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Disposition kinetics and *in vitro* plasma protein binding of cefpirome in cattle

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ABSTRACT

The disposition of cefpirome after single intramuscular (i.m.) administration (10 mg.kg^{-1}) was investigated in five male cross-bred calves and *in vitro* plasma protein binding was determined. The concentration of cefpirome in the plasma was estimated by the microbiological assay technique. Binding of cefpirome to plasma proteins was determined at different concentration levels by the equilibrium dialysis technique. The peak plasma level of cefpirome after i.m. administration to cattle was attained at 45 min post-dose and the drug was detected in plasma above MIC of $0.5 \mu\text{g.mL}^{-1}$ for up to 10 h. The drug disposition followed a one-compartment open model. The values of $t_{1/2\text{Ka}}$, $t_{1/2\beta}$ and AUC were $0.21 \pm 0.01 \text{ h}$, $2.06 \pm 0.02 \text{ h}$ and $31.7 \pm 0.95 \mu\text{g.mL}^{-1}\text{.h}$, respectively. Cefpirome was bound to the plasma proteins to the extent of 26.0 ± 2.84 percent at the concentration range of $1\text{-}100 \mu\text{g.mL}^{-1}$. The binding capacity of cefpirome to plasma proteins and the dissociation rate constant of the protein-drug complex were $3.71 \times 10^{-8} \pm 0.31 \times 10^{-8} \text{ mole.g}^{-1}$ and $3.43 \times 10^{-7} \pm 0.46 \times 10^{-7} \text{ mole}$, respectively.

Key words: calves, cefpirome, disposition, protein binding

Introduction

Cephalosporins are among the most widely used group of antibacterials in veterinary and human medical practice. Cefpirome, a new fourth generation cephalosporin, possesses an extended spectrum of activity against resistant organisms such as *Pseudomonas* spp. (SULTANA and ARAYNE, 2007; OZBEK and OTUK, 2010). It is commonly used in humans to treat bacterial meningitis and infections of the lower respiratory tract, skin and urinary tract (PRESCOTT, 2006). Cefpirome has the clinical advantage of being highly stable to hydrolysis by several β -lactamases including Amp C β -lactamases that confer resistance to a wide variety of β -lactam antibiotics and, therefore, it is clinically useful

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against organisms producing Amp C-type β -lactamases (PRESCOTT, 2006; AHMED and SHIMAMOTO, 2008). In view of the species variation in the disposition kinetic data of antimicrobials, it is considered important to investigate the disposition kinetics of drugs in different animal species and under different environmental conditions. The disposition kinetics of ceftiofime have been described in rabbits (MRESTANI et al., 2003), rats (ISERT et al., 1992), dogs (ISERT et al., 1992; KITA et al., 1992), monkeys (KLESEL and SEEGER, 1983), buffalo calves (RAJPUT et al., 2007a,b; RAJPUT et al., 2008) and humans (SAUERMAN et al., 2005). It has been emphasized that the pharmacokinetic data of a drug generated in one species cannot be extrapolated to other species. Since there is no information available on the pharmacokinetic behaviour of ceftiofime in cross-bred calves, the present study was undertaken to investigate the disposition kinetics after single intramuscular administration and *in vitro* plasma protein binding of ceftiofime in cross-bred calves.

Materials and methods

Experimental animals and drug administration. The study was conducted on five healthy male cross-bred calves between 6-12 months of age and weighing 80-120 kg. The animals were dewormed and kept under observation for 2 weeks of acclimatization before commencement of the experiment. During the experimental period, the animals were maintained on concentrate feed and were allowed to graze freely. Water was provided *ad libitum*. The average daily temperature in the shed was about 25 °C during the experimental period. The experimental protocol followed the ethical guidelines on the proper care and use of animals and was approved by the Institutional Animal Ethics Committee. Ceftiofime (Ceftiofime, Orchid Chemicals and Pharmaceuticals Ltd, India) was administered by a single intramuscular (i.m.) injection into the lateral neck region at the dose rate of 10 mg.kg⁻¹.

