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Pharmacokinetics of cefotaxime in hepatic-dysfunctioned buffalo calves

Suresh Kumar Sharma[1]*, Anil Kumar Srivastava[1], and Milind Devidas Deore[2]

[1]*Department of Pharmacology and Toxicology, College of Veterinary Science Punjab Agricultural University, Ludhiana, India*

[2]*Bombay Veterinary College, Parel, Mumbai, India*

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ABSTRACT

The pharmacokinetics, urinary excretion and dosage regimen of cefotaxime after its single intravenous administration (10 $mg.kg^{-1}$) was investigated in hepatic-dysfunctioned buffalo calves. Hepatic-dysfunction was induced by intramuscular administration of paracetamol (250 $mg.kg^{-1}$ body weight on day 1, followed by two subsequent doses of 50 $mg.kg^{-1}$ body weight on day 3 and 5). At 1 min, the concentration of cefotaxime in plasma was 69.6 ± 1.54 $\mu g.ml^{-1}$ which rapidly declined to 11.5 ± 0.41 $\mu g.ml^{-1}$ at 15 min. The drug was detected upto 5 h. The elimination half-life and volume of distribution were 0.94 ± 0.02 h and 1.48 ± 0.07 $L.kg^{-1}$, respectively. The distribution half-life and AUC were 0.055 ± 0.003 h and 9.20 ± 0.47 $\mu g.ml^{-1}.h$, respectively. The total body clearance (Cl_B) and tissue/plasma (T/C) ratio were 1.1 ± 0.06 $L.kg^{-1}.h^{-1}$ and 11.5 ± 0.89, respectively. Approximately 3% of the total administered dose of cefotaxime was recovered in urine within 24 h after administration. Cefotaxime was bound to plasma proteins of hepatic-dysfunctioned buffalo calves to the extent of 31-35.2%. A satisfactory intravenous dosage regimen for cefotaxime in hepatic-dysfunctioned buffalo calves would be 13 mg/kg body weight at 6 h intervals.

Key words: buffalo calves, cefotaxime, dosage regimen, hepatic dysfunction, pharmacokinetics

Introduction

Cefotaxime, a semisynthetic bactericidal cephalosporin, is effective against a wide variety of Gram-positive and Gram-negative microorganisms (NEU et al., 1979). Pharmacokinetics of chemotherapeutic agents are markedly altered in disease conditions (LESAR and ZASKE 1984; HARY et al., 1989; TOTH et al., 1991; SINGH et al., 1998;

* Contact address:
Dr. Suresh Kumar Sharma, Associate Professor, Department of Pharmacology and Toxicology, College of Veterinary Science, Punjab Agricultural University, Ludhiana - 141 004, India, Phone +91 161 2401960 Ext. 366; Fax +91 161 2400822, +91 161 2400945; E-mail: sureshpan2000@yahoo.com

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CHAUDHARY et al., 1999), hence the dosage regimen obtained in healthy subjects cannot be extrapolated in clinical cases to treat diseased animals. Since liver is the main site of biotransformation and elimination of drugs, hepatic dysfunction certainly poses a potential therapeutic problem by altering the disposition kinetics of antimicrobial drugs.

The purpose of this study was to determine the disposition kinetic variables of cefotaxime and its urinary excretion in hepatic-dysfunctioned buffalo calves following intravenous administration. From the disposition kinetic data, recommendations were made for optimal dosage regimens of cefotaxime in hepatic-dysfunctioned buffalo calves.

Materials and methods

Animals and treatment. Five healthy male buffalo calves ranging between 1 and 1.5 years of age with an average weight of 65.4 kg were used. The animals were housed in an 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*. Hepatic dysfunction was induced by intramuscular administration of paracetamol. The dosage schedule of paracetamol was 250 $mg.kg^{-1}$ body weight on day 1, followed by 2 subsequent doses of 50 $mg.kg^{-1}$ body weight on day 3 and 5. The extent of hepatic dysfunction was determined by regular estimation of plasma levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP) and cholesterol at every 24 h, intervals. On the basis of above biochemical parameters, day 6 after administration of first dose of paracetamol, was taken as the time of full onset of hepatic dysfunction. Once hepatic dysfunction was set, cefotaxime was administered by single intravenous injection into the jugular vein at 10 $mg.kg^{-1}$ body weight, in a 10% solution with sterilized distilled water.

