PHARMACOKINETIC PROFILE OF SINGLE DOSE INTRAVENOUS ADMINISTRATION OF CEFTIZOXIME IN FEMALE MEHSANA GOATS

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ABSTRACT

Ceftizoxime is the third generation cephalosporin, extensively used in veterinary medicine. It has larger volume of distribution, good penetration into tissues, and useful for the treatment of mastitis which is resistant to other antibiotics. Keeping in view of generating pharmacokinetic data of ceftizoxime in different domestic animals, the present study was planned to investigate pharmacokinetics of ceftizoxime in goats (n = 6) at the dose rate of 10 mg kg^{-1} body weight following single dose intravenous administration. Drug concentration in plasma was determined using High Performance Liquid Chromatography (HPLC) with UV detector. The values of C_{max}, AUC and MRT were 44.40 ± 2.09 μg ml^{-1}, 121.22 ± 15.40 μg.h.ml^{-1} and 11.44 ± 1.30 h, respectively. The longer elimination half-life (8.92 ± 1.11h) along with smaller Cl_B (0.09 ± 0.01 L h^{-1} kg^{-1}) showed slower excretion of the drug from animal body.

Keywords: Pharmacokinetics, Ceftizoxime, Mehsana female goat, HPLC.

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INTRODUCTION

Mastitis is the disease of economic importance of livestock and decreases milk production. Many antibiotics are reported to be resistant to this disease. Ceftizoxime is a novel drug for mastitis in veterinary medicine with better effectiveness (Salih and Ahmed, 2011). It possess better activity against anaerobes, broader spectrum of activity against Gram negative bacteria (Barriere and Flaherty, 1984) and extended activity against *Pseudomonas spp*. (Vaden and Reviere, 2001).

Besides mastitis, it can be used for the treatment of the infections of respiratory tract, urogenital tract, skin, soft tissues, bones and joints. It penetrates the cerebrospinal fluid in sufficient concentration due to greater lipid solubility (Mandell and Sande, 1991). It is resistant to hydrolysis by β-lactamase. Ceftizoxime is not metabolized in the body and is excreted predominantly by glomerular filtration (Facca *et al*., 1998).

Pharmacokinetic studies on ceftizoxime have been investigated in sheep (Rule *et al.,* 2000), Black Bengal goat (Karmakar *et al.,* 2011), calves (Singh *et al*., 2008), laboratory animals (Murakawa *et al.,* 1986) and humans (Neu and Srinivasan, 1981). Results from these studies have clearly revealed that there is variation in pharmacokinetics of ceftizoxime in the various species and breed. Therefore, before use of ceftizoxime, its pharmacokinetic properties should be determined in target species like Mehsana goats under local environment in which the drug is to be used clinically.

MATERIALS AND METHODS

The experiment was conducted on six female mehsana goats of 2-4 years of age (weight 25-40 kg) after obtaining permission from Institutional Animal Ethics Committee (IAEC). Ceftizoxime (Zoctim®; a product of Intas pharmaceuticals Ltd) was administered intravenously in jugular vein at the dose rate of 10 mg kg^{-1} body weight. About 4-5 ml of blood samples were collected from jugular vein (contra-lateral) in heparinized test tubes at 0 min (pre-administration), 2 min, 5 min, 15 min , 30 min , 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h and 96 h post intravenous administration of drug. The plasma samples were separated after centrifugation of blood samples at 1660 revolutions per minute for 10 minutes. The plasma samples were transferred to cryo-vials (2 ml capacity) then stored at –4ºC until assayed for ceftizoxime concentration using HPLC procedure. All the reagents used for the analysis were of HPLC grade.

HPLC assembly was equipped with isocratic solvent delivery pump (Model K 501) and UV detector (Model K 2501). Chromatographic separation was performed by using reverse phase Thermo C_{18} column (Zorbax, ODS; 25 cm x 4.6 mm ID) at room temperature. The mobile phase was a mixture of acetonitrile and water (65:35). Mobile phase was filtered by 0.45 µm filter paper by using vacuum pump and degassed by using sonicator to allow sucking into HPLC system and pumped into column at a flow rate of 0.8 ml min^{-1} at ambient temperature. The effluent was monitored at 260 nm wavelength. The retention time of ceftizoxime was 5.2 min with total run time of 10 minutes.

