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PHARMACOKINETICS OF CEFTRIAXONE IN NORMAL AND SALMONELLA TYPHIMURIM INFECTED GOATS

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ABSTRACT

The pharmacokinetic parameters of ceftriaxone in blood, urine and milk following intravenous and intramuscular (single & repeated) administrations were estimated in normal and experimentally Salmonella typhimurum infected goats. Following a single intravenous injection of 20 mg ceftriaxone/kg b.wt. in normal goats, ceftriaxone could be detected therapeutically for 8 hours post intravenous injection. The serum concentration – time curve of ceftriaxone following intravenous injection showed that the drug obeyed a two compartments open model. The intramuscular bioavailability of ceftriaxone in normal goats was 61.28%. Intramuscular injection of 20 mg ceftriaxone per kilogram body weight twice daily for five consecutive days in normal and Salmonella typhimurium infected goats revealed a lower significant serum ceftriaxone concentration after the first, third, fifth, seventh, ninth doses in Salmonella typhimurium infected goats compared with normal goats.. The high milk concentrations of ceftriaxone in lactating goats after repeated intramuscular administrations, suggested that ceftriaxone could be used for treatment of mastitis caused by Salmonella typhimurium and other sensitive microorganisms to ceftriaxone in lactating goats. The high concentrations of ceftriaxone in urine after repeated intramuscular administrations, suggested that ceftriaxone is a suitable antimicrobial for treatment of urinary tract infections caused by Salmonella typhimurium and other sensitive microorganisms to ceftriaxone in goats.

KEYWORDS: Pharmacokinetics, ceftriaxone, goats.

INTRODUCTION

Ceftriaxone is a third-generation semi-synthetic bactericidal cephalosporin antibiotic, resistant to various types of bacterial β-lactamases. It has excellent activity against gram negative bacteria as well as a wide range of gram-positive and some anaerobic bacteria, including enterobacteriaceae, Streptococcus pneumoniae, Haemophilus inflfl uenzae, Pseudomonas aeruginosa and other non-enterococcal streptococci.[1,2,3] Like other cephalosporin, ceftriaxone bind to the penicillin-binding proteins (PBP) by covalent bond and inactivate transpeptidase enzymes, thereby inhibiting the peptidoglycan synthesis leading to inhibition of the cell wall synthesis.[4] It has rapid absorption and wide distribution in tissues as well as body fluids, after parenteral administration in animals.[5] The drug thus seems to be useful in the treatment of a variety of bacterial infections, including meningitis, septicemia, pyoderma, colibacillosis, surgical prophylaxis and urinary tract, respiratory tract, wound, soft tissue and joint infections.[2]

Clinical pharmacology of ceftriaxone was investigated in human,[6] sheep,[7,8] goats,[9,10,11] buffulo calves,[12,13] calves,[14] domestic cats,[15] cross bred cow calves.[16] Little literature was found concerning the pharmacokinetics of ceftriaxone in goats. Thus, the aim of present work was undertaken to study the pharmacokinetic parameters of ceftriaxone after intravenous and intramuscular injection in normal and experimentally Salmonella typhimurium infected goats, also the bioavailability of ceftriaxone was calculated after a single intramuscular injection in normal goats.

MATERIAL AND METHODS

Drug

Ceftriaxone is a member of third generation cephalosporins, ceftriaxone sodium was used in this study under the trade name **(Cefaxone®).** It is available as glass vial containing 1000 mg ceftriaxone. it was produced by **Pharco** company**,** Egypt**.**

Experimental animals

Four clinically normal lactating baladi four experimentally infected goats and lactating goats were used for each drug in this investigation. The body weight and age of the tested goats ranged from 20-26 kg and from 2 to 3 years old (for normal goats) and from 22 – 29 kg and from 2.5 to 3.5 years old for experimentally infected goats. They were housed in hygienic stable fed on barseem, drawa and concentrate. Water was provided ad-libitum.

Grouping of goats

Group (1)

It included 4 normal post-partum lactating goats. Each goat was injected intravenously into the left jugular vein ceftriaxone. These goats were left for 15 days after the intravenous injection to insure complete excretion of ceftriaxone from bodies of goats. Then each goat was injected intramuscularly into the gluteus medius muscle with the same dose of ceftriaxone. The aim of intramuscular injection to calculate the bioavailability of ceftriaxone in normal goats.

Group (2)

It included 4 normal post-partum lactating goats. Each goat was injected intramuscularly into the gluteus medius muscle with 20 mg/kg b.wt. ceftriaxone for five consecutive days.

Group (3)

It included 4 experimentally infected post-partum lactating goats with twenty four hours peptone water culture of enterpathogen Salmonella typhimurium which were cultured on nutrient agar plates for 24 hours, then suspension of culture were collected by sterile saline. By opacity tube, the required concentration of $2X10^9$ micro-organisms/ml was obtained. Each of the four goats received orally a 10 ml suspension containing $2x10^9$ organism/ml. The clinical symptoms of bacteraemia; as fever and diarrhea appeared after 48-72 hours of injection with Salmonella typhimurium suspension.[17] Each goat was injected intramuscularly into the gluteus medius muscle with ceftriaxone per kilogram body weight, 48 hours after experimental infection with samlonella Typhmurium for five consecutive days**.**

Collection of samples

Blood samples

Blood samples were collected from right jugular vein following a single intravenous injection of ceftriaxone in normal goats blood samples were collected after 5 min, 10 min,15 min, 30 min, 1, 2, 4, 8 and 12 hours of administration. Blood samples following the second, third, fourth and fifth intramuscular doses were collected before and 10 min, 15 min, 0.50, 1, 2, 4, 8 and 12 hours post injection. Blood samples taken from goats were allowed to clot and the serum separated by centrifugation, collected and divided in to two parts, the first part was used for assay of ceftriaxone and the second part was used for creatinine assay. All serum samples were stored at – 20°C until assay for ceftriaxone and creatinine.

Urine samples

The urine sample was taken by using rubber balloon catheter (Folatex No. 41.585.12). The goats were catheterized and bladder was evacuated before each experiment. Following injection of ceftriaxone (single intravenous, single intramuscular and repeated intramuscular administration) in goats (normal and experimentally infected), urine samples were taken after 0.25, 0.50, 1, 2, 4, 8, 12, 24 and 48 hours of administrations. Urine sample which was taken at 0.25 h was discarded. Urine samples from goats of group (1) group (2), group (3) were collected and divided into two parts: the first part was used for assay of ceftriaxone and the second part was used for creatinine assay. All urine samples were stored at - 20°C until assay for ceftriaxone. After the end of each experiment, the urinary bladder was irrigated with 15 milliliters potassium permanganate solution 1: 5000 as antiseptic agent.

