Intramuscular Pharmacokinetics and Milk Levels of Ceftriaxone in Endometritic Cows

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ABSTRACT

Disease conditions are known to alter the pharmacokinetics of antibacterials in bovines. Ceftriaxone is effective for the treatment of bacterial endometritis particularly caused by Gram-negative pathogens. In this regard, the plasma pharmacokinetics and milk levels of ceftriaxone were studied in healthy and endometritic cows following single intramuscular administration. Peak plasma drug levels of 11.2 ± 0.329 and 4.68 ± 0.261 $\mu g.ml^{-1}$ attained at 30 minutes were found in healthy and endometritic cows, respectively. The drug was detected above the minimum inhibitory concentration (MIC) after up to 6 h of dosing and the disposition followed a one-compartment open model. The values of Vd_{area} (apparent volume of distribution), AUC (area under the plasma drug concentration-time curve), $t_{1/2\beta}$ (elimination half life) and P/C ratio (ratio of drug present in peripheral versus central compartment) were 0.67 ± 0.13 $L.kg^{-1}$, 21.3 ± 0.86 $\mu g.ml^{-1}.h$, 1.42 ± 0.13 h and 1.07 ± 0.25, respectively, in healthy cows and 1.35 ± 0.19 $L.kg^{-1}$, 12.4 ± 0.56 $\mu g.ml^{-1}.h$, 1.69 ± 0.47 h and 0.92 ± 0.39, respectively, in endometritic cows. The use of antibacterial drugs that could penetrate into the udder parenchyma in therapeutic levels is of considerable importance in severe infectious conditions of the udder. Ceftriaxone was secreted into milk up to 36 h of administration. An appropriate intramuscular dosage for ceftriaxone, would be 13 $mg.kg^{-1}$ repeated at 6 h intervals for the treatment of endometritis in cows.

Keywords: Ceftriaxone, Endometritis, Intramuscular, Milk, Pharmacokinetics, Cows.

INTRODUCTION

Ceftriaxone is effective in a variety of infections including meningitis, septicemia, pyoderma, colibacillosis, surgical prophylaxis and infections of the urinary tract, respiratory tract, wounds, soft tissues and joints (1). It is characterized by its excellent activity against Gram-negative pathogens including Salmonella, Shigella, Proteus, Klebsiella, Enterobacter, Pasteurella, *Escherichia coli* and *Neisseria meningitidis*. The relatively low Minimum Inhibitory Concentration (MIC) of ceftriaxone against Gram-negative bacteria makes it suitable for use in bacterial endometritis associated with Gram-negative pathogens, most of which are resistant to the other commonly used antibiotics (2). The use of antibacterial drugs that could penetrate into the udder parenchyma in therapeutic levels is of considerable importance, particularly in severe and life-threatening infectious conditions of the udder (3).

There is meager information on the penetration of ceftriaxone from blood into milk. Although, some data are avail-

able for ceftriaxone concentration in the milk of goats (4) and ewes (3), there is no report of its levels in cow milk. Furthermore, disease conditions have been reported to markedly alter the pharmacokinetics of antibacterials in bovines (5, 6, 7, 8). Disposition kinetics of ceftriaxone after intramuscular dosing has been conducted in buffalo calves (9, 10), ewes (3), goats (4, 11, 12), camels (13) and dogs (14). However, there is little information on the pharmacokinetics of ceftriaxone in cattle species, except one study following intravenous administration in endometritic cows conducted earlier in our laboratory (15). In view of the paucity of pharmacokinetic data of intramuscular ceftriaxone during endometritic condition in cattle, the present study was undertaken to determine the pharmacokinetics and milk excretion of administration.

