VETERINARSKI ARHIV 81 (4), 423-432, 2011

Effect of *E. coli* endotoxin induced fever on the pharmacokinetic profile and dosage regimen of ceftriaxone in sheep (*Ovis aries*)

Rajeev Ranjan[1], Birendra K. Roy[1], Amita Ranjan[1]*, and Sanjeet K. Singh[2]

[1]*Department of Pharmacology and Toxicology, Ranchi College of Veterinary Science and Animal Husbandry, Birsa Agriculture University, Ranchi, Jharkhand, India*

[2]*Department of Livestock Production and Management, Ranchi College of Veterinary Science and Animal Husbandry, Birsa Agriculture University, Ranchi, Jharkhand, India*

RANJAN, R., B. K. ROY, A. RANJAN, S. K. SINGH: Effect of *E. coli* endotoxin induced fever on the pharmacokinetic profile and dosage regimen of ceftriaxone in sheep (*Ovis aries*). Vet. arhiv 81, 423-432, 2011.

ABSTRACT

The effect of fever was studied on the pharmacokinetics of ceftriaxone (CTRX) following intravenous administration at the rate of 50 mg/kg b.m. in Chhotanagpuri sheep. Fever was induced by intravenous administration of *E. coli* serovar O126:B8 lipopolysaccharide, and plasma CTRX concentration was estimated by HPLC. The plasma drug concentration versus time curve best fitted a two compartment open model. The maximum plasma drug concentration was 16.33 per cent lower in febrile sheep (FS) in comparison to normal sheep (NS). In FS, $t_{1/2}\alpha$ was lower, while $t_{1/2}\beta$ was higher than in NS. Vd_{area} and P: C ratio was higher in FS, but Cl_B and AUC did not differ significantly between the two groups. The results of the present study indicate that CTRX has greater distribution in the peripheral compartment during pyrexia. High values of K_{12}/K_{21} ratio also indicated rapid drug distribution in various body fluids and compartments. The suitable dosage regimen of CTRX in FS by the intravenous route was calculated to be 15 mg/kg b.m. at a 5 h interval.

Key words: ceftriaxone, *E. coli*-endotoxin, pharmacokinetics, pyrexia, sheep

Abbreviations: A, zero time drug concentration at distribution phase; B, zero time drug concentration at elimination phase; α, regression coefficient for distribution phase; β, regression coefficient for elimination phase; CTRX, Ceftriaxone; HPLC, High performance liquid chromatography; C_0, Initial plasma concentration, C^0p, theoretical zero time plasma drug concentration; $t_{1/2}$ α, half life of distribution phase; $t_{1/2}$ β, half life of elimination phase; AUC, area under the plasma concentration curve; MRT, mean residence time ; Cl_B total body clearance; Vd_{area}, volume of distribution in total area under curve; K_{21}, rate of drug diffusion from peripheral to central compartment; K_{12}, rate of drug diffusion from the central to peripheral compartment; K_{el}, elimination rate constant from central compartment; P/C ratio, peripheral/central compartment drug concentration ratio.

*Corresponding author:

Amita Ranjan, Research Scholar, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana - 141 004, Punjab, India, Phone: +91 946 518 7263; Fax: +91 161 2400 822; E-mail: amita_pharma@rediffmail.com

ISSN 0372-5480
Printed in Croatia

Introduction

Ceftriaxone (CTRX) is a third generation cephalosporin, which is used extensively in veterinary clinical practice, because of its broad spectrum antibacterial activity, low toxicity and resistance to β-lactamases produced by gram-positive as well as gram-negative bacteria (ANGEHRN et al., 1980; CLEELAND and SQUIRES et al., 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).

For better response in clinical practice, knowledge of the pharmacokinetic-pharmacodynamic parameters of a drug is essential. The pharmacokinetic profile of CTRX varies with animal species, disease conditions and route of administration (DARDI and SHARMA, 2004; SAR et al., 2006; GOUDAH, 2008). Fever, one of the most common manifestations of many infectious diseases, is reported to change heart rate, renal blood flow, hepatic and splanchnic blood flow (KASTING et al., 1982). The pharmacokinetic profile of many drugs changes during fever (WILSON et al., 1984; CHAUDHARY et al., 1999). There seems to be no recent report available on the effect of fever on the pharmacokinetics of ceftriaxone in sheep. Therefore, the present study was aimed to study the pharmacokinetics and recommend an optimal dose of ceftriaxone in febrile sheep.

