VETERINARSKI ARHIV 82 (6), 555-565, 2012

The pharmacokinetics of ceftazidime in *E. coli* lipopolysaccharide induced febrile buffalo calves

Suresh K. Sharma*, and Shah A. Ul Haq

Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, India

SHARMA, S. K., S. A. UL HAQ: The pharmacokinetics of ceftazidime in *E. coli* lipopolysaccharide induced febrile buffalo calves. Vet. arhiv 82, 555-565, 2012.

ABSTRACT

The pharmacokinetic properties of ceftazidime, a third generation cephalosporin, were investigated in experimentally induced febrile buffalo calves (n=5) after a single intravenous administration at a dose rate of 10 mg/kg body weight. The fever was induced by a single/repeated intravenous injection of *E. coli* lipopolysaccaride (1 µg/kg). Ceftazidime concentrations in the plasma and urine were determined by microbiological assay. Ceftazidime disposition was best fitted by a bi-compartmental open model with first-order elimination. At 2.5 min, the concentration of ceftazidime in the plasma of the febrile animals was 152.3 ± 6.77 µg/mL and the drug was detected up to 14 h. The elimination half-life and volume of distribution were 3.73 ± 0.42 h and 0.26 ± 0.05 L/kg, respectively. The distribution half-life, AUC and total body clearance (Cl_B) were 0.24 ± 0.03 h, 217.3 ± 23.4 µg/mL.h and 47.9 ± 4.57 mL/kg/h, respectively. Urinary excretion of ceftazidime was less than 28 percent after 32 h of administration of the drug in the febrile animals. An efficacy predictor, measured as the time over which the active drug exceeds the bacteria minimum inhibitory concentration (T>MIC), was calculated. T>MIC was 73% of the recommended dosing interval (8h) for bacteria with a MIC_{90}≤4 µg/mL.

Key words: buffalo calf, ceftazidime, dosage regimen, fever, pharmacokinetics

Introduction

Ceftazidime is an aminothiazolyl third generation cephalosporin antimicrobial agent. It is active against some susceptible gram-negative bacilli (*Escherichia coli, Proteus* spp.*, Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp.*)*, gram-positive pathogens (*Staphylococcus* spp., *Streptococcus* spp.*)* and is very active against *Pseudomonas aeruginosa* (ALBARELLOS et al., 2008). Amongst the documented reasons contributing to drug resistance are inappropriate dosage regimens. Rational antibiotic therapy requires

*Corresponding author:

Suresh Kumar Sharma, B.V.Sc., A.H., M.V.Sc., PhD, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, Guru Angad Dev. Veterinary and Animal Sciences University, Ludhiana - 141 004, India, Phone: + 91 161 241 4032; E-mail: sureshksharma@gadvasu.in

ISSN 0372-5480
Printed in Croatia

dosage regimens to be optimized, not only for clinical efficacy, but also to minimize the selection and spread of resistant pathogens. Pharmacokinetic studies of antimicrobial agents, which provide a basis for the determination of satisfactory dosage regimen, are relevant, when they are undertaken in the species in which the drugs are to be used clinically. There have been some limited data published on the pharmacokinetics of ceftazidime in animals. Pharmacokinetic data of ceftazidime has been reported in many animal species, including mice (KITA et al., 1992), rats (KITA et al.,1992; MATSUI et al., 1984), rabbits (ABD-EL-ATY et al., 2001; CARBON et al., 1984; KITA et al.,1992; SAKATA et al., 1984), monkeys (KITA et al., 1992; MATSUI et al., 1984), calves (SOBACK and ZIV, 1989), sheep (RULE et al., 1991), cows (RULE et al., 1996), dogs (KITA et al., 1992; MOORE et al., 2000; MATSUI et al., 1984) and cats (ALBARELLOS et al., 2008). The pharmacokinetics of chemotherapeutic agents are markedly altered in disease conditions (DARDI et al., 2005; SHARMA et al., 2005; TOTH et al., 1991), hence the dosage regimen obtained in healthy subjects cannot be extrapolated to clinical cases to treat diseased animals. Fever, which is one of the most common manifestations of many infectious diseases, is reported to induce a series of biochemical and physiological alterations in cells (MONSHOUWER et al., 1996). So, a study on the influence of fever on the pharmacokinetics of antibiotics is essential. The purpose of this study was to determine the pharmacokinetic variables of ceftazidime in febrile buffalo calves following intravenous administration. From the pharmacokinetic data, recommendations were made for an optimal dosage regimen of ceftazidime in febrile buffalo calves.

