Disposition kinetics and urinary excretion of cefpirome after intravenous injection in buffalo calves

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We investigated the disposition kinetics and urinary excretion of cefpirome in buffalo calves after a single intravenous administration of 10 mg/kg. Also, an appropriate dosage regimen was calculated. At 1 min after injection, the concentration of cefpirome in the plasma was 57.4 ± 0.72 μg/ml, which declined to 0.22 ± 0.01 μg/ml at 24 h. The cefpirome was rapidly distributed from the blood to the tissue compartment as shown by the high distribution coefficient values (8.67 ± 0.46/h), and by the drug's rate of transfer constant from the central to the peripheral compartment, K_{12} (4.94 ± 0.31/h). The elimination half-life and the volume of distribution were 2.14 ± 0.02 h and 0.42 ± 0.005 l/kg, respectively. Once the distribution equilibrium was reached between the tissues and plasma, the total body clearance (Cl_B) and the ratio of the drug present in the peripheral to the central compartment (T/P ratio) were 0.14 ± 0.002 l/kg/h and 1.73 ± 0.06, respectively. Based on the pharmacokinetic parameters we obtained, an appropriate intravenous cefpirome dosage regimen for treating cefpirome-sensitive bacteria in buffalo calves would be 8.0 mg/kg repeated at 12 h intervals for 5 days, or until persistence of the bacterial infection occurred.

Key words: buffalo, cefpirome, cephalosporins, dosage, pharmacokinetics

Introduction

Cefpirome is a cephalosporin that was recently introduced, and is frequently used for empirical therapy in severely ill patients in the intensive care, oncology, and transplantation units [20]. It has potent bactericidal activity against a broad range of gram-negative and gram-positive organisms, including *Pseudomonas aeruginosa* and methicillin susceptible *Staphylococcus* spp. It is also highly active against *Haemophillus influenzae* type B and many members of the *Enterobacteriaceae* family [3]. Cefpirome, however, does not target anaerobic bacteria; hence, it spares the intestinal flora, unlike other antibiotics [7]. The disposition kinetics of cefpirome have been investigated in humans [18], rabbits [13], rats [8], dogs [11], and monkeys [12]. However, there is no information available on cefpirome's pharmacokinetics in buffaloes. Given the marked species variations that are found in the kinetic data of antimicrobial drugs, the present study was undertaken to determine the disposition kinetics, urinary excretion, and appropriate dosage regimen for cefpirome in buffalo calves, following a single intravenous administration.

Materials and Methods

The experiment was performed on 5 healthy male buffalo calves, 6-12 months old and weighing 90-122 kg. The animals were adapted to the laboratory conditions for 2 weeks prior to the study's commencement, and were provided seasonal green fodder, wheat straw, and water *ad libitum*. The average daytime temperature in the shed was approximately 25°C during the experimental period. The experimental protocol followed the ethical guidelines on the proper care and use of animals. Cefpirome (Orchid Chemicals & Pharmaceuticals, India) was administered at a dose rate of 10 mg/kg of body weight into the left jugular vein. Blood samples were then drawn from the contra lateral 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 administration of drug. The plasma was separated by centrifugation at 3,000 rpm at room temperature and stored at −20°C until analysis, which usually took place the day after collection.

To examine the urinary excretion of cefpirome, the same animals were placed into metabolic stalls designed in such a way that all the urine voided by the animals was collected without contamination or spillage. The urine samples were collected after predetermined time intervals of 2, 4, 6, 8, 10, 12, 14, and 24 h after drug administration. The volume of urine was measured, and after filtration, 10 ml samples were

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taken for analysis.

The concentrations of cefpirome in the plasma and urine samples were determined by a standard microbiological bioassay technique [2] using *Escherichia coli* (MTCC 739) as the test organism. The test organisms were cultured on medium No. 1 at 37°C for 24 h, and a suspension was prepared in sterile normal saline. The assay plates were prepared by putting a seed layer (25 ml) of medium No. 11 on the flat bottoms of assay Petri dishes that had 100 ml capacities. A desired amount of bacterial suspension was added to the seed layer to obtain clear bacterial growth and the required zone of inhibition dimensions using a cefpirome reference concentration of 0.25 µg/ml. Preliminary experiments were conducted to determine the actual amount of bacterial suspension to be used in the preparation of the seed layer. After solidification of the media, 6 wells were punched at equal distances using a punching machine (designed and standardized in our laboratory). Three alternating cylindrical wells were filled with one plasma or urine sample and the remaining 3 cylindrical wells were filled with a standard solution of cefpirome (0.25 µg/ml). These assay plates were incubated at 32°C for 6 h. At the end of incubation the diameter of the zone of inhibition of each well was measured with Antibiotic Zone Reader (Fisher Scientific, USA). For each sample, 9 replicates were analyzed. This method could detect a minimum of 0.05 µg/ml of cefpirome.

