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Subcutaneous pharmacokinetics and dosage regimen of cefotaxime in buffalo calves (*Bubalus bubalis*)

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The pharmacokinetics and dosage regimen of cefotaxime following its single subcutaneous administration (10 mg/kg) were investigated in buffalo calves. Plasma and urine samples were collected over 10 and 24 h post administration, respectively. Cefotaxime in plasma and urine was estimated by microbiological assay technique using *E. coli* as test organism. The pharmacokinetic profiles fitted one-compartment open model. The peak plasma levels of cefotaxime were 6.48 ± 0.52 μg/ml at 30 min and the drug was detected upto 10 h. The absorption half-life and elimination half-life were 0.173 ± 0.033 h and 1.77 ± 0.02 h, respectively. The apparent volume of distribution and total body clearance were 1.17 ± 0.10 l/kg and 0.45 ± 0.03 l/kg/h, respectively. The urinary excretion of cefotaxime in 24 h, was 5.36 ± 1.19 percent of total administrated dose. A satisfactory subcutaneous dosage regimen for cefotaxime in buffalo calves would be 13 mg/kg repeated at 12 h intervals.

Key words: buffalo calf, cefotaxime, dosage regimen, pharmacokinetics

Introduction

Cefotaxime was the first of the third generation cephalosporins to be released in the market. It is broad spectrum antibiotic and highly resistant to the action of β-lactamase enzyme. Against gram negative micro organisms, it exhibits greater *in vitro* activity than any of the previous cephalosporins [14]. Pharmacokinetic studies of antimicrobial agents, which provide a basis for the determination of their satisfactory dosage regimen, are relevant when they are undertaken in the species in which the drugs are to be used clinically. The pharmacokinetics of cefotaxime have been investigated in humans [11], rats [10], Sheep [8,9], dogs [7], cats [13], goats [2,5] cattle [16,17] and buffaloes [18]. The purpose of this study was to determine the pharmacokinetics, urinary excretion and appropriate dosage regimen of cefotaxime in buffalo calves after a single subcutaneous administration. Recently, in Veterinary practice, administration of antibiotics by subcutaneous route has been found very effective [4].

Materials And Methods

Five healthy male buffalo calves ranging between 1 and 1.5 years of age with an average weight of 91 kg were used in the present study. The animals were kept in the departmental animal shed with concrete floor and adequate ventilation. A constant supply of water was maintained in the shed. All the animals were acclimatized in the animal shed under uniform conditions and were maintained on green fodder and wheat straw and water *ad libitum*. On the day of experiment, the animals were kept in standard metabolic stalls, designed so that all the urine passed by the animals over a particular period could be collected without any contamination or spillage. Cefotaxime Sodium (Claforan; Hoechst Marion Roussel, India) was given by subcutaneous route at the dose rate of 10 mg/kg body weight as a 10% freshly prepared solution in sterilized distilled water. Blood samples (5 ml each) were withdrawn from the jugular vein into heparinized glass test tubes before administration and at 1, 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60 and 90 min and 2, 3, 4, 5, 6, 7, 8 and 10 h after administration of the drug. Plasma was collected after centrifugation at 2000 × *g* for 15 min at room temperature and kept at –20°C until analysis, usually the next day. The urine samples were collected at 4, 8, 12, 16, 20 and 24 h after drug administration. The volume of urine was measured and approximately 8-10 ml was frozen for drug analysis.

The concentration of cefotaxime in the plasma and urine were estimated by employing the microbiological assay technique [1,19] using *Escherichia coli* (ATCC 25922) as

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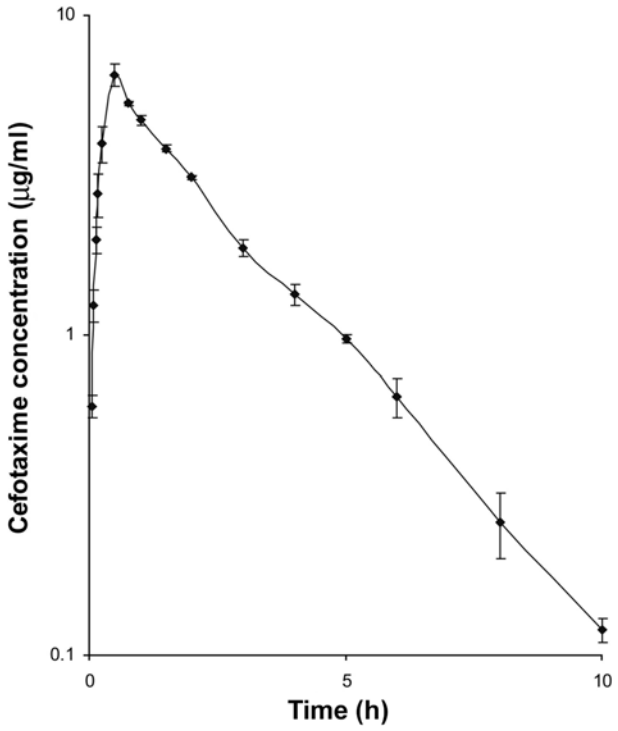