Ceftizoxime was extracted using ice - cold acetonitrile. A 300 µl of sample was mixed with 300 µl ice - cold acetonitrile. After thorough mixing with vortex mixture (30 sec), mix were centrifuged (5 min) at 3,000 RPM at 4°C using refrigerated centrifuge machine. Supernatant thus obtained was collected and 100 µl was injected into HPLC machine. The pharmacokinetic analysis was done by the non-compartment model with the use of "PK Solver Software" (Zhang *et al.,* 2010).

RESULTS AND DISCUSSION

Initially, the measured plasma concentration of ceftizoxime after single dose IV

administration (10 mg kg^{-1}) showed the level of 44.40 ± 2.09 μg ml^{-1} achieved at 0.0333 h (2 min). There after plasma level of the drug diminished gradually and retained at the level of 1.50 ± 0.26 μg ml^{-1} up to 24 h. The pharmacokinetic parameters calculated from plasma concentrations of ceftizoxime after its single dose IV administration in goats are presented in Table 1. The Semi logarithmic plot of mean plasma concentration of ceftizoxime against time following IV administration is presented in Figure 1.

The mean peak plasma concentration of ceftizoxime was 44.40 μg ml^{-1} which is higher in other species like 61.9 μg ml^{-1} in dog, 78.0 μg ml^{-1} in monkey whereas lower ceftizoxime peak concentration was found in mouse as 27.6 g ml^{-1} (Murakawa *et al.*, 1986).

The mean elimination rate constant (β) calculated was 0.09 ± 0.01 h^{-1} which is comparatively similar to β value of 0.12 ± 0.003 h^{-1} as reported in Black Bengal goat (Karmakar *et al.,* 2011) whereas higher values have been reported in sheep (Rule *et al.,* 2000), dog, mouse, rat and monkey (Murakawa *et al.*, 1986) as 0.70 , 0.653 , 2.60, 2.08 and 0.939 h^{-1}, respectively. A low value of elimination rate constant observed following IV administration of the drug, in the present study, indicates that the drug is slowly eliminated from the body of goat.

The mean value of elimination half-life of ceftizoxime was found to be 8.92 h in the present study. This was slightly higher than the value of $t_{1/2\beta}$ reported as 6.24 h in Black Bengal goat (Karmakar *et al*., 2011) and much higher than the values of $t_{1/2\beta}$ reported as 1.1 ± 0.4 h in sheep (Rule *et al.,* 2000) and 0.93 ± 0.21 h in human (Quintiliani and Nightingale, 1982). This value of $t_{1/2\beta}$ was also much higher than the values of $t_{1/2\beta}$ reported in dog, mouse, rat and monkey (Murakawa *et al*., 1986) as 1.06, 0.267, 0.333 and 0.738 h, respectively. The mean apparent volume of distribution (Vd_{area}) and volume of distribution at steady state (Vd_{ss}) were calculated to be 0.374 ± 0.825 and 0.329 ± 0.659 L kg^{-1}, respectively. The value of $Vd_{(area)}$ was higher as compared to 0.49 L kg^{-1} in goats (Karmakar *et al*., 2011), whereas, Shaktidevan *et al.* (2005) reported comparative lower value as 0.21 L kg^{-1} in goats following IV administration of ceftizoxime. The result indicates moderate distribution of ceftizoxime into various body fluids and tissues of goats following IV administration. In the present study mean value of AUC was 121.22 ± 15.40 μg h ml^{-1} which is similar to that reported in dog by Murakawa *et al.* (1986) as 100.0 μg h ml^{-1}. The Mean Resident Time (MRT) following single dose IV administration of the drug was calculated to be 11.44 ± 1.30 h in Mehsana female goats. The values of MRT for ceftizoxime was found slight lower in Black Bengal goats (Karmakar *et al.,* 2011) and sheep (Rule *et al.,* 2000) as 7.58 ± 0.2 h and 4.0 h, respectively following IV administration of the drug.

Based on the formulae [D= Cp. Vd ($e^{+\beta t}$)] proposed by Baggot (2001), it was calculated that optimised IV dose of ceftizoxime in Mehsana goats would be 7.5 mg/kg body weight to be repeated every 48 hours to treat infections caused by susceptible bacteria having MIC value equal to or less than 0.30 μg/ml.

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REFERENCES

Baggot, J.D. (2001). Chapter 4: Some aspects of dosage, clinical selectivity and stereoisomerism. In: The physiological Basis of Veterinary Clinical Pharmacology. 1st edn. Blackwell Sciences, UK. pp. 137-146.