The pharmacokinetic parameters were calculated manually by the computed least-square linear regression technique [6]. Different estimates of the distribution volume were obtained from the following equation:

$$Vd_{area} = \frac{Dose\ (mg/kg)}{\beta \cdot AUC}$$

$$Vd_B = \frac{Dose\ (mg/kg)}{B}$$

$$Vd_{ss} = \frac{Dose\ (mg/kg) \cdot AUMC}{AUC^2}$$

The priming (D) and maintenance (D') doses of cefpirome at various dosage intervals for maintaining different MICs was calculated from the equations:

$$D = Cp(min)^\propto \cdot Vd_{area} \cdot (e^{\beta\tau})$$
$$D' = Cp(min)^\propto \cdot Vd_{area} \cdot (e^{\beta\tau} - 1)$$

Where β is the elimination rate constant, τ is the dosage interval, and $Cp(min)^\propto$ is the minimum inhibitory concentration of cefpirome against common animal pathogens.
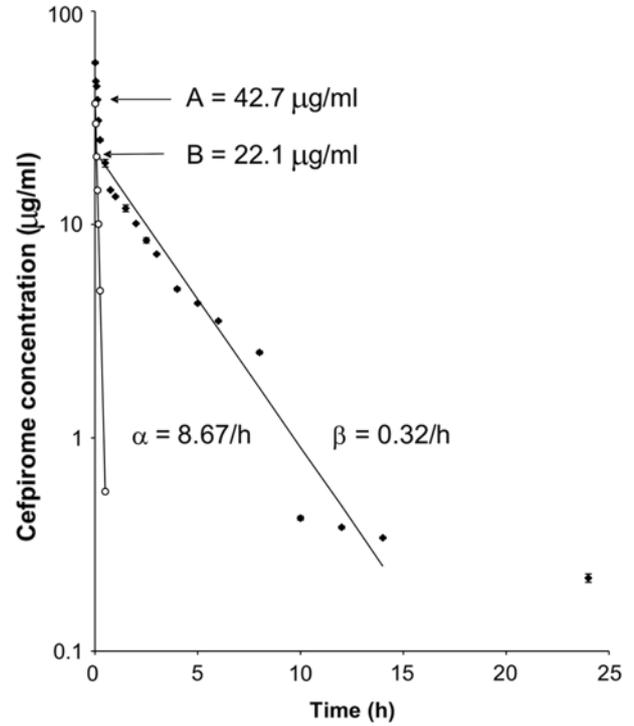
Fig. 1. Semilogarithmic plot of the plasma concentration-time profile of cefpirome in buffalo calves following a single intravenous dose of 10 mg/kg body weight. Values given are mean ± SE of 5 animals. The data were analyzed using a two-compartment open model. Distribution (α) and elimination (β) phases are represented by least-square regression lines. The calculated points (o) of the distribution phase were obtained by the feathering off technique.

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 intravenous injection was 57.4 ± 0.72 µg/ml, which declined rapidly to 13.5 ± 0.11 µg/ml at 1 h. The drug was detected in plasma for up to 24 h after dosing (0.22 ± 0.01 µg/ml). The calculated pharmacokinetic parameters that described the distribution and elimination pattern of cefpirome are presented in Table 1. Table 2 summarizes the urinary excretion data of cefpirome after a single intravenous administration. The optimum cefpirome doses were calculated using the various dosage intervals, the different desired plasma concentrations ranging from 0.05 to 0.5 µg/ml, and the values for β and Vd_{area} from Table 1. These optimum doses are presented in Table 3.