Milk samples

The udder was completely evacuated before drug administration and milk samples were collected by hand stripping from both teats. Following injection of ceftriaxone (single intravenous, single intramuscular and repeated intramuscular administration) in goats (normal and experimentally infected), milk samples were taken after 0.50, 1, 2, 4, 8, 12, 24 and 48 hours of administrations. Milk sample which was taken at 0.25 h was discarded The udder of each goat in all groups was completely evacuated before drug administration and after each milk samples. Milk samples from goats of all groups were allowed to clot (by mixing equal volumes of milk and 25% trichloroacetic acid) and centrifuged. The skim milk was collected and stored at – 20°C until assay for ceftriaxone.

Analytical Procedure

Assay of ceftriaxone

Ceftriaxone was assayed in goats serum, distalled water and goats milk by microbiological method using agar well diffusion method by using of **Escherichia coli ATCC** (American type culture collection 25922) as tested microorganism, which was obtained from Microbiological Department, Animal Health Institute, Doky, Giza, Egypt.).[18] Concentrations of ceftriaxone in biological fluids were determined by modification of the agar – plate diffusion method[19] using Escherichia coli ATCC25922 as assay organism and Muller Hinton agar media.

Assay of samples

According to,[20] three plates were used for each sample. Six pores were made, three of them were filled with reference concentration while the other three pores were filled with the serum, milk or urine samples in triplicate manner. The plates were incubated at 37°C for 18 hours then the diameter of inhibitory zones were measured. The diameter of inhibitory zones of samples were corrected by using the zone diameter of the reference concentration in the same manner as previously discussed either by addition or subtraction. From the standard curve the concentrations corresponding to the corrected values of the inhibitory zones were obtained.

Drug clearance

Clearance of the tested drug from the blood of goats was estimated according to the following equation.

$$\text{Drug clearance/10 kg. b. wt.} = \frac{\text{Drug concentration in urine (µg/ml) X rate of diuresis (ml/min) Body weight (Kg)}}{\text{Drug concentration in serum (µg/ml) } \mathbf{X} \text{ 10}}$$

Assay of creatinine in serum and urine

Creatinine was assayed by[21] and performed by kit manufactured by Diamond diagnostics company.

Creatinine clearance

The creatinine clearance (ml/min./10 kg.b.w.t) for goats was calculated by the following equation.

$$\text{Creatinine clearance /10 kg.b.w.t} = \frac{\text{Creatinine concentration in urine (mg/L) X rate of diuresis (ml/min) Body weight (Kg)}}{\text{Creatinine concentration in serum (mg/L) } \mathbf{X} \text{ 10}}$$

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated by using Winonlin, version 1.2 and other parameters according to.[22,23]

Statistical Analysis

The data were calculated as mean ± standard error. All statistical analysis were carried out according to[24] using the scientific calculator CASIO fx 120.

RESULTS

Following a single intravenous injection of 20 mg ceftriaxone/kg b.wt. in normal goats, ceftriaxone could be detected therapeutically for 8 hours post intravenous injection. The serum concentration – time curve of ceftriaxone following intravenous injection showed that the drug obeyed a two compartments open model (Figure 1). The disposition kinetics of ceftriaxone following a single intravenous, intramuscular injection were recorded in table (1).

Intramuscular injection of 20 mg ceftriaxone per kilogram body weight twice daily for five consecutive days in normal and Salmonella typhimurium infected goats revealed a lower significant serum ceftriaxone concentration after the first, third, fifth, seventh, ninth doses in Salmonella typhimurium infected goats compared with normal goats. The pharmacokinetic parameters of ceftriaxone after repeated intramuscular injection in normal were compared to those in Salmonella typhimurium infected goats (Table 2) and (Figure 2 & 3).

The highest concentrations of ceftriaxone in milk were recorded 4 hours after each intramuscular dose (Table 3) with a significant lower value in Salmonella typhimurium infected goats compared with normal goats. The calculated milk/serum concentrations ratios of ceftriaxone after repeated intramuscular injection (Table 4).

The amount of urine (ml/min) voided after repeated intramuscular injection of 20 mg/kg bwt. Twice daily of ceftriaxone for five consecutive days in normal and experimentally Salmonella typhimurium infected goats were recorded in table (5). The mean peak urine concentrations of ceftriaxone (Table 6) were reached 2 hours after each intramuscular dose with a lower significant concentration in Salmonella typhimurium infected goats compared with normal goats. Urine/serum concentration ratios of ceftriaxone after repeated intramuscular injection in normal and experimentally Salmonella typhimurium infected goats were calculated and illustrated in table (7). Creatinine clearance (ml/min/10 kg bwt.) expressing glomerular filtration rate from blood of goats was shown in table (8). The rate of ceftriaxone clearance (ml/min/10 kg bwt.) from blood of goats was shown in table (9). The ratio between ceftriaxone clearance and creatinine clearance was calculated and illustrated in

table (10). The data revealed a significant lower ratio in Salmonella typhimurium infected goats compared with normal goats after the third, fifth, seventh, ninth doses.

Table (1): Pharmacokinetics parameters of ceftriaxone (µg/ml) following a single intravenous and intramuscuer injection of 20 mg/kg b.wt in normal goats (n=4).

Parameters	Unit	Intravenous_ (X±S. E.)	Intramusculer_ (X±S. E.)
C°	µg/ml	**123.23**±1.213	--------
A	µg/ml	**1.54± 69.84**	**92.01±0.654**
α	h^{-1}	**0.196± 6.65**	**0.667±0.007**
$T_{0.5\ (\alpha)}$	H	**0.002± 0.104**	**1.04±0.011**
K_{12}	h^{-1}	**3.53±0.151**	**0.211±0.027**
K_{21}	h^{-1}	**2.95±0.048**	**0.074±0.006**
V_{dss}	l/kg	**0.355±0.004**	--------
B	µg/ml	**53.41±0.616**	**56.07±0.295**
β	h^{-1}	**0.316±0.001**	**0.038±0.0006**
$(t_{0.5(\beta)}$	H	**5.19±0.099**	**18.04±0.303**
Cl_{tot}	l/kg/h	**0.048±0.0007**	**0.043±0.005**
AUMC	µg/ml/h	**2999.74±93.6**	--------
MRT	H	**7.30± 0.141**	--------
AUC	µg/ml/h	**410.145±5.54**	**250.8±8.47**
F	**%**	--------	**61.28±1.82**
K_{01}	h^{-1}	--------	**0.653±0.016**
$(T_{0.5(k01}$	h^{-1}	--------	**1.06±0.027**
$(T_{max}$(calc)	H	--------	**1.57±0.025**
$(C_{max}$(calc	µg/ml	--------	**40.015±0.429**

