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Cefotaxime pharmacokinetics in male buffalo calves following multiple dosing

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ABSTRACT

The pharmacokinetic pattern of cefotaxime following its repeated dosing was studied in buffalo calves. Cefotaxime was given at a dose rate of 13 mg/kg, first by intravenous route (i.v.) followed by intramuscular (i.m.) administration, 8 hourly for 5 days. Plasma levels of cefotaxime equivalent at different pre-determined time intervals were estimated. At 1 min, after first i.v. injection, plasma level was 71.7 ± 6.01 $\mu g.ml^{-1}$, which gradually declined and drug was detected up to 8 h (0.09 ± 0.05 $\mu g.ml^{-1}$). Plasma concentration of cefotaxime equivalent at 15, 20, 30 and 480 min following all repetitions was almost the same. After final intramuscular injection, peak plasma concentration (11.0 ± 0.24 $\mu g.ml^{-1}$) was detected at 20 min, which declined to 0.08 ± 0.04 $\mu g.ml^{-1}$ at 8 h. On comparing the data on plasma levels of repeated intramuscular injections with first intravenous injection, it was revealed that repeated intramuscular injections of cefotaxime have no prolonged therapeutic effect and lack any cumulative effect. Perusal of kinetic determinants of cefotaxime following first i.v. injection and last i.m. injection revealed no significant difference in relation to β, $t_{1/2\beta}$, AUC, $Vd_{(area)}$ and Cl_B. Such lack of variation indicated that repeated administration of cefotaxime did not alter its disposition kinetics.

Key words: buffalo calves, cefotaxime, multiple dosing, pharmacokinetics

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Introduction

Cefotaxime was the first of the third generation cephalosporins to be released onto the market It is effective against a wide range of Gram-positive and Gram-negative microorganisms (NEU, 1982). Generally, antimicrobials are used after repeated administration to treat various bacterial infections. Therefore, pharmacokinetic studies of antimicrobial agents are relevant when they are undertaken after repeated administration, in the species in which the drugs are to be used clinically. The pharmacokinetics of cefotaxime have been investigated after single injection in humans (KAMPF et al., 1984); rats (HAKIM et al., 1989); sheep (GUERRINI et al., 1983, 1985, 1986); dogs (GUERRINI et al., 1986); cats (McELORY et al., 1986); goats (ATEF et al., 1990) and cattle (SHARMA and SRIVASTAVA 1994; SHARMA et al., 1995). However, similar information after repeated administration is not available in buffalo. The purpose of this study was to determine the pharmacokinetics of cefotaxime in buffalo calves after repeated administration.

Materials and methods

Healthy male buffalo calves (n=3), 1-1.5 year old and having an average body mass of 95 kg were housed in the departmental animal shed with a concrete floor, and provided with green fodder and water *ad libitum*. Each animal was acclimatized for 2 weeks before the start of the experiment. Cefotaxime sodium (Claforan®, Hoechst Marion Roussel Ltd., Mumbai, India) was given at a dose rate of 13 mg/kg b.m., intravenously followed by 13 mg/kg by intramuscular administration at 8 h intervals for 5 days, 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, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min after first intravenous injection, 15, 20, 30, 480 min after subsequent intramuscular injections and at 1, 2.5, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480 and 600 min after final intramuscular injection. 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.

Concentration of cefotaxime equivalent in plasma was estimated using the microbiological assay technique (SIMON and JONGYIN, 1970; ARRET et al., 1971) using *Escherichia coli* (ATCC 25922) as the test organism. This method detected both the parent compound and its active metabolites. The assay could detect a minimum of 0.1 µg/ml of cefotaxime equivalent. 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. Plasma concentration–time data for each buffalo calf were determined according to the computed least squares regression technique. Kinetic parameters were calculated as described by GIBALDI and PERRIER (1982).

Results

Mean plasma concentrations of cefotaxime equivalent in buffalo calves at various time intervals, after first i.v. and last i.m. doses of 13 mg/kg b.m., are shown in Table 1.

