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Pharmacokinetics of ceftriaxone in calves

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ABSTRACT

The pharmacokinetics of ceftriaxone was determined after a single intravenous and intramuscular administration at the dose rate of 10 mg/kg in crossbred cow calves. The drug concentration in plasma was quantified through High Performance Liquid Chromatography with UV detection. Following intravenous administration the drug was rapidly distributed ($t_{1/2\alpha}$: 0.13 ± 0.01 h; $Vd_{(area)}$: 0.44 ± 0.07 L/kg) and eliminated ($t_{1/2\beta}$: 1.58 ± 0.06 h) from the body with a clearance rate of 3.15 ± 0.41 mL/min/kg. Following intramuscular administration, the peak plasma drug concentration (C_{max}) was 15.34 ± 2.39 µg/mL at 0.25 hours (T_{max}) suggesting very rapid absorption. The drug was extensively distributed ($Vd_{(area)}$: 1.16 ± 0.15 L/kg) and slowly eliminated ($t_{1/2\beta}$: 5.02 ± 0.51 hours; $Cl_{(B)}$: 2.71 ± 0.29 mL/min/kg) following intramuscular administration. The absolute bioavailability of ceftriaxone was 47.0 ± 5.0% following intramuscular injection. However, it can be used at a dosage of 10 mg/kg intramuscularly, repeated at twelve-hourly intervals, for the treatment of susceptible bacteria infections in calves.

Key words: pharmacokinetics, bioavailability, ceftriaxone, intravenous, intramuscular, cow calves

Introduction

Ceftriaxone is a third-generation semi-synthetic bactericidal cephalosporin antibiotic, resistant to various types of bacterial β-lactamases. It has excellent activity against gram-negative bacteria as well as a wide range of gram-positive and some anaerobic bacteria, including enterobacteriaceae, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and other non-enterococcal streptococci (NEU et al., 1981; RICHARDS et al, 1984; BROGDEN and WARD, 1988). It has rapid absorption and wide distribution in tissues as well as body fluids, after parenteral administration in animals (CHRIST, 1991). The drug thus seems to be useful in the treatment of a variety of bacterial

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infections, including meningitis, septicemia, pyoderma, colibacillosis, surgical prophylaxis and urinary tract, respiratory tract, wound, soft tissue and joint infections (RICHARDS et al., 1984). Pharmacokinetic studies of a drug are essential for its judicious use in animals. Despite the great potential for clinical use of the drug in veterinary medicine, the data on its pharmacokinetics following intravenous and intramuscular administration in cow calves are limited (SOBACK and ZIV, 1988; JOHAL and SRIVASTAVA, 1998, 1999). Therefore, the objective of the present study was to determine the pharmacokinetics and bioavailability of ceftriaxone following a single intravenous and intramuscular administration at a dose rate of 10 mg/kg body mass in crossbred calves.

Materials and methods

Experimental animals. The experiment was done on six healthy, male, domestic crossbred (Kankrej × Jersey) calves weighing 55-105 kg (aged 6-9 months). The calves were kept under constant observation for two weeks before commencing the experiment, without any antibiotic treatment. They were subjected to clinical examination during this period, in order to exclude the possibility of any disease. They were housed in sheds with concrete floors and were maintained on concentrate, green fodder and dry grass. Water was provided *ad libitum.*

Chemicals. Ceftriaxone sodium (Vetaceph Injection containing sterile ceftriaxone sodium USP equivalent to 1 g ceftriaxone) was obtained from Unichem Laboratories Ltd., Mumbai, India. Acetonitrile and Methanol (HPLC grade), N-acetyl -N, N, N-trimethyl ammonium bromide, Orthophosphoric acid (88%) were procured from Loba chemical Ltd, Mumbai, India and Ranbaxy Fine Chemicals Ltd., New Delhi, India.