Materials and methods

Animals. Five healthy male buffalo calves, ranging between 6-12 months of age and weighing between 85 and125 kg body weight, were used. The animals were housed in an animal shed with a concrete floor and adequate ventilation. The animals were determined to be clinically healthy before the study. All the animals were acclimatized to the animal shed under uniform conditions and were maintained on green fodder, wheat straw and water *ad libitum.* They did not receive any drug treatment before the study. For the collection of urine, the experimental animals were kept in metabolic stalls of standard size, from 12h before the start of experiment and for the entire study. The metabolic stalls are designed in such a way that urine voided by animals can be collected at any time interval without any spillage. Before the start of the experiment, permission for experiments on these animals was obtained from the Institutional Animal Ethics Committee (IAEC).

Experimental design. Fever was induced by single/repeated intravenous administration of *E. coli* lipopolysaccaride at the dose rate of 1μg/kg b.m. (DARDI et al., 2005). Once fever was induced ceftazidime was injected intravenously to these five animals at a dose rate of 10 mg/kg of ceftazidime, in a 10% solution with sterilized distilled water. Blood

samples (4-5 mL each) were drawn from the contralateral jugular vein into heparanized glass test tubes before administration and at 2.5, 5, 10, 15, 30, 45 and 60 minutes and 2, 3, 4, 5, 6, 7, 8, 10, 12 and 14 h after administration of drug.

Bioassay. The concentrations of ceftazidime in the plasma and urine were estimated by employing the microbiological assay technique (ARRET et al., 1971) using *Escherichia coli* (MTCC 739) as the test organism. Three alternate wells on assay plates were filled with reference concentration (5 µg/mL) and the remaining three with an unknown concentration of the drug. Three plates were used for each concentration. These assay plates were incubated at 37 ^{o}C for a period of 24 hours. At the end of incubation, the diameters of the zones of inhibition were measured and the ceftazidime concentrations in the samples were calculated from the standard curve and expressed as µg/mL. The bioassay method used in this work could not distinguish between the parent compound and its active metabolites, if they exist. However, it measured the overall microbiological activity of the drug. The standard curve of ceftazidime in buffalo calf plasma was linear between 1 to 5 µg/mL. The value of the coefficient of determination (r^2) of the standard curve was 0.99. The drug could be detected up to a minimum limit of 1 µg/mL. The ceftazidime recovery exceeded 96% from plasma and urine over the concentration range of 5 to 200 µg/mL. The intra-day and inter-day coefficients of variance were less than 3%.

Pharmacokinetic analysis. 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 two- compartment open model (GIBALDI and PERRIER, 1982). T>MIC (%) was calculated as per following equation (ALBARELLOS et al., 2008):

$$T>MIC\ (\%) = \ln(dose/V_d \times MIC) \times t_{1/2}\ \ln 2 \times 100/\text{inter-dose interval}$$

Results

The effect of *E. coli* lipopolysaccharide on body temperature was recorded. The dose of lipopolysaccaride caused fever within 2-3 hours and fever persisted for 14 hours. At least 1.1 ^{0}C increase of temperature from the normal temperature was taken as the time of ceftazidime administration. The mean plasma concentrations of ceftazidime as a function of time in febrile buffalo calves were plotted on a semilogarithmic scale (Fig. 1**)**. At 2.5 minutes the mean plasma concentration of ceftazidime was 152.3 ± 6.77 µg/mL, which rapidly declined to a plasma concentration of 88.4 ± 4.07 µg/mL at 15 minutes. The levels gradually decreased to 2.10 ± 0.37 µg/mL at 14 hours. The various pharmacokinetic parameters for ceftazidime in buffalo calves in which fever was induced before administration of drug are given in Table 1. The elimination half life ($t_{1/2\beta}$), volume of distribution ($Vd_{(area)}$) and total body clearance in febrile animals were 3.73 ± 0.42 h, 0.26 ± 0.05 L/kg and 47.9 ± 4.57 mL/kg/h, respectively. The cumulative percent of the

total dose excreted in the urine of febrile animals (Table 2) was 27.6 ± 10.2 percent within 32 hours. The calculated T>MIC (%) of ceftazidime for three dosing intervals (8, 12 and 24 h) are presented in Table 3.

