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Research Article

Effect of Ceftriaxone after Single Intramuscular Administration in Endometritis Cow

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ABSTRACT

Pharmacokinetics and distribution of Ceftriaxone in various biological fluids were undertaken post I.M. dose (10mg.kg^{-1}) in Endometritic cows. Peak concentration of 27.05 ±1.03 and 132.86 ±2.62 µg.ml^{-1} were attained up to 2 and 6 hrs in plasma and uterine fluid, respectively. The therapeutic concentration (µg.ml^{-1}) were maintained up to 12 and 48 hrs, respectively in plasma and uterine fluid. Distribution half life ($t_{1/2}$ α) and elimination half life ($t_{1/2}$ β) of 0.83± 0.01and 2.05 ±0.10hrs were noted in the present study. Vd $_{area}$ of 0.26 ±0.01L.kg^{-1} obtained for Ceftriaxone in Endometritic denoted its wide distribution in the body. The present investigation suggested a loading dose (D) of 10 mg.kg^{-1} followed by a maintenance dose (Do) of 11.33 mg.kg^{-1} at the dosage interval (y) of 26 hrs for maintaining therapeutic concentration (MIC) of 0.38 µg.ml^{-1}*

Key words: *Dairy industry, Endometritis, Diseases, Bovine Reproductive organs*

INTRODUCTION

Dairy industry is expanding vastly now a day due to high production of milk. The economic viability of any herd mainly depends upon normal reproduction in farm animals. Diseases of bovine reproductive organs cause infertility, which ultimately leads to substantial economic losses to the dairy cattle industry. The incidence of bovine endometritis varies from 15 to 57 %, and the variability mainly depends on sanitation practiced during per partum and immediate postpartum period. Therefore to achieve the desired clinical response & successful treatment of genital infections, a suitable dosage of a drug generally must be administered by an appropriate route. The Ceftriaxone sodium is a third generation cephalosporin, having a broad-spectrum activity, low toxicity, and resistant against a wide range of β- lactamases induced in the bacterial population. Its disposition kinetic and efficacy has been evaluated to determine therapeutic plasma and uterine fluid concentrations after intramuscular administration in animals.

The experiments were performed in six Endometritic cows of 4-6 years of age 2 to 3 parity and average weight 350-450 kg.

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The animals were housed in the departmental shed which had a concrete floor and were provided green fodder and water *ad libitum*. Each animal was quarantined for two week before the start of the experiment and collected uterine soabs for bacterial examination before and after treatment of endometritic cows . Ceftriaxone sodium (10 mg/kg) as a 10% solution with sterilized, distilled water was injected into the jugular vein of these six animals. Blood samples (4-5 ml) each were withdrawn from the contra lateral jugular vein into heparinised glass test tubes at 0, 10, 20, 30, 45 minutes, 1, 2, 4, 6, 8, 12, 24 hrs and uterine fluid at 0, 15, 30, minutes , 1, 2, 3, 6, 8, 12, 24, 36, 48, & 72 hrs after administration of the drug. Plasma and uterine fluid were collected after centrifugation at 2000 rpm for 15 minutes at room temperature and kept at -20^0 C until analysis, usually the next day / same day. The animals were kept in standard stall, which were designed so that all the uterine fluid passed by the animals was collected in a test tube without contamination or spillage.

The level of Ceftriaxone sodium concentration in all the experimental sample of blood plasma and uterine fluid collected at graded time interval were estimated by spectrophotometer method as described by Sar *et al*.[17], on using computer based double bean U.V. spectrophotometer. Concentration of Ceftriaxone was then calculated from standard curve already prepared earlier and expressed as µg/ml. The different pharmacokinetic parameter data was analysis by computer programming (Pharmkit).

RESULTS AND DISCUSSIONS

The present study on endometritis deals with the isolation of etiological agents, their antibacterial susceptibility test as well as disposition studies of the important antimicrobial agent namely Ceftriaxone sodium in plasma and uterine fluid. Based on the above noted studies treatments were carried out with Ceftriaxone by intramuscular (I.M) routes. Efficacy of the treatment was judged on the basis of bacteriological report and conception rates. Further, on the basis of disposition kinetic of Ceftriaxone, the doses regimen was also calculated. The estrual discharge of all the endometritic cows was mucopurulent in nature which became clear in all the cases after treatment with Ceftriaxone. The result was in agreement with the finding of Saini *et al*.[16], & Deari *et al*.[9]. Shaktaval *et al*., also stated that most of the cows with endometritis gave purulent discharge before treatment.