Barriere, S.L. and Flaherty, J.F. (1984). Third generation cephalosporins: A critical evaluation. Clinical Pharmacology. 3**:** 351-373.

Facca, B., Frame, B. and Triesenberg, S. (1998). Population pharmacokinetics of ceftizoxime administered by continuous infusion in clinically ill adult patients. Antimicrobial Agents Chemotherapy. 42: 1783-1787.

Karmakar, U., Datta, B., Patra, P.H., Prashant, M., Suman, S., Sar, T., Chakraborty, A. and Mandal, T. (2011). Disposition kinetics of ceftizoxime in healthy and mastitic goats after intravenous administration. Pharmacology Online. **3**: 935-946.

Mandell, G.L. and Sande, M.A. (1991). Penicillins, cephalosporins and other β-lactam antibiotics. In: The Pharmacological Basis of Therapeutics. Gilman, A.G., Rall, T.W., Nies, A.S. and Tayler, P. (Eds.) Goodman and Gilman's Maxwell Macmillan, Singapore, pp. 1065-1097.

Murakawa, T., Sakamoto, H., Fukada, S., Nakamoto, S., Hirose, T., Itoh, N. and Nishida, M. (1986). Pharmacokinetics of ceftizoxime in animals after parental dosing. Antimicrobial Agents Chemotherapy. 17: 157-164.

Neu, H.C. and Srinivasan, S. (1981). Pharmacology of ceftizoxime compared with that of cefamandole. Antimicrobial Agents and chemotherapy. 20(3): 366-369.

Quintiliani, R., and Nightingale, C.H. (1982). Comparative pharmacokinetics of ceftizoxime and other third-generation cephalosporins in humans. Journal of Antimicrobial Chemotherapy. *10* (suppl C): 99-104.

Rule, R., Lacchini, R., Quiroga, G., Moreno, L. and Buschiazzo, P. (2000). Pharmacokinetics and penetration into tissue fluid of ceftizoxime in normal and hyperthermic sheep. Small Ruminant Research. 37: 43-49.

Salih, R.R. and Ahmed, F.A. (2011). Treatment trial of bovine bacterial mastitis in Khartoum State, Sudan. World's Veterinary Journal. 1(1): 20-24.

Shakthidevan, R. K., Jha, K. C., Sar, T. K., Das, S. K., Chatterjee, U. S.,Chakraborty, A.K. and Mandal, T. K. (2005). Effect of induced surgical stress and acute renal failure on disposition kinetics of ceftizoxime in goats. Indian Journal of Pharmacology. **37**: 186-188.

Singh, R., Chaudhary, R. K. and Dumka, V. K. (2008). Influence of paracetamol on the pharmacokinetics and dosage regimen of ceftizoxime in cross bred calves. Israel Journal of Veterinary Medicine. **63** (3): 72-76.

Vaden, S. L. and Riviere, J. E. (2001). Penicillins and related β-lactam antibiotics. In: Veterinary Pharmacology and Therapeutics Adams, H.R. (ed.), 8th edn. Iowa State University Press, Ames, USA, **pp.** 818-827.

Zhang, Y., Huo, M., Zhou, J., and Xie, S. (2010). PK Solver : An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs. Biomedical, 99: 306 -314.

Table 1

Pharmacokinetic parameters of ceftizoxime after single dose intravenous administration in goats

Pharmacokinetic Parameters	Unit	Mean ± SE
Cp^o	$\mu g\ ml^{-1}$	47.72 ± 2.14
β	h^{-1}	0.09 ± 0.01
$t_{1/2\beta}$	h	8.92 ± 1.11
AUC	$\mu g\ h\ ml^{-1}$	121.22 ± 15.40
AUMC	$\mu g\ h^2\ ml^{-1}$	1402.98 ± 222.37
MRT	h	11.44 ± 1.30
$V_{d(area)}$	$L\ kg^{-1}$	0.374 ± 0.825
$V_{d(ss)}$	$L\ kg^{-1}$	0.329 ± 0.659
Cl_B	$L\ h^{-1}\ kg^{-1}$	0.09 ± 0.01

Cp^o = Concentration of drug in plasma at zero time,

β= Elimination rate constant,

$t_{1/2\beta}$ = elimination half-life,

AUC= Area under curve,

AUMC= Area under first moment of curve,

MRT= Mean residence time,

$V_{d(area)}$= Apparent volume of distribution,

$Vd_{(ss)}$ = Volume of distribution at steady state, and

Cl_B = Total body clearance.