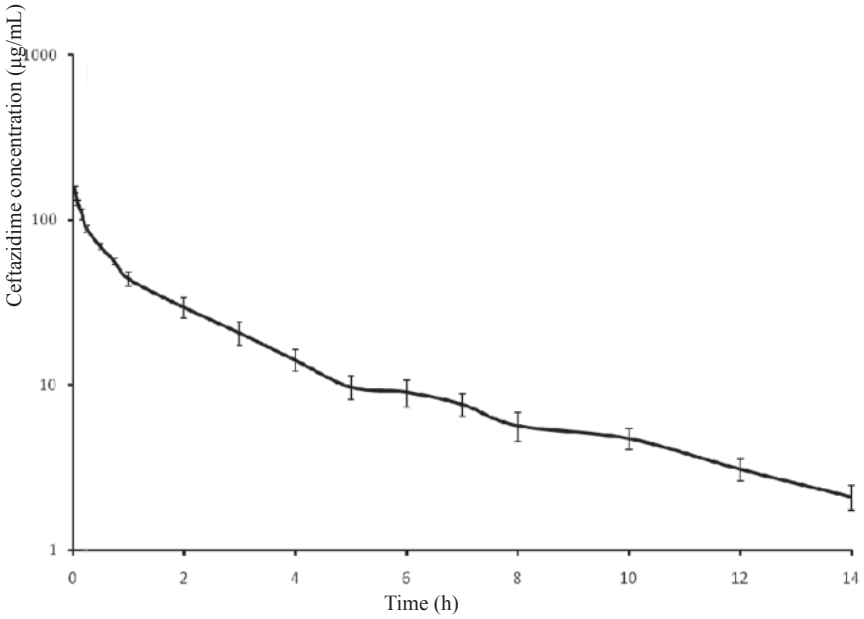

Fig. 1. A semi logarithmic plot of plasma levels of ceftazidime after a single intravenous dose of 10 mg/kg b.m. in febrile buffalo calves. Values given are mean ± SE of 5 animals.

Table 1. Pharmacokinetic parameters of ceftazidime in febrile buffalo calves (n=5) after a single intravenous injection of 10 mg/kg body weight.

Parameter[a]	Unit	Mean ± SE
C_p^o	µg/mL	163.2 ± 5.87
A	µg/mL	132.2 ± 5.71
B	µg/mL	31.04 ± 5.27
α	h^{-1}	3.07 ± 0.32
β	h^{-1}	0.19 ± 0.02
$t_{1/2\alpha}$	h	0.24 ± 0.03
$t_{1/2\beta}$	h	3.73 ± 0.42
K_{el}	h^{-1}	0.23 ± 0.02
K_{12}	h^{-1}	2.29 ± 0.26
K_{21}	h^{-1}	0.74 ± 0.13
$K_{12/K21}$ ratio	-	3.66 ± 1.07
AUC	µg/mL.h	217.3 ± 23.4
AUMC	$\mu g.mL^{-1}.h^2$	952.9 ± 176.4
$V_{d(area)}$	L/kg	0.26 ± 0.05
$V_{d(SS)}$	L/kg	0.20 ± 0.02
Cl_B	mL/kg/h	47.9 ± 4.57

[a] Kinetic parameters as described by Gibaldi and Perrier (1982). C_p^o = plasma drug concentration immediately following intravenous injection of a single dose; A, B = zero-time plasma drug concentration intercepts of regression lines of distribution and elimination phases, respectively; α and β = distribution and elimination rate constants, respectively; $t_{1/2\alpha}$ = distribution half life; $t_{1/2\beta}$ = elimination half life; K_{el} = elimination rate constant from central compartment; K_{12}, K_{21} = rate of transfer of drug from central (blood) to peripheral (tissues) compartment and vice-versa; AUC = total area under plasma drug concentration-time curve; AUMC = total area under the first moment plasma drug concentration-time curve; $V_{d(area)}$ = apparent volume of distribution, based on area under curve; Vd(ss) = apparent volume of distribution, based on steady state plasma levels; Cl_B = total plasma clearance.