Materials and methods

The present study was conducted in female Chhotanagpuri sheep (n = 12), of 2 to 2.5 years age and 13-15 kg body mass. Animals were housed in the departmental shed for 30 days acclimatization. Animals were fed with a balanced ration, green fodder and fresh water was provided *ad libitum*. The experiment was conducted as per the guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals, Government of India.

Animals were randomly divided into two groups (n = 6 each), group I served as the afebrile normal sheep model (experiment I), while group II served as the febrile sheep model (experiment II).

Experiment I

Drug administration and sample collection. A single intravenous injection of CTRX (Injection WOCFF 3 g, Wockhardt Pvt. Ltd. Mumbai, India) at the rate of 50 mg/kg body mass was given to 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 venipuncture at an interval of 0.04, 0.08, 0.16, 0.25, 0.33, 0.50, 0.75, 1, 2, 3, 4 and 6 hours after drug administration. Plasma was harvested and stored at -20 °C until drug assay.

Drug assay. The concentrations of CTRX were estimated by high performance liquid chromatography (SAR et al., 2006). The chromatographic system, Cecil 4100 (Cecil Instrumentation, Cambridge) was used. The mobile phase consisted of acetonitrile and water (40:60) and tetraheptyl ammonium bromide (0.32 per cent) as an ion pairing agent. The concentration of CTRX was scanned at 280 nm wavelength. The limit of quantization was 1.56 µg/mL and mean (± SE) absolute recovery of CTRX was 118.23 ± 8.93 per cent. The intra-assay and inter-assay coefficients of variation in the present study were found to be 7.65.and 9.5 per cent respectively.

Experiment II

Induction of fever. Fever was induced by intravenous administration of *E. coli* serotype O126:B8 lipopolysaccharide (LPS) at the rate of 0.2 µg/kg body mass. After 5 hours, half of the initial LPS dose was repeated intravenously for maintenance of the fever up to 12 hours.

Drug administration, sample collection and drug assay. A single dose of CTRX at the rate of 50 mg/kg body mass was injected intravenously after an hour of LPS administration. The rest of the procedures, including sample collection and drug assay, were similar to those followed in experiment I.

Pharmacokinetic analysis. Various pharmacokinetic parameters were calculated as per the standard methods (BAGGOT, 1977; NOTARI, 1980). The intravenous dose rate (mg/kg body mass) and dose interval (h) of CTRX in febrile sheep were calculated as per the formulae given by SHARGEL and ANDREW (1985).

Calculation of dosage regimen and P/C ratio.

The dose and dosing interval of CTRX was calculated by the standard method (SHARGEL and ANDREW, 1985).

$$Cp_{max} = (Dose/Vd) / 1\text{-}e^{-\beta.r}$$

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

Where,

r = interval for dose repeat, β = overall elimination rate constant

P/C ratio = $(K_{12} / K_{21}^{-\beta})$

Statistical analysis. Different pharmacokinetic parameters and plasma drug concentrations at different observation periods were statistically analyzed using the Student *t*-test (SNEDECOR and COCHRAN, 1984).

Results

In group I animals, rectal temperature varied within the normal range during the entire experimental period. In group II animals, a rise in rectal temperature (39.4 - 40.5

ºC) was observed one hour after the LPS administration, and it was maintained up to 12 hours.

Plasma CTRX concentration, as a function of time in normal (NS) and febrile sheep (FS) following its single intravenous administration, was plotted on a semi logarithmic scale (Fig. 1). Plasma drug concentration versus time profile showed a biphasic disposition curve. The data was best fitted to a bi-exponential equation according to a two-compartment open model. Plasma drug concentration (C_0) in FS observed after 2.5 minutes of drug administration was about 16.33 per cent lower than that of NS. A gradual decline in drug concentration occurred thereafter and fell below the detection limit after 3 hours. Mean plasma drug concentration in NS remained significantly ($P<0.01$) higher from corresponding levels in FS up to half an hour and thereafter, levels in NS were recorded significantly ($P<0.01$) lower than corresponding levels in FS.