Experimental and assay procedures. Before the start of experiment, the animals were kept in metabolic stalls of standard size. The stalls were prepared in such a way that all the urine voided by animals could be collected over the chosen time intervals without any contamination or spillage. Following the administration of cefotaxime, blood samples (5 ml) were withdrawn from the contralateral jugular vein into heparinized glass test tubes before administration and at 1, 2.5, 5, 7.5, 10, 15, 30, 45, 60, 90 min and 2, 3, 4 and 5 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 analysis.

Analytical procedure. The plasma activities of asparate aminotransferase and alkaline phosphatase were determined by the method of WOOTTON (1964). Plasma level of cholesterol was determined by procedure of WYBENGA et al. (1970). The concentration of cefotaxime in the plasma and urine were estimated by employing the microbiological assay

technique (ARRET et al., 1971) using Escherichia coli (ATCC 25922) as the test organism. This method detected both parent and active metabolities of cefotaxime. The assay could detect a minimum of 0.1 $\mu g.ml^{-1}$ of cefotaxime. The standard curve of cefotaxime in buffalo calf plasma was linear between 0.1 to 0.6 $\mu g.ml^{-1}$. The value of correlation coefficient (r) and coefficient of variation were 0.99 and 4.8%, respectively. Kinetic parameters were determined according to the method of computed least squares (GIBALDI and PERRIER, 1982). The in vitro plasma protein binding was determined by an equilibrium dialysis technique at plasma concentration of 2, 5, 10, 25, 50 and 100 $\mu g.ml^{-1}$.

Results

The plasma activities of AST, ALP and cholesterol level after paracetamol administration are presented in Table 1.

Table 1. Effect of repeated administration of paracetamol* employed to induce hepatic-dysfunction, on plasma activity of aspartate aminotransferase, alkaline phosphatase and plasma levels of cholesterol in buffalo calves

Time after paracetamol administration (days)	Aspartate aminotransferase (n mol pyruvate formed.$min^{-1}.ml^{-1}$)	Alkaline phosphatase (n mol pyruvate formed.$min^{-1}.ml^{-1}$)	Cholesterol (mg.100 ml^{-1})
0	32.5 ± 1.06 (100)	21.3 ± 0.88 (100)	59.9 ± 1.39 (100)
1	50.6 ± 1.70 (156)**	31.0 ± 0.54 (146) **	64.2 ± 1.36 (107) **
2	54.0 ± 3.34 (166) **	70.3 ± 4.71 (330) **	67.2 ± 0.76 (112) **
3	61.7 ± 2.96 (190) **	77.5 ± 2.27 (364) **	65.5 ± 1.81 (109) **
4	70.3 ± 2.37 (216) **	66.6 ± 2.21 (313) **	70.0 ± 0.63 (117) **
5	76.5 ± 2.56 (235) **	54.8 ± 4.17 (257) **	72.3 ± 1.38 (121) **
6	81.8 ± 1.09 (252) **	76.0 ± 2.46 (357) **	76.5 ± 1.03 (128) **
7	78.6 ± 1.39 (242) **	75.9 ± 3.44 (356) **	74.9 ± 2.26 (125) **
8	74.1 ± 1.27 (228) **	68.7 ± 4.49 (323) **	75.5 ± 2.12 (126) **
9	65.7 ± 2.76 (202) **	64.9 ± 3.17 (305) **	76.4 ± 1.62 (128) **
10	57.7 ± 2.94 (178) **	54.3 ± 4.22 (255) **	75.7 ± 1.50 (126) **
12	51.9 ± 1.59 (160) **	46.5 ± 2.22 (218) **	75.8 ± 1.49 (126) **
14	45.9 ± 3.07 (141) **	37.6 ± 2.21 (176) **	75.8 ± 1.49 (126) **

The values given are mean ± SE of results obtained from 5 animals. Figures in parentheses indicate the percentage of corresponding control (0 day) values taking the values of 0 day as 100 per cent. *The dosage schedule of paracetamol was 250 $mg.kg^{-1}$ i/m on day 1; followed by 50 $mg.kg^{-1}$ i/m on day 3; followed by 50 $mg.kg^{-1}$ i/m on day 5. **Significantly ($P<0.05$) different as compared to corresponding value of 0 day.