Table 1. Plasma levels of cefotaxime equivalent (µg.ml^{-1}) following repeated* administration of cefotaxime at a dose rate of 13 mg.kg^{-1} b.m. in buffalo calves

Time after cefotaxime administration (min)	First injection (i.v.)	Thirteenth injection (i.m.)
1	71.7 ± 6.01	1.60 ± 0.05
2.5	53.6 ± 1.82	2.69 ± 0.07
5	38.4 ± 0.43	4.36 ± 0.38
10	23.5 ± 0.90	7.27 ± 0.41
15	15.7 ± 2.11	9.58 ± 0.42
20	12.5 ± 0.90	11.0 ± 0.24
30	9.83 ± 0.75	10.2 ± 0.41
45	5.58 ± 0.61	7.73 ± 0.24
60	3.71 ± 0.12	6.26 ± 0.35
90	2.62 ± 0.22	4.43 ± 0.08
120	2.05 ± 0.21	2.68 ± 0.22
180	1.23 ± 0.18	1.60 ± 0.05
240	0.66 ± 0.21	1.22 ± 0.10
300	0.40 ± 0.11	0.48 ± 0.02
360	0.35 ± 0.11	0.30 ± 0.09
420	0.15 ± 0.07	0.16 ± 0.02
480	0.09 ± 0.05	0.08 ± 0.04

Values given are mean ± SE of 3 animals

*First injection was given intravenously, followed by intramuscular route at 8 hour intervals for 5 days

Table 2. Pharmacokinetic parameters of cefotaxime following its repeated* administration at a dose rate of 13 mg.kg^{-1} body mass in buffalo calves

Parameter[a]	Unit	First injection (intravenous)	Thirteenth injection (intramuscular)
$C_p°$	µg.ml^{-1}	82.9 ± 7.59	-
A^1	µg.ml^{-1}	-	7.72 ± 1.66
A	µg.ml^{-1}	77.2 ± 7.73	-
B	µg.ml^{-1}	5.76 ± 0.30	8.13 ± 1.44
Ka	h^{-1}	-	10.6 ± 1.62
α	h^{-1}	10.4 ± 1.22	-
β	h^{-1}	0.54 ± 0.06	0.542 ± 0.052
t½Ka	h	-	0.068 ± 0.009
t½α	h	0.069 ± 0.009	-
t½β	h	1.31 ± 0.13	1.30 ± 0.13
K_{12}	h^{-1}	5.15 ± 0.94	-
K_{21}	h^{-1}	1.25 ± 0.02	-
K_{12}/K_{21}	Ratio	4.14 ± 0.80	-
AUC	µg.ml^{-1} x h	18.3 ± 0.98	14.0 ± 1.28
AUMC	µg.ml^{-1} x h²	21.6 ± 3.80	27.3 ± 1.72
$Vd_{(area)}$	L x kg^{-1}	1.34 ± 0.09	1.30 ± 0.06
$Vd_{(B)}$	L x kg^{-1}	2.27 ± 0.12	1.73 ± 0.36
Cl_B	ml.kg^{-1} x h^{-1}	713.6 ± 38.06	707.0 ± 83.6
T/P	Ratio	7.62 ± 1.29	-
F	%	-	76.7 ± 13.3

*In repeated administration of cefotaxime, the first injection was given intravenously, followed by intramuscular route at 8 hour intervals for 5 days. The disposition kinetics parameters were calculated after first i.v. and final i.m. administration.

[a]Kinetic parameters are as described by Gibaldi and Perrier (1982).

C_p^0 = plasma drug concentration at time zero after intravenous dose; A^1, A and B are zero intercepts of absorption, distribution and elimination phase, respectively; Ka, α and β are absorption rate constant, distribution rate constant and elimination rate constant, respectively, $t_{1/2}$Ka = absorption half-life; $t_{1/2}\alpha$ = distribution half life; $t_{1/2}\beta$ = 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; AUC = total area which is under plasma drug concentration – time curve; AUMC = total area under the first moment curve; $Vd_{(area)}$ = apparent volume of distribution, $Vd_{(B)}$ = volume of distribution based on zero-time plasma drug concentration intercept of elimination phase; T/P = tissue/plasma drug concentration ratio; F = bioavailability.