Discussion

In buffalo calves, the disposition of cefpirome in plasma after IV administration was best described by a 2-compartment open pharmacokinetic model. Similarly, cefpirome was

Table 1. Disposition kinetic parameters of cefpirome in buffalo calves following a single intravenous administration

Pharmacokinetic Parameter	Calf number					Mean ± SE
	1	2	3	4	5	
Cp^0 (µg/ml)	66.2	62.4	65.6	70.2	59.9	64.8 ± 1.75
$t_{1/2\alpha}$ (h)	0.08	0.09	0.08	0.07	0.08	0.08 ± 0.004
$t_{1/2\beta}$ (h)	2.17	2.17	2.17	2.10	2.10	2.14 ± 0.02
K_{12}/K_{21} (ratio)	1.64	1.44	1.57	1.68	1.44	1.56 ± 0.05
AUC (µg · h/ml)	72.7	74.5	74.4	74.6	69.9	73.2 ± 0.90
AUMC (µg · h²/ml)	210.7	216.7	216.8	212.5	199.3	211.2 ± 3.21
Vd_{area} (l/kg)	0.43	0.42	0.42	0.41	0.43	0.42 ± 0.005
Vd_B (l/kg)	0.47	0.45	0.45	0.43	0.46	0.45 ± 0.006
Vd_{SS} (l/kg)	0.40	0.39	0.39	0.38	0.41	0.40 ± 0.004
Cl_B (l/kg/h)	0.14	0.13	0.13	0.13	0.14	0.14 ± 0.002
K_{el} (/h)	0.91	0.84	0.88	0.94	0.86	0.89 ± 0.02
MRT (h)	2.90	2.91	2.92	2.85	2.85	2.89 ± 0.01
T/P (ratio)	1.85	1.62	1.76	1.85	1.60	1.73 ± 0.06
tC_{ther} (h)	7.04	7.04	7.04	6.81	6.81	6.95 ± 0.06

Cp^0 = plasma drug concentration at zero time; $t_{1/2\alpha}$ and $t_{1/2\beta}$ = half-lives of distribution and elimination phases, respectively; K_{12} and K_{21} = 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} = 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; T/P = ratio of the drug present in the peripheral to central compartment; tC_{ther} = duration of therapeutic concentration of drug.

Table 2. Urinary excretion of cefpirome in healthy buffalo calves following a single intravenous administration

Time interval (h)	Amount excreted (mg)	Per cent of total dose excreted	Time interval (h)	Cumulative amount excreted (mg)	Cumulative per cent of total dose excreted
0-2	356.5 ± 55.3	31.6 ± 5.16	0-2	356.5 ± 55.3	31.6 ± 5.16
2-4	179.5 ± 30.8	17.0 ± 3.45	0-4	464.7 ± 62.5	42.3 ± 4.82
4-6	133.5 ± 35.0	12.9 ± 4.30	0-6	571.5 ± 32.6	52.7 ± 0.63
6-8	54.0 ± 13.8	5.10 ± 0.64	0-8	593.1 ± 34.3	54.7 ± 1.18
8-10	23.8 ± 2.85	2.08 ± 0.27	0-10	607.4 ± 39.2	55.9 ± 1.44
10-12	14.5 ± 5.21	1.30 ± 0.52	0-12	616.0 ± 40.6	56.7 ± 1.51
12-14	10.3 ± 2.90	0.96 ± 0.22	0-14	622.2 ± 40.0	57.3 ± 1.34
14-24	12.4 ± 0.95	1.15 ± 0.10	0-24	634.6 ± 40.1	58.5 ± 1.31

reported as best fitting a 2-compartment open model after intravenous administration in humans [14]. Also, this model has been described for the disposition of ceftazidime in cows [17], and cefepime in foals [5], and dogs [15].

At 1 min after injection, the plasma level (57.4 ± 0.72 µg/ml) was approximately 147-fold higher than the minimum therapeutic level of cefpirome (0.39 µg/ml), and the drug was detected above the MIC for up to 14 h. In humans, a high serum level of 44.4 µg/ml was attained at 0.2 h following a 1 g intravenous dose of cefpirome [10]. Similarly, a peak serum level of 47-49 µg/ml was reported in humans receiving 1 g of cefpirome intravenously [16]. A C_{max} of 2.13 µg/ml in the pouch exudate of rats was achieved after intravenous administration of cefpirome at a dose rate of 40 µg/kg [1]. The minimum therapeutic plasma concentration of cefpirome against most common pathogens in animals has been reported as 0.05-0.39 µg/ml [1,9]. Due to the influence of

certain unavoidable factors *in vivo*, and to cover most of the susceptible microorganisms, the higher MIC range (0.39 µg/ml) of cefpirome has been taken into consideration for this discussion.

The low distribution half-life ($\tau_{1/2\alpha}$) value of cefpirome (0.08 ± 0.004 h) indicated the drug's rapid distribution from the central to peripheral compartments in buffalo calves. The rapid distribution of cefpirome was further confirmed by the high K_{12}/K_{21} ratio (1.56 ± 0.05).