Drug administration and sample collection. The calves were randomly allocated to receive either an intravenous or intramuscular injection of ceftriaxone sodium at the dose rate of 10 mg/kg. A washout period of 2 weeks was observed between treatments. The intravenous injection was administered in the jugular vein. Blood samples (5 mL each) were collected through an intravenous catheter fixed in the contra-lateral jugular vein, in heparinized glass test tubes, before administration and at 2, 5, 10, 15, 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, and 36 hours after intravenous administration. The intramuscular injection was administered in the gluteal muscles. Blood samples were collected before administration and at 2, 5, 10, 15, 30 minutes and 1, 2, 4, 6, 8, 12, 24 and 36 hours after the intramuscular administration of the drug. Plasma was separated by centrifugation at 3000 g for 10 minutes at room temperature, stored at -20 °C and analyzed within 24 h.

Analytical assay of ceftriaxone and pharmacokinetic analysis. Plasma ceftriaxone concentration was determined by the High Performance Liquid Chromatography (HPLC) assay, with minor modifications (HAKIM et al., 1988). The HPLC system (Merck-Hitachi LaChrom) consists of an isocratic pump (L-7110) with an online degasser (L-

7612), interface (D-7000), UV detector (7400), autosampler (7200), sample cooler (L-7200), chromatography data station software (D-7000) and multi HSM-manager. Chromatographic separation was done using Lichrocart RP-18 column (250 mm × 4 mm) at room temperature.

Samples (250 µL) were deproteinized by the addition of acetonitrile (500 µL), and vortexed for one minute, followed by centrifugation at 3000 g for 10 minutes. A clear supernant fluid was decanted into a glass insert (automatic sampler vessels) from which 50 µL was injected into the HPLC system. The mobile phase consisted of a mixture of buffer and acetonitrile (62:38). The buffer was prepared by dissolving 1.78 g di-sodium hydrogen phosphate dihydrate and 1.0 g N-acetyl -N, N, N-trimethyl ammonium bromide in 950 mL HPLC water, pH (7.0) was adjusted with orthophosphoric acid. The mobile phase was filtered through a 0.45 µm Millipore filter. The mobile phase was pumped through a column at a flow rate of 1.0 mL/min, at an ambient temperature of 25 °C. The elute was monitored at a wavelength of 254 nm. All chemicals used in the present study were of HPLC grade. Ceftriaxone standards (0.19, 0.26, 0.52, 1.68, 4.93, 14.94, 49.79, 76.59, 90.11, 100.12 µg/mL) were prepared by serial dilutions of stock solution (100.12 µg/mL) in the drug-free plasma of calves. A calibration curve was prepared for drug concentrations ranging from 0.19 to 100.12 µg/mL and was used to quantify the drug concentration in samples. The calibration curve was prepared daily. The assay was sensitive and reproducible, and linearity was observed from 0.19 to 100.12 µg/mL ($R^2 \geq 0.99$). The lower limit of quantification of assay was 0.19 µg/mL. Precision and accuracy were determined using quality control (QC) samples at concentrations of 1.68, 14.94, and 100.12 µg/mL (5 replicates each, per day). The intraday and interday coefficients of variation (COV%) for 5 QC samples were satisfactory, with relative standard deviations (RSD) of less than 7.5%. Intraday and interday variations were within acceptable limits. Different pharmacokinetic parameters were calculated by the least square linear regression technique described by GIBALDI and PERRIER (1982). The formulas used to compute various pharmacokinetic parameters were as follows.

a) Half-life: distribution, elimination and absorption phases:

i) $t_{1/2\alpha} = \frac{0.693}{\alpha}$

ii) $t_{1/2\beta} = \frac{0.693}{\beta}$

iii) $t_{1/2k(a)} = \frac{0.693}{k_{(a)}}$

b) $AUC_{(0 - t)}$, the area under plasma drug concentration - time curve from time zero to time of last observed concentration and AUMC, the area under the first moment of the plasma drug concentration - time curve were calculated by the trapezoidal rule. Where as $AUC_{(t - \infty)}$ was calculated through dividing the last observed concentration by the elimination rate constant (β). $AUC_{(0 - \infty)}$ was calculated by the summation of $AUC_{(0 - t)}$ and $AUC_{(t - \infty)}$.