Sample collection. Blood samples (6 mL) were collected into heparinized glass centrifuge tubes by jugular venipuncture at time intervals of 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 of administration of ceftiofime. Plasma was separated and stored at -20 °C until analyzed for ceftiofime, which was usually done on the next day after collection.

Analytical method. The concentration of ceftiofime in plasma was estimated by the microbiological assay technique (ARRET et al., 1971) using *Escherichia coli* (microbial type culture collection; MTCC 739) as the test organism, as detailed in previously published reports (RAJPUT et al., 2007b). This method detected both the parent compound and its active metabolites. The assay could detect a minimum of 0.05 $\mu\text{g.mL}^{-1}$ of the antimicrobial active compound.

Pharmacokinetic analysis. The concentrations of ceftiofime in the plasma were plotted on a semi-logarithmic scale as a function of time and the pharmacokinetic parameters were

calculated manually for each animal by the least square regression technique (GIBALDI and PERRIER, 1982).

Plasma protein binding. *In vitro* binding of cefpirome to plasma proteins was determined by employing the equilibrium dialysis technique (KUNIN et al., 1959). Various concentrations of cefpirome (1, 10, 20, 50 and 100 $\mu\text{g.mL}^{-1}$) were prepared in plasma taken from untreated cattle. Each dialyzing bag filled with 5 mL of plasma, containing a known amount of the drug, was then immersed in separate tubes containing 5 mL of phosphate buffer and the tubes were incubated at 37 °C for 24 h with occasional shaking. At the end of the incubation period, the buffer as well as the contents of the dialysing bags, were analyzed separately for the concentration of cefpirome. For each concentration three separate sets of experiments were conducted. The extent of *in vitro* plasma protein binding of cefpirome was calculated by the equation:

$$\text{Percent of cefpirome bound to plasma protein} = \frac{\text{CP}' - \text{CB}}{\text{CP}} \times 100$$

Where, CP' is the concentration of cefpirome in the plasma after incubation, CB is the concentration of cefpirome in the phosphate buffer after incubation and CP is the concentration of cefpirome in the plasma before incubation. The constants for binding of cefpirome to plasma proteins were obtained as described by PILLOUD (1973) to describe the capacity and nature of the binding characteristics of the drug.

Results

The plasma levels of cefpirome at different time intervals are presented in Fig. 1. The plasma concentration of cefpirome at 1 min after a single i.m. injection was $0.31 \pm 0.01 \mu\text{g.mL}^{-1}$, and it gradually increased until the peak plasma concentration ($10.1 \pm 0.05 \mu\text{g.mL}^{-1}$) was observed at 45 min. The pharmacokinetic parameters that described the absorption and elimination pattern of cefpirome were calculated and are presented in Table 1. Table 2 summarizes the parameters of *in vitro* plasma protein binding of cefpirome.

Table 1. Disposition kinetic parameters of cefpirome in cross-bred calves (n = 5) after a single intramuscular dose of 10 mg.kg⁻¹ body weight

Parameter	Animal number					Mean ± SE
	1	2	3	4	5	
A' (µg.mL ⁻¹)	14.4	12.8	13.7	12.7	12.2	13.1 ± 0.40
B (µg.mL ⁻¹)	13.2	11.6	12.6	11.2	11.2	12.0 ± 0.39
Ka (h ⁻¹)	3.09	3.40	3.13	3.77	3.19	3.32 ± 0.13
β (h ⁻¹)	0.33	0.34	0.35	0.33	0.33	0.34 ± 0.01
t _{1/2Ka} (h)	0.22	0.20	0.22	0.18	0.22	0.21 ± 0.01
t _{1/2β} (h)	2.10	2.04	1.98	2.10	2.10	2.06 ± 0.02
AUC (µg.mL ⁻¹ .h)	35.3	30.5	31.7	30.7	30.3	31.7 ± 0.95
AUMC (µg.mL ⁻¹ .h ²)	119.7	99.6	101.6	102.3	102.0	105.1 ± 3.69
MRT (h)	3.39	3.27	3.21	3.33	3.37	3.31 ± 0.03
C _{max} (µg.mL ⁻¹)	10.1	10.1	9.98	10.2	10.3	10.1 ± 0.05
t _{max} (h)	0.75	0.75	0.75	0.75	0.75	0.75 ± 0.00