Table 2. Urinary excretion of ceftazidime in febrile buffalo calves following a single intravenous injection (10 $mg.kg^{-1}$ body weight)

Time interval (h)	Amount excreted (mg)	Percent of total dose excreted	Time interval (h)	Cumulative amount excreted (mg)	Cumulative percent of total dose excreted
0-4	6.56 ± 5.93	0.59 ± 0.50	0 - 4	6.56 ± 5.94	0.59 ± 0.50
4-8	206.4 ± 89.7	22.3 ± 9.30	0 - 8	209.8 ± 92.2	22.6 ± 9.44
8-12	25.2 ± 4.57	2.85 ± 0.47	0 - 12	234.9 ± 96.6	25.4 ± 9.83
12-20	18.75 ± 1.25	2.68 ± 0.17	0 - 20	244.3 ± 95.0	26.8 ± 9.88
20-24	10.0 ± 4.67	1.47 ± 0.76	0 - 24	247.3 ± 96.1	27.2 ± 10.1
24-28	4.12 ± 0.04	0.61 ± 0.02	0 - 28	248.4 ± 95.5	27.3 ± 10.1
28-32	5.22 ± 2.37	0.77 ± 0.36	0 - 32	250.3 ± 96.1	27.6 ± 10.2

Values given are mean ± SE of the results obtained from 4-5 animals unless otherwise stated

Table 3. Time above ceftazidime minimum inhibitory concentration (T >MIC) expressed as percentage of the inter-dose interval (8, 12 or 24 h) for febrile buffalo calves (10 mg/kg)

	Inter-Dose Interval (h)		
MIC ($\mu g.mL^{-1}$)	8	12	24
0.1	192.4	128.3	64.1
0.25	162.8	108.5	54.3
0.3125	155.5	103.7	51.8
0.5	140.4	93.6	46.8
0.625	133.1	88.8	44.4
1	118.0	78.6	39.3
2	95.6	63.7	31.9
4	73.2	48.8	24.4
8	50.8	33.8	16.9

Discussion

Evaluation of the results of plasma ceftazidime levels against time indicated that the pharmacokinetics of ceftazidime in febrile buffalo calves, after intravenous administration, are best described by the two-compartment open model. The plasma concentration-time data were adequately described by the equation:

$C_p = Ae^{-\alpha t} + Be^{-\beta t}$

where Cp is ceftazidime concentration in plasma at time 't'. A and B are zero time intercepts of the distribution and elimination phase of the plasma concentration time curve. α and β are the distribution and elimination rate constants, respectively, and 'e' represents the base of natural logarithm. The disposition of ceftazidime following intravenous injection has been reported to follow a 2-compartment open model in rats (MATSUI et al., 1984), unweaned calves (SOBACK and ZIV, 1989), sheep (RULE et al., 1991), non-lactating cows (RULE et al., 1996), rabbits (ABD-EL-ATY et al., 2001) and cats (ALBARELLOS et al., 2008). In contrast, ceftazidime followed a three compartment open model in lactating cows (RULE et al., 1996).

Plasma concentrations of ceftazidime after IV administration remained greater than 2μg/mL for 14 h. A comparison of plasma levels of ceftazidime in febrile animals with that in healthy animals (SHAH AHSAN UL HAQ, 2010), indicated that the plasma levels of ceftazidime in febrile buffalo calves were almost similar to healthy buffalo calves. In contrast to this study, lower concentrations have been reported of cefepime in febrile cross-bred calves (PAWAR and SHARMA, 2008), gentamicin in febrile goats (AHMAD et al., 1994) and human beings (PENINGTON et al., 1975), cefazolin in febrile goats (ROY et al., 1992), cefuroxime (CHAUDHARY et al., 1999) and ceftriaxone (DARDI et al., 2005) in buffalo calves. The high values of the distribution rate constant α ($3.07 \pm 0.32\ h^{-1}$) indicated

