

## The influence of *E. coli* lipopolysaccharide induced fever on the plasma kinetic of ceftriaxone in Black-Bengal goats

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### ABSTRACT

The pharmacokinetic profile of ceftriaxone was studied in healthy and febrile Black Bengal goats after its single intramuscular administration at the dose rate of 50 mg/kg body mass. The fever was induced by intravenous administration of *E. coli* serovar O126:B8 lipopolysaccharide (1 µg/kg, IV) and the plasma drug concentration was analyzed using HPLC. The plasma drug concentration versus time curve best fitted the two compartment open model. At 1 min the ceftriaxone concentrations in healthy and febrile animals were  $40.58 \pm 0.94$  µg/mL and  $32.83 \pm 0.92$  µg/mL, respectively and the drug could be detected up to 8 h in healthy goats and up to 4 h in febrile goats. The elimination half-life of ceftriaxone in febrile animals ( $0.95 \pm 0.02$  h) was lower than healthy animals ( $2.30 \pm 0.19$  h). Volume of distribution was higher in febrile animals ( $0.72 \pm 0.01$  L/kg) in comparison to healthy animals ( $0.15 \pm 0.07$  L/kg). Total body clearances in healthy and febrile animals were  $5.08 \pm 0.14$  and  $8.82 \pm 0.31$  mL/kg/h, respectively, suggesting extensive clearance of the drug in febrile animals. The intramuscular dose of ceftriaxone in febrile animals was calculated as 6 mg/kg body mass, to be repeated at a 6 h interval. Results of the present study indicated that the drug distribution is altered by fever.

**Key words:** ceftriaxone, dosage- regimen, fever, goat, pharmacokinetics

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### Introduction

Ceftriaxone (CTX) is a third generation cephalosporin used extensively in veterinary clinical practice because of its broad spectrum antibacterial activity, low toxicity and resistance to enzyme β-Lactamases (ANGEHRN et al., 1980; CLEELAND and SQUIRES,

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1984). This drug has high potential application in septicemia, bacteremia, lower respiratory tract infection, urinary tract infection, peritonitis, enteritis and soft tissue infections, because of its excellent penetration into the extra vascular space (PATEL and KAPLAN, 1984; TAN et al., 1984).

The pharmacokinetics of different antimicrobials are reported to vary during different disease conditions (BURROW, 1985; FRAZIER et al., 1988). Likewise, the kinetic profile of CTX varies with animal species, disease conditions and route of drug administration (SAR et al., 2006; GOUDAH, 2008). Fever is the most important clinical manifestation of many infectious diseases in goats and is reported to induce biochemical and physiological alterations in cells (VAN MIERT, 1987; LOHUIS et al., 1988). The pharmacokinetic profile of many drugs changes during fever (WILSON et al., 1984; CHAUDHARY et al., 1999). Despite the great potential for clinical use in veterinary medicine, the effect of fever on the pharmacokinetics of CTX after intramuscular administration in goats has not been studied so far. Therefore, the present study aimed to determine the pharmacokinetics of CTX in Black-Bengal goats following its intramuscular administration.

#### Materials and methods

The study was conducted on ten healthy, female Black Bengal goats, 1.5 to 2 years old, weighing 12-14 kg. The goats were kept under observation and periodical clinical examination for two weeks before commencing the experiment to exclude the possibility of any disease. They were maintained on balanced ration, green fodder and dry grass, and water was provided *ad libitum*. The experiment was conducted as per the guidelines of the Institutional Animal Ethics Committee.

Animals were randomly divided into two equal groups. Group I served as the afebrile healthy goat model, while group II served as the febrile goat model. Ceftriaxone sodium (WOCEF 3 g) was obtained from Wockhart Pvt. Ltd, Mumbai, India. Acetonitrile and Methanol (HPLC grade), N-acetyl-N, N- trimethyl ammonium bromide, sodium citrate, dibasic potassium phosphate ( $\text{KH}_2\text{PO}_4$ ) and monobasic potassium phosphate ( $\text{K}_2\text{HPO}_4$ ) were procured from Loba chemical Ltd., Mumbai, India and Ranbaxy fine chemical Ltd., New Delhi, India. A single intramuscular injection of ceftriaxone sodium at the dose rate of 50 mg/kg body mass was administered in the gluteal muscles of each experimental animal. Rectal temperature was recorded prior to drug administration and thereafter at hourly intervals. About 2 mL of blood sample was collected in separate heparinized vials by jugular vein puncture at an interval of 0.08, 0.16, 0.25, 0.33, 0.50, 0.75, 1, 2, 3, 4, 6 and 8 h after drug administration. The plasma was separated by centrifugation at 3000 rpm for 10 minutes and stored at -20 °C until drug analysis. Fever was induced by intravenous administration of *E. coli* serotype 0126:B8 lipopolysaccharide (LPS) at the rate of 0.2 µg/kg body mass. After 5 hours, half of the initial LPS dose was repeated for maintenance