C $^{\circ}$Drug concentration in the serum at zero time immediately after a single intravenous injection (µg/ml). **A & B**: Zero time plasma drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (µg/ml). **α & β**: Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h^{-1}). **T0.5 (α)**: Distribution half – life (h). **t0.5 (β)**: Elimination half – life (h). **K12**: First – order transfer rate constant for drug distribution from Central to peripheral compartment (h^{-1}). **K21**: First order transfer rate constant for drug distribution from Peripheral to central compartment (h^{-1}). **V_{dss}:** The apparent volume of distribution which was calculated by steady – state method (ml/kg). **AUMC:** Area under moment curve. **MRT:** Mean residence time. **AUC:** Total area under the serum drug concentration versus time curve from t = 0 to t = α after administration of a single dose. **F**: Bioavailability. **Cmax:** maximum drug concentration; **Tmax:** time of maximum observed concentration in blood.

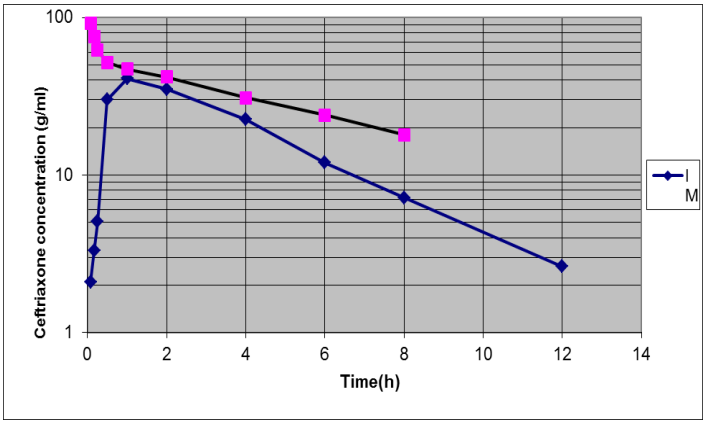

Figure (1): Arthimatic plot of Serum concentrations of ceftriaxone (µg/ml) in normal goats following a single intramuscular injection (♦—♦) previously given the same doseby a single intravenous injection (■—■) of 20 mg ceftriaxone/kg.b.wt (n=4).

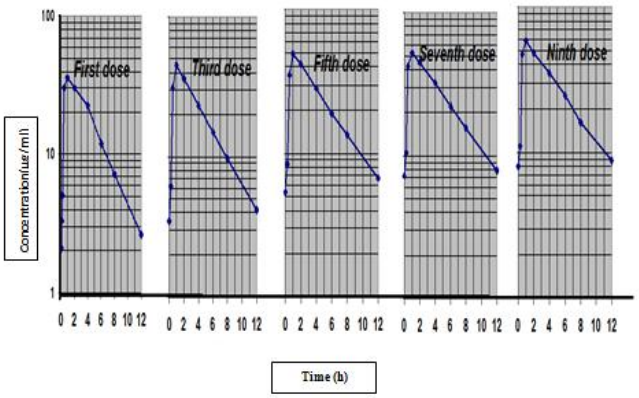

Figure (2): Semilogarthmic graph depicting the time course of ceftriaxone in serum of normal goats following repeated ntramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days. (n=4).

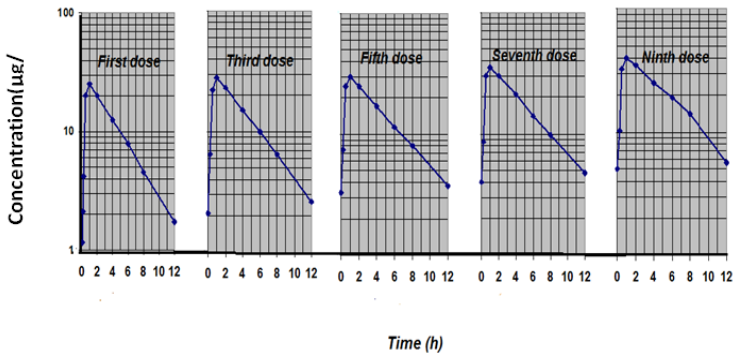

Figure (3): Semilogarthmic graph depicting the time course of ceftriaxone in serum of experimentally Salmonella typhimurim infected goats following repeated ntramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days. (n=4).

Table (2): Pharmacokinetic parameters of ceftriaxone (µg/ml) in normal and experimentally Salmonella typhimurim infected goats following repeated ntramuscular injection of 20 mg ceftriaxone /kg.b.wt. twice dialy for five consecutive days. (n=4).