A' and B, zero-time plasma concentration intercepts of regression lines of absorption and elimination phases, respectively; Ka and β, absorption and elimination coefficients, respectively, in the mono-exponential equation that describes the plasma concentration-versus-time data; t_{1/2Ka} and t_{1/2β}, half-lives of absorption and elimination phases, respectively; AUC, area under the plasma concentration-time-curve; AUMC, area under the first moment of the plasma concentration-time-curve; MRT, mean residence time of drug in body; C_{max}, maximum plasma concentration; t_{max}, time required to attain peak plasma level.

Table 2. *In vitro* binding and kinetic constants of binding of cefpirome to plasma proteins of cross-bred calves (n = 5)

Exp. No.	Extent of binding (%)					Association rate constant, β _i (mole.g ⁻¹)	Dissociation rate constant, K _β (mole)
	Concentration of cefpirome (µg.mL ⁻¹)						
	1	10	20	50	100		
1	47.0	19.1	25.2	17.6	23.8	3.96 × 10 ⁻⁸	4.34 × 10 ⁻⁷
2	48.0	17.7	22.8	18.7	25.8	4.07 × 10 ⁻⁸	2.98 × 10 ⁻⁷
3	29.0	41.9	12.2	21.7	19.7	3.09 × 10 ⁻⁸	2.96 × 10 ⁻⁷
Mean ± SE	41.3 ± 6.17	26.2 ± 7.84	20.1 ± 3.99	19.3 ± 1.25	23.1 ± 1.80	3.71 × 10 ⁻⁸ ± 0.31 × 10 ⁻⁸	3.43 × 10 ⁻⁷ ± 0.46 × 10 ⁻⁷

Overall Mean ± SE of extent of binding = 26.0 ± 2.84%.