of the fever up to 12 hours. A single dose of CTX at the rate of 50 mg/kg body mass was injected intramuscularly after an hour of LPS administration. Blood samples were collected in the heparinized vials after 0.08, 0.16, 0.25, 0.33, 0.50, 0.75, 1, 2, 3, 4, 6 and 8 h of drug administration and plasma was separated. The CTX concentrations in plasma samples were estimated by High Performance Liquid Chromatography (HPLC) assay (SAR et al., 2006). The HPLC system, Cecil 4100 (Cecil Instrumentation, Cambridge), UV detector and column RPC-18 were used. The mobile phase consisted of acetonitrile and water (40:60) and tetraheptyl ammonium bromide (0.32 per cent) as ion pairing agent. The concentration of CTX was scanned at 280 nm wave length. The mobile phase was pumped through a column at a flow rate of 1.0 mL/min, at an ambient temperature of 35<sup>o</sup> C. The sample (20 µL) was injected into HPLC with the help of 25 µL loop of Hamilton syringe. In the present study, the LOD (limit of detection) value of CTX in the plasms by HPLC was 3.66 µg/mL, whereas the LOQ (limit of quantification) value was 2.50 µg/mL. The inter and intra assay variations were 6.5 and 5.7% respectively. Various pharmacokinetic parameters were determined by computerized software programming 'Pharmakit', J. I. P. M. E. R., Ponducherry, India. Different pharmacokinetic parameters were statistically analyzed by the standard method (SNEDECOR and COCHRAN, 2004).

The intramuscular dose rate (mg/kg body mass) and the dose interval (h) of CTX in febrile goats were estimated using the kinetic data (SHARGEL and ANDREW, 1985):

$$Cp_{\max}/Cp_{\min} = 1/e^{-\beta \cdot r}$$

Where; r = interval for dose repeat; β = Overall elimination rate constant;  $Cp_{\max} = (\text{Dose}/Vd)/1 - e^{-\beta \cdot r}$ ;  $Cp_{\max}$  and  $Cp_{\min}$  are maximum and minimum concentrations of drug respectively in plasma.

## Results

The plasma CTX concentrations in healthy and febrile goats were plotted on semi-logarithmic scale (Fig. 1). In the group I animals, rectal temperature varied within the normal range during the entire experimental period. In group II animals, a rise in rectal temperature (39.2 - 40.4 °C) was observed one hour after the LPS administration, and remained elevated up to 12 hours. The drug concentration in plasma could be detected for up to 8 hours in healthy goats and up to 4 hours in febrile goats. Evaluation of the drug concentration data revealed that the pharmacokinetics of CTX was best described by a two- compartment open model. Initially, during the distribution phase, a rapid fall in plasma drug concentration was observed. Thereafter, it gradually declined during the elimination phase to reach a level below the detection limit after 6 hours. The various pharmacokinetic parameters of CTX in healthy and febrile goats are summarized in Table 1. In febrile goats  $A$ ,  $C^0_p$ ,  $\alpha$ ,  $\beta$ ,  $Cl_B$  and  $Vd_{\text{area}}$  were significantly ( $P < 0.05$ ) higher, while  $t_{1/2\alpha}$ ,  $t_{1/2\beta}$ , AUC and MRT were significantly ( $P < 0.05$ ) lower in comparison to healthy goats.

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Table 1. Pharmacokinetic profile of ceftriaxone following a single intramuscular administration in healthy and febrile goats

Parameter	Group I (Healthy goats)	Group II (Febrile goats)	P value
A ( $\mu\text{g/mL}$ )	$48.18 \pm 0.40$	$69.54 \pm 2.58$	0.001
B ( $\mu\text{g/mL}$ )	$50.54 \pm 5.60$	$73.26 \pm 1.16$	0.014
$C_p^0$ ( $\mu\text{g/mL}$ )	$43.81 \pm 0.75$	$60.44 \pm 1.20$	0.000
$\alpha$ ( $\text{h}^{-1}$ )	$4.96 \pm 0.22$	$15.99 \pm 0.51$	0.000
$\beta$ ( $\text{h}^{-1}$ )	$0.30 \pm 0.02$	$0.73 \pm 0.01$	0.000
$t_{1/2\alpha}$ (h)	$0.14 \pm 0.00$	$0.03 \pm 0.00$	0.000
$t_{1/2\beta}$ (h)	$2.30 \pm 0.19$	$0.95 \pm 0.02$	0.002
AUC( $\text{mg/L.h}$ )	$163.40 \pm 5.43$	$90.01 \pm 8.80$	0.001
MRT (h)	$3.27 \pm 0.10$	$1.34 \pm 0.04$	0.000
$Cl_B$ ( $\text{ml/kg/min}$ )	$5.08 \pm 0.14$	$8.82 \pm 0.31$	0.000
$Vd_{\text{area}}$ (L/kg)	$0.15 \pm 0.07$	$0.72 \pm 0.01$	0.020