The low Vd_{area} (0.42 ± 0.005 l/kg) in buffalo calves indicated the limited distribution of cefpirome into various body fluids and tissues. Low values of Vd_{area} have been also reported in mice (0.26 l/kg) and dogs (0.22 l/kg) after single intravenous administration of cefpirome [11]. However, our results are in contrast to the high Vd_{area} (1.3 ± 0.06 l/kg) value that was reported after the repeated administration of cefotaxime in buffalo calves [19]. Furthermore, the T/P ratio

Table 3. Doses of cefpirome (mg/kg) at various intervals for different MICs in buffalo calves

MIC (μg/ml)	Dose	Dosage interval (h)				
		8	10	12	16	24
0.05	D	0.28	0.54	1.03	3.77	50.6
	D'	0.26	0.52	1.01	3.75	50.6
0.19	D	1.07	2.05	3.92	14.4	192.3
	D'	0.99	1.97	3.84	14.3	192.2
0.29	D	1.64	3.13	5.98	21.9	293.5
	D'	1.51	3.01	5.86	21.8	293.4
0.39	D	2.20	4.21	8.05	29.4	394.7
	D'	2.04	4.05	7.88	29.3	394.5
0.5	D	2.76	5.39	10.3	37.7	506.1
	D'	2.56	5.18	10.1	37.5	505.9

D = Priming dose, D' = Maintenance dose

of 1.73 ± 0.06 that we observed when the distribution equilibrium was reached between tissues and plasma reflected higher cefpirome concentrations in the body fluids and tissues as compared to the plasma of the buffalo calves.

The high AUC (73.2 ± 0.90 μg · h/ml) and AUMC (211.2 ± 3.21 μg · h²/ml) values reflected that a vast body area was covered by cefpirome in the buffalo calves. Similarly, high AUC values following single intravenous injection of cefpirome were reported to be 75.6 μg · h/ml in rabbits [9], 20.1 μg · h/ml in mice, 103 μg · h/ml in dogs [11], 18.9 μg · min/ml in rabbits [13], and 16.5 g · min/l in humans [18].

The total body clearance (Cl_B) of cefpirome, which represents the sum of the metabolic and excretory processes, was 0.14 ± 0.002 l/kg/h in the buffalo calves. Comparable values of Cl_B were reported for cefpirome in dogs (3.2 ml/kg/min), guineapigs (1.57 ml/kg/min), and humans (1.8 ml/kg/min) following single intravenous injections [11]. Also, similar value of Cl_B was reported after intravenous injection of ceftriaxone (0.26 l/kg/h) in buffalo calves [4].

The elimination half-life of cefpirome in the buffalo calves was 2.14 ± 0.02 h. Previously reported values of $\tau_{1/2\beta}$ have been 0.47 h in rabbits [9], 0.4 h in rats [8], 0.19 h in mice [11], 0.9 and 1.1 h in dogs [8,11], and 1.95 h in humans [16].

The elimination rate constant of cefpirome from the central compartment (K_{el}) was 0.89 ± 0.02/h for the buffalo calves. The values of MRT and tC_{ther} of cefpirome were 2.89 ± 0.01 h and 6.95 ± 0.06 h, respectively. Others have reported K_{el}, MRT, and tC_{ther} values for ceftriaxone in buffalo calves as 2.28/h, 2.04 h, and 25.1 h, respectively, [4].

The highest urinary excretion amount of the drug was at 0-2 h (356.5 ± 55.3 mg), which gradually declined to 12.4 ± 0.95 mg at 14-24 h. About 58.5% of the administered dose was recovered in the urine within 24 h of administration. In contrast, very high amounts of cefpirome were detected in the urine of dogs (80%) and rats (90%) within 24 h after IV

dosing of cefpirome [8, 12]. However, Mrestani *et al.* [13] reported a very low amount of cefpirome, only 2%, in rabbit urine within 6 h after intraduodenal administration. A similar level of urinary excretion was reported for ceftriaxone in buffalo calves, where 49% of the administered dose was recovered in the urine within 8 h [4].

The main objective of this pharmacokinetic study was to compute the most appropriate dosage regimen of cefpirome for buffalo calves. The most appropriate priming and maintenance doses of cefpirome to maintain a MIC of 0.39 mg/ml at a dosage interval of 12 h would be 8.05 and 7.88 mg/kg, respectively. Under field conditions, a dose of 8.0 mg/kg may be needed at repeated 12 h intervals for 5 days, or until persistence of the bacterial infection occurs.

Acknowledgments

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