Before treatment the uterine discharges of all the endometritic cows were positive to white side test. The uterine discharge of endometritic cows remain rich in leukocyte & cellular debris to give colour reaction to the white site test. The bacterial load was recorded to be 247.66 x 10^6 /ml which ranged from 190 to 301 X10^6 /ml in the uterine discharge of endometritic cows. The values were in accordance with the finding of Deori *et al*.[9], The mean bacterial colonies counts decreased to the minimum at 6 hours (5.33± 0.66 X 10^6 / ml) after I.M. administration of drug and again increased gradually reaching to 81.16 ± 1.24 X10^6 / ml of uterine fluid after I.M. of drug at 72 hours. The difference in bacterial activity might be due to the action of Ceftriaxone which inhibited the bacterial organism in the uterus. The difference in bacterial activity might be due to the action of Ceftriaxone which inhibited the bacterial organism in the uterus. The above observation of the study was in agreement with finding of Black *et al*.[7], and Hawk *et al*., Whereas at the lower concentration of Ceftriaxone or below of MIC levels (0.38 µg/ml) in uterine fluid, the bacterial colonies gradually increased in the uterine discharge of Endometritic animals. Ceftriaxone is a third generation semisenthetic broad spectrum bactericidal cephalosporin which is effective against a wide Variety of gram positive and gram negative microorganisms.

Following I.M. administration of Ceftriaxone the mean peak serum levels of drug (27.2 05± 1.03 µg/ml) was attained at 2 hour & the drug was detectable up to 12 hour.

The therapeutic level of the drug was maintained in plasma between 10 minutes to 12 hour. The $t_{½}$ half life of the drug in plasma after I.M .administration was recorded as 2.05 ± 0.10 hour. Johal and Srivastava[12] also recorded mean plasma concentration of Ceftriaxone (18.8 ± 0.68 µg/ml) at 30 minutes after I.M. administration of drug in cross bred calves. The drug was detected up to 10 hour. Rebuelto *et al.*[14], observed the peak serum concentration of Ceftriaxone as 115.10 ± 10.96 µg/ml when ejected intramuscularly to dogs. Ringger *et al.*[15], administered Ceftriaxone in horses through intravenously route at a dose of 50 mg/kg body weight and recorded that the CP_{max} was 144.7µg/ml at 15 minutes, where as when the route of administration was intramuscularly , Albarellos *et al.*[2], estimated peak serum level of Ceftriaxone as 54.40 ± 12.92µg/ml in cat. Thus it can be concluded from the fore going literature that, in addition to dose and route of administration the physiological status of the animals is capable of modifying the plasma profile of Ceftriaxone. Following I.M. injection of Ceftriaxone, the drug appeared in uterine fluid at 15 minutes post drug administration and the peak level was attained at 6 hour (132.86 ± 2.62µg/ml). The therapeutic levels of the fluid between 15 minutes to 48 hours. Al-guedaway *et al.*[1], studied the distribution of gentamycin between plasma and uterine content following I.M. administration and noted that gentamycin was rapidly absorbed from the site and it first appeared in uterine lumen as early as 15 minutes and peak uterine concentration was achieved at 6 hours. Bhatt[6] also detected gentamycin in healthy and diseased uterine tissue after I.M. administration in higher doses. Ayliffe and Noakes[5] noted the peak level of Benzyl penicillin at 15 & 60 minutes in plasma and endometrium , respectively following I.M. administration of the drug in cows . According to them the drug persisted at a higher level and for a longer period of time in uterine tissue than in serum. High endometrial ampicillin concentrations immediately after systemic administration have been reported[4]. Haddad *et al.*[10], studied the endometrial tissue concentration of gentamycin after single I.M. injection @ 5 mg/kg body weight and observed the levels to range from 17.54 to 56.11µg/g of tissue . Jayachandran *et al.*[11], studied distribution of streptomycin in uterine fluid of buffaloes after I.M. injection of streptomycin (10 mg/kg) and observed that the drug was detectable up to 12 hours in uterine fluid . They also noted that the endometrial concentration exceeded the MIC for most Gram positive & Gram negative organisms, and aerobes frequently isolated from mares with endometritis. Bretzlaff[8] also opined that concentrations of most antibiotics are greater & more homogenously distributed in genital tract tissue after systemic injection than after intrauterine administration. The present study revealed that significant decrease in plasma drug concentration while significant increase in uterine fluid level at most of the time interval following drug administration were noted in cases of cows suffering from endometritis . The higher concentration of the drug in endometritis may be due to increase in permeability of the drug caused by inflammatory changes of the uterine membrane. It is well known that inflammation of any tissue may increase the size of the pores of the tissue membranes[13]. Such increase was noted by Ames *et al.*[3], also. There is also some evidence that antibiotics have a high affinity for inflammatory exudates when administered parenterally, which in cows might ensure high tissue levels in the endometrium during uterine infections .