MATERIALS AND METHODS

Experimental animals and drug administration

The experiment was performed in two groups of 8 healthy and 8 endometritis-affected crossbred cows between 3 to 9 years age which had calved at least once. Endometritic cows were selected on the basis of history of repeat breeding, thorough per-rectal examination and physicochemical characteristic of cervical mucus. Cows with history of repeat breeding, purulent or muco-purulent estrual discharge or containing white flakes and positive reaction to white side test (16) were considered positive for endometritis. All the cows were examined per-rectally to rule out any anatomical or reproductive disorders. Animals were kept under loose housing system in clean and hygienic experimental and milking paddocks with brick flooring, asbestos roofing and sufficient space for the free movement of the animals. All the animals were fed on a ration consisting of concentrate mixture and green fodder with free access to fresh water. The experimental protocol followed the ethical guidelines on the proper care and use of animals and was approved by the Institutional Animal Ethics Committee vide Director Resident Instructions SKUAST (J), Order No. AUJ/DRI/07-08/D-08/2612-13 dated 18-1-2008. Ceftriaxone (Ceftriaxone sodium; Intacef-3, Intas Pharmaceuticals, Ahmedabad, India) was administered as 10 % solution at dose rate of 6.72 $mg.kg^{-1}$ body weight intramuscularly.

Collection, processing and storage of samples

Blood samples were collected just before and after drug administration from the jugular vein into heparinized glass tubes at different time intervals viz. 0, 1, 5, 10, 15, and 30 min and at 1, 2, 4, 6, 8, 12 and 24 h with the help of a plastic catheter placed and secured before the administration of drug. Plasma was separated by centrifugation at 8000 rpm for 10 minutes and stored at -20°C for analysis to be conducted on the following day of sample collection. Collection of milk was carried out manually at 12, 24, 36 and 48 hours after intramuscular administration of the drug. The udder was completely evacuated before the start of the experiment. The samples were kept in -20°C until analysis.

Analytical methods

The concentration of ceftriaxone in samples was determined by microbiological assay technique using *Escherichia coli* (ATCC 25922) as the test organism (17). The test organism was cultured on antibiotic medium no. 1 at 37°C for 24 h and a suspension was prepared in sterile normal saline. Preliminary experiments were conducted to determine the actual amount of bacterial suspension to be used in the preparation of seed layer. The bacterial suspension of 0.5 naphlometer reading was diluted 30 times with sterile normal saline and 100 µl of the dilute suspension was transferred to each petri-plate with the help of Cornwell Continuous Pipetting Device (Becon Dickinson, USA). After solidification of the media, six wells of 9 mm diameter each were punched at equal distance with the help of a punching device. Three alternative wells were filled with one plasma sample and the remaining three wells with a reference solution of ceftriaxone (0.1 $\mu g.ml^{-1}$). These assay plates were incubated at 34°C for 6 h. At the end of incubation period, the diameter of zone of inhibition of each well was measured with Fisher Lilly Antibiotic Zone Reader (Fisher Scientific Company, USA). Nine replicates were analyzed for each sample. The assay could detect a minimum drug concentration of 0.01$\mu g.ml^{-1}$ without differentiating between the parent drug and its metabolites.

Pharmacokinetic analysis

The concentrations of ceftriaxone in plasma were plotted on a semi-logarithmic scale as a function of time and the pharmacokinetic parameters were calculated manually for each animal using least square regression technique (18) by applying the formulae: $\beta = 2.303 \times m$ where m, the regression coefficient was calculated by least square regression technique and B was the zero-time plasma drug concentration intercept of the regression line. A' and Ka were calculated by

the method of residual yields, $t_{½\beta}$ = 0.693/Rate constant of elimination, AUC = A/α + B/β, AUMC= A/α² + B/β², MRT = AUMC/AUC, Vd_{area} = Dose /β × AUC, Cl_B = β × Vd_{area} × 1000 (18). The mean values and standard error (Mean ± SE) of pharmacokinetic variables were obtained by averaging the variables calculated for drug disposition after drug administration to each animal.

Statistical analysis

The mean values and standard errors (Mean ± SE) of drug levels in plasma and milk as well as the pharmacokinetic variables in endometritic cows were compared with the corresponding values obtained in healthy animals. The differences between two means based on individual observations were determined by Student's t-test. The significance was assessed at P<0.05 and P<0.01 levels.