c) $Vd_{(area)}$, the apparent volume of distribution:

$$Vd_{(area)} = \frac{Dose}{\beta \times (AUC)} \qquad \text{(For intravenous injection)}$$

$$Vd_{(area)} = \frac{Dose \times F}{\beta \times (AUC)} \qquad \text{(For intramuscular injection)}$$

d) $Vd_{(ss),}$ the volume of distribution of drug at steady state:

$$Vd_{(ss)} = \frac{Dose \times AUMC}{(AUC)^2}$$

e) Cl_B, the total body clearance of drug:

$$Cl_B = \beta \times Vd_{(area)} \times 1000$$

f) MRT, the mean residence time:

$$MRT = \frac{AUMC}{AUC}$$

g) F, the fraction of drug absorbed after non-vascular administration:

$$F = \frac{\text{Dose (i/v)} \times \text{AUC (i/m)}}{\text{Dose (i/m)} \times \text{AUC (i/v)}}$$

Statistical analysis. The obtained results were presented as Mean ± SE The standard error of the mean was calculated according to SNEDECOR and COCHRAN (1976).

Results

The semi-logarithmic plot of the plasma drug concentration as a function of time following the intravenous and intramuscular administration of ceftriaxone exhibited biexponential decline in the plasma drug concentration and could be best fitted to a two-compartment open model. The drug was detected in plasma up to 8 and 12 hours following intravenous and intramuscular administration, respectively. The comparative disposition of ceftriaxone following single dose intravenous and intramuscular administration in cow calves is presented in Fig. 1.

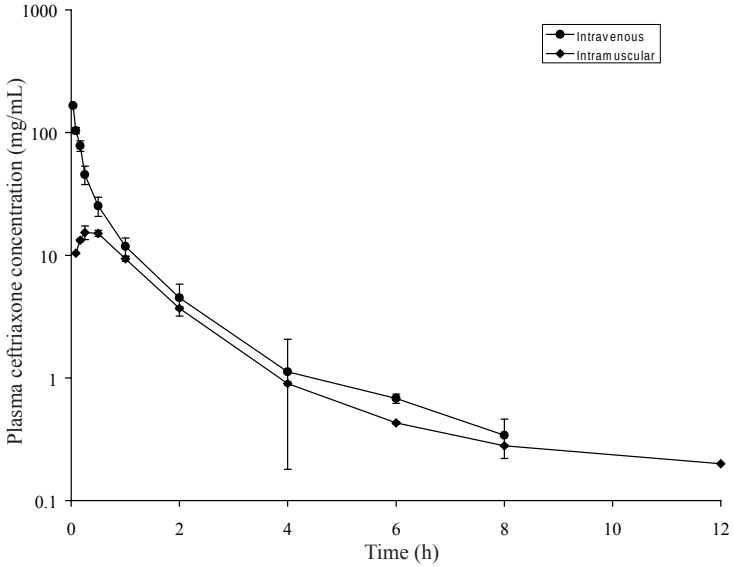

Fig. 1. Semilogarithmic plot of ceftriaxone concentration in plasma versus time following single dose intravenous and intramuscular administration at the dose rate of 10 mg/kg of body mass in cow calves. Each point represents mean ± SE of six calves.

Following intravenous administration of the drug, the elimination half-life ($t_{1/2\beta}$), total body clearance (Cl_B), apparent volume of distribution ($Vd_{(area)}$) and area under curve ($AUC_{(0 - \infty)}$) were 1.58 ± 0.06 h, 3.15 ± 0.41 mL/min/kg, 0.44 ± 0.07 L/kg and 57.35 ± 7.04 µg.h/mL, respectively. Following intramuscular administration, a peak plasma concentration of 15.34 ± 2.39 µg/mL was observed at 0.25 h. The values of elimination half-life ($t_{1/2\beta}$), mean residence time (MRT) and area under curve ($AUC_{(0 - \infty)}$) were 5.02 ± 0.51 h, 2.67 ± 0.13 h and 28.15 ± 2.02 µg.h/mL, respectively. The bioavailability of the drug following intramuscular injection was 47.0 ± 5.0%. Various pharmacokinetic parameters calculated from the plasma concentration of ceftriaxone after single dose intravenous and intramuscular administrations in cow calves are summarized in Table 1.