that ceftazidime is rapidly distributed into various body fluids and tissue compartments. Ceftazidime shows rapid distribution reflected by the rate constant. This process in buffalo calves seems to be faster than in unweaned calves (SOBACK and ZIV, 1989), but slower than in lactating and non- lactating cows (RULE et al., 1996), dogs (MATSUI et al., 1984) and cats (ALBARELLOS et al., 2008). The rapid distribution of ceftazidime is further substantiated by the high values of K_{12}/K_{21} (3.66 ± 1.07). The elimination half-life of ceftazidime in febrile animals (3.73 ± 0.42 h) is similar to that reported in healthy (3.42 ± 0.21 h) animals (SHAH AHSAN UL HAQ, 2010), but longer than the values reported in unweaned calves (SOBACK and ZIV, 1989), sheep (RULE et al., 1991), dogs and mice (KITA et al., 1992), lactating and non-lactating cows (RULE et al., 1996), rabbits (ABD-EL-ATY et al., 2001) and cats (ALBARELLOS et al., 2008).

The volume of distribution at steady state ($Vd_{(ss)}$) is the constant that expresses the amount of the drug in the body at steady state as a proportion of the corresponding expected plasma concentration at steady state (TOUTAIN and BOUSQUET-MELOU, 2004). The relatively low volume of distribution at steady state in febrile buffalo calves (0.2 ± 0.02 L/kg) was as expected for a beta lactam antibiotic. This value was consistent with that reported in healthy buffalo calves (SHAH AHSAN UL HAQ, 2010), dogs (MATSUI et al., 1984) and cats (ALBARELLOS et al., 2008), but, was smaller than reported in unweaned calves (SOBACK and ZIV, 1989), sheep (RULE et al., 1991), lactating and non-lactating cows (RULE et al., 1996). The value of $Vd_{(ss)}$ in healthy buffalo calves, dogs, cats, unweaned calves, sheep, lactating and non-lactating cows was 0.18 ± 0.01, 0.21 ± 0.0007, 0.18 ± 0.04, 0.29 ± 0.06, 0.35 ± 0.21, 0.49 ± 0.14 and 0.39 ± 0.21 L/kg, respectively.

While comparing the total body clearance in febrile animals with that of healthy animals (SHAH AHSAN UL HAQ, 2010), it was found that the value of Cl_B in febrile animals (47.9 ± 4.57 mL/kg/h) is not significantly different as compared to healthy animals (39.5 ± 1.15 mL/kg/h). Endotoxin causes hepatic and renal dysfunction (WILKINSON, 1977) as well as hemodynamic depression (VAN MIERT, 1973). Due to the significant alterations in hepatic function, the levels of various enzymes, responsible for the metabolism of these antimicrobials, are altered and change the elimination and biotransformation pattern of the drug during fever (SINGH et al., 1997). Since ceftazidime is not significantly metabolized, is excreted unchanged primarily in urine by the glomerular filteration process (ALBARELLOS et al., 2008; SOBACK and ZIV, 1989) and is poorly bound to plasma proteins, this may be the reason why febrile conditions did not affect the pharmacokinetics of ceftazidime.

Ceftazidime is mostly eliminated by glomerular filtration (ALBARELLOS et al., 2008; SOBACK and ZIV, 1989). The cumulative percent of total dose excreted in the urine of febrile animals was 27.6 ± 10.2 percent within 32 hours. In contrast to our findings, the cumulative percent of ceftazidime excreted in the urine of rats and dogs (MATSUI et al., 1984) and mice (KITA et al., 1992) was 97.1, 86.3 and 77.9 percent, respectively. The peak urine level of the drug (410.9 ± 89.1 µg/mL) was detected at 8 h and there after the level

remained at ≥10μg/mL in the urine up to 32 hours from administration. The concentration of ceftazidime in the urine of buffalo calves remained higher than the MIC (0.25 to 8 μg/mL) of most microorganisms (ALBARELLOS et al., 2008; MOORE et al., 2000; SOBACK and ZIV, 1989) sensitive to the drug up to 32h. This suggested that use of ceftazidime in buffalo calves might achieve successful bacterial killing in urinary tract infections caused by microorganisms having susceptibility of ≤10 μg/mL.