Parameters	Unit عبه	Dose									
		First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
		N	S	N	S	N	S	N	S	N	S
A	g/mlµ	76.35±1.76	14.24±0.172***	54.30±1.25	14.61±0.214***	59.23±1.26	14.10±0.243***	63.73±1.47	13.52±0.132***	74.09±1.21	12.69±0.073***
A	h^{-1}	1.33±0.033	0.786±0.028***	±0.0231.21	0.848±0.025***	±0.0261.22	0.823±0.006***	±0.0411.77	0.720±0.008***	±0.0080.396	0.651±0.049**
$T_{0.5(\alpha)}$	H	±0.0120.522	0.885±0.030***	0.569±0.012	0.818±0.024***	0.567±0.12	0.841±0.007	0.392±0.007	0.962±0.011***	1.75±0.015	1.06±0.008***
K_{ab}	h^{-1}	1.36±0.027	2.22±0.100***	1.22±0.026	2.48±0.060***	1.20±0.028	2.67±0.039***	1.81±0.033	2.03±0.075*	1.68±0.047	2.48±0.019***
$T_{0.5(ab)}$	H	0. 510±0.012	0.314±0.014***	0.0569±0.011	0.279±0.005***	0.567±0.011	0.252±0.009***	0.383±0.008	0.342±0.012*	0.412±0.009	0.278±0.002***
K_{12}	h^{-1}	0.239±0.005	0.116±0.003***	0.394±0.008	0.117±0.004***	0.424±0.009	0.113±0.0027***	0.402±0.008	0.430±0.008*	0.378±0.007	0.627±0.008***
K_{21}	h^{-1}	0.998±0.023	0.761±0.039**	0.660±0.013	0.683±0.020	0.651±0.013	0.666±0.019	1.30±0.023	1.41±0.021**	0.962±0.022	1.21±0.013***
T_{max}	H	1.23±0.023	0.910±0.032**	1.19±0.023	1.10±0.077	1.22±0.025	1.06±0.037*	1.12±0.024	1.04±0.047	1.29±0.026	1.15±0.035*
C_{max}	g/mlµ	40.65±0.825	24.79±0.547***	42.43±0. 870	27.13±0.781***	47.74±0.854	31.17±0.965***	51.35±0.860	34.40±0.363***	61.08±1.40	41.82±0.628***
B	g/mlµ	63.29±1.39	32.56±0.918***	47.09±0.990	31.85±0.909***	51.17±1.13	31.90±0.688***	65.11±1.30	41.99±0.702***	71.95±1.42	49.44±0.820***
β	h^{-1}	0.272±0.006	0.249±0.918	0.195±0.005	0.214±0.009	0.167±0.004	0.181±0.0035*	0.178±0.004	0.181±0.002	0.189±0.0043	0.164±0.003**
$T_{0.5\beta}$	H	2.55±0.050	2.77±0.056*	3.55±0.075	3.25±0.139	4.15±0.081	3.82±0.074*	3.88±0.089	3.81±0.047	3.67±0.086	4.23±0.079**
C_{ltot}	L/kg/h	0.693±0.014	1.71±0.060***	0.675±0.013	1.54±0.064***	0.503±0.011	1.33±0.022***	0.426±0.009	1.09±0.004***	0.429±0.009	0.879±0.015***
AUC	g/ml/hµ	202.92±4.87	121.75±1.44***	241.35±5.55	152.81±2.39***	307.05±6.01	178.60±1.55***	342.59±7.20	217.84±0.888***	407.75±8.08	283.58±2.15***

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

Table (3): Milk concentrations of ceftriaxone (µg/ml) in normal and experimentally Salmonella typhimurim infected goats following repeated ntramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days. (n=4).

Time of administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S	N	S	N	S	N	S	N	S
Before	------	----------	0.74±0.012	0.500±0.040	0.885±0.14	0.887±0.013	1.55±0.132	1.25±0.104*	2.00±0.408	1.97±0.205
0.50	--------	----------	1.55±0.132	1.00±0.00**	1.97±0.205	1.55±0.132	2.00±0.408	1.97±0.205	2.2±0.108	2.00±0.408
1	5.20±0.166	1.00±0.00***	5.82±0.118	1.55±0.132***	6.00±0.408	2.5±0.204***	6.4±0.163	3.00±0.408***	7.00±0.408	5.26±0.166***
2	6.91±0.176	2.00±0.408***	7.00±0.408	2.75±0.061***	7.55±0.221	5.82±0.118***	7.92±0.114	5.82±0.118***	9.00±0.408	6.40±0.163***
4	12.25±0.595	5.26±1.66***	13.52±0.205	6.00±0.408***	14.00±0.408	6.40±0.163***	14.75±0.322	6.40±0.163***	15.12±0.125	9.00±0.408***

6	2.75±0.061	1.55±0.132***	3.00±0.408	2.75±0.06	3.5±0.353	3.00±0.408	3.92±0.125	3.00±0.408	4.00±0.408	3.50±0.353
8	0.887±0.013	0.500±0.040***	1.00±0.00	0.825±0.062*	1.55±0.1	1.25±0.104	2.00±0.408	1.25±0.104	3.5±0.353	3.00 ±0.408
12	0.73±0.020	0.422±0.00***	0.825±0.078	0.730±0.02	1.25±0.104	1.00±0.00*	1.55±0.132	1.00±0.00***	2.2±0.108	2.00±0.408

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

Table (4): Milk/serum concentrations ratios of ceftriaxone in normal and experimentally Salmonella typhimurim infected goats following repeated intramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice daily for five consecutive days. (n=4).

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S	N	S	N	S	N	S	N	S
Before	…….	--------	0.205±0.002	0.232±0.016	0.16±0.026	0.365±0.0064***	0.21±0.019	0.307±0.026*	0.25±0.063	0.400±0.049
0.50	--------	---------	0.049±0.005	0.067±0.016	0.055±0.006	0.575±0.0062***	0.042±0.010	0.062±0.0062	0.042±0.0025	0.057±0.125
1	0.122±0.004	0.039±0.005***	0.126±0.028	0.08±0.017	0.122±0.008	0.088±0.0054***	0.117±0.004	0.08±0.012	0.115±0.0064	0.127±0.0062
2	0.19±0.004	0.097±0.020**	0.193±0.012	0.112±0.0025***	0.179±0.006	0.182±0.054*	0.17±0.004	0.21±0.004***	0.185±0.010	0.18±0.008***
4	0.54±0.027	0.415±0.017***	0.572±0.01	0.395±0.016***	0.494±0.015	0.285±0.082*	0.45±0.009	0.33±0.021***	0.425±0.005	0.357±0.020***
6	0.222±0.002	0.196±0.016	0.201±0.03	0.272±0.015	0.180±0.017	0.257±0.037	0.175±0.006	0.207±0.022	0.16±0.016	0.18±0.015
8	0.117±0.002	0.107±0.0094	0.102±0.001	0.122±0.0062*	0.14±0.022	0.152±0.011	0.122±0.024	0.200±0.044	0.212±0.020	0.212±0.033
12	0.275±0.009	0.252±0.032	0.195±0.012	0.272±0.125	0.185±0.015	0.265±0.0064**	0.192±0.014	0.325±0.027**	0.25±0.01	0.372±0.042*

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

Table (5): The amount of urine (ml/min) voided in normal and experimentally Salmonella typhimurim infected goats following repeated intramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days. (n=4).