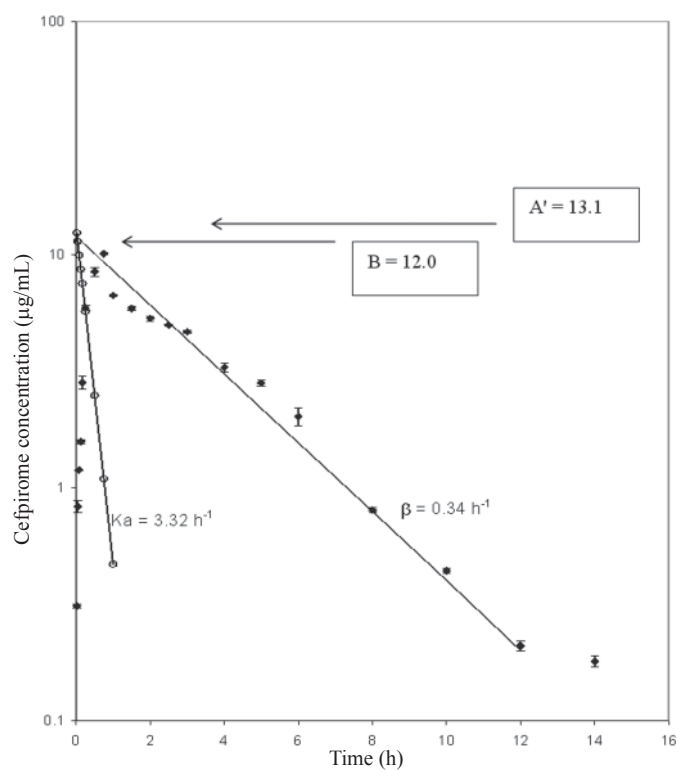


Fig. 1. Semilogarithmic plot of plasma concentration-time profile of cefpirome in cross-bred calves following a single intramuscular dose of 10 mg.kg^{-1} body weight. Values given are mean \pm SE of 5 animals. Data was analyzed according to the one-compartment open model. Absorption (K_a) and elimination (β) phases are represented by the least square regression lines. The calculated points (o) of the absorption phase were obtained by the residual method.

Discussion

The evaluation of the results on the observed plasma levels of cefpirome indicated that the data may be best fitted to the one-compartment open model and the pharmacokinetics were described by the equation: $C_p = Be^{-\beta t} - A'e^{-k_a t}$. The mono-compartment model has also been used to describe the disposition pattern of cefpirome (RAJPUT et al., 2007b) and ceftriaxone (GOHIL et al., 2009) in buffalo calves and ceftizoxime in calves (SINGH et al., 2008) following single i.m. administration. The rapid attainment of peak cefpirome concentration in plasma suggested that this drug rapidly entered into systemic circulation

following i.m. administration. A similar peak plasma level of ceftiofime ($9.04 \mu\text{g.mL}^{-1}$) was produced at 0.5 h after i.m. administration in buffalo calves (RAJPUT et al., 2007b). The minimum therapeutic plasma concentration of ceftiofime against human pathogens has been reported to be $0.05\text{-}0.39 \mu\text{g.mL}^{-1}$ (ARAI et al., 1988) but such values for ceftiofime have not been determined against animal isolates. Another fourth-generation cephalosporin, ceftiofime, is active against pathogens generally found in animal infections and possesses a potency and spectrum comparable to ceftiofime (MURPHY et al., 1994). The minimum inhibitory concentration (MIC_{90}) of ceftiofime against animal pathogens, including *E. coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Pasteurella*, *Salmonella* and *Streptococcus* species, have been reported in the range of $0.03\text{-}1.0 \mu\text{g.mL}^{-1}$ (AL-TAHER, 2010). In this study, a concentration of $0.5 \mu\text{g.mL}^{-1}$ was considered as the reference plasma level for ceftiofime.

The study of kinetic determinants of ceftiofime following i.m. administration revealed a low value of absorption half-life, $t_{1/2ka}$ (0.21 ± 0.01 h) in the present study, which was similar to the low $t_{1/2ka}$ of 0.19 h reported for ceftiofime in buffalo calves (RAJPUT et al., 2007b), further confirming that after i.m. administration, absorption of ceftiofime is very rapid. Rapid absorption after i.m. injection has also been reported for ceftiofime and ceftiofime in crossbred calves (ISMAIL, 2005; SINGH et al., 2008) and ceftiofime in buffalo calves (GOHIL et al., 2009). The high values of AUC ($31.7 \pm 0.95 \mu\text{g.mL}^{-1}\cdot\text{h}$) AUMC ($105.1 \pm 3.69 \mu\text{g.mL}^{-1}\cdot\text{h}^2$) in the present study were comparable to the values of AUC ($28.7 \pm 1.9 \mu\text{g.mL}^{-1}\cdot\text{h}$) and AUMC ($107.7 \pm 6.7 \mu\text{g.mL}^{-1}\cdot\text{h}^2$) of ceftiofime in buffalo calves (RAJPUT et al., 2007b). Similarly, high values of AUC have also been reported in dogs ($103 \mu\text{g.mL}^{-1}\cdot\text{h}$), rabbits ($18.9 \mu\text{g. min.mL}^{-1}$) and man ($16.5 \text{ g.min.L}^{-1}$) for ceftiofime (KITA et al., 1992; MRESTANI et al., 2003; SAUERMAN et al., 2005).