The efficacy of treatment with a bacteriostatic antibiotic requires the persistence of sufficient concentration in the genital tract for a sufficient time to allow the elimination of pathogens from the uterine environment. In this study, Ceftriaxone concentration in uterine fluid remained above MIC level for more than 24 hours following I.M. administration. This study indicated that after systemic administration to endometritic cows, Ceftriaxone was rapidly found in genital tract secretions at concentration, which were sufficiently high and persistent to suggest its clinical evolution in the treatment of

endometritis in cows. It seems reasonable to conclude that systemic, rather than I.U. treatment would achieve adequate concentration of Ceftriaxone in blood serum and endometrial tissue, which would be necessary in instance of severe septic metritis. Also, systemic administration is easier and eliminates the risk of damage to the genital tract & of introducing new microorganisms into the site of infection.

Table 1. Plasma concentrations (µg/ml) of Ceftriaxone Sodium in endometritic Cows after single dose I.M. administration @ 10 mg/ kg, b.wt.

Time intervals(hr)	No. of Animals						Mean ± S.E.
	1	2	3	4	5	6	
0.166	0.05	1.10	1.00	0.08	0.07	1.00	0.55± 0.21
0.333	1.15	1.50	1.55	1.55	1.15	1.60	1.42 ± 0.08
0.500	4.50	4.55	3.95	4.60	4.75	4.80	4.52 ± 0.12
0.750	8.10	8.00	8.15	8.15	10.00	9.50	8.65± 0.35
1.00	11.50	10.85	15.00	15.10	14.50	14.25	13.53± 0.76
2.00	24.50	23.25	29.10	28.00	28.30	29.15	27.05± 1.03
4.00	15.10	16.75	16.20	15.50	16.25	16.50	16.05 ± 0.25
6.00	7.50	7.05	7.30	8.75	7.00	8.25	7.65 ± 0.28
8.00	3.15	3.00	2.90	3.50	3.45	3.35	3.22 ± 0.10
12.00	0.85	0.90	0.75	0.70	0.75	0.08	0.67 ± 0.03
24.00	BDL	BDL	BDL	BDL	BDL	BDL	BDL

Table 2. Uterine fluid concentration (µg/ml) of ceftriaxone sodium in endometritic cows (n=6) after single dose I.M. administration @ 10 mg/kg, b.wt.

Time intervals(hr)	No. Of Animals						Mean ± S.E.
	1	2	3	4	5	6	
0.250	1.80	1.75	3.00	3.25	1.80	3.00	2.43 ± 0.29
0.50	4.50	4.50	6.75	5.15	4.50	6.00	5.23 ± 0.38
1.00	21.00	21.00	18.75	22.50	18.75	22.25	20.70 ± 0.66
2.00	48.45	48.80	48.15	48.75	48.85	49.00	48.71 ± 0.11
6.00	126.45	129.25	144.00	136.50	129.00	132.00	132.86 ± 2.62
8.00	112.50	114.00	114.50	113.95	114.00	112.75	113.61± 0.32
12.00	54.50	52.50	51.00	52.50	54.25	46.50	51.87± 1.19
24.00	37.20	37.50	37.30	37.75	37.25	37.50	37.41 ± 0.08
36.00	24.00	24.50	23.75	23.50	24.25	24.50	24.08 ± 0.16
48.00	6.00	6.15	5.25	5.55	6.00	6.15	5.85 ± 0.15
72.00	0.08	0.07	0.03	0.07	0.04	0.05	0.06 ± 0.007