Following i.v. injection, peak plasma concentration (71.7 ± 6.01 µg/ml) at 1 min declined rapidly during the initial disposition phase. Prior to administration of the second injection (i.e. at 8 h after i.v. injection),

concentration of drug in plasma was 0.09 ± 0.05 μg/ml. Plasma concentration of cefotaxime equivalent at 15, 20, 30 and 480 min following all repetitions (second to twelfth i.m. injection) was 7.65-11.2, 8.25-12.5, 7.94-10.1 and 0 (not detected) -0.47 μg/ml, respectively. After the thirteenth i.m. injection a high concentration (1.60 ± 0.05 μg/ml) of the drug was detected in plasma as early as 1 min post-injection. Peak plasma concentration (11.0 ± 0.24 μg/ml) was observed at 20 min after injection. The drug was detected for up to 8 h. Pharmacokinetic parameters describing the absorption, distribution and elimination of cefotaxime equivalent in buffalo calves following first i.v. and thirteenth i.m. administration are presented in Table 2.

Discussion

Evaluation of results of plasma drug concentration of cefotaxime equivalent after first i.v. injection revealed that the disposition of cefotaxime equivalent was adequately described by a bi-exponential equation, $C_p=Ae^{-\alpha t}+Be^{-\beta t}$, corresponding to 2-compartment open model, while after thirteenth i.m. injection it was described by mono-exponential equation, $C_p=Be^{-\beta t}-A^1e^{-Kat}$. The disposition of cefotaxime following intravenous injection has been reported to follow the 2-compartment open model in humans (KEMMERICH et al., 1983); dogs (GUERRINI et al., 1986), and goats (ATEF et al., 1990).

The high value of distribution rate constant α (10.4 ± 1.22 h^{-1}) indicated that cefotaxime is rapidly distributed into the various body fluids and tissue compartments. The rapid distribution of cefotaxime was further substantiated by the high value of K_{12}/K_{21} (4.14 ± 0.80). Calculated values for the apparent volume of distribution (1.34 ± 0.09 $L.kg^{-1}$) and the high tissue/plasma ratio (7.62 ± 1.29) of cefotaxime indicate good penetration of drug into the body tissue. However, a lower value of $Vd_{(area)}$ (0.48 L/kg) has been reported in dogs (GUERRINI et al., 1986). The elimination half-life of cefotaxime in buffalo calves was 1.31 ± 0.13 h, which is considerably longer than the half-life of cats, dogs, sheep and goats, but shorter than that of cow calves. The elimination half-lives of cefotaxime in cats (McELROY et al., 1986); dogs (GUERRINI et al., 1986); sheep (GUERRINI et al., 1983), and goats (ATEF et al., 1990) have been reported to be 0.98, 0.74,

0.38 and 0.36 h, respectively. The total body clearance of cefotaxime in calves is calculated to be 0.71 ± 0.038 L/kg/h, which did not vary significantly from the data reported in dogs, sheep and cow calves. The values of Cl_B in dogs (GUERRINI et al., 1986); sheep (GUERRINI et al., 1983), and cow calves (SHARMA et al., 1995) have been calculated to be 0.63, 0.65 and 0.81 ± 0.10 L/kg/h.

On comparing data on plasma levels of repeated intramuscular injection with first intravenous injection it was revealed that repeated intramuscular injection of cefotaxime has no prolonged therapeutic effect and a lack of cumulative effect. Perusal of kinetic determinants of cefotaxime following first i.v. injection and last i.m. injection revealed no significant difference in relation to β, $t_{1/2\beta}$, AUC, $Vd_{(area)}$ and Cl_B. Such lack of variation indicated that repeated administration of cefotaxime did not alter its disposition kinetics.

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References

ARRET, B., D. P. JOHNSON, A. KRISHBAUM (1971): Outline of details for microbiological assay of antibiotics: Second revision. J. Pharm. Sci. 60, 1689-1694.

ATEF, M., A. RAMADAN, N. A. AFIFI, S. A. H. YOUSSEF (1990): Pharmacokinetic profile of cefotaxime in goats. Res. Vet. Sci. 49, 34-38.

GIBALDI, M., D. PERRIER (1982): Pharmacokinetics. Marcel and Dekker Inc., New York.

GUERRINI, V. H., L. J. FILIPPICH, P. B. ENGLISH, D. W. A. BOURNE (1983): Pharmacokinetics of cefotaxime in sheep. Am. J. Vet Res. 44, 1488-1491.

GUERRINI, V. H., L. J. FILIPPICH, P. B. ENGLISH, G. R. CAO, D. W. A. BOURNE (1985): Effect of probenecid on the pharmacokinetics of cefotaxime in sheep. J. Vet. Pharm. Ther. 8, 38-46.