The elimination of ceftiofime was rapid, with a $t_{1/2\beta}$ of 2.06 ± 0.02 h following i.m. administration in crossbred calves. Short elimination half-lives have also been reported for ceftiofime after i.v. (2.14 h) and i.m. (2.39 h) administration and ceftiofime (3.0 h) following i.v. administration in buffalo calves (RAJPUT et al., 2007a,b; JOSHI and SHARMA, 2009) and for ceftiofime (1.44 h) and ceftiofime (3.02 h) after i.m. administration in calves (ISMAIL, 2005; SINGH et al., 2008). The value of MRT in crossbred calves following i.m. administration of ceftiofime (3.31 ± 0.03 h) in the present study was in accordance with the values of MRT (3.76 h) observed after i.m. administration of ceftiofime in buffalo calves (RAJPUT et al., 2007b), however it was longer than the MRT of ceftiofime (1.55 h) reported after intravenous (i.v.) administration in cattle (KUMAR et al., 2010).

The extent of plasma protein binding of ceftiofime varied from 12.2 to 48.0 percent with an overall mean of 26.0 ± 2.84 percent. The calculated values of the capacity of ceftiofime to bind with plasma proteins of crossbred calves (β_1) and the dissociation rate constant of protein drug complex (K_p) were $3.71 \times 10^{-8} \pm 0.31 \times 10^{-8} \text{ mol.g}^{-1}$ and $3.43 \times 10^{-7} \pm$

0.46×10^{-7} mol, respectively. The binding of the drug to plasma proteins was weak and reversible, which was evident from the lower value of β_i than the value of K_β . These results are in accordance with the 30.7% binding of cefpirome to the plasma proteins of buffalo calves (RAJPUT et al., 2007b), however a low value of plasma protein binding of cefpirome has been reported at 10 percent in humans (STEINER et al., 2004) and 8.8 percent in rats (ARAI et al., 1988). A marked inter-species difference has been reported in the binding of cephalosporins to plasma proteins in animals. A plasma protein binding study of six cephalosporins in animals revealed high protein binding in rat, monkey, and human plasma, whereas in dog plasma, protein binding was markedly lower (RICHTER et al., 1998). Similarly the plasma protein binding of cefoperazone in calves has been reported to be nearly one fourth of that in humans (GUPTA et al., 2008).

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SAŽETAK

Istražena je raspodjela ceftiofima i njegovo *in vitro* vezanje na proteine plazme u petero muške bivolje teladi nakon jednokratne intramuskularne primjene u dozi od 10 mg/kg. Koncentracija ceftiofima u plazmi bila je procijenjena pomoću mikrobioloških testova. Njegovo vezanje na proteine plazme određeno je za različite koncentracije pomoću dijalize. Vršna razina ceftiofima u plazmi nakon intramuskularne primjene postignuta je 45 minuta nakon davanja, a lijek je u plazmi bio dokazan iznad MIC od 0,5 µg/mL do 10 sati nakon davanja. Raspodjela lijeka bila je sukladna modelu otvorenosti jednog odjeljka. Vrijednost $t_{1/2Ka}$ iznosila je $0,21 \pm 0,01$ h, $t_{1/2\beta}$ $2,06 \pm 0,02$ h, a AUC $31,7 \pm 0,95$ µg/mL/h. Ceftiofom se vezao na proteine plazme u visini od $26,0 \pm 2,84$ % u razmaku koncentracije od 1-100 µg/mL. Sposobnost vezanja ceftiofima na proteine plazme bila je $3,71 \times 10^{-8} \pm 0,31 \times 10^{-8}$ mol/g, a konstanta njegova oslobađanja od kompleksa protein-lijek iznosila je $3,43 \times 10^{-7} \pm 0,46 \times 10^{-7}$ mola.

Ključne riječi: telad, ceftiofom, raspodjela, vezanje na proteine