Table 1. Pharmacokinetic profile of ceftriaxone following its single intravenous administration (50 mg/kg body mass) in healthy (n = 6) and febrile sheep (n = 6)

Pharmacokinetic parameter	Normal sheep	Febrile sheep	*t*-value
A (µg/mL)	207.16 ± 12.15	257.84 ± 12.85	2.87*
B (µg/mL)	67.90 ± 1.91	43.16 ± 1.75	9.56**
C^0p (µg/mL)	275.06 ± 10.65	301.00 ± 12.66	1.57^{NS}
α (h^{-1})	11.79 ± 0.83	17.01 ± 0.36	5.79**
β (h^{-1})	1.17 ± 0.04	0.76 ± 0.03	7.99^{NS}
$t_{½}α$ (h)	0.06 ± 0.00	0.04 ± 0.00	5.40**
$t_{½}β$ (h)	0.60 ± 0.02	0.92 ± 0.03	8.00**
AUC (mg/L.h)	75.71 ± 1.66	72.26 ± 3.10	0.98^{NS}
MRT (h)	0.63 ± 0.03	1.04 ± 0.04	7.80**
Cl_B (mL/kg/min)	11.28 ± 0.24	11.49 ± 0.48	0.40^{NS}
Vd_{area} (L/kg)	0.58 ± 0.01	0.91 ± 0.03	9.36**
K_{21} (h^{-1})	3.77 ± 0.14	3.09 ± 0.12	3.76^{NS}
K_{12} (h^{-1})	5.55 ± 0.59	10.50 ± 0.35	7.20**
K_{el} (h^{-1})	3.64 ± 0.18	4.17 ± 0.14	2.32*
P/C	1.97 ± 0.27	4.55 ± 0.30	6.40**

**P<0.01; *P<0.05; NS = Non-significant

The pharmacokinetic parameters are summarized in Table 1. In febrile sheep, the half life of the distribution phase was lower, while the half life of the elimination phase was higher in comparison to NS (control). However, total body clearance of the drug

did not differ significantly between the two groups. Also, no significant difference was observed in the area under the plasma concentration curve (AUC) between the groups. The volume of distribution in the total area under curve was significantly ($P<0.01$) higher in the febrile group. The peripheral/central compartment drug concentration ratio was significantly ($P<0.01$) higher in FS.

The suitable dosage regimen for CTRX in FS was calculated to be 15 mg/kg body mass at 5 hour intervals.

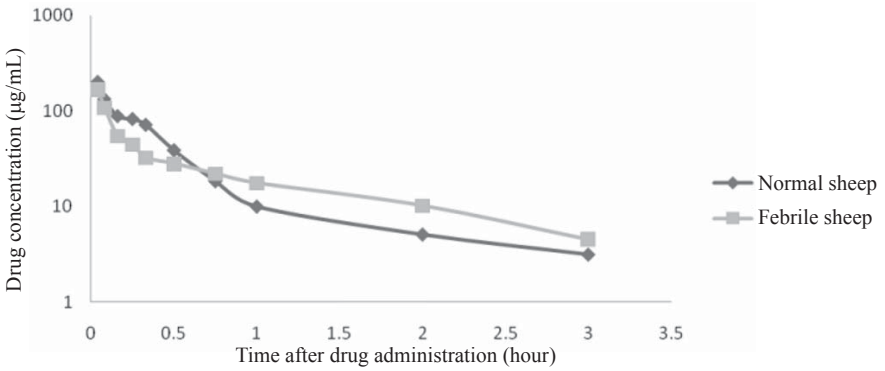

Fig. 1. Semilogarithmic plot of plasma ceftriaxone (CTRX) concentration versus time in normal and febrile sheep after intravenous administration of CTRX

Discussion

E. coli LPS is widely used to induce pyrexia in sheep and to study the effects of fever on the pharmacokinetic profile of different drugs (WILSON et al., 1984; RULE et al., 2000). When injected intravenously, it interacts with various cellular components of blood such as neutrophils, basophils, eosinophils, monocytes and other fixed macrophages, resulting in the release of endogenous pyrogens and hence induces a febrile condition (DINARALLO, 1979).