Table 1. Pharmacokinetics of ceftriaxone after single dose intravenous and intramuscular administration in cow calves (10 mg/kg)

Pharmacokinetic parameters	Unit	Intravenous (Mean ± SE)	Intramuscular (Mean ± SE)
Cp^0	µg/mL	177.60 ± 6.16	-
$t_{1/2\,\alpha}$	h	0.13 ± 0.01	-
$t_{1/2\beta}$	h	1.58 ± 0.06	5.02 ± 0.51
$AUC_{(0 - t)}$	µg.h/mL	56.59 ± 6.34	26.69 ± 1.78
$AUC_{(0 - \infty)}$	µg.h/mL	57.35 ± 7.04	28.15 ± 2.02
AUMC	µg.h^2/mL	61.65 ± 7.80	74.34 ± 3.86
$Vd_{(area)}$	L/kg	0.44 ± 0.07	1.16 ± 0.15
$Vd_{(ss)}$	L/kg	0.20 ± 0.03	-
$Cl_{(B)}$	mL/min/kg	3.15 ± 0.41	2.71 ± 0.29
MRT	h	1.08 ± 0.03	2.67 ± 0.13
F	%	-	47.0 ± 5.0
C_{max}	µg/mL	-	15.34 ± 2.39
T_{max}	h	-	0.25

Cp^o: Theoretical concentration of drug in the plasma at zero time, $t_{1/2\alpha}$: half-life of distribution phases, $t_{1/2\beta}$: elimination half-life, $t_{1/2K(a)}$: absorption half-life, $AUC_{(0 - t)}$: the area under plasma drug concentration - time curve from time zero to time of last observed concentration, $AUC_{(0 - \infty)}$: area under the plasma concentration-time curve from time zero to infinity, AUMC: area under first of moment curve, $Vd_{(area)}$: volume of distribution of drug based on area, $Vd_{(ss)}$: volume of distribution of drug at steady-state, $Cl_{(B)}$: total body clearance, MRT: mean residence time, F: bioavailability, C_{max}: maximum drug concentration; T_{max}: time of maximum concentration observed in plasma

Discussion

Following intravenous administration, a plasma ceftraiaxone concentration of 0.34 ± 0.05 μg/mL was maintained for 8 hours above MIC (0.03 -0.2 μg/mL) of the drug against pathogenic bacteria of calves. JOHAL and SRIVASTAVA (1999) reported similar plasma levels in cross-bred calves; however SOBACK and ZIV (1988) reported a concentration of 0.1 μg/mL up to 10 hours following intravenous injection in neonatal calves. A peak plasma concentration of 15.34 ± 2.39 μg/mL was observed following intramuscular injection, which is lower than the concentrations of 20.3 ± 0.92, 23.6, and 23.16 ± 2.94 μg/mL reported in cross-bred calves, goats and sheep, respectively (JOHAL and SRIVASTAVA, 1998; ISMAIL, 2005, GOUDAH et al., 2006). A therapeutic ceftriaxone concentration (≥ 0.2 μg/mL) was maintained in plasma for up to 12 hours following intramuscular injection in cow calves, which is longer than that observed in other studies (SOBACK and ZIV, 1988).

Following intravenous administration of the drug, higher values of distribution rate constants and low values of elimination rate constants observed in the present study indicated that the drug was rapidly distributed and then relatively slowly eliminated in calves, which is in agreement with the high distribution rate constants (8.56 ± 1.69 h^{-1}) and low elimination rate constants (0.30 ± 0.02 h^{-1}) observed in buffalo calves (GAIKWAD, 2001). The elimination half-life of the drug following intravenous administration in calves was 1.58 ± 0.06 h. This is in agreement with the half-life of ceftriaxone reported in sheep (1.7 and 1.75 ± 0.02 h) (GUERRINI et al., 1985; GOUDAH et al., 2006), calves (1.39 ± 0.04 h) (SOBACK and ZIV, 1988), goats (1.44 h) (ISMAIL, 2005) and horses (1.62 ± 0.42 h) (RINGGER et al., 1996). However, a longer elimination half-life of 4.39 ± 0.63 h has been reported in calves (JOHAL and SRIVASTAVA, 1999). The total body clearance of ceftriaxone in calves was 3.15 ± 0.41 mL/min/kg, which supports similar observations reported in sheep, calves, goats and mares (GUERRINI et al., 1985; SOBACK and ZIV, 1988; GARDENER and AUCOIN, 1994; ISMAIL, 2005; GOUDAH et al., 2006). However, faster clearance of the drug (5.16 ± 0.16 mL/min/kg) has been also observed in calves (JOHAL and SRIVASTAVA, 1998). The values of elimination half-life and total body clearance suggest faster elimination of cetriaxone following intravenous administration in cow calves. The apparent volume of distribution (0.44 ± 0.07 l/kg) of ceftriaxone in the present study was lower than the apparent volume of distribution of 1.19 ± 0.19 and 1.39 ± 0.08 l/kg reported in cow and buffalo calves (JOHAL and SRIVASTAVA, 1998; GAIKWAD, 2001), respectively.