GUERRINI, V. H., P. B. ENGLISH, L. J. FILIPPICH, J. SCHNEIDER, D. W. A. BOURNE (1986): Pharmacokinetic evaluation of slow-release cefotaxime suspension in the dog and sheep. Am. J. Vet Res. 47, 2057-2061.

HAKIM, L., D. W. A. BOURNE, E. J. TRIGGS (1989): Disposition of cefotaxime and its metabolite, desacetyl-cefotaxime in rat; application of a pharmacokinetic protein binding model. Xenobiotica 19, 815-822.

KAMPF, D., K. BORNER, M. MOLLER, M. KESSEL (1984): Kinetic interactions between azolocillin, cefotaxime and cefotaxime metabolites in normal and impaired renal function. Clin. Pharmacol. Ther. 35, 214-220.

KEMMERICH, B., H. LODE, G. BELMEGA, I. JENDROSCHEK, K. BORNER, P. KOEPPE (1983): Comparative pharmacokinetics of cefoperazone, cefotaxime and moxalactam. Antimicrob. Agents Chemother. 23, 429-434.

McELORY, D., W. R. RAVIS, C. H. CLARK (1986): Pharmacokinetics of cefotaxime in the domestic cat. Am. J. Vet. Res. 47, 86-88.

NEU, H. C. (1982): The new beta lactamase stable cephalosporins. Ann. Intern. Med. 97, 408-419.

SHARMA, S. K., A. K. SRIVASTAVA (1994): Pharmacokinetics and dosage regimen of cefotaxime in crossbred calves following single intramuscular administration. Vet. Res. Comm. 18, 313-318.

SHARMA, S. K., A. K. SRIVASTAVA, M. S. BAL (1995): Disposition kinetics and dosage regimen of cefotaxime in crossbred male calves. Vet. Res. 26, 168-173.

SIMON, H. J., E. JONGYIN (1970): Microbioassay of antimicrobial agents. Appl. Microbiol. 19, 573-579.

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SAŽETAK

Istražene su farmakokinetičke osobine cefotaksima u bivolske teladi nakon njegove višekratne primjene. Cefotaksim je bio dan u dozi od 13 mg/kg t.m. prvi puta intravenski (i.v.), a potom intramuskularno (i.m.) s razmacima od 8 sati i to tijekom 5 uzastopnih dana. U pokusu je određivana koncentracija cefotaksima u krvnoj plazmi u različitim, prethodno određenim, vremenskim razmacima. Jednu minutu nakon i.v. injekcije razina cefotaksima u plazmi bila je 71.7 ± 6.01 mg/ml te se postupno smanjivala, a niske koncentracije ovog cefalosporina utvrđene su sve do 8 sati nakon davanja (0.09 ± 0.05 mg/ml). Razine cefotaksima u plazmi bile su nepromijenjene 15, 20, 30 i 480 minuta nakon opetovanog davanja. Po posljednjoj i.m. injekciji vršna razina u plazmi utvrđena je nakon 20 minuta (11.0 ± 0.24 mg/ml), a po isteku 8 sati iznosila je 0.08 ± 0.04 mg/ml. Usporedbom vrijednosti koncentracije cefotaksima u plazmi nakon ponovljene i.m. primjene, s koncentracijama poslije prvog i.v. davanja, moglo se utvrditi da opetovane i.m. injekcije cefotaksima ne produžuju njegov terapijski učinak, tj. da se ovaj antibiotik ne kumulira u organizmu. Pažljivim promatranjem kinetičkih pokazatelja cefotaksima nakon njegove prve intravenske i posljednje intramuskularne injekcije utvrđeno je da nema signifikantnih razlika u vrijednostima kao što su: konstanta eliminacije (β), poluvrijeme eliminacije lijeka iz plazme ($t_{1/2\beta}$), površina ispod koncentracijske krivulje lijeka u plazmi (area under the curve - AUC), prividni volumen raspodjele ($Vd_{(area)}$) i ukupni klirens lijeka iz organizma (Cl_B). Nedostatak promjena u navedenim farmakokinetičkim pokazateljima ukazuje da višekratna primjena cefotaksima nije mijenjala kinetiku dispozicije ovog cefalosporinskog antibiotika treće generacije.

Ključne riječi: bivolska telad, cefotaksim, višekratna primjena, farmakokinetika