

Pharmacokinetics of ceftazidime in buffalo calves following intravenous and intramuscular administration

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Summary

The pharmacokinetic parameters of ceftazidime, a third generation cephalosporin, were investigated in six buffalo calves after single intravenous (IV) and intramuscular (IM) administration at a dose rate of 10 mg/kg body weight. Ceftazidime concentrations in plasma and urine were determined by microbiological assay. Ceftazidime disposition was best fitted by a two-compartmental and a one-compartmental open model with first-order elimination after IV and IM dosing, respectively. After IV administration, distribution was rapid ($t_{1/2\alpha} = 0.15 \pm 0.01$ h) with an area under the ceftazidime plasma concentration/time curve ($AUC_{0-\infty}$) of 253.9 ± 7.8 $\mu\text{g/ml.h}$ and a steady state volume of distribution ($V_{d(ss)}$) of 0.18 ± 0.01 L.kg⁻¹. The elimination half life ($t_{1/2\beta}$) and total body clearance were 3.4 ± 0.2 h and 39.5 ± 1.2 ml/kg/h, respectively. Following intramuscular administration, the absorption half life ($t_{1/2ka}$), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), $AUC_{0-\infty}$ and bioavailability were 0.25 ± 0.04 h, 45.8 ± 2.7 $\mu\text{g/ml}$, 0.75 h, 207.9 ± 9.9 $\mu\text{g/ml.h}$ and $81.7 \pm 5.9\%$, respectively. Urinary excretion of ceftazidime was less than 55% 36 h post administration. *In vitro* plasma protein binding of ceftazidime was $13.1 \pm 1.1\%$. To maintain minimum therapeutic concentration of 4 $\mu\text{g/ml}$, a satisfactory dosage regimen of ceftazidime in buffalo calves would be 9.4 mg/kg to be repeated at 12 h intervals. In conclusion, ceftazidime (10 mg/kg, IM) shows favorable pharmacokinetic behavior in buffalo calves.

Key words: Buffalo calves, Ceftazidime, Dosage regimen, 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 very active against *Pseudomonas aeruginosa* (Albarellos *et al.*, 2008). Rational antibiotic therapy requires 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. Pharmacokinetic data of ceftazidime has been reported in many animal species, including mice (Kita *et al.*, 1992), rats (Matsui *et al.*, 1984; Kita *et al.*, 1992), rabbits (Carbon *et al.*, 1984; Sakata *et al.*, 1984; Kita *et al.*, 1992; Abd-El-Aty *et al.*, 2001), monkeys (Matsui *et al.*, 1984; Kita *et al.*, 1992), calves (Soback and Ziv, 1989), sheep (Rule *et al.*, 1991), cows (Rule *et al.*, 1996), dogs (Matsui *et al.*, 1984; Kita *et al.*, 1992; Moore *et al.*, 2000), cats (Albarellos *et al.*, 2008) and goats (Rule *et al.*, 2011). However, to the best of our knowledge, pharmacokinetic studies in buffalo calves have not been reported. As the usefulness of an antibacterial agent

depends on its efficacy, safety and pharmacokinetic disposition in the target animal, the aim of the present study was to investigate the pharmacokinetics of ceftazidime following single intravenous and intramuscular administration in buffalo calves.

Materials and Methods

Six healthy male buffalo calves ranging between 6-12 months of age and weighing between 85-125 kg were used. The animals were housed in an animal shed with concrete floor and adequate ventilation. All animals were clinically healthy before the beginning of the study. Animals were acclimatized under uniform conditions and maintained on green fodder, wheat straw and water *ad libitum*. They were not under any drug treatment before the study. For the collection of urine, the experimental animals were moved to metabolic stalls of standard size, 12 h before the start of the experiment and kept there for the entire study. The metabolic stalls were designed in such a way that urine voided by animals could be collected at any time interval without any spillage. Before the start of experiment, permission for experiments on these animals was obtained from the Institutional Animal Ethics Committee (IAEC).

The study was performed in two phases, using a cross over design with a washout period of 30 days. Before repeating the drug in the same animals, blood samples

were collected and assayed for being drug-free. 10% aqueous solutions of ceftazidime-pentahydrate (Glaxo India Limited) were administered by either the intravenous or the intramuscular route at single doses of 10 mg/kg body weight. Animals were randomly assigned to receive intravenous or intramuscular doses first. Intravenous injection of ceftazidime was given into the jugular vein and intramuscular administration was performed in the lower third region of the neck muscles.