Evaluation of results indicated that the pharmacokinetics of CTRX after its intravenous administration in both NS and FS followed a two compartment open model. Following single intravenous CTRX administration, plasma drug concentration declined rapidly with time. Drug concentrations remained higher in NS in comparison to FS for up to half an hour, but the trend reversed thereafter. This may be correlated to temperature variation in pyrectic sheep. Following *E. coli* LPS administration, the temperature rises initially and then declines gradually. In comparison to normal animals, lower plasma drug concentration during pyrexia has been reported for CTRX in buffalo calves (DARDI et al., 2005), enrofloxacin in cross-bred bovine calves (AHANGAR and SRIVASTAVA, 2000),

gentamycin in goats (AHMAD et al., 1994), oxytetracycline in goats (MANNA et al., 1993) and cefuroxime in buffalo calves (CHAUDHARY et al., 1999). On the contrary, higher plasma levofloxacin concentrations in febrile goats in comparison to normal animals were reported in the recent past (MISHRA, 2006). During fever, the kidneys show certain biochemical changes leading to impaired drug excretion. Reduced cardiac output further impairs the renal blood flow and hence renal drug excretion (BLATTEIS et al., 1988). This mechanism could be more pertinent for levofloxacin, which is mainly excreted by the renal route. Decreased drug elimination during fever has also been reported for other drugs (SONG et al., 1972; TRENHOLME et al., 1976).

The normal pharmacokinetic profile of CTRX has been studied in many animal species including cats (ALBARELLOS et al., 2007) goat (ISMAIL, 2005), camel (GOUDAH, 2008) and dogs (REBUELTO et al., 2002). In all these studies, drug disposition kinetics after intravenous administration best fitted a two compartment open model.

Many pharmacokinetic parameters (apparent volume of distribution and rate constants of distribution phases) of CTRX during pyrexia have been reported to differ from that observed in normal buffalo calves following single intravenous CTRX administration (DARDI et al., 2005). However, there seems to be no report available on changes in CTRX pharmacokinetics in sheep during pyrexia. It is well established that the kinetics of many antibiotics including cephalosporines (ACHARYA et al., 1994; DARDI et al., 2005), aminoglycosides (TARDIF et al., 1990) and fluoroquinolones (WAXMAN et al., 2003) changes during fever induced by *E. coli* LPS administration.

The $t_{½}\beta$ in FS was higher than that observed in NS. Likewise, a higher value of $t_{½}\beta$ was reported in febrile goats following intravenous administration of CTRX (SINGH et al., 2004). Higher $t_{½}\beta$ in febrile animals can be attributed to the effects of endotoxin on the normal physiology. Endotoxin causes hepatic and renal dysfunctions (WILKINSON et al., 1974) along with haemodynamic depression (VAN MIERT, 1973). The haemodynamic depression may be responsible for slower drug elimination in febrile animals; while alterations in hepatic function may cause lower normal drug metabolism and transformation.

The high values of distribution rate, constant in FS as well as NS, indicated that CTRX was rapidly distributed into various body fluid and tissue compartments. The rapid distribution of CTRX was further substantiated by high values of K_{12}/K_{21} ratio in buffalo calves (DARDI et al., 2005). Similar observations were reported in febrile calves following intravenous administration of enrofloxacin (AHANGAR and SRIVASTAVA, 2000) and cephaloridine (SINGH et al., 1997).

Significantly higher values of AUC for cefepime in healthy buffalo calves in comparison to febrile animals have been reported in the past (PAWAR and SHARMA, 2008). Likewise, DARDI et al. (2005) also reported higher AUC for CTRX in healthy buffalo calves in comparison to those observed in febrile animals. However, in the present study

the values of AUC did not differ significantly between the two groups, although it was numerically higher in NS. It has been suggested that low urine flow and a shift to a more acidic pH favour possible tubular reabsorption of lipophilic weak acids (VAN MIERT, 1990). A reduction in pH of urine has been reported during fever in goats (VAN GOGH et al., 1989), which may explain the possible cause of a reduction in AUC during fever, observed in the present study and in other reports.