RESULTS

Figure 1 displays the mean plasma drug concentration-time profile of ceftriaxone after intramuscular dose of 6.72 mg.kg^{-1} body weight in healthy and endometritic cows. In healthy cows, the plasma concentration of ceftriaxone was 2.13 ± 0.33 µg.ml^{-1} at 1 min which attained peak level of 11.2 ± 0.33 µg.ml^{-1} at 30 min and the drug levels above minimum inhibitory concentration (MIC) were detected in plasma for up to 6 h. In endometritic cows, the plasma drug concentration at 1 min was 1.81 ± 0.27 µg.ml^{-1}, and the peak plasma concentration (4.68 ± 0.26 µg.ml^{-1}) was observed at 30 min. The drug levels above the minimum inhibitory concentration (MIC) were detected in plasma for up to 6 h. Based on plasma level of ceftriaxone in healthy and endometritic cows, various pharmacokinetic parameters were calculated and are presented in Table 1.

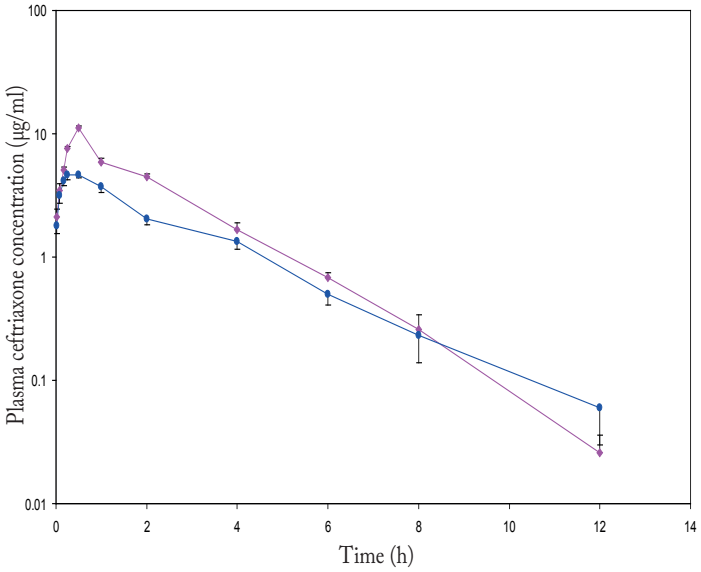

Figure 1: Semilogarithmic plot of plasma concentration-time profile of ceftriaxone in healthy and endometritic cows following its single intramuscular administration of 6.72 mg.kg^{-1} body weight. Values are presented as mean ± SE of 8 animals. The data was analyzed according to one-compartment open model.

Evaluation of results of plasma drug concentration of ceftriaxone after intramuscular injection in healthy and endometritic cows revealed that the disposition of ceftriaxone best fitted one-compartment open model adequately described by the exponential equation, $C_p = Be^{-\beta\tau} - A'e^{-K_a\tau}$. In healthy animals, the drug was rapidly absorbed into systemic circulation from the intramuscular site of administration as was evident from the high absorption rate constant (Ka) which was 3.88 ± 0.79 h^{-1} and the C_{max} of 11.2 ± 0.33 µg.ml^{-1} was attained at 0.5 h. The values of elimination rate constant (β)

Table 1: Disposition parameters of ceftriaxone in healthy and endometritic cows (n = 8) following its single intramuscular administration of 6.72 mg.kg^{-1} body weight

Parameter	Unit	Mean ± SE	
		Healthy	Endometritic
C_{max}	µg.ml^{-1}	11.2 ± 0.33	4.68 ± 0.26**
t_{max}	h	0.5	0.5
A'	µg.ml^{-1}	10.7 ± 2.52	4.56 ± 1.07
Ka	h^{-1}	3.88 ± 0.79	3.16 ± 1.84
B	µg.ml^{-1}	11.9 ± 0.49	6.74 ± 0.96**
β	h^{-1}	0.49 ± 0.07	0.47 ± 0.26
$t_{1/2\beta}$	h	1.42 ± 0.13	1.69 ± 0.47
AUC	µg.ml^{-1}.h	21.3 ± 0.86	12.4 ± 0.56**
AUMC	µg^2.ml^{-1}.h	47.4 ± 1.90	32.20 ± 1.46**
Vd_{area}	L.kg^{-1}	0.67 ± 0.13	1.35 ± 0.19*
Cl_B	L.kg^{-1}.h^{-1}	0.33 ± 0.11	0.56± 0.14
MRT	h	2.27 ± 0.15	2.55 ± 0.31
td	h	5.31 ± 0.26	4.66 ± 0.78
P/C	ratio	1.17 ± 0.32	0.91 ± 0.38