Blood samples (4-6 ml) were taken from contra lateral jugular vein into heparinized glass test tubes before administration and at different time intervals viz. 2.5, 5, 10, 15, 30, 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 h in each group. Plasma from the samples was separated by centrifugation at 2000 g for 15 min and stored at -20°C till analysis, usually the next day. Urine was collected at 4, 8, 12, 16, 20, 24, 28, 32, 36 h after administration of drug. The urine voided by animals was filtered. Its volume was recorded and approximately 5 ml urine sample was stored at -20°C till analysis.

Determination of ceftazidime concentration

The concentration of ceftazidime in plasma and urine was estimated by employing the microbiological assay technique (Arret *et al.*, 1971) using *E. 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 drug. Three plates were used for each sample. Plates were incubated at 37°C for a period of 24 h. At the end of incubation, the diameters of zones of inhibition were measured and the ceftazidime concentrations in 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 existed. However, it measured the overall microbiological activity of the drug. The standard curve of ceftazidime in buffalo calf plasma and urine was linear between 1 and 5 µg/ml. The correlation coefficient of standard curves was 0.99. The drug could be detected up to a minimum limit of 1 µg/ml for plasma and urine. The ceftazidime recovery exceeded 96% 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. Two-compartmental and one-compartmental open models were found to best fit the data, following intravenous and intramuscular administration, respectively. The kinetic parameters were calculated from the formulae derived for a single and two compartmental open model (Gibaldi and Perrier, 1982). The dosage regimen (D) of ceftazidime was also determined based on kinetic data (Baggot, 1977) by using following formulae:

$$D = C_p (\text{min}) \cdot V_d (e^{\beta\tau})$$

where,

C_p (min): The minimum therapeutic concentration of ceftazidime

τ : The dosage interval and other parameters are defined in Table 1

Table 1: Pharmacokinetic parameters of ceftazidime in buffalo calves (n=6) after a single intravenous and intramuscular injection (10 mg/kg body weight)

Parameter ^a	Unit	Route of administration	
		Intravenous	Intramuscular
C_p^0	µg/ml	189.4±6.9	-
A	µg/ml	145.6±6.3	-
B	µg/ml	45.4±3.2	-
A'	µg/ml	-	51.5±4.3
α	h ⁻¹	4.63±0.4	-
β	h ⁻¹	0.21±0.01	0.24±0.02
K_a	h ⁻¹	-	3.04±0.46
$t_{1/2\alpha}$	h	0.15±0.01	-
$t_{1/2\beta}$	h	3.42±0.21	3.01±0.28
$t_{1/2K_a}$	h	-	0.25±0.04
K_{12}	h ⁻¹	3.37±0.28	-
K_{21}	h ⁻¹	1.23±0.12	-
$AUC_{0-\infty}$	µg/ml.h	253.9±7.8	207.9±9.9
$AUMC_{0-\infty}$	µg/ml.h ²	1185.1±134.9	1057.8±170.2
$V_{d(\text{area})}$	L/kg	0.19±0.01	-
$V_{d(B)}$	L/kg	0.23±0.01	-
$V_{d(ss)}$	L/kg	0.18±0.01	-
Cl_B	ml/kg/h	39.5±1.2	39.2±1.2
MRT	h	4.61±0.39	4.97±0.57
F	%	-	81.7±5.9

Kinetics parameters are as described by Gibaldi and Perrier (1982). C_p^0 : The expected plasma drug concentration at zero time; A', A and B: Zero time plasma drug concentration intercept of regression line of absorption, distribution and elimination phase, respectively; k_a , α and β : Hybrid rate constants representing the slopes of absorption, distribution and elimination phases, respectively; $t_{1/2k_a}$: Absorption half life; $t_{1/2\alpha}$: Distribution half life; $t_{1/2\beta}$: Elimination half life; K_{12} and K_{21} : Rate constant of drug transfer from central to peripheral compartment and from peripheral to central compartment, respectively; $AUC_{0-\infty}$: Total area under the plasma concentration time curve; $AUMC_{0-\infty}$: Total area under the first moment curve; $V_{d(\text{area})}$: Apparent volume of distribution, based on area under the curve; $V_{d(B)}$: Volume of distribution based on zero time plasma drug concentration intercept of elimination phase; $V_{d(ss)}$: Volume of distribution at steady state; Cl_B : Total body clearance; MRT: Mean residence time; F: Systemic bioavailability following intramuscular administration