Following the intramuscular administration of ceftriaxone in calves, the elimination half-life in the present study was 5.02 ± 0.51 h, which supports an elimination half-life of 6.54 ± 0.87 h reported in calves (JOHAL and SRIVASTAVA, 1998). However, a shorter elimination half-life of ceftriaxone has been reported in buffalo calves, dogs, goats and sheep (GAIKWAD, 2001; REBUELTO et al., 2002; ISMAIL, 2005; GOUDAH et al., 2006).

Following the intravenous and intramuscular administration of the drug, the variability in plasma drug concentration observed at 4 hours may be due to individual variation in elimination of the drug. The bioavailability of ceftriaxone following intramuscular administration was 47.0 ± 5.0%, which is close to the bioavailability of 40.0 ± 2.84% obtained in calves (JOHAL and SRIVASTAVA, 1998). However, higher bioavailability of ceftriaxone following intramuscular administration has been reported in cow calves, buffalo calves, goats and sheep (SOBACK and ZIV, 1988; GAIKWAD, 2001; ISMAIL, 2005; GOUDAH et al., 2006). For *Salmonella, Escherichia coli* and *Pasteurella multocida* isolated from calves, ceftriaxone has MIC_{90} of 0.03 -0.2 μg/mL (SOBACK and ZIV, 1988). In spite of relative low intramuscular bioavailability, a therapeutically effective plasma concentration is attained at 5 minutes and maintained for 12 hours. The pharmacokinetic characteristics of ceftriaxone in cow calves following intravenous and intramuscular administration indicates this favorable pharmacokinetic profile, hence the drug may be used to treat susceptible bacterial infections in cow calves.

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SAŽETAK

Farmakokinetika ceftriaksona određivana je u križane teladi nakon njegove jednokratne intravenske i intramuskularne primjene u dozi od 10 mg/kg. Koncentracija lijeka u plazmi određivana je tekućinskom kromatografijom visokog učinka s UV zrakama. Raspodjela lijeka bila je brza nakon intravenske primjene ($t_{1/2\alpha}$: 0,13 ± 0,01 h; $Vd_{(area)}$: 0,44 ± 0,07 L/kg), a izlučivanje ($t_{1/2\beta}$: 1,58 ± 0,06 h) iz tijela s klirensom od 3,15 ± 0,41 mL/min/kg. Nakon intramuskularne primjene vršna koncentracija u plazmi iznosila je (C_{max}) 15,34 ± 2,39 µg/mL tijekom 0,25 sati (T_{max}) što upućuje na vrlo brzu apsorpciju. Raspodjela lijeka bila je izrazito dobra ($Vd_{(area)}$ 1,16 ± 0,15 L/kg), a izlučivanje sporo ($t_{1/2\beta}$: 5,02 ± 0,51 sati; $Cl_{(B)}$: 2,71 ± 0,29 mL/min/kg) nakon intramuskularne primjene. Apsolutna biološka raspoloživost nakon intramuskularne primjene ceftriaksona iznosila je 47,0 ± 5,0%. Međutim, on se može rabiti u dozi od 10 mg/kg i.m. te ponavljati u razmacima od 12 sati radi liječenja bakterijskih zaraza u teladi.

Ključne riječi: farmakokinetika, biološka raspoloživost, ceftriakson, telad, intravenska primjena, intramuskularna primjena