*P<0.05, **P<0.01, C_{max} and t_{max} = peak plasma drug concentration and time required to attain the peak concentration, respectively; A¢ and B = zero-time plasma drug concentration intercepts of the regression lines of absorption and elimination phases, respectively; Ka and β = absorption and elimination rate constants, respectively; $t_{½\beta}$= elimination half-life; AUC = area under the plasma concentration-time curve; AUMC = area under the first moment of plasma concentration-time curve, Vd_{area} = apparent volume of distribution; Cl_B = total body clearance; MRT = mean residence time; td = total duration of pharmacological effect, P/C ratio = ratio of drug present in peripheral versus central compartment.

Table 2: Levels of ceftriaxone in milk of healthy and endometritic cows (n=8) following a single intramuscular dose of 6.72 mg.kg^{-1} body weight

Time after ceftriaxone administration (h)	Drug levels in milk (µg/ml)	
	Healthy cows	Endometritic cows
12	313.6 ± 110.2	148.1 ± 63.7
24	36.9 ± 15.1	3.43 ± 1.24**
36	1.99 ± 0.88	0.93 ± 0.45
48	ND	ND

ND = Not detected, *P<0.05, **P<0.01

and half-life of elimination ($t_{½\beta}$) were 0.49 ± 0.07 h^{-1} and 1.42 ± 0.13 h, respectively, indicating rapid elimination of the drug. The apparent volume of distribution (Vd_{area}) was 0.67 ± 0.13 L.kg^{-1}, reflecting moderate tissue distribution. Area under curve (AUC) was 21.3 ± 0.86 µg.ml^{-1}.h and area under mean curve (AUMC) was 47.4 ± 1.90 µg^2.ml^{-1}.h. The total body clearance (Cl_B) which represents the sum of all metabolic and excretory processes was 0.33 ± 0.11 L.kg.$^{-1}$h^{-1}. The mean residential time (MRT) was calculated to be 2.27 ± 0.15 h and the ratio of amount of drug in peripheral to that in central compartment (P/C) was 1.17 ± 0.32 showing that greater fraction of the drug was available to produce antibacterial activity at the site of infection.

In endometritic cows, some of the values of various pharmacokinetic parameters were different from their corresponding values in healthy animals. The absorption rate constant (3.16 ± 1.84 h^{-1}) was similar to the corresponding value in healthy cows, however a lower C_{max} of 4.68 ± 0.26 µg.ml^{-1} was attained in the endometric cows at 0.5 h compared to the healthy cows (p<0.01). The values of β and $t_{½\beta}$ were 0.47 ± 0.26 h^{-1} and 1.69 ± 0.47 h and similar to the healthy cows. Vd_{area} was 1.35 ± 0.19 L.kg^{-1}. AUC was 12.36 ± 0.56 µg.ml^{-1}.h and area under mean curve AUMC was 32.20 ± 1.46 µg^2.ml^{-1}.h both of which parameters were significantly different from the healthy cows (p<0.001). The total body clearance was 0.56 ± 0.14 L.kg.$^{-1}$h^{-1}, mean residential time (MRT) was calculated to be 2.55 ± 0.31 h and the P/C ratio was 0.91 ± 0.38, all three being similar to those of the healthy coms.

The milk levels of ceftriaxone at various time intervals after its single intramuscular administration in healthy and endometritic cows are given in Table 2. Initially at 12 h of drug administration, the drugs levels were higher (313.6 ± 110.2 µg/ml) in healthy than during endometritis (148.1 ± 63.7 µg/ml). Subsequently the higher milk drugs levels were maintained up to 36 h in healthy animals (1.99 ± 0.88 µg/ml) compared to endometritic cows (0.93 ± 0.45 µg/ml). Thereafter, the drug was not detected in the milk of both healthy as well as of endometritic cows.