Table 3. Pharmacokinetic profile of Ceftriaxone sodium in plasma and uterine fluid after single dose I.M. (10 mg/kg. b. wt.) administration in Endometritic cows

Kinetic Parameter	**Mean ± S.E.** (N=6, Plasma)	**Mean ± S.E.** (N=6, Uterine fluid)
A (µg/ml)	49.74 ± 5.71	402.29±20.14
B (µg/ml)	49.73 ± 5.70	402.20±20.14
C^oP (µg/ml)	99.48 ±11.42	804.501±40.30
α (h^{-1})	0.82 ± 0.01	0.27± 0.01
β (h^{-1})	0.33± 0.01	0.10 ± 0.002
$t_{½}$ α (h)	0.83 ± 0.01	2.55 ± 0.12
$t_{½}$ β (h)	2.05 ± 0.10	6.36 ± 0.10
AUC (mg/L.L)	111.09 ±2.47	2137 ± 7.20
MRT	3.91± 0.05	17.15 ± 0.09
Cl_B ml/kg/hr.	1.47 ± 0.03	0.08 ± 0.00
Vd_{area} (L)	0.26 ± 0.01	0.04± 0.001
K_{21} (h^{-1})	0.57± 0.008	0.18 ± 0.004
K_2 (h^{-1})	0.47 ± 0.01	0.15 ± 0.001
K_{12} (h^{-1})	0.11 ± 0.01	0.04 ± 0.005
T/P	0.45 ± 0.02	0.55 ± 0.03
FC	0.69 ± 0.01	0.68 ±0.01
CP_{max}(µg/ml)/ Cu_{max}(µg/ml)	27.05 ± 1.03	132.86 ± 2.62