In vitro plasma protein binding

In vitro binding of ceftazidime to plasma protein was determined by employing the equilibrium dialysis technique (Kunin *et al.*, 1959). The dialyzing bags (4°A pore size), 10 cm long were washed and soaked overnight in distilled water. The various concentrations of ceftazidime e.g. 6.25, 12.5, 25, 50, 100 and 200 µg.ml⁻¹ were prepared in plasma taken from untreated animals. Each dialyzing bag was knotted on one end before filling with 5 ml of plasma containing known amount of drug and the other end was then securely tied. Each bag was immersed in separate tubes containing 5 ml of distilled water and the tubes were incubated at 37°C for 24 h with occasional shaking. At the end of incubation period

water as well as contents of the dialyzing bags were separately analysed for the concentration of ceftazidime. For each concentration, three separate sets of experiments were conducted. The extent of *in vitro* plasma protein binding of ceftazidime was calculated by the following equation.

$$\text{Percent of ceftazidime bound to plasma proteins} = \frac{(C_p' - C_w)}{C_p} \times 100$$

where,

C_p' = Concentration of ceftazidime in plasma after incubation

C_w = Concentration of ceftazidime in distilled water after incubation

C_p = Concentration of ceftazidime in plasma before incubation

Results

Clinical examination of all animals before and after each trial did not reveal any abnormalities. No adverse reactions were observed after a single IV or IM administration of ceftazidime in the animals studied. The mean plasma concentration-time profiles of ceftazidime following IV and IM administrations are presented in Fig. 1. Mean \pm SE values of pharmacokinetic parameters estimated from the curve fitting are shown in Table 1. The cumulative percent of total dose excreted in urine (Table 2) after IV and IM administration was 54.0 ± 6.3

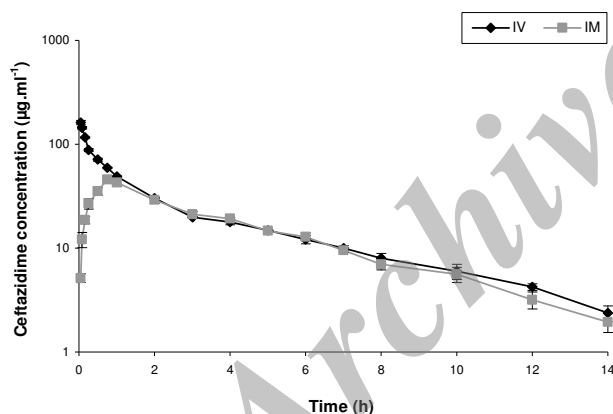


Fig. 1: A semi-logarithmic plot of plasma levels versus time profile of ceftazidime after a single intravenous and intramuscular dose of 10 mg/kg body weight in buffalo calves (n=6)

Table 2: Cumulative percent of ceftazidime excreted in urine of buffalo calves following a single intravenous and intramuscular injection (10 mg/kg body weight)

Time interval (h)	Intravenous	Intramuscular
0-4	25.7 \pm 6.6	21.8 \pm 2.7
0-8	43.7 \pm 7.1	38.0 \pm 3.5
0-2	47.2 \pm 7.2	44.6 \pm 2.3
0-16	51.2 \pm 6.6	49.0 \pm 2.0
0-20	52.8 \pm 6.5	49.3 \pm 1.9
0-24	53.7 \pm 6.3	49.7 \pm 1.9
0-28	53.7 \pm 6.3	50.1 \pm 2.0
0-32	53.9 \pm 6.3	50.3 \pm 2.0
0-36	54.0 \pm 6.3	50.5 \pm 2.0

Values given are mean \pm SE of the results obtained from 3-6 animals

Table 3: Dosage regimen (mg/kg) of ceftazidime to maintain specified plasma ceftazidime concentration in buffalo calves

Desired plasma concentration ($\mu\text{g/ml}$)	Dosage interval (h)	
	8	12
0.1	0.1	0.2
0.5	0.5	1.2
1	1.0	2.4
2	2.0	4.7
4	4.0	9.4
8	8.0	18.9

and $50.5 \pm 2.0\%$, respectively within 36 h. Taking 8 and 12 h as convenient dosage interval (τ) and the minimum therapeutic plasma concentration of 0.1, 0.5, 1, 2, 4 and 8 $\mu\text{g}\cdot\text{ml}^{-1}$ and using the values of β and V_d (area) of Table 1, the dosage regimens for ceftazidime were computed in buffalo calves and presented in Table 3.

Discussion

In the present study plasma ceftazidime concentration decreased in a bi-exponential manner following intravenous injection, which demonstrates the presence of distribution and elimination phases. Plasma concentration of ceftazidime after IV administration remained greater than MIC (0.25 $\mu\text{g/ml}$) for 14 h. Ceftazidime shows rapid distribution reflected by the rate constant.