The mean plasma concentrations of cefotaxime as a function of time in hepatic-dysfunctioned buffalo calves were plotted on a semilogarithmic scale (Fig. 1). At 1 min the mean plasma concentration of cefotaxime was 69.6 ± 1.54 $\mu g.ml^{-1}$, which rapidly declined to 11.5 ± 0.41 $\mu g.ml^{-1}$ at 15 min. Thereafter it gradually disappeared from plasma and at 5 h only a concentration of 0.04 ± 0.02 $\mu g.ml^{-1}$ of cefotaxime was detected. Table 2 presents the calculated values of the pharmacokinetic parameters in hepatic-dysfunction buffalow calves. Table 3 shows the urinary excretion of cefotaxime in hepatic-dysfunctioned buffalo calves.

Table 2. Pharmacokinetic parameters of cefotaxime in buffalo calves (n = 5) in which hepatic-dysfunction was induced by repeated administration of paracetamol and subsequently cefotaxime was administered in a single intravenous dose of 10 $mg.kg^{-1}$ body weight

Parameter	Unit	Mean ± SE
$C_p°$	$\mu g.ml^{-1}$	84.1 ± 2.30
A	$\mu g.ml^{-1}$	82.1 ± 2.48
B	$\mu g.ml^{-1}$	2.04 ± 0.25
α	h^{-1}	12.8 ± 0.76
β	h^{-1}	0.742 ± 0.017
$t_{½\alpha}$	h	0.055 ± 0.003
$t_{½\beta}$	h	0.94 ± 0.02
K_{12}	h^{-1}	3.24 ± 0.18
K_{21}	h^{-1}	1.03 ± 0.04
K_{12}/K_{21}	Ratio	3.15 ± 0.12
K_{10}	h^{-1}	9.29 ± 0.71
AUC	$\mu g.ml^{-1}.h$	9.20 ± 0.47
V_c	$L.kg^{-1}$	0.12 ± 0.003
$V_{d(area)}$	$L.kg^{-1}$	1.48 ± 0.07
Cl_B	$L.kg^{-1}.h^{-1}$	1.1 ± 0.06
T/C	Ratio	11.5 ± 0.89
Td	h	5.28 ± 0.12

$C_p°$ = plasma drug concentration at time zero after intravenous dose; A and B are zero intercepts of distribution and elimination phase, respectively; α and β are distribution and elimination rate constants, respectively, $t_{½\alpha}$ = distribution half-life; $t_{½\beta}$ = elimination half-life; K_{12} and K_{21} are rate constants of drug transfer from central to peripheral and from peripheral to central compartments, respectively; K_{10} = rate constant for elimination of drug from central compartment; AUC = area under the plasma drug concentration – time curve; V_c = Volume of central compartment; $Vd_{(area)}$ = apparent volume of distribution, Cl_B = total plasma clearance; T/C = ratio of drug concentration between peripheral and central compartment; td = duration of therapeutic plasma concentration.