In recent years, substantial efforts have been devoted to elucidating systematically the dynamic relationship between pharmacokinetic and pharmacodynamic variables. The main concept of this pharmacokinetic-pharmacodynamic approach is to use the concentration-effect relationship of the drug of interest in dosage adjustment and product development in a logical way, and minimize trial-and-error approaches (MEIBOHM and DERENDORF, 1997). Accordingly, several efficacy indices or surrogate markers that take both pharmacokinetic and pharmacodynamic information into account have been defined and used to describe the antibacterial activity of various classes of antimicrobial agents (HYATT et al., 1995; SANCHEZ-RECIO et al., 2000). In these approaches, the pharmacokinetic parameter is usually the serum concentration of the anti-infective agent, and the pharmacodynamic parameter is almost exclusively the MIC (SCHENTAG, 1999a and 1999b). Various empirical pharmacokinetic/pharmacodynamic indices have been proposed (ALIABADI and LEES, 2000; HYATT et al., 1995) to predict the success or failure of therapy. Three appear to be sufficient to predict drug effectiveness: T >MIC (therapeutic time) when antibiotics are time-dependent, AUIC (AUC/MIC), and C_{max}/MIC (inhibitory ratio) when antibiotics are concentration-dependent. For β-lactam antibiotics, the most important pharmacokinetic- pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the duration that the unbound concentration of an antibiotic remains above the MIC as a percentage of the dosing interval (%T>MIC) (ANDES and CRAIG 2002; CRAIG 1998). For cephalosporins, a T >MIC 35-40% of the inter dose interval has been established as optimal for bacteriostatic action, while a T >MIC of 60-70% is necessary for bactericidal effect (CRAIG, 1998; TOUTAIN et al., 2002). The MIC values of ceftazidime are 0.25 μg/mL for *E. coli*, 4 μg/mL for *Pseudomonas aeruginosa* and 8 μg/mL for *Staphylococcus spp*. for human and animal strains (ALBARELLOS et al., 2008; MOORE et al., 2000; SOBACK and ZIV, 1989). There is no published information regarding ceftazidime MIC's against the most important pathogens isolated from buffalo calves. In this study, ceftazidime administrations at a dose of 10 mg/kg seem to be equally suitable for the inter-dose intervals proposed (8 h) against bacterial isolates with MIC ≤ 4μg/mL. Furthermore, clinical controlled trials are mandatory to establish proper ceftazidime dosing schedules in this species.

In conclusion, on the basis of the results reported above, ceftazidime (10 mg/kg) shows favorable pharmacokinetic behavior in febrile buffalo calves, but needs to be evaluated for clinical efficacy and safety in buffalo species before issuing final recommendations.

It would appear to be a good therapeutic tool for the treatment of most of the infections produced by Gram-negative and Gram-positive susceptible bacteria in buffalo calves.

Acknowledgements

The financial assistance provided by Council of Scientific & Industrial Research, New Delhi (India) in the form of a research grant (Scheme No: 37(1395)/10/EMR-II) is gratefully acknowledged.

References

ABD-EL-ATY, A. M., A. GOUDAH, K. ABO-EL-SOOUD (2001): Pharmacokinetics, intramuscular bioavailability and tissue residue profiles of ceftazidime in a rabbit model. Deutsche Tierärztl. Wochenschr. 108, 168-171.

AHMAD, A. H., H. S. BAHGA, L. D. SHARMA (1994): Pharmacokinetics of gentamicin following single doseintravenous administration in normal and febrile goats. J. Vet. Pharmacol. Therap. 17, 369-373.

ALBARELLOS, G. A., L. A. AMBROS, M. F. LANDONI (2008): Pharmacokinetics of ceftazidime after intravenous and intramuscular administration to domestic cats. Vet. J. 178, 238-243.

ALIABADI, F. S., P. LEES (2000): Antibiotic treatment for animals: Effect on bacterial population and dosage regimen optimisation. Int. J. Antimicrob. Agents 14, 307-313.

ANDES, D., W. A. CRAIG (2002): Animal model of pharmacokinetics and pharmacodynamics: A critical review. Int. J. Antimicrob. Agents 19, 261-268.

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

CARBON, C., F. DROMER, N. BRION, A. C. CREMIEUX, A. CONTREPOIS (1984): Renal disposition of ceftazidime illustrated by interference by probenecid, furosemide, and indomethacin in rabbits. Antimicrob. Agents Chemother. 26, 373-377.