A = Zero time intercept of distribution phase; B = Zero time intercept of elimination phase;  $\alpha$  = Distribution / absorption rate constant;  $\beta$  = Elimination rate constant;  $t_{1/2\alpha}$  = Distribution/absorption half life;  $t_{1/2\beta}$  = Elimination half life;  $Vd_{\text{area}}$  = Apparent volume of distribution;  $Cl_B$  = Total body clearance, AUC = Total area under the time concentration curve,  $C_p^0$  = Zero time plasma concentration, MRT = Mean residence time

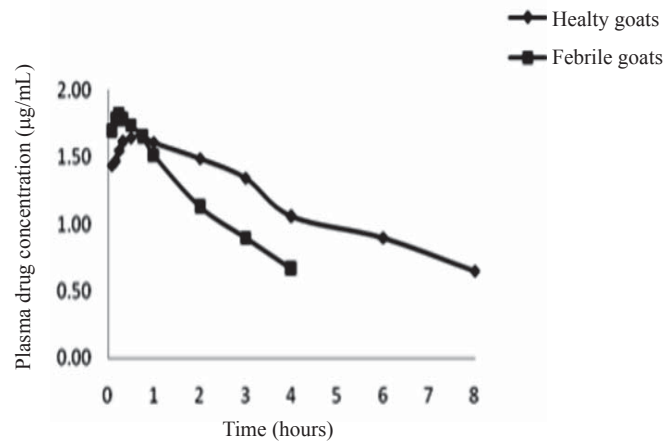


Fig. 1. A semi logarithmic plot of plasma CTX concentration versus time profile in healthy and febrile

### Discussion

The peak plasma CTX concentration ( $45.98 \pm 0.92 \mu\text{g/mL}$ ) was observed at 0.75 h after its intramuscular administration in healthy goats. Likewise, in buffalo calves, peak plasma concentration of CTX was also observed 0.5 h after its intramuscular administration (GOHIL et al., 2009). The high value of the distribution rate constant ( $\alpha$ )  $15.99 \pm 0.51 \text{ h}^{-1}$  in febrile animals indicated that CTX is rapidly distributed into various body fluid and tissue compartments. This may be due to increased capillary permeability, caused by different chemical mediators released during the fever (YANG and LEE, 2008). The pharmacokinetics of CTX best fitted in the two compartment open model, after its intramuscular administration (KUMAR et al., 2010).

In accord with the present finding, PAWAR and SHARMA (2008) reported higher value of cefepime in the B (zero time intercept of elimination phase) than the A (zero time intercept of distribution) phase in cross-bred calves. In febrile goats, the half-life of the distribution phase and the half-life of the elimination phase were lower in comparison to healthy goats, suggesting rapid clearance of the drug in febrile animals. The lower elimination half-life of CTX in febrile female goats was supported by the findings of ISMAIL (2005a) who reported lower elimination half-life of cefepime in cross-bred calves. This difference in elimination half-life could be due to differences in the age, sex and breed of the animals. The elimination half-life of CTX had been reported as 1.76 h in ewes (ISMAIL, 2005b) and 2.1 h in horses (GUGLICK et al., 1998). Hyperthermia causes alterations in renal function (MUSTAFA et al., 2007). Tachycardia and increased total cardiac output may be the possible reasons behind increased renal perfusion and glomerular filtration (RULE et al., 2000), enhancing rapid elimination of the drug.

The volume of distribution ( $V_{d_{\text{area}}}$ ) for CTX in febrile goats was higher than the reported value of  $V_{d_{\text{area}}}$  in horses (0.225 L/kg) (GUGLICK et al., 1998). The high value of  $V_{d_{\text{area}}}$  in female goats suggested that CTX is distributed principally through extracellular fluid space. In concurrence with the results of the present study, an increase in  $V_{d_{\text{area}}}$  in febrile animals was also reported for other cephalosporin antibiotics including cefuroxime (CHAUDHARY et al., 1999) and cefotaxime (SHARMA et al., 2006). In the present study the AUC was higher in healthy animals. DARDI et al. (2005) also reported higher AUC for CTX in healthy buffalo calves in comparison to febrile animals. Similarly, a decrease in AUC following intramuscular administration of cefazolin in febrile goats was reported by ROY et al. (1994).