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S S	N	S	N N	S	N	S	N	S
Before	--------	----------	1.08±0.008	1.08±0.013	1.18±0.067	1.18±0.066	1.30±0.028	1.30±0.030	1.26±0.034	±0.03725.00
0.50	0.272±0.014	0.287±0.017	0.33±0.012	0.340±0.024	0.33±0.012	0.312±0.02	±0.060.48	0.45±0.060	0.0800.57±	0.577±0.069
1	0.697±0.015	0.719±0.031	0.655±0.010	0.635±0.032	0.675± 0.009	0.672±0.011	0.697±0.006	0.68±0.081	0.692±0.014	0.712±0.019
2	0.762±0.041	0.737±0.027	0.702±0.018	0.722±0.019	0.715±0.02	0.715±0.011	±0.0050.74	0.732±0.011	0.787±0.021	0.837±0.025
4	0.38±0.01	0.380±0.004	0.397±0.009	0.400±0.057	0.405±0.011	0.402±0.075	0.452±0.02	0.447±0.022	0.507±0.021	0.535±0.095
6	0.365±0.006	0.350±0.005	0.37± 0.007	0.372±0.047	±0.0040.38	0.380±0.007	0.405±0.002	0.400±0.010	0.432±0.008	0.437±0.0094
8	0.335±0.005	0.302±0.004	0.345±0.005	0.340±0.004	0.352±0.007	0.355±0.086	0.395±0.009	0.380±0.012	0.410±0.008	0.397±0.028
12	0.362±0.016	0.327±0.006	0.372±0.106	0.362±0.086	0.367±0.004	0.365±0.064	0.380±0.008	0.385±0.0064	0.380±0.010	0.385±0.01

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

Table (6): Urine concentrations of ceftriaxone (µg/ml) in normal and experimentally Salmonella typhimurim infected goats following repeated intramuscular injection of 20 mg ceftriaxone /kg.b.wt. twice dialy for five consecutive days . (n=4)

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S	N	S	N	S	N	S	N	S
Before	------	----------	18.15±0.287	3.7±0.811***	55.5±7.98	18.3±0.3**	81±3.24	73.5±2.87***	112.5±1.5	112.5±1.50
0.50	168±5.47	10.2±1.60***	208.5±9.91	54.00±2.73***	241.5±3.57	105.75±6.4***	249±5.74	169.5±7.88**	262.5±3.74	241.5±3.57**
1	224.25±8.94	69.75±2.25***	241.5±3.57	102.00±5.47	270.5±4.71	169.5±6.18***	280.5±3.5	224.25±12.25**	292.3±4.79	260.25±7.87*
2	248.25±6.16	102±5.47***	264.5±9.17	163.5±5.61***	292.3±4.79	235.5±2.59***	296.4±4.15	285.75±7.38	301.2±.346	292.95±7.65
4	118.5±4.5	60±2.12***	151.5±7.08	84.75±3.09***	198±8.48	169.5±7.88	241.5±3.57	234.75±15.64	248.2±6.16	234.75±4.30
6	85.5±1.93	13.12±0.552***	121.5±4.5	66.75±3.09**	159±1.73	114±9.48***	193.5±9.60	153±5.19**	235.5±2.59	190.5±4.5***
8	50.25±1.43	9.07±0.951***	72±2.44	61.81±3.39*	136.5±6.65	73.5±2.95**	150±3.4	133.5±12.29	196.5±13.5	153±10.24*
12	13.125±0.552	3.735±0.458***	39±2.12	15.3±1.30***	75±1.73	52.5±2.95	96±8.74	117.25±15.51	120±3.46	135±5.19**

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

Table (7): Urine/serum concentrations ratios of ceftriaxone following repeated ntramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days in normal and experimentally Salmonella typhimurim infected goats (n=4).

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S S	N	S	N	S	N	S	N	S
Before	------	-------	4.146±1.16	1.75±0.380	10.50±1.58	5.33±0.260*	11.25±0.484	18.85±1.59**	14.48±0.743	22.9± 1.63***
0.50	5.59±0.181	0.510±0.081***	6.67±0.306	2.45±0.092**	6.83±0.106	4.22±0.206	±0.1495.87	5.8±0.242*	±0.1555.55	7.41±0.063***
1	5.34±0.248	2.79±0.121***	±0.1105.32	3.60±0.303***	±0.0855.47	5.65±0.243***	±0.1445.35	6.37±0.373	±0.0654.95	6.51±0.243***
2	±0.1687.04	5.08±0.186***	7.27±0.256	2.17±0.303***	±0.1306.95	9.42±0.166***	±0.1046.55	8.62±0.180***	±0.0476.22	8.36±0.150***
4	±0.1485.50	4.8±0.164*	6.41±0.241	5.65±0.223	±0.2857.00	9.99±0.542**	±0.0757.37	10.06±0.710**	±0.1587.00	9.39±0.235***
6	6.42±0.644	1.67±0.101***	±0.3628.1	6.19±0.483*	±0.2528.3	9.93±0.921	±0.3978.77	10.97±0.641*	2±0.1889.5	10.05±0.418**
8	±0.2046.97	2.055±0.311***	±0.2517.33	8.86±0.408*	±0.55910.1	9.25±0.593	9.95±0.415	11.71±0.980	±0.75312.18	10.91±0.649
12	±0.2744.96	2.27±0.452**	±0.3959.26	5.80±0.397***	±0.26711.16	14.18±1.09*	12.22±1.24	17.94±0.228***	±0.32713.86	23.92±1.29***

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

Table (8): Creatinine clearance (ml/min/10kg.b.wt) following repeated intramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days in normal and experimentally Salmonella typhimurim infected goats (n=4).

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S	N	S	N	S	N	S	N	S
Before	------	----------	17.24±1.79	6.95±0.634**	12.02±0.777	6.69±0.672**	6.72±0.817	4.81±0.409	22.65±1.67	11.15±0.703***
0.50	0.458±0.037	2.95±0.124***	1.03±0.106	0.802±0.099	0.699±0.092	0.547±0.055	2.51±0.707	0.718±0.141**	1.47±0.305	0.703±0.091*
1	1.03±0.166	2.14±0.234**	4.755±0.582	2.47±0.110**	3.73±0.499	1.61±0.146**	2.64±0.217	1.31±0.099**	1.61±0.093	1.01±0.075**
2	1.69±0.454	2.63±0.399	9.72±1.05	4.51±0.223**	2.87±0.499	1.87±0.563	2.67±0.217	1.73±0.501	3.87±0.340	1.57±0.198**

4	2.92±0.742	1.23±0.057	11.9±1.53	3.28±0.253**	6.82±0.584	3.83±0.299**	4.36±0.599	1.73±0.501*	3.46±0.444	1.84±0.095*
6	2.64±0.294	1.05±0.057**	5.48±0.901	3.53±0.393	4.22±0.314	3.08±0.234*	6.63±0.584	2.41±0.186***	4.11±0.661	2.21±0.242*
8	4.04±0.419	2.06±0.160**	4.56±0.340	2.28±0.175***	0.773±0.049	1.06±0.207	7.53±0.676	3.19±0.273***	4.76±0.339	2.61±0.295**
12	6.055±0.176	2.40±0.218***	3.77±0342	2.17±0.143**	2.35±0.337	2.09±0.189	6.69±0.476	32.64±0.153***	4.09±0.434	3.10±0.218

*Between normal and diseased.