Fig. 1. Semilogarithmic plot of plasma concentration-time profile of cefotaxime in buffalo calves following a single subcutaneous dose of 10 mg/kg body weight. Values given are mean ± SE of 5 animals.

the test organism. The assay could detect a minimum of 0.1 µg/ml of cefotaxime. The standard curve of cefotaxime in buffalo calf plasma was linear between 0.1 to 0.6 µg/ml. The value of correlation coefficient (r) was 0.99. The plasma concentration - time data for each buffalo calf were determined according to the computed least squares regression technique. The kinetic parameters were calculated from the formulae derived for a one - compartment open model [6,15]. Based on the kinetic data, the dosage regimen of cefotaxime were also determined [3].

Results

The mean plasma concentrations of cefotaxime as a function of time were plotted on a semilogarithmic scale (Fig. 1). At 2.5 min, after subcutaneous administration, the mean plasma concentration was 0.60 ± 0.05 µg/ml. The peak drug concentration of 6.48 ± 0.52 µg/ml was achieved at 30 min of injection which gradually declined to 0.12 ± 0.01 µg/ml at 10 h.

The various pharmacokinetic parameters are presented in Table 1. The absorption half-life and elimination half-life were 0.173 ± 0.033 h and 1.77 ± 0.02 h, respectively. The apparent volume of distribution and total body clearance were 1.17 ± 0.10 l/kg and 0.45 ± 0.03 l/kg/h, respectively. Table 2 summarizes the urine concentration and extent of

Table 1. Pharmacokinetic parameters of cefotaxime in buffalo calves (n = 5) after a single subcutaneous dose of 10 mg/kg body weight

Parameter	Unit	Mean ± SE
A*	µg/ml	6.90 ± 0.45
Ka	/h	4.61 ± 0.93
$t_{½Ka}$	h	0.173 ± 0.033
B	µg/ml	6.33 ± 0.53
β	/h	0.392 ± 0.004
$t_{½β}$	h	1.77 ± 0.02
AUC	µg.h/ml	14.3 ± 0.91
AUMC	$µg.h^2/ml$	40.5 ± 2.80
$Vd_{(area)}$	l/kg	1.17 ± 0.10
$Vd_{(B)}$	l/kg	1.63 ± 0.15
Cl_B	l/kg/h	0.45 ± 0.03
MRT	h	2.83 ± 0.05
t_d	h	9.97 ± 0.09

Note: Kinetic parameters are as described by Gibaldi and Perrier (1982). A* and B = Zero-time plasma drug concentration intercept of the regression line of absorption and elimination phases, respectively; Ka and β are the absorption and elimination rate constants, respectively; $t_{½Ka}$ = absorption half-life; $t_{½β}$ = elimination half-life; AUC = area under the plasma concentration-time curve; AUMC = area under the first-moment curve; $Vd_{(area)}$ = apparent volume of distribution based on AUC; $Vd_{(B)}$ = Volume of distribution based on zero-time plasma drug concentration intercept of elimination phase; Cl_B = total body clearance; MRT = mean residence time; t_d = duration of therapeutic plasma concentration.

Table 2. Urine concentration and urinary excretion of cefotaxime in buffalo calves after a single subcutaneous dose of 10 mg/kg body weight

Time interval (h)	Conc. (µg/ml)	Percent of total dose excreted
0-4	14.3 ± 9.71	0.12 ± 0.09
4-8	27.2 ± 11.9	1.40 ± 1.09
8-12	54.2 ± 18.8	2.84 ± 1.11
12-16	29.6 ± 12.4	2.40 ± 1.25
16-20	3.67 ± 1.87	0.38 ± 0.14
20-24	1.45 ± 0.46	0.04 ± 0.02
0-24	-	5.36 ± 1.19

The values given are mean ± SE of the results obtained from 3-5 animals.

urinary excretion cefotaxime in buffalo calves. At the end of 24 h, the urinary excretion of cefotaxime was 5.36% of total administered dose. Taking 8 and 12 h as convenient dosage intervals (t), with minimum therapeutic plasma concentration [Cp $(min)^{\infty}$] of 0.05, 0.1, 0.2, 0.4 and 0.6 µg/ml and using the values of β and $V_{d(area)}$ of Table 1, the dosage regimens for cefotaxime were computed and are presented in Table 3.

