and was used for estimation of the drug concentrations. The dose of cefpirome used in the present study was comparable to the dosage used by previous workers in micro pig [14], mice, rats, rabbits, dogs and monkeys [7] and humans [15].

The concentration of cefpirome in plasma was estimated by a standard microbiological bioassay technique [16] using *Escherichia coli* (MTCC 739) as test organism obtained from Institute of Microbial Technology, Chandigarh, India. The test organism was cultured on antibiotic medium no. 1 at 37°C for 24 h and a suspension was prepared in sterile normal saline. About 20 ml of molten seed layer containing bacterial suspension was poured on a petri dish with the help of Cornwell Continuous Pipetting Device (Becton Dickinson, New Jersey, USA). Preliminary experiments were conducted to determine the actual amount of bacterial suspension to be used in the preparation of

seed layer. After solidification of the media, six wells were punctured at equal distance with the help of a punching device.

Three alternative wells were filled with one plasma sample and the remaining three wells with a standard reference solution of cefpirome ($0.25 \mu\text{g}\cdot\text{ml}^{-1}$). These assay plates were incubated at 34°C for 6 h. At the end of incubation period, the diameters of zone of inhibition of each well was measured with a Fisher Lilly Antibiotic Zone Reader (Fisher Scientific Company, New Jersey, USA). Nine replicates were analyzed for each sample. The repeatability of this method was excellent and within-day error estimated was less than 2%. The minimum detection level was $0.05 \mu\text{g}\cdot\text{ml}^{-1}$. The diameter of zones of inhibition was measured and concentration of cefpirome was expressed as $\mu\text{g}\cdot\text{ml}^{-1}$ of plasma.

Based on diameter of zone of inhibition of the reference concentrations, the plasma levels of cefpirome were calculated and expressed as $\mu\text{g}\cdot\text{ml}^{-1}$. Pharmacokinetic parameters were calculated manually by the least square regression technique [17]. The mean values and standard error (SE) of pharmacokinetic variables were obtained by averaging the variables calculated for drug disposition after iv drug administration to each animal.

Table 1. Pharmacokinetic parameters of cefpirome in febrile (*E. coli* endotoxin 1 $\mu\text{g.kg}^{-1}$, iv) cow calves after a single intravenous dose of 10 mg.kg^{-1} body weight

| Parameter | Unit | Mean \pm SE |
|---------------------------|----------------------------------|------------------|
| Cp^0 | $\mu\text{g.ml}^{-1}$ | 49.7 \pm 1.19 |
| A | $\mu\text{g.ml}^{-1}$ | 37.5 \pm 1.53 |
| B | $\mu\text{g.ml}^{-1}$ | 12.2 \pm 0.52 |
| $t_{1/2\alpha}$ | h | 0.06 \pm 0.003 |
| $t_{1/2\beta}$ | h | 1.90 \pm 0.03 |
| K_{12}/K_{21} | ratio | 2.39 \pm 0.15 |
| AUC | $\mu\text{g.ml}^{-1}.\text{h}$ | 36.6 \pm 0.82 |
| AUMC | $\mu\text{g.ml}^{-1}.\text{h}^2$ | 90.9 \pm 1.89 |
| Vd_{area} | L.kg^{-1} | 0.75 \pm 0.02 |
| Vd_B | L.kg^{-1} | 0.83 \pm 0.03 |
| Vd_{ss} | L.kg^{-1} | 0.68 \pm 0.02 |
| Cl_B | $\text{L.kg}^{-1}.\text{h}^{-1}$ | 0.27 \pm 0.006 |
| K_{el} | h^{-1} | 1.36 \pm 0.06 |
| MRT | h | 2.49 \pm 0.02 |
| P/C | ratio | 2.73 \pm 0.18 |
| td | h | 10.1 \pm 0.14 |

Cp^0 , plasma drug concentration at zero time; A and B, zero-time plasma concentration intercepts of regression lines of distribution and elimination phases, respectively; $t_{1/2\alpha}$ and $t_{1/2\beta}$, half-lives of distribution and elimination phases, respectively; K_{12} and K_{21} , micro rate constants defined in the two compartment model; AUC, area under the plasma concentration-time-curve; AUMC, area under the first moment of the plasma concentration-time-curve; Vd_{area} , Vd_B and Vd_{ss} , apparent volume of distribution from AUC, elimination phase and steady state plasma level, respectively; Cl_B , total body clearance of the drug; K_{el} , elimination rate constant from the central compartment; MRT, mean residence time of drug in body; P/C, ratio of the drug present in the peripheral to central compartment; td, total duration of pharmacological effect.