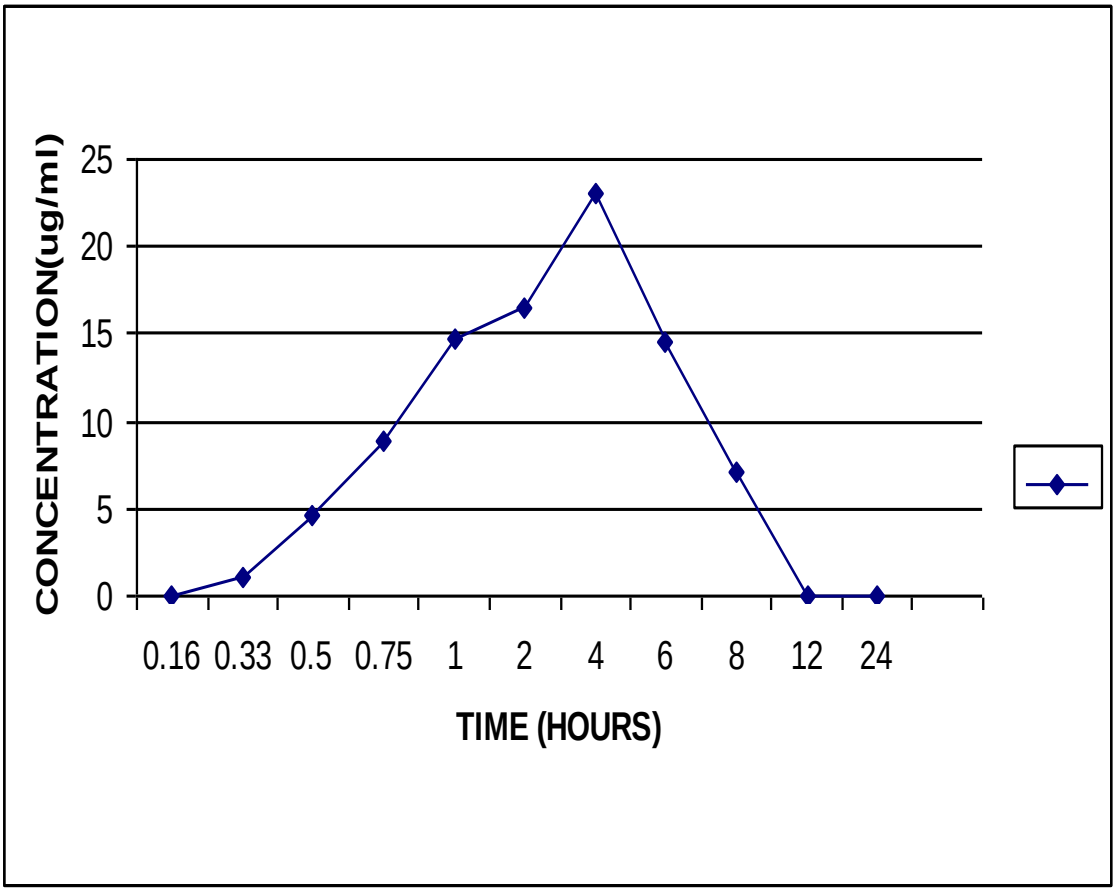

Fig. 1. Semi logarithmic plot of line and the mean plasma Ceftriaxone concentration Vs time in endometritic cows after single dose (10mg/kg) I.M. administration

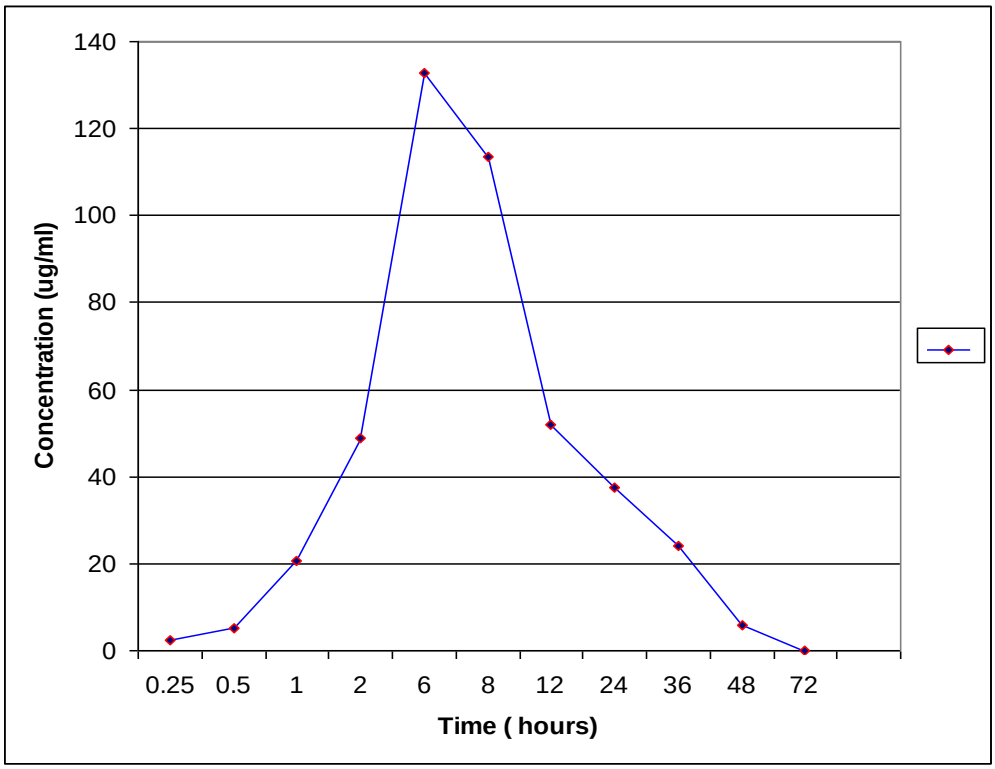

Fig. 2. Semi logarithmic plot of line and the mean uterine fluid Ceftriaxone concentration Vs time in endometritic cows after single dose (10mg/kg) I.M. administration

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