Using convenient dosage interval and the values of β and $Vd_{(area)}$ of endometritic cows, the priming (D) and maintenance (D') doses of ceftriaxone to maintain the minimum therapeutic concentration of were calculated from following equations:

$$D = C_p(min)^{\mu}.Vd\ (e^{\beta\tau})$$

$$D' = C_p\ (min)^{\mu}.\ Vd\ (e^{\beta\tau}-1)$$

Where, $C_p(min)^{\mu}$ is the desired minimum therapeutic plasma level of ceftriaxone, β is elimination rate constant, Vd is apparent volume of distribution and τ is the dosing interval (19).

Based on the results presented, the priming and maintenance doses of ceftriaxone were calculated from the pharmacokinetic data obtained in healthy animals as 9.02 and 8.71 mg.kg^{-1}, respectively at an interval of 6 h for bacterial susceptible to ceftriaxone with an MIC of 0.5 µg.ml^{-1} However in endometric cows, in order to maintain a minimum therapeutic plasma concentration of 0.5 µg.ml^{-1}, an appropriate intramuscular dosage regimen of ceftriaxone in endometritic cows was 13.2 mg.kg^{-1} followed by 12.6 mg.kg^{-1} at 6 h intervals.

DISCUSSION

Disposition of ceftriaxone has also been reported to follow a one-compartment open model in camels, goats and ewes (3, 11, 12, 13). The peak plasma level of the drug in healthy cows was approximately 22 fold higher than the MIC of ceftriaxone, however a lower peak plasma level was attained at the same time in endometritic cows. The plasma level of ≥ 0.2 µg.ml^{-1} for third generation cephalosporins is considered adequate against most species of sensitive bacteria including *Enterobacteriaceae* spp. (20). However, a plasma concentration of 0.25-2.0 µg.ml^{-1} has been reported as the minimum inhibitory concentration (MIC_{90}) for cephalosporins against common animal pathogens (21). MIC_{90} of ceftriaxone against various species of bacteria lies in the range of 0.01-0.50 ug.ml^{-1} (2). In this discussion, the higher value of MIC (0.5 µg.ml^{-1}) has been taken into consideration.

The values of various pharmacokinetic variables of ceftriaxone obtained following intramuscular injection in the

present study were distinct from their corresponding values reported in different species of domestic animals (Table 3).

The significantly (P<0.05) large Vd_{area} in endometritic cows (1.35 ± 0.19 $L.kg^{-1}$) in comparison to that in healthy animals (0.67 ± 0.13 $L.kg^{-1}$) indicated greater distribution of the drug during endometritis. In agreement to the present results, an increase in Vd_{area} of ceftriaxone was also noted following intravenous injection in endometritic cows (15). The observed increase in the apparent volume of distribution could be attributed to the increased perfusion of the uterine endometrium during the inflammatory condition.

The significantly (P<0.01) lower AUC of ceftriaxone in endometritic cows (12.4 ± 0.56 $\mu g.ml^{-1}.h$) in comparison to its corresponding value in healthy cows (21.3 ± 0.86 $\mu g.ml^{-1}.h$), following intramuscular administration, in this study, is in agreement with the decrease in AUC from 62.2 ± 23.3 to 37.0 ± 17.1 $\mu g.ml^{-1}.h$ observed during endometritis after intravenous injection of the same dose of ceftriaxone in cows (15). The significant (P<0.01) decrease in C_{max} (from 11.2 ± 0.33 $\mu g.ml^{-1}$ to 4.68 ± 0.26 $\mu g.ml^{-1}$) and AUC of ceftriaxone during endometritis may possibly be due to the inflammatory condition where more blood flow is diverted to the uterine endometrium and hence reduced vascularity at the intramuscular site of administration of the drug.