Discussion

Evaluation of the results on observed plasma levels of cefotaxime indicated that the data can be best fitted to one-

Table 3. Calculated subcutaneous dosage regimen of cefotaxime, required to maintain specified plasma cefotaxime concentration in buffalo calves

Desired plasma concentration (μg/ml)	Dosage interval (h)	Priming doses (mg/kg)	Maintenance doses (mg/kg)
0.05	8	1.35	1.29
0.05	12	6.45	6.40
0.1	8	2.69	2.58
0.1	12	12.9	12.8
0.2	8	5.38	5.16
0.2	12	25.8	25.6
0.4	8	10.8	10.3
0.4	12	51.6	51.2
0.6	8	16.1	15.5
0.6	12	77.4	76.8

compartment open model with the exponential equation $Cp = Be^{-\beta t} - A^1e^{-Kat}$, where Cp is the cefotaxime concentration at time t, A^1 and B are zero-time intercepts of absorption and elimination phases of the plasma concentration-time curves, respectively, Ka and β are the absorption and elimination rate constants, respectively, and e represents the base of natural logarithms.

The minimum therapeutic plasma concentration was maintained from 2.5 to 10 h. The minimum inhibitory concentration (MIC_{90}) of cefotaxime has been reported to be 0.016-1 μg/ml [12]. The rapid appearance of cefotaxime in the plasma suggests that this drug quickly enters into the systemic circulation following subcutaneous administration, and this is further confirmed by the high value for the absorption rate constant (4.61 ± 0.93/h).

The elimination half-life of cefotaxime in buffalo calves was 1.77 ± 0.02 h, which was shorter than its half-life in cow calves, but longer than that reported in cats, dogs, sheep and goats. The elimination half-lives of cefotaxime in cow calves [17], cats [13], dogs [7], sheep [9] and goats [2] have been reported to be 3.48, 0.98, 0.74, 0.38 and 0.36 h, respectively. The total body clearance of cefotaxime in buffalo calves is calculated to be 0.45 ± 0.03 l/kg/h, which is lesser than from the data reported in cattle, dogs and sheep. The values of total body clearance (Cl_B) in cattle [17], dogs [7] and sheep [9] have been calculated to be 0.81, 0.63 and 0.65 l/kg/h respectively. The total body clearance of cefotaxime in cat [13] has been reported to be 0.17 l/kg/h, which is approximately 2.5 fold lower than the values in buffalo calves calculated in the present study. The results of the present study revealed marked species differences in the pharmacokinetic behaviour of cefotaxime.

In the present study, 5.36 ± 1.19 percent of the total administered dose of cefotaxime was recovered in urine of buffalo calves within 24 h. Similar result was also reported in crossbred calves, where approximately 4.5 percent of the total administered dose of cefotaxime was recovered in urine within 12 h [17].

The ultimate objective of the present study was to determine a satisfactory subcutaneous dosage regimen of cefotaxime in buffalo species. Judicious use of an antibiotic is not based solely on its pharmacokinetic behaviour. It also depends on its clinical efficacy. But it is also not axiomatic to extrapolate the data of dosage regimen from one species to other species of animal without conducting the detailed pharmacokinetic study. A suitable dosage regimen for cefotaxime in buffalo calves was computed from the kinetic data of present study. The primary (D) and maintenance (D') doses were calculated by following equations:

$$D = Cp\,(min)^{\infty}.\ Vd(e^{\beta\tau})$$
$$D' = Cp\,(min)^{\infty}.\ Vd(e^{\beta\tau}-1)$$

In clinical practice, the most suitable dosage schedule of cefotaxime for a minimum therapeutic plasma concentration ($Cp\,(min)^{\infty}$) of 0.1 μg/ml, would be 12.9 mg/kg followed by 12.8 mg/kg repeated at 12 h intervals or it would be 13 mg/kg repeated at 12 h intervals.

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