*P< 0.05 **P<0.01 *** P<0.001.

Table (9): Ceftriaxone clearance (ml/min/10kg.b.wt following repeated intramuscular injection of 20 mg ceftriaxone /kg.b.wt. twice in normal and experimentally Salmonella typhimurim infected goats (n=4).

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S	N	S	N	S	N	S	N	S
Before	----------	--------	0.173±2.16	0.668±0.157**	1.03± 4.80	2.38±0.222	0.547±5.60	8.95±1.13*	0.557±6.84	10.48±1.21*
0.50	0.602±0.074	0.190±0.137*	0.847±0.103	0.300±0.028**	0.860±0.068	0.473±0.037**	1.10±0.233	0.936±0.162	1.22±0.270	1.56±0.251
1	1.49±0.327	0.616±0.153*	±0.1031.33	0.883±0.054**	1.422±0.139	1.37±0.115	1.43±0.098	1.57±0.178	1.33±0.121	1.66±0.079
2	1.87±0.132	1.28±0.153*	2.07±0.137	1.83±0.149	1.78±0.278	2.43±0.180	1.84±0.13	2.22±0.093	1.89±0.169	2.54±0.272
4	0.76±0.047	0.654±0.065	0.063±0.977	0.821±0.072	1.08±0.092	1.44±0.100*	1.28±0.15	1.61±0.129	1.36±0.118	1.81±0.136
6	0.992±0.064	0.212±0.022***	1.14±0.140	0.897±0.052	1.22±0.125	1.35±0.118	1.35±0.096	1.52±0.200	1.65±0.181	1.60±0.177
8	0.896±0.084	0.229±0.046***	70.97±0.096	1.08±0.071	1.37±0.146	0.891±0.272	1.44±0.106	1.63±0.242	2.05±0.283	1.53±0.049
12	±0.04450.68	0.264±0.043***	±0.1841.34	0.773±0.094*	1.56±0.127	1.86±0.159	1.81±0.332	2.49±0.150	2.03±0.230	3.40±0.522*

*Between normal and diseased.

*P< 0.05 **P<0.01 *** P<0.001.

N= Normal S= Salmonella infected.

Table (10): Ceftriaxone clearance/creatinine clearance following repeated ntramuscular injection of 20 mg ceftriaxone/kg.b.wt. twice dialy for five consecutive days in normal and experimentally Salmonella typhimurim infected goats (n=4).

Time of a administration (h)	Dose									
	First_ (X±S. E.)fi		Third_ (X±S. E.)		Fifth_ (X±S. E.)		Seventh_ (X±S. E.)		Ninth_ (X±S. E.)	
	N	S S	N	S	N	S	N	S	N	S
Before	----------	-------	0.127±0.001	0.099±0.020	0.279±0.047	0.358±0.018	0.864±0.098	1.83±0.116***	0.305±0.013	0.934±0.083***
0.50	1.08±0.062	0.018±0.003***	0.813±0.031	0.361±0.011***	1.26±0.068	0.876±0.063**	0.458±0.029	1.31±0.0414***	0.819±0.044	2.20±0.115***
1	0.909±0.187	0.324±0.011*	0.287±0.025	0.331±0.009	0.407±0.041	0.858±0.052***	0.546±0.027	1.18±0.068***	0.818±0.029	1.64±0.078
2	2.66±1.77	0.512±0.077	0.220±0.029	0.409±0.020**	0.686±0.050	1.69±0.464	0.329±0.027	2.32±1.28	0.488±0.005	1.61±0.044***
4	0.362±0.041	0.528±0.028*	0.083±0.006	0.235±0.014***	0.160±0.008	0.381±0.027***	0.296±0.007	0.948±0.062***	0.394±0.005	0.933±0.024***
6	0.382±0.028	0.20±0.013**	0.214±0.006	0.238±0.019	0.286±0.008	0.446±0.034**	0.204±0.006	0.639±0.066***	0.411±0.028	0.726±0.018***
8	0.222±0.006	0.109±0.185	0.213±0.0018	0.477±0.015***	1.74±0.083	0.524±0.146***	0.192±0.009	0.508±0.052***	0.425±0.036	0.609±0.072
12	0.098±0.018	0.111±0.021	0.354±0.018	0.351±0.022	0.706±0.103	0.891±0.056	0.265±0.030	0.942±0.004	0.496±0.012	1.08±0.128**

***Between normal and diseased.**

***P< 0.05 **P<0.01 *** P<0.001.**

N= Normal S= Salmonella infected.

DISCUSSION

In the present investigation intravenous injection of 20 mg ceftriaxone/kg.b.wt. in normal goats, the drug showed high serum level (92± 0.408 µg/ml) at 5 minutes post-injection, then its concentration was decreased gradually till reached its minimum level (18 ±0.816µg/ml) at 8hours post-injection.

In the present investigation, the intravenous injection of 20 mg ceftriaxone/kg.b.wt. In normal goats, showed that the drug disposition best fitted a two-compartments- open model, a compartment of plasma and rapid equilibrating tissues, and a deeper slower compartment. The obtained result is consistent with those reported for ceftriaxone in lactating goats,[9] lactating ewe[25], domestic cat[15], calves[26] and patanwadi sheep.[8] Also this phenomenon is in agreement with those reported for other cephalosporines as ceftazidime in a rabbit[27], cefepime in dog and neonatal foals[28], ewes[29], ceftriaxone in goats[9], cefipime in calves[30], ceftiofur in cross-bred friesian cattle[31], cefipime in calves[32], ceftiofur in cows[33], cefpirome in cross-bred calves[3], cefazidime in goats[35] and cefquinome in sheep and goats.[36] cefipime in chickens.[37]

Ceftriaxone was distributed after intravenous injection with a distribution phase (α) equal to 6.56 per hour with a short distribution half – life [$t_{0.5\ (\alpha)}$] equal to 0.104 hour. The shorter distribution half-life of ceftriaxone in goats suggested the rapid distribution of the drug in body tissue and fluid and that nearly similar to that recorded for ceftriaxone in lactating goats(0.12 hour)[9], for ceftriaxone in lactating ewes (0.152 hour)[2] and for ceftriaxone in calves(0.13hour).[26]

The rapid distribution of ceftriaxone in goats is supported by high rate constant of transfer of the drug from central to peripheral compartment [K_{12} = 3.53 h^{-1}] as compared to the rate constant of transfer of the drug from peripheral to central compartment [K_{21}= 2.95 h^{-1}]. This value is nearly similar to those reported for cefotaxime in goats (K_{21}=3.27 h^{-1}).[38] On contrast this value was higher than those recorded for ceftriaxone in lactating goats ($K_{21=}$1.43 h^{-1})[9], in lactating ewes ($K_{21=}$1.25 h^{-1})[25] and in domestic cats ($K_{21=}$1.54 h^{-1}).[15]