The elimination half-life (1.69 ± 0.47 h) and MRT (2.55 ± 0.31 h) of ceftriaxone in endometritic cows was longer than the $t_{½\beta}$ (1.42 ± 0.13 h) and MRT (2.27 ± 0.15 h) in healthy cows, although not statistically significant this possibly reflects a slower elimination of the drug during endometritis. Consistent with the present observation, prolongation in elimination half-life from 1.02 ± 0.07 h to 1.56 ± 0.25 h and MRT from 1.55 ± 0.25 h to 2.14 ± 0.34 h was seen after intravenous injection of ceftriaxone in endometric cows in comparison to healthy animals (15).

Total body clearance of ceftriaxone, which represents the sum of metabolic and excretory processes was 0.33 ± 0.11 $L.kg^{-1}.h^{-1}$ in healthy cows and 0.56 ± 0.14 $L.kg^{-1}.h^{-1}$ in endometritic cows, and statistically similar for both groups. A similar difference in Cl_B after intravenous injection from 0.3 ± 0.09 $L.kg^{-1}.h^{-1}$ to 0.56± 0.14 $L.kg^{-1}.h^{-1}$ was observed of the same dose of ceftriaxone during endometritis in cows (15).

High levels of ceftriaxone were attained in the milk of both healthy and endometric cows up to 36 h of administration. Lower concentration of the drug was recovered in the milk of endometritic cows as compared to that of healthy cows throughout the milking period with significant (P<0.01) differences at 24 h. No drug could be detected in milk of both healthy and endometritic cows after 48 h of dosing. A similar trend was noted in the concentration of ceftriaxone after intravenous administration where higher drug levels were recovered in milk of endometritic cows than that of healthy cows throughout the milking period (15). In contrast, lower concentration of ceftriaxone (0.19 $\mu g.ml^{-1}$) has been reported at 12 h following intramuscular dose of 10 $mg.kg^{-1}$ in ewes (3).

The pharmacokinetic data was used to determine an appropriate intramuscular dosage regimen of ceftriaxone for cows suffering from endometritis. Taking 6 h as a dosage interval (τ), with a minimum therapeutic plasma level (Cp_{min}^{μ}) of 0.5 $\mu g.ml^{-1}$ and using the values of β and Vd_{area} of endometritic cows from Table 2, a suitable intramuscular dosage regimen for ceftriaxone, would be 13 $mg.kg^{-1}$ repeated at 6 h intervals for the treatment of endometritis in cows. This dose was higher than the intravenous dose of 9 $mg.kg^{-1}$ at 6 h

Table 3: Pharmacokinetics of ceftriaxone in different species of animals in relation to these variables in healthy and endometritic cows.

Species	C_{max} ($\mu g.ml^{-1}$)	t_{max} (h)	Ka (h^{-1})	Vd_{area} ($L.kg^{-1}$)	AUC ($\mu g.ml^{-1}.h$)	$t_{½\beta}$ (h)	MRT (h)	Reference
Healthy cows	11.2	0.5	3.88	0.67	21.3	1.42	2.27	Present finding
Endometritic cows	4.68	0.5	3.16	1.35	12.4	1.69	2.55	
Calves	-	-	-	1.91	32.6	1.94	-	2,22
Buffalo calves	15.8	0.5	15.1		40.0	4.38, 4.96	2.63	9,10,23
Camels	21.5	1.03	2.39	-	91.9		2.96	13
Ewes	23.2	0.75	2.15	-	77.0	1.77	3.02	3
Goats	-	-	4.12	-	52.9, 77.5	0.98, 1.44, 2.03	2.76, 1.65	4, 11, 12
Dogs	-	-	-	-	-	1.17	-	14

C_{max} and t_{max} = peak plasma drug concentration and time required to attain the peak concentration, respectively; Ka = absorption rate constant; $t_{½\beta}$= elimination half-life; AUC = area under the plasma concentration-time curve; Vd_{area} = apparent volume of distribution; MRT = mean residence time.

intervals suggested for endometritis in cows (15). Lack of any significant adverse effect, rapid absorption and high value of Vd (area) revealed that in the treatment of mild to moderate bacterial infections, IM administration of ceftriaxone may be recommended for efficacy.

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