RESULTS

In all the animals there was significant rise in body temperature within 2-3 h of injection of endotoxin. The highest body temperature was $103.9 \pm 0.41^\circ\text{F}$ ($3-4^\circ\text{F}$ above normal) at 6 h following endotoxin administration, which then declined slowly and remained above normal range up to 14 h. The temperature became normal after 14-24 h of endotoxin administration.

Fig 1 shows the semilogarithmic plot of the mean plasma concentrations of cefpirome at different time intervals following single dose iv administration of 10 mg.kg^{-1} in febrile calves. At 1 min, the cefpirome concentration was $46.50 \pm 0.40 \mu\text{g.ml}^{-1}$ which rapidly decline to $11.80 \pm 0.15 \mu\text{g.ml}^{-1}$ at 45 min and the drug was detected in plasma up to 14 h. Evaluation of the results on observed plasma levels revealed that the disposition pattern of cefpirome best fitted two compartment open model kinetics and was adequately described by the bi-exponential equation $\text{Cp} = \text{Ae}^{-\alpha t} + \text{Be}^{-\beta t}$, where Cp is the drug concentration at time t, A and B are zero-time plasma concentration intercepts of the biphasic disposition curve, e is the base of the natural logarithm, α and β are hybrid rate constants related to the slopes of the distribution and elimination, respectively.

Based on the plasma levels, various pharmacokinetic parameters pertaining to the distribution and elimination of cefpirome in cross-bred calves were calculated and presented in Table 1.

DISCUSSION

The levels of cefpirome above the minimum therapeutic plasma concentration were maintained in plasma from 1 min to 12 h of administration. The MIC_{90} of cefpirome against most common pathogens has been

reported to be 0.05-0.39 $\mu\text{g.ml}^{-1}$ [18] but such values have not been established specifically against animal isolates. Another fourth generation cephalosporin, cefquinome is active against pathogens generally responsible for animal infections and possesses antimicrobial spectrum and potency comparable to cefpirome [19]. MIC_{90} of cefquinome against common animal pathogens have been reported in the range of .03-1.0 $\mu\text{g.ml}^{-1}$ [20]. In the present discussion, a concentration of 0.25 $\mu\text{g.ml}^{-1}$ has been considered as the reference plasma level of cefpirome.

The pattern of disappearance of drug from plasma of febrile cross-bred calves followed 2 compartment open model. Similarly, the disposition pattern of another cephalosporin, ceftizoxime also followed two compartment open model in febrile cow calves [21].

The low value of distribution half-life (0.06 ± 0.003 h) indicated that cefpirome is rapidly distributed into various body fluids and tissue compartments of febrile calves. This correlated well with the rapid decline of drug in the early phase. The high value of K_{12}/K_{21} ratio (2.39 ± 0.15) indicated rapid transfer of drug from central to peripheral compartments in febrile calves. The high value of AUC ($36.6 \pm 0.82 \mu\text{g.ml}^{-1}.\text{h}$) and AUMC ($90.9 \pm 1.89 \mu\text{g.ml}^{-1}.\text{h}^2$) showed that vast area of the body was covered by cefpirome concentration. Extensive tissue distribution was reflected by the high value of Vd_{area} ($0.75 \pm 0.02 \text{L.kg}^{-1}$). A high P/C ratio (2.73 ± 0.18) established in the present study, indicated that cefpirome is present in greater concentration in peripheral than in central compartment in febrile calves. Similar to our findings, high value of AUC ($31.5 \mu\text{g.ml}^{-1}.\text{h}$), AUMC ($59.8 \mu\text{g.ml}^{-1}.\text{h}^2$), Vd_{area} (0.92L.kg^{-1}) and P/C ratio (5.23) of another cephalosporin, ceftizoxime were reported in febrile cow calves [21].

The elimination half-life of 1.9 ± 0.03 h and Cl_B of $0.27 \pm 0.006 \text{L.kg}^{-1}.\text{h}^{-1}$ in febrile calves, reflected rapid

elimination and body clearance of the drug. In agreement to our findings, high values of Cl_B ($0.41 \text{ L.kg}^{-1}\text{h}^{-1}$) and $t_{1/2\beta}$ (2.04 h) have also been reported for ceftriaxone in febrile buffalo calves [12]. The values of K_{el} , MRT and td of ceftiofime in febrile calves in the present study were $1.36 \pm 0.06 \text{ h}^{-1}$, $2.49 \pm 0.02 \text{ h}$ and $10.1 \pm 0.14 \text{ h}$, respectively. Comparable values of $t_{1/2\beta}$, Cl_B , K_{el} , MRT and td were also reported as 1.97 h, $327.1 \text{ ml.kg}^{-1}\text{h}^{-1}$, 2.58 h^{-1} , 1.84 h and 6.55 h, respectively for ceftiofime in febrile calves [21].

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