Higher values of Vd_{area} in FS in comparison to NS indicated that CTRX was more extensively distributed in various body fluids and tissues in FS. It occurred perhaps due to the increased capillary permeability caused by different chemical mediators released during the fever (YANG and LEE, 2008). Hyperthermia causes alterations in renal function (MUSTAFA et al., 2007). Tachycardia and increased total cardiac output may be the possible reasons behind the increased renal perfusion and glomerular filtration (RULE et al., 2000).

In accordance to our present findings, PAWAR and SHARMA (2008) also observed higher values of Vd_{area} in febrile buffalo calves in comparison to healthy ones after intravenous administration of cefepime. Higher values of Vd_{area} in febrile animals have also been reported for other antibiotics such as oxytetracycline (SINGH et al., 1998), cefuroxime (CHAUDHARY et al., 1999) and cefotaxime (SHARMA et al., 2006).

The P/C ratio observed in this study indicated a high distribution of drug to tissues (AHANGAR and SRIVASTAVA, 2000). The higher P/C ratio in FS indicated that the drug has greater distribution in peripheral compartment during pyrexia. The high value of the K_{12}/K_{21} ratio also substantiated the rapid distribution of CTRX into various body fluids and tissue compartments (DARDI et al., 2005).

Calculation of a suitable dosage regimen of CTRX in febrile sheep on the basis of pharmacokinetic parameters was the ultimate objective of the present study. A minimum therapeutic plasma CTRX concentration of 1.0 μg/mL has been shown to be the most effective against the majority of sensitive Gram-positive and Gram-negative pathogens (PERRY and SCHENTAG, 2001). Intravenous administration of CTRX 15 mg/kg at 5 h interval appeared to be the suitable dosage regimen in febrile sheep. This dose is slightly less that the dosage of CTRX recommended in febrile buffalo calves (DARDI et al., 2005).

References

ACHARYA, G., C. CREVOISIER, T. BUTLER, M. HO, M. TIWARI, K. STOECKEL, C. A. BREDLEY (1994): Pharmacokinetics of ceftriaxone in patients with typhoid fever. Antimicrob. Agents Ch. 38, 2415-2418.

AHANGAR, A. H., A. K. SRIVASTAVA (2000): Pharmacokinetics of enrofloxacin in febrile crossbred bovine calves. Indian J. Pharmacol. 32, 305-308.

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

ALBARELLOS, G. A., V. E. KREIL, M. F. LANDONI (2007): Pharmacokinetics of ceftriaxone after intravenous, intramuscular and subcutaneous administration to domestic cats. J. Vet. Pharmacol. Ther. 30, 345-352.

ANGEHRN, P., P. J. PROBST, R. L. THEN (1980): Ro-13-9904, a long-acting broad-spectrum cephalosporin: *In vitro* and *In vivo* studies. Antimicrob. Agents Ch. 18, 913-921.

BAGGOT, J. D. (1977): Principles of drug disposition in domestic animals. In: The Basis of Veterinary Clinical Pharmacology, Ist ed., W. B. Saunders Company, Philadelphia.

BLATTEIS, C. M., J. R. HALES, A. A. FAWCETT, T. A. JR. MASHBURN (1988): Fever and regional blood flows in wethers and parturient ewes. J. Appl. Physiol. 65, 165-172.

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.

CLEELAND, R., E. SQUIRES (1984): Antimicrobial activity of ceftriaxone: A review. Am. J. Med. 77, 3-11.

DARDI, M. S., S. K. SHARMA (2004): Pharmacokinetics and dosage regimen of ceftriaxone in buffalo calves. Vet. Res. Commun. 28, 331-338.

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.

DINARALLO, C. A. (1979): Production of endogenous pyrogen. Proceedings of the Meetings of Federation of European Biochemical Societies 38, pp. 52-56.

GOUDAH, A. (2008): Pharmacokinetic parameters of ceftriaxone after single intravenous and intramuscular administration in camels (*Camelus dromedarius*). Res. Vet. Sci. 84, 483-489.

ISMAIL, M. M. (2005): Pharmacokinetics, urinary and mammary excretion of ceftriaxone in lactating goats. J. Vet. Med. A 52, 354-358.