The apparent volume of distribution of ceftriaxone was (0.355±0.004L/Kg), this value is nearly similar to that recorded for cefaronide in sheep(0.39 L/Kg)[7], cefotaxime in dog (0.48 l/kg)[39], in goat (0.51 l/kg)[40], for caphalexin in buffalo calves (0.41 L/kg)[41], for cefipime in ewes and calves (0.32 l/kg) (0.43L/kg)[29] and[30] respectively. For ceftriaxone in domestic cats (0.57L/kg).[15] in camel (0.32L/kg).[42] On the other hand this result is differ than that reported for cefotaxime in buffalo calves (1.17L/kg).[43] High value of the volume of distribution suggested extensive penetration power. Drug with volume of distribution greater than one liter/kilogram indicated wide distribution or extensive tissue binding or both.[44] The apparent volume of distribution in the present study indicated moderate tissue penetrating power. This result agreed with[15] for ceftriaxone in domestic cats.

Ceftriaxone is eliminated in the current study following a single intravenous injection with elimination half –life [$t_{0.5(\beta)}$] equal to 5.19 hours. This observation is nearly agreed with the data recorded for ceftizoxime in goats (6.24hours).[45] On contrast this value was longer than that reported for ceftriaxone in lactating ewe (1.75hours)[25], for cefaronide in sheep (1.7 hours).[7] For cephalexin in buffulo calves (2.16hours)[41], for ceftriaxone in healthy horse (1.62hours)[46], also this value is longer than that recorded for ceftriaxone in lactating goats (1.44hours)[9], for cefipime in goats (1.86hours).[47]

The rate of total body clearance of ceftriaxone following a single intravenous injection is 0.048 l/kg/h, which equal to data reported for ceftizoxime in lactating goats (0.05L/kg/h).[45] On contrast this value is lower than that reported for ceftriaxone in buffulo calves, lactating goats, buffulo calves (Bubalus bubalis), goats (capra hircus), patanwadi sheep (0.26 L/kg/h), (3.95 L/kg/h), (4.40 L/kg/h) (4.50 L/kg/h), (3.91 L/kg/h)[12,9,13,11,8] respectively.

The variation in total body clearance might be attributed to specific interspecies variation, handling of the drug, method used, healthy status of the animal.[48]

The difference between values calculated for pharmacokinetic parameters may be attributed to animal species, the drug formulation employed, the age, the size or sex o, l, lf the animal or even inter individual variation and also due to method of analysis of the drug.[49]

Following a single intramuscular injection of 20 mg ceftriaxone/kg bwt. In normal goats, the drug reached its peak serum concentrations after one hour of injection with value of(41µg/ml). Ceftriaxone could be detected in serum in a therapeutic level (2.63µg/ml) at 12 hours post-injection. The reported peak serum concentrations neerly similar to that reported for cephalexin in buffulo calves (45.7 µg/ml).[41] These results is differed than those reported for ceftriaxone in cross breed calves (18.8 µg/ml at 30 min[16], in Kangro breed of goats (Capra Hircus) (26.40 µg/ml at 20 min.[10][50] found after intramuscular administration of ceforazone peak plasma concentration was (9.76 µg/ml) at 45min. This result was also higher than that recorded for ceftriaxone in buffalo calves (15.8 µg/ml).[13]

The calculated maximum serum concentration (C_{max}) is (40.015 µg/ml) at maximum time (t_{max}) of 1.57 hours. The reported (C_{max}) agreed with the data reported for cefipime in goats (49.32 µg/ml.[47] The reported maximum serum concentration (C_{max}) is higher than that reported for ceftriaxone in lactating goats(23.6 µg/ml)[9], in lactating ewes (17.22 µg/ml[25], in

goats (21.51 µg/ml)[11], for cefquinome in camels (1.23 µg/ml)[51], for ceftriaxone in calves (15.34 µg/ml)[26], in patanwadi sheep (15.53 µg/ml)[8], for cefpirome in cattle (10.1 µg/ml).[52] And for ceftiofur in chickens (25.94 µg/ml).[37] On the other hand the result was lower than that reported by[6] who observed the maximum serum concentration (C_{max}) of ceftriaxone in human after ntramuscular administration was (80.5 µg/ml), also it was lower than that reported for ceftriaxone in dog (115.10 µg/ml)[53], in domestic cats (54.40 µg/ml)[15] and for ceftazoxime in goats (88.78 µg/ml).[45]

The reported [t_{max}] is neerly similar to that reported for ceftriaxone (1.04hours)in lactating ewes by.[25] On contrast it is longer than those reported for ceftriaxone in dogs (1.29hours).[53], for ceftriaxone in lactating goats (0.7hours)[9], also the result was longer than that reported for ceftriaxone in domestic cats (0.33hours)[15], in buffulo calves (0.5 hours)[13] and for cefpirome in cattle (0.75hours).[52] The reported [t_{max}] is shorter than those reported for cefquinome in camels (4.25hours)[51], in sheep and goats (2.61 and 2.62 hours)[36] and for ceftiofur in chickens (2.51 hours).[37]

The elimination half life [$t_{0.5(\beta)}$]

following a single intramuscular administration was 18.04 hours. This value is nearly agreed with that recorded for cefquinomein camels (10.24hours)[52], On contrast this result is longer than that reported for cephalexin in buffalo calves (2.43hours)[41], for ceftriaxone in lactating ewes (1.77hours)[25], in buffalo calves (4.38hours)[13], in goats (2.03 hours)[11] and for cefipime in goats (1.65 hours).[47]

The rate of total body clearance of ceftriaxone following a single intramuscular injection is 0.043l/kg/h. This value was lower than that reported for ceftriaxone in buffulo calves (4.01L/kg/h)[13], in goats (3.04 L/kg/h)[11] and in sheep (2.22 L/kg/h).[8]

Bioavailability is the fraction of the drug administered by non vascular rout that gains accesses to the systemic circulation. The obtained result revealed that the calculated systemic bioavailability percent was 61.28%. It is equal to that recorded for cefpirome in cow calves (61%).[54] It is nearly equal to that recorded for ceftriaxone in sheep (64%).[8] On the other hand, this value is higher than those recorded for cefperazone in crossbred calves (48.1%)[50], for ceftriaxone in goats (59%)[11], in calves (47%).[55] On contrast, this value is lower than those reported for cefotaxime in two cats 98.2 and 93%)[57], for cephradine in goats