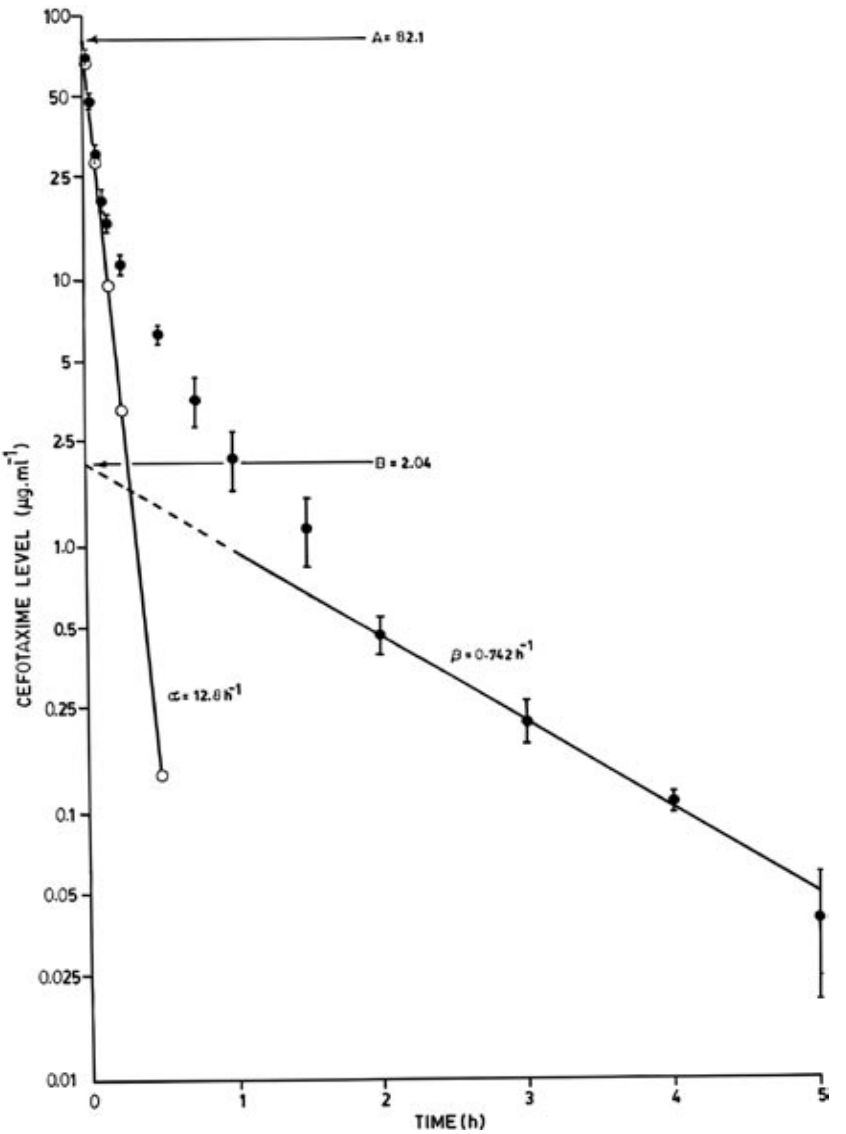

Fig. 1. A semilogarithmic plot of plasma levels of cefotaxime after a single intravenous dose of 10 mg.kg^{-1} body weight in hepatic-dysfunctioned buffalo calves. Values given are mean ± SE of 5 animals. Data were analysed according to two compartment open model. The calculated points (O) of the distribution phase are obtained by feathering techniques.

Taking 4, 6 and 8 h as convenient dosage intervals (τ), with a minimum therapeutic concentration [$C_p(min)^{\infty}$] of 0.05, 0.1, 0.2 and 0.4 μg.ml^{-1} and using the values of β and $Vd_{(area)}$ of table 2, the dosage regimen for cefotaxime in hepatic-dysfunctioned buffalo calves were computed and are presented in Table 4.

Table 3. Urinary excretion of cefotaxime in buffalo calves in which hepatic-dysfunction was induced by repeated administration of paracetamol and subsequently cefotaxime was administered in a single intravenous dose of 10 mg/kg body weight

Time interval (h)	Cumulative percent of total dose excreted
0-4	0.58 ± 0.28
0-8	2.85 ± 0.22
0-12	3.01 ± 0.28
0-16	3.12 ± 0.25
0-20	3.14 ± 0.26
0-24	3.15 ± 0.26

The values given are mean ± SE of the results obtained from 4-5 animals.

