

Pharmacokinetics of thiamphenicol in normal and *Pasteurella multocida* infected lactating goats

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Abstract

The pharmacokinetic parameters of thiamphenicol following intravenous and intramuscular (single & repeated) administrations were estimated in normal and experimentally *Pasteurella multocida* infected goats. Following a single intravenous injection of 30 mg thiamphenicol /kg b.wt. in normal goats, thiamphenicol could be detected therapeutically for 24 hours post intravenous injection. The serum concentration – time curve of thiamphenicol following intravenous injection showed that the drug obeyed a two compartments open model. The intramuscular bioavailability of thiamphenicol in normal goats was 66.63 %. Intramuscular injection of 30 mg thiamphenicol per kilogram body weight once daily for five consecutive days in normal and *Pasteurella multocida* infected goats revealed a lower significant serum thiamphenicol concentration in *Pasteurella multocida* infected goats compared with normal goats, also it's found that: marked significant decrease in (k_1 , K_{12} , K_{21} , $T_{0.5(\alpha)}$, $T_{0.5(\beta)}$, T_{max} and CL_{tot} in normal compared with infected goats, on the other hand a significant increase in C_{max} , AUC , C_0 , B and β in normal compared with infected goats. Thiamphenicol was cleared by all clearance processes (CL_{tot}) in the body at significant faster rates in *Pasteurella multocida* infected goats than in normal goats. The concentrations of thiamphenicol in milk were significantly lower in *Pasteurella multocida* infected goats than in normal goats. The mean peak urine concentrations of thiamphenicol were reached 4 hours after each intramuscular dose with a lower significant concentration in *Pasteurella multocida* infected goats than in normal goats.

Keywords: Pharmacokinetics; Thiamphenicol; *Pasteurella multocida*; Lactating Goats.

1. Introduction

Thiamphenicol is a derivative of chloramphenicol, in which the