CHAUDHARY, R. K., A. K. SRIVASTAVA, S. RAMPAL (1999): Modification of the pharmacokinetics and dosage of cefuroxime by endotoxin-induced fever in buffalo calves. Vet. Res. Commun. 23, 361-368.

CRAIG, W. A. (1998): Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. 26, 1-12.

DARDI, M. S., S. K. SHARMA, A. K. SRIVASTAVA (2005): Pharmacokinetics and dosage regimen of ceftriaxone in *E. coli* lipopolysaccharide induced fever in buffalo calves. J. Vet. Sci. 6, 147-150.

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

HYATT, J. M., P. S. MCKINNON, G. S ZIMMER, J. J. SCHENTAG (1995): The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. Clin. Pharmacokinet. 28, 143-160.

KITA, Y., T. YAMAZAKI, A. IMADA (1992): Comparative pharmacokinetics of SCE-2787 and related antibiotics in experimental animals. Antimicrob. Agents Chemother. 36, 2481-2486.

MEIBOHM, B., H. DERENDORF (1997): Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. Int. J. Clin. Pharmacol. Therap. 35, 401-413.

MONSHOUWER, M., R. F. WITKAMP, S. M. NIJMEIJER, L. A. VANLEENGOOD, H. C. VERNOOY, J. H. VERHEIJDEN, A. S. J. P. A. M. VAN MIERT (1996): A lipopolysaccharide-induced acute phase response in the pig is associated with a decrease in hepatic cytochrome P450-mediated drug metabolism. J. Vet. Pharmacol. Therap. 19, 382-388.

MATSUI, H., M. KOMIYA, C. IKEDA, A. TACHIBANA (1984): Comparative pharmacokinetics of YM-13115, ceftriaxone and ceftazidime in rats, dogs and Rhesus monkeys. Antimicrob. Agents Chemother. 26, 204-207.

MOORE, K. W., L. A. TREPANIER, S. J. LAUTZENHISER, J. P. FIALKOWSKI, E. ROSIN (2000): Pharmacokinetics of ceftazidime in dogs following subcutaneous administration and continuous infusion and the association with *in vitro* susceptibility of *Pseudomonas aeruginosa*. Am. J. Vet. Res. 61, 1204-1208.

PAWAR, Y. G., S. K. SHARMA (2008): Influence of *E. coli* lipopolysaccharide induced fever on the plasma kinetics of cefepime in cross-bred calves. Vet. Res. Commun. 32, 123-130.

PENINGTON, J. E., D. C. DALE, H. Y. REGNOLDS, J. D. HACLOWRY (1975): Gentamicin sulfate pharmacokinetics, plasma levels of gentamicin in blood during fever. J. Infect. Dis.132, 270-275.

ROY, B. K., K. P. YADAV, M. C. BANERJEE 1992. Effect of pyrogen induced fever on the pharmacokinetics of cefazolin in goats. Indian J. Pharmacol. 24, 51.

RULE, R., G. H. QUIROGA, M. RUBIO, H. O. BUSCHIAZZO, P. M. BUSCHIAZZO (1996): The pharmacokinetics of ceftazidime in lactating and non lactating cows. Vet. Res. Commun. 20, 543-550.

RULE, R., M. RUBIO, M. C. PERELLI (1991): Pharmacokinetics of ceftazidime in sheep and its penetration into tissue and peritoneal fluids. Res. Vet. Sci. 5, 233-238.

SAKATA, Y., G. H. MCCRACKEN, M. L. THOMAS, K. D. OLSEN (1984): Pharmacokinetics and therapeutic efficacy of imipenem, ceftazidime, and ceftriaxone in experimental meningitis due to an ampicillin- and chloramphenicol-resistant strain of *Haemophilus influenzae* Type b. Antimicrob. Agents Chemother. 25, 29-32.

SANCHEZ-RECIO, M. M., C. I. COLINO, A. SANCHEZ-NAVARRO (2000): A retrospective analysis of pharmacokinetic/pharmacodynamic indices as indicators of the clinical efficacy of ciprofloxacin. J. Antimicrob. Chemother. 45, 321-328.

SCHENTAG, J. J. (1999a): Antimicrobial action and pharmacokinetics/ pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance. J. Chemother. 11, 426-439.