(73.9%)[58], for ceftazidime in a rabbit (96.6%)[27], for ceftriaxone in lactating goats (85%)[9], in lactating ewes (83.6%)[25], in domestic cats 85.72%[15], for cefipime in goats 86.45%[47], for ceftriaxone in buffulo calves 70.2%[13] and for ceftiofur in chickens 88.90%.[37]

Repeated intramusculer adminsteration of ceftriaxone in normal and Salmonella typhimurium infected goats twics dialy for five days revealed that the drug could be detected in a therapeutic level for 12hours following repeated intramuscular administrations and exceeded the minimum inhibitory concentration(MIC_{90})of ceftriaxone(0.2mg/ml).[59]

The relative higher serum concentrations of ceftriaxone after the last dose compared to the first doses indicated the accumulation of ceftriaxone in blood during multiple dosing at 12 hours intervals for five consecutive days. These observations agreed with data reported by[36], on comparing the data of serum levels of repeated intramuscular injections with first intramuscular injection, it was revealed that repeated intramuscular injections of cefquinome have cumulative effect in both species sheep and goats.

The obtained result is inconsistent with that reported by[56] who found that,when cefotaxime was administered repetitively in patients, the ratio of maximal serum levels after the last dose to those after the first dose demonstrated minimal accumulation of intact drug and by[60] who found that a lack of cumulative effect after repeated intramuscular injection of cefotaxime in buffalo calves.

The study showed that the blood concentrations of ceftriaxone in Salmonella typhimurium infected goats are significantly lower than those in normal goats following repeated intramuscular injection. These lower blood concentrations in Salmonella typhimurium infected goats might be attributed to the higher penetrating power of ceftriaxone to the diseased tissues.[48] This phenomenon is similar to data recorded by[61] who suggested that Salmonella typhimurium infection in red sokoto goats significantly altered plasma kinetics of ceftriaxone. These alterations might be due to fever and inflammation induced by infections.[59] proved that, the serum concentrations of cephradine following intramuscular administrations of 10 mg/kg bwt. Twice daily for five consecutive days, peaked 2 hours after each intramuscular dose with a lower significant values recorded in Escherichia-coli infected goats than in normal goats.Also similer to that reported by[62] who observed that the maximum plasma drug concentration of ceftriaxone was 16.33 per cent lower in febrile sheep

in comparison to normal sheep,On contrast[43] reported that peak plasma level of cefotaxime in febrile buffalo calves was higher than healthy buffalo calves.

In this study, the total body clearance (CL_{tot}) in normal goats are significantly lower than in Salmonella typhimurium infected goats. This result supported by[61] and[63], fever and inflammation are cardinal features in bacterial infection, which may in turn caused an increase in heart rate and cardiac output, increasing blood flow to the liver and kidneys, all these could lead to increased in the rate at which the drug was delivered to both organs which were important sites of drug excretion. This might somewhat explain the increase in the total body clearance in infected goats. This result is differ than that reported by[64] who observed that the clearance of ceftriaxone was significantly reduced in infected mice than in non infected animals.

The highest concentrations of ceftriaxone in milk are recorded 4 hours after each intramuscular injection with a significant lower value in Salmonella typhimurium infected goats than in normal goats. This might be attributed to accumulation of drug in the inflammed tissues.[48] This result is similar to those reported by[65,59] who found that milk concentrations of gentamicin and cephradine were significantly lower in infected goats and cattle than in normal ones, respectively.

The mechanism of blood-milk passage of ceftriaxone could be explained on the basis of the non-ionic passive diffusion principle.[66] reported that, most drug cross-lipid membranes by passive diffusion in the unbound non–ionized state and the extent of diffusion is greatly influenced by the physicochemical properties of the drug.[67,68]

Almost all drugs passed into milk from maternal plasma by passive diffusion, the milk/serum ratio was affected by the composition of the milk (aqueous, lipid, protein and pH) and the physicochemical characteristics of the drug (protein binding, lipophilicity and pKa).[69] Milk contains substantially more lipid and less protein than serum and is slightly more acidic. Therefore, drugs which tend to concentrated in milk are weak bases, with low serum protein binding and high lipid solubility. Ceftriaxone have three ionization groups: carboxylic, amide and aminothiazole, also possesses an hydroxytriazinone group as new and additional ionization center[70], these compounds are sufficiently lipid- soluble to be able to penetrate tissues.

The dose of ceftriaxone used in the present study induced therapeutically concentrations in milk. These concentrations suggested that, ceftriaxone would be efficacious in treatment of mastitis caused by sensitive organisms in lactating goats at dose 20 mg/kg bwt. Twice daily for 3-5 days.

The study showed that, the urine concentrations of ceftriaxone are greater than the concurrent serum concentrations following intramuscular injection. This observation is similar to those reported in cows after cephapirin administrations.[71]

In the present study, urine concentrations of ceftriaxone increased with the repetition of dosing. This observation supported by[72] after repeated intramuscular administrations of ceftriaxone in healthy volunteeres.

The mean peak urine concentrations of ceftriaxone were reached 2 hours after each intramuscular injection. The lower urine ceftriaxone concentrations in Salmonella typhimurium infected goats than in normal goats might be attributed to the accumulation of the drug in the inflamed tissues.[48]

The ratio between ceftriaxone clearance and creatinine clearance revealed a significant lower ratio in Salmonella typhimurium infected goats than in normal goats at different time of sampling. This indicates that glomerular filteration seemed to be the main pathway of ceftriaxone elimination. This observation supported by[59] who found that, the ratio between cephradine clearance from blood of goats to creatinine clearance showed a marked decrease in Escherichia-coli infected goats than in normal goats. This indicated that glomerular filteration seemed to be the main pathway of cephradine elimination with a limited rate of tubular reabsorption.

CONCLUSION

The intramuscular bioavailability of ceftriaxone in normal goats was 61.28%. This value referred a better absorption of ceftriaxone from its site of intramuscular administration. The high milk concentrations of ceftriaxone in lactating goats after repeated intramuscular administrations, suggested that ceftriaxone could be used for treatment of mastitis caused by Salmonella typhimurium and other sensitive microorganisms to ceftriaxone in lactating goats. The high concentrations of ceftriaxone in urine after repeated intramuscular administrations, suggested that ceftriaxone is a suitable antimicrobial for treatment of urinary tract infections

caused by Salmonella typhimurium and other sensitive microorganisms to ceftriaxone in goats.

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