KASTING, N. W., W. L. VEALE, K. E. CORPER (1982): Fever and its role in disease: Rationale for antipyretics. In: Pyretics and Antipyretics (A. S. Milton, Ed.). Springer-Verlag, New York.

MANNA, S., T. K. MONDAL, A. K. CHAKRABORTY, R. D. GUPTA (1993): Modification of deposition kinetics of paracetamole by oxytetracycline and endotoxin induced fever in goats. Indian J. Anim. Sci. 64, 248-252.

MISHRA, V. K. (2006): Pharmacokinecs of Levofloxacin in Healthy and Febrile Goats. M. V. Sc. Thesis, Birsa Agriculture University, Ranchi, India.

MUSTAFA, S., A. H. ELGAZZAR, H. ESSAM, S. GOPINATH, M. MATHEW (2007): Hyperthermia alters kidney function and renal scintiography. Am. J. Nephrol. 27, 315-321.

NOTARI, R. E. (1980): Biopharmaceutics and Clinical Pharmacokinetics, 3rd ed., Marcel Dekkar INC., New York.

PATEL, I. H., S. A. KAPLAN (1984): Pharmacokinetic profile of ceftriaxone in man. Am. J. Med. 77, 17-25.

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.

PERRY, T. R., J. J. SCHENTAG (2001): Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. Clin. Pharmacokinet. 40, 685-694.

REBUELTO, M., G. ALBARELLOS, L. AMBROS, V. KREIL, L. MONTOYA, R. BONAFINE, P. OTERO, R. HALLU (2002): Pharmacokinetics of ceftriaxone administered by the intravenous, intramuscular or subcutaneous routes to dogs. J. Vet. Pharmacol. Ther. 25, 73-76.

RULE, R., R. LACCHINI, G. QUIROGA, L. MORENO, P. BUSCHIAZZO (2000): Pharmacokinetics and penetration into tissue fluid of ceftizoxime in normal and hyperthermic sheep. Small Ruminant Res. 37, 43-49.

SAR, T. K., T. K. MANDAL, S. K. DAS, A. K. CHAKRABORTY, A. BHATTACHARYYA (2006): Pharmacokinetics of ceftriaxone in healthy and mastitic goats with special reference to its interaction with polyherbal drug (Fibrosin). Int. J. Appl. Res. Vet. Med. 4, 142-154.

SHARGEL, L., B. C. Y. ANDREW (1985): Applied Biopharmaceutics and Pharmacokinetics. Appletun Century, New York.

SHARMA, S. K., A. K. SRIVASTAVA, M. D. DEORE (2006): Effect of *E. coli* lipopolysaccharide induced fever on the disposition pattern of cefotaxime in buffalo calves. Vet. Arhiv. 76, 537-545.

SINGH, K. P., A. H. AHMAD, V. AHUJA, K. PRADEEP, A. ZAFAR, K. PRANVENDRA, S. K. HORE (2004): Evaluation of pharmacokinetics of ceftriaxone along with diclofenac sodium following intravenous and intramuscular routes of administration in febrile goats. Proceedings of 4th Annual Conference of Indian Society for Veterinary Pharmacology and Toxicology. pp. 60.

SINGH, R. P., A. K. SRIVASTAVA, S. K. SHARMA, D. C. NAURIYAL (1998): Influence of *Escherichia coli* endotoxin induced fever on the pharmacokinetics and dosage regimen of oxytetracycline in cross-bred calves. Acta Vet. Hung. 46, 95-100.

SINGH, R. P., A. K. SRIVASTAVA, S. K. SHARMA, D. C. NAURIYAL (1997): Pharmacokinetics and urinary excretion of cephaloridine in febrile crossbred calves. Indian J. Anim. Sci. 67, 949-952.

SNEDECOR, G. W., W. G. COCHRAN (1984): Statistical Methods, 9th ed., Iowa State Univ. Press, Ames, U. S. A.

SONG, C. S., N. A. GELB, S. M. WOLFF (1972): The influence of pyrogen-induced fever on salicylamide metabolism in man. Clin. Invest. 51, 2959-2966.

TAN, J. S., S. J. SALSTROM, T. M. FILE (1984): Diffusibility of the newer cephalosporines into human interstitial fluids. Am. J. Med. 77, 33-36.