Table 4. Dosage regimen of cefotaxime in hepatic-dysfunctioned buffalo calves, at various dosage intervals for microorganisms of different susceptibility

MTC	Dosage interval (h)		
(μg/ml)	4	6	8
0.05	1.44 (1.36)	6.35 (6.30)	28.0 (27.9)
0.1	2.88 (2.73)	12.7 (12.6)	56.0 (55.9)
0.2	5.76 (5.46)	25.4 (25.1)	112.0 (111.7)
0.4	11.5 (10.9)	50.8 (50.2)	224.0 (223.4)

Values are expressed as mg/kg body weight. Values of maintenance doses are given in parentheses.
MTC- Minimum therapeutic plasma concentration

Discussion

Hepatic-dysfunction was produced by repeated administration of paracetamol (250 mg.kg^{-1} body weight im on day 1, followed by 50 mg.kg^{-1} b.wt on day 3 and 5). Paracetamol was also reported to produce hepatic injury in man (PROUDFOOT and WRIGHT, 1970), experimental animals (MITCHELL et al., 1973), sheep (BHAUMIC et al., 1995) and buffalo calves (KUMAR, 1999).

The plasma activities of AST, ALP and cholesterol level after paracetamol administration remained significantly high upto 14th day. The elevation in AST activity may be attributed to its release from ruptured hepatocytes or escape though membranes because of altered permeability, which is caused by hepatotoxic effects of paracetamol. The increase in ALP activity may be due to production in response to hepatic necrosis and injury to intrahepatic bile canaliculi. Hypercholesterolaemia may be due to utilization of volatile fatty acids by damaged liver for glycogenesis which entered in the circulation. The decreased metabolism/ excretion of cholesterol by liver may be another contributing factor.

Evaluation of the mean plasma concentrations of cefotaxime as a function of time in hepatic-dysfunctioned buffalo calves revealed biphasic decline of plasma drug concentration and were fitted in 2-compartment open model. The disposition of cefotaxime was adequately described by a bi-exponential equation, $Cp = Ae^{-\alpha t}+Be^{-\beta t}$. Cefotaxime, after intravenous administration has also been reported to follow two-compartment open model in man (KEMMERICH et al., 1983), dogs (GUERRINI et al., 1986), goats (ATEF et al., 1990) and healthy buffalo calves (SHARMA, 2000).

The high value of rate constant α (12.8 ± 0.76 h^{-1}) and volume of distribution (1.48 ± 0.07 $L.kg^{-1}$) indicated that cefotaxime is rapidly and extensively distributed into various body fluids and tissues. The elimination half-life of cefotaxime in hepatic-dysfunctioned buffalo calves was 0.94 ± 0.02 h which was considerably lesser than its half-life in healthy cow calves and buffalo calves. The elimination half-life of cefotaxime in healthy cow calves (SHARMA et al., 1995) and buffalo calves (SHARMA, 2000) have been reported to be 3.48 ± 1.17 h and 1.19 ± 0.05 h, respectively. In accordance to the result, the value of the total body clearance of cefotaxime in hepatic-dysfunctioned buffalo calves (1.1 ± 0.06 $L.kg^{-1}.h^{-1}$) was higher as compared to healthy crossbred calves and buffalo calves. The values of Cl_B in healthy crossbred calves (SHARMA et al., 1995) and buffalo calves (SHARMA, 2000) have been calculated to be 0.81 ± 0.10 and 0.68 ± 0.04 $L.kg.^{-1}.h^{-1}$, respectively. The results of the present study revealed marked differences in kinetic behaviour of cefotaxime as compared to healthy buffalo calves.

The precise mechanisms for enhanced drug clearance in hepatic-dysfunctioned patients remain to be elucidated. Recently, it has been reported that during hepatic dysfunction, the phase I mixed function oxidases are selectively affected i.e. cytochome P450 (CYP), 1A2 and CYP2CB have enhanced activity while other CYP isoforms such as CYP2C9 and CYP3A4 remain unaffected. Increased activities of phase II enzymes i.e glucuronyl transferase, acetyl transferase and sulfotransferase have also been demonstrated. So the increased hepatic clearance of drugs during hepatic dysfunction may be the consequence of disease specific changes in both enzyme activity and/or drug transport within the liver (REY et al., 1998).