SCHENTAG, J. J. (1999b): Pharmacokinetic and pharmacodynamic surrogate markers: studies with fluoroquinolones in patients. Am. J. Health- System Pharmacy 56, S21-S24.

SHAH AHSAN UL HAQ (2010): Disposition kinetics and bioavailability of ceftazidime in buffalo calves. M.V.Sc Thesis. Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, India.

SHARMA, S. K., A. K. SRIVASTAVA, M. D. DEORE (2005): Pharmacokinetics of cefotaxime in hepatic-dysfunctioned buffalo calves. Vet. Arhiv 75, 339-348.

SINGH, R. P., A. K. SRIVASTAVA, S. K. SHARMA, D. C. NAURIYAL (1997): Disposition kinetics, urinary excretion and dosage regimen of sulfadimidine in febrile crossbred calves. Indian J. Anim. Sci. 67, 866-867.

SOBACK, S., G. ZIV (1989): Pharmacokinetics of ceftazidime given alone and in combination with probenecid to unweaned calves. Am. J. Vet. Res. 50, 1566-1569.

TOTH, A., H. Y. ABDALLAH, R. VENKATARAMANAN, L. TEPERMAN, G. HALSF, M. RABINOVITCH, G. J. BURCKAT, T. E. STARLZ (1991): Pharmacokinetics of ceftrioxone in liver - transplant recipients. J. Clin. Pharmacol. 31, 722-728.

TOUTAIN, P. L., A. BOUSQUET-MELOU (2004): Volumes of distribution. J. Vet. Pharmacol. Therap. 27, 441-453.

TOUTAIN, P. L., J. R. E. DEL CASTILLO, A. BOUSQUET-ME´LOU (2002): The pharmacokinetic-pharmacodynamic approach to a rational dosage regimen for antibiotics. Res. Vet. Sci. 73, 105-114.

VAN MIERT, A. S. J. P. A. M. (1973): Clinical symptoms induced by *E. coli* endotoxin in goats. J. Vet. Med. A 20, 614-623.

WILKINSON, S. P. (1977): Endotoxins and liver diseases. Scand. J. Gastroenterol. 12, 385-386.

Received: 18 December 2011
Accepted: 8 June 2012

SHARMA, S. K., S. A. UL HAQ: Farmakokinetika ceftazidima u bivolske teladi s vrućicom uzrokovanom lipopolisaharidom bakterije *E. coli*. Vet. arhiv 82, 555-565, 2012.

SAŽETAK

Farmakokinetička svojstva ceftazidima, cefalosporinskog antibiotika treće generacije, istražena su u febrilne bivolske teladi (n=5) nakon njegove jednokratne intravenske primjene u dozi od 10 mg/kg tjelesne mase. Vrućica je u teladi bila pokusno izazvana jednokratnim odnosno ponovljenim intravenskim davanjem lipopolisaharida bakterije *E. coli* u dozi od 1 mg/kg. Koncentracija ceftazidima u plazmi i mokraći određena je mikrobiološkim postupkom. Farmakokinetičko ponašanje ceftazidima u febrilnih životija opisano je u dva modela. Za 2,5 minuta koncentracija ceftazidima u plazmi febrilnih životinja iznosila je 152,3 ± 6,77 µg/mL, a lijek se mogao dokazati sve do 14 sati nakon primjene. Poluvrijeme njegova izlučivanja iznosilo je 3,73 ± 0,42 h, a količina raspodjele 0,26 ± 0,05 L/kg. Poluvrijeme njegove raspodjele bilo je 0,24 ± 0,03 h, površine ispod koncentracijske krivulje u plazmi 217,3 ± 23,4 µg/mL.h, a ukupni klirens iz organizma 47,9 ± 4,57 mL/kg/h. Izlučivanje ceftazidima mokraćom bilo je manje od 28% nakon 32 sata od primjene. Predviđena učinkovitost lijeka, izmjerena kao vrijeme u kojem je aktivna supstancija bila iznad minimalne inhibicijske koncentracije (T>MIC), bila je 73% od preporučenog razmaka primjene (8h) za bakterije s MIC_{90}≤4 µg/mL.

Ključne riječi: bivolska telad, ceftazidim, doziranje, vrućica, farmakokinetika