TARDIF, D., D. BEAUCHAMP, M. G. BERGERON (1990): Influence of endotoxin on the intracortical accumulation kinetics of gentamicin in rats. Antimicrob. Agents Ch. 34, 576-580.

TRENHOLME, G. M., R. L. WILLIAMS, K. H. RIECKMANN, H. FRISCHER, P. E. CARSON (1976): Quinine disposition during malaria and during induced fever. Clin. Pharmacol. Ther. 19, 459-467.

VAN GOGH, H., A. D. WATSON, J. F. M. NOUWS, J. NIEUWENHUIJS, A. S. VAN MIERT (1989): Effect of tick-borne fever (*Ehrilichia phagocytophila*) and trypanosomiasis (*Trypanosoma brucei* 1066) on the pharmacokinetics of sulfadimidine and its metabolites in goats. Drug Metab. Dispos. 17, 1-6.

VAN MIERT, A. S. J. P. A. M. (1990): Influence of febrile disease on the pharmacokinetics of veterinary drugs. Ann. Rech. Vet. 21 (Suppl 1), 11-28.

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.

WAXMAN, S., M. D. SAN-ANDRES, F. GONZALEZ, J. J. DE-LUCAS, M. I. SAN-ANDRES, C. RODRIGUEZ (2003): Influence of *E. coli* endotoxin induced fever on the pharmacokinetic behaviour of marbofloxacin after intravenous administration in goats. J. Vet. Pharmacol. Ther. 26, 65-69.

WILKINSON, S. P., B. G. GAZZARD, V. ARROYO (1974): Relation of renal impairment and haemorrhagic diathesis to endotoxemia in hepatic failure. Lancet 1, 521-524.

WILSON, R. C., D. D. GOETSCH, T. H. HUBER (1984): Influence of endotoxin induced fever on the pharmacokinetics of gentamicin in ewes. Am. J. Vet. Res. 45, 2495-2497.

YANG, K. H., M. G. LEE (2008): Effects of endotoxin derived from Escherichia coli lipopolysaccharide on the pharmacokinetics of drugs. Arch. Pharm. Res. 31, 1073-1086.

Received: 9 June 2010
Accepted: 29 October 2010

RANJAN, R., B. K. ROY, A. RANJAN, S. K. SINGH: Učinak vrućice uzrokovane endotoksinom bakterije *E. coli* na farmakokinetiku i doziranje ceftriaksona u ovaca (*Ovis aries*). Vet. arhiv 81, 423-432, 2011.

SAŽETAK

Istraživan je učinak vrućice na farmakokinetiku ceftriaksona (CTRX) nakon njegove intravenske primjene u dozi od 50 mg/kg tjelesne mase u ovaca pasmine Chhotanagpuri. Vrućica je bila uzrokovana intravenskom primjenom lipopolisaharida serovara O126:B8 bakterije *E. coli*. Koncentracija cefriaksona u plazmi bila je određivana visokotlačnom tekućinskom kromatografijom. Koncentracija lijeka u plazmi u odnosu na vremensku krivulju bila je najsličnija modelu dvaju odjeljaka. Najveća koncentracija lijeka bila je 16,33% manja u febrilnih ovaca u odnosu na nefebrilne. U febrilnih je ovaca $t_{1/2}\alpha$ bio manji, a $t_{1/2}\beta$ veći nego u nefebrilnih. Prividni volumen raspodjele (V_{darea}) i omjer P:C bili su veći u febrilnih ovaca dok se ClB (ukupni klirens lijeka iz organizma) i AUC (površina ispod koncentracijske krivulje lijeka u plazmi) nisu značajno razlikovali između dviju skupina. Rezultati ovog istraživanja naznačuju da ceftriakson ima bolju raspodjelu u perifernom odjeljku za vrijeme vrućice. Velike vrijednosti odnosa K_{12}/K_{21} također upućuju na brzu raspodjelu lijeka u različitim tjelesnim tekućinama i odjeljcima. Izračunato je da je ceftriakson u febrilnih ovaca najbolje davati intravenski u dozi od 15 mg/kg tjelesne mase u razmaku od pet sati.

Ključne riječi: ceftriakson, *E. coli*, endotoksin, farmakokinetika, vrućica, ovce