At the end of 24 h, the urinary excretion was 3% of total administered dose, which was similar to that of healthy buffalo calves (SHARMA, 2000). In healthy crossbred calves, following a single intravenous administration of cefotaxime (10 $mg.kg^{-1}$) approximately 4.5% of drug was recovered in urine within 12 h (SHARMA et al., 1995). TOTH et al. (1991) have also reported that the fraction of the administered dose of ceftriaxone excreted in urine of liver transplant recipients did not differ markedly from that of normal subjects.

The extent of binding of cefotaxime to plasma protein of hepatic-dysfunctioned buffalo calves was 32.5 ± 2.07 per cent. Similar to this, cefotaxime was reported to bind plasma proteins of human (NEU, 1982) and crossbred calves (SHARMA and SRIVASTAVA 1994) to the extent of 36-40 and 30.2 per cent, respectively.

The method of detection used in this study did not distinguish between the parent drug and its metabolites. So the plasma levels of the drug are actually the efficacies of both parent drug and its active metabolites. So the possibility of altered metabolism in diseased liver is there. But ultimate objective of the present study was to determine a satisfactory dosage regimen of cefotaxime in hepatic-dysfunctioned buffalo calves. It is not axiomatic to compute the dosage regimen of cefotaxime to be used effectively in clinical practice, without having first conducted a detailed pharmacokinetic study. Thus the appropriate dosage schedule of cefotaxime on the basis of its pharmacokinetic data was calculated for hepatic-dysfunctioned buffalo. The maintenance dose (D_1) was calculated according to equation:

$$D_1 = C_p(min)^{\infty}. Vd_{(area)} (e^{\beta\tau}-1)$$

The priming dose (D) is obtained by omitting –1 from the above equation. With a minimum therapeutic plasma concentration (MTC) of cefotaxime as 0.1 $\mu g.ml^{-1}$, which has been shown to be most effective against the majority of sensitive Gram-positive and Gram-negative pathogens (BARRIERE and FLAHERTY, 1984), in practice the suitable dosage schedule of cefotaxime in hepatic-dysfunctioned buffalo calves would be 13 mg/kg to be repeated at 6 h intervals.

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SAŽETAK

Istražena je farmakokinetika, izlučivanje mokraćom i doziranje cefotaksima u bivolske teladi s poremećenom jetrenom funkcijom nakon njegove jednokratne intravenske primjene u količini 10 $mg.kg^{-1}$. Jetrena disfunkcija bila je prouzročena intramuskularnom primjenom paracetamola u količini 250 $mg.kg^{-1}$ tjelesne mase prvog dana, a zatim po 50 $mg.kg^{-1}$ tjelesne mase trećega i petoga dana. Koncentracija cefotaksima u plazmi iznosila je u prvoj minuti 69,6 ± 1,54 $\mu g.ml^{-1}$, a u petnaestoj minuti smanjila se na 11,5 ± 0,41 $\mu g.ml^{-1}$. Lijek se mogao dokazati pet sati nakon primjene. Poluvrijeme njegova izlučivanja iznosilo je 0.94 ± 0,02 h, a volumen distribucije 1,48 ± 0,07 $L.kg^{-1}$. Poluvrijeme distribucije bilo je 0,055 ± 0,003 h, a AUC 9,20 ± 0,47 $\mu g.ml^{-1}.h$. Ukupni tjelesni klirens iznosio je 1,1 ± 0,06 $L.kg^{-1}.h$., dok je odnos tkivo/plazma bio 11,5 ± 0,89. Oko 3% ukupno primijenjene doze cefotaksima dokazano je u mokraći unutar 24 sata nakon davanja. Cefotaksim je bio vezan od 31 do 35,2% na bjelančevine plazme u teladi s poremećenom jetrenom funkcijom. Zadovoljavajuće doziranje cefotaksima u bivolske teladi s poremećenom jetrenom funkcijom bilo bi 13 mg/kg tjelesne mase u razmaku od 6 sati.

Ključne riječi: bivolska telad, cefotaksim, doziranje, jetrena disfunkcija, farmakokinetika