It was found that the value of  $Cl_B$  in febrile animals was significantly ( $P < 0.05$ ) higher as compared to healthy animals. However, the value of  $Cl_B$  as calculated in the present study was less than the values reported in foals, cow calves and dogs. The value of  $Cl_B$  reported in foals, dog (GARDNER and PAPICH, 2001) and cow calves (ISMAIL, 2005a) was 78, 129.6, and 66  $\text{mL.kg}^{-1}$ , respectively. Contrary to the present findings JOSHI and SHARMA (2007) reported that  $Cl_B$  does not differ significantly during fever.

Fever, one of the most common manifestations of many infectious diseases, is reported to change the heart rate and renal, hepatic and splanchnic blood flow (KASTING et al., 1982). Fever is also associated with significant alterations in hepatic function, leading to changes in levels of various enzymes responsible for the metabolism of antimicrobials. Therefore, elimination and biotransformation patterns of antimicrobials may change during fever (SINGH et al., 1997). Changes in the permeability of the biological membrane barrier and/or tissue and plasma pH during fever may cause alteration in the distribution pattern of different drugs. These changes may be more important in patients suffering from encephalitis, infectious proctitis, arthritis and mastitis. For example, certain antibiotics may quickly attain high concentration in joint fluid during endotoxin induced synovial inflammation (FIRTH et al., 1988).

Calculation of a suitable dosage regimen of CTX in febrile goats, on the basis of pharmacokinetic parameters, was another objective of the present study. A minimum therapeutic plasma CTX concentration of 1.0 µg/mL has been shown to be effective against most gram positive as well as gram negative bacteria. For example, MIC<sub>90</sub> of CTX for *Salmonella*, *Escherichia coli* and *Pasteurella multocida* isolated from calves was found to be 0.03-0.2 µg/mL (SOBACK and ZIV, 1988).

From the data obtained from the present study, it may be concluded that the pharmacokinetics of CTX changes during fever in goats. CTX can be recommended to be given by intramuscular route at the dose rate of 6 mg/ kg body mass every 6 hours in febrile goats.

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**KUMAR, N., B. K. ROY, A. RANJAN: Utjecaj vrućice prouzročene lipopolisaharidom bakterije *E. coli* na kinetiku ceftriaksona u plazmi crnih bengalskih koza. *Vet. arhiv* 83, 479-486, 2013.**

**SAŽETAK**

Istraživana je farmakokinetika ceftriaksona u zdravih i febrilnih crnih bengalskih koza nakon njegove jednokratne intramuskularne primjene u dozi od 50 mg/kg tjelesne mase. Vrućica je bila prouzročena intravenskom primjenom lipopolisaharida (1 µg/kg) serovara O126:B8 bakterije *E. coli*. Koncentracija lijeka u plazmi bila je određivana tekućinskom visokotlačnom kromatografijom. Koncentracija lijeka u plazmi u odnosu na vremensku krivulju najviše je odgovarala modelu dvaju otvorenih odjeljaka. Koncentracija ceftriaksona u zdravih životinja nakon minute bila je  $40,58 \pm 0,94$  µg/mL, a u febrilnih  $32,83 \pm 0,92$  µg/mL. Lijek se nakon primjene mogao dokazati do osam sati u zdravih te do 4 sata u febrilnih koza. Poluživot izlučivanja ceftriaksona u febrilnih koza bio je manji ( $0,95 \pm 0,02$  h) nego u zdravih ( $2,30 \pm 0,19$  h). Obujam raspodjele bio je veći ( $0,72 \pm 0,01$  L/kg) u febrilnih u usporedbi sa zdravima ( $0,15 \pm 0,07$  L/kg). Ukupan tjelesni klirens u zdravih životinja bio je  $5,08 \pm 0,14$ , a u bolesnih  $8,82 \pm 0,31$  mL/kg/h što upućuje na ekstenzivan klirens lijeka u febrilnih životinja. Izračunato je da intramuskularna doza ceftriaksona u febrilnih životinja iznosi 6 mg/kg tjelesne mase svakih 6 sati. Rezultati istraživanja upućuju na zaključak da se raspodjela lijeka mijenja kod vrućice.

**Ključne riječi:** ceftriakson, doziranje, vrućica, koza, farmakokinetika

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