The elimination half life ($t_{1/2\beta}$) of ceftazidime in buffalo calves was longer than 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 relatively low volume of distribution at steady state in buffalo calves (0.18 ± 0.01 L/kg) was expectable from a beta lactam antibiotic. This value was consistent with that reported in dogs (Matsui *et al.*, 1984) and cats (Albarellos *et al.*, 2008), but was smaller than that reported in unweaned calves (Soback and Ziv, 1989), sheep (Rule *et al.*, 1991) and lactating and non-lactating cows (Rule *et al.*, 1996). The total body clearance (Cl_B) of ceftazidime in buffalo calves (39.5 ± 1.2 ml/kg/h) was smaller than dogs (Matsui *et al.*, 1984), unweaned calves (Soback and Ziv, 1989), lactating and non-lactating cows (Rule *et al.*, 1996), and cats (Albarellos *et al.*, 2008). Species differences are relatively common and are frequently related to inter-species variation, assay method used, blood sampling intervals, the health status and the age of the animal, dosing frequency, dose extrapolation, etc.

Ceftazidime plasma disposition curves after IM administration were best fitted by a one-compartmental open model. The plasma concentration-time curve after IM administration documented C_{\max} (45.8 ± 2.7 $\mu\text{g/ml}$) at 0.75 h, indicating a fast absorption. Plasma drug concentration above minimum therapeutic level (0.25 $\mu\text{g/ml}$) was detected up to 14 h of administration. The elimination half life ($t_{1/2\beta}$) of ceftazidime after IM (3.01 ± 0.28 h) administration was similar to the half life after IV

administration, suggesting that absorption does not interfere with terminal half life.

Bioavailability plays an important role in therapeutic efficacy of a drug. It refers to the percent of drug absorbed from extravascular site of administration to central compartment for pharmacological action. On the basis of area under the plasma concentration-time curve and elimination rate constant of ceftazidime after single intravenous and intramuscular administration in buffalo calves, the bioavailability ($81.7 \pm 5.9\%$) was of the order of that reported for rabbits, cows and cats (Rule *et al.*, 1996; Abd-El-Aty *et al.*, 2001; Albarellos *et al.*, 2008), which demonstrates high absorption of drug from the intramuscular injection site. Rapid absorption and high value of bioavailability shows that intramuscular administration of ceftazidime is likely to be as effective as intravenous injection in the treatment of mild to moderate bacterial infections.

Ceftazidime is mostly eliminated by glomerular filtration (Soback and Ziv, 1989; Verhagen *et al.*, 1994; Albarellos *et al.*, 2008). The cumulative percent of total dose excreted in urine within 36 h after IV and IM administration was $54.0 \pm 6.3\%$ and $50.5 \pm 2.0\%$, respectively. Incomplete and variant urinary ceftazidime recovery may be explained by several hypotheses: (i) 36-h urine collection was inadequate to collect 100% of the excreted dose, (ii) degradation of ceftazidime in urine and blood may occur either *in vivo* or *in vitro*, (iii) ceftazidime may be metabolized, or (iv) the drug may be excreted through an alternate pathway such as bile. Hypothesis (iii) is unlikely because no metabolites of ceftazidime have been identified either by HPLC assay or by bioautography (Harding, 1981). Since faecal ceftazidime concentrations were not measured, it is impossible to rule out biliary excretion as an elimination pathway. Peak urinary level of drug after IV ($1154 \pm 218 \mu\text{g/ml}$) and IM ($973 \pm 218 \mu\text{g/ml}$) administration was detected at 4 h and thereafter remained $\geq 10 \mu\text{g/ml}$ in urine up to 36 h post administration. The concentration of ceftazidime in urine of buffalo calves remained higher than the MIC (0.25 to $8 \mu\text{g/ml}$) of most microorganisms (Soback and Ziv, 1989; Moore *et al.*, 2000; Casellas *et al.*, 2003; Rhomberg *et al.*, 2004; Albarellos *et al.*, 2008) sensitive to the drug up to 36 h. This suggests that use of ceftazidime in buffalo calves might achieve successful bacterial killing in urinary tract infections caused by microorganisms having susceptibility $\leq 10 \mu\text{g/ml}$.

The extent of protein binding directly affects the pharmacokinetics and therapeutic efficacy of a drug. Pharmacological action depends on the capability of a drug to bind to its target receptors in tissue. At plasma concentration of 6.25 to $200 \mu\text{g/ml}$, the extent of plasma protein binding of ceftazidime ranged from 8.8 to 17.9% with a mean \pm SE of $13.1 \pm 1.1\%$. Protein binding of ceftazidime in buffalo calves was not concentration dependent. Since these proteins are large molecules, drugs that are bound to proteins cannot pass out of vascular space. Thus, plasma protein binding has the effect of restricting the distribution of drugs. As plasma protein binding increases, the extent of distribution

decreases. However, in the present study, other physicochemical properties may permit the extensive penetration into extravascular sites. Further, low plasma protein binding supports the therapeutic effectiveness of ceftazidime in a wide variety of infections because non protein bound antibiotic produces antimicrobial activity.

The main objective of the present study was to determine a satisfactory dosage regimen of ceftazidime in buffalo calves. It is not axiomatic to compute the dosage regimen of ceftazidime to be used effectively in clinical practice for the treatment of mild to severe bacterial infections, without having first conducted a detailed pharmacokinetic study. The MIC values of ceftazidime are $0.25 \mu\text{g/ml}$ for *E. coli*, $4 \mu\text{g/ml}$ for *Pseudomonas aeruginosa* and $8 \mu\text{g/ml}$ for *Staphylococcus* spp. for human and animal strains (Soback and Ziv, 1989; Moore *et al.*, 2000; Casellas *et al.*, 2003; Rhomberg *et al.*, 2004; Albarellos *et al.*, 2008). With minimum therapeutic plasma concentration of ceftazidime as $4.0 \mu\text{g/ml}$, the most convenient and suitable dosage regimen of ceftazidime in buffalo calves was 9.4 mg/kg to be repeated at 12 h intervals.

In conclusion, ceftazidime (10 mg/kg , IM) shows favorable pharmacokinetic behavior in buffalo calves, but needs to be evaluated for clinical efficacy and safety in disease conditions in this species before issuing final recommendations. It seems 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. Although, further studies are necessary to examine the MIC values of this agent for important pathogens that affect buffalo calves.

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پارامترهای فارماکوکینتیک داروی سفتازیدیم که یک سفالوسپورین نسل سوم است، در شش گوساله گاومیش به دنبال تزریق منفرد وریدی و ماهیچه‌ای با دوز 10 mg/kg مورد ارزیابی قرار داده شد. غلظت سفتازیدیم در پلاسما و ادرار با روش میکروبیولوژیک تعیین شد. الگوی کینتیک پس از تزریق وریدی، با مدل دو بخشی و پس از تزریق ماهیچه‌ای با مدل یک بخشی منطبق شد. پخش دارو در تزریق وریدی سریع بوده ($t_{1/2\alpha} = 0/15 \pm 0/01$ h) و سطح زیر منحنی غلظت پلاسمایی/زمان ($AUC_{0-\infty}$) برابر شد با $253/9 \pm 7/8 \mu\text{g/ml.h}$ حجم پخش دارو در شرایط پایا روند ($Vd_{(ss)}$) مقدار $0/18 \pm 0/01 \text{ L.kg}^{-1}$ برآورد شد. نیمه عمر حذفی دارو و پاکسازی تام به ترتیب برابر بودند با $0/2 \pm 0/2$ h و $3/4$ و $39/5 \pm 1/2 \text{ ml/kg/h}$ به دنبال تزریق ماهیچه‌ای، نیمه عمر جذب دارو ($t_{1/2ka}$)، اوج غلظت پلاسمایی (C_{max})، زمان لازم برای رسیدن به اوج غلظت پلاسمایی (T_{max})، $AUC_{0-\infty}$ و زیست فراهمی دارو به ترتیب عبارت بودند از $0/25 \pm 0/04$ h، $45/8 \pm 2/7 \mu\text{g/ml}$ ، $0/75$ h، $207/9 \pm 9/9 \mu\text{g/ml.h}$ و $81/7 \pm 7/5/9$ دفع ادراری سفتازیدیم $13/1 \pm 1/1$ برآورد شد. به منظور حفظ غلظت درمانی 4 mg/kg رژیم دوزاژ مناسب سفتازیدیم در گوساله‌های گاومیش 9/4 mg/kg هر 12 ساعت می‌باشد. در کل، داروی سفتازیدیم (10 mg/kg)، تزریق ماهیچه‌ای، رفتار فارماکوکینتیک مناسبی در گوساله‌های گاومیش نشان می‌دهد.

واژه‌های کلیدی: گوساله‌های گاومیش، سفتازیدیم، رژیم دوزاژ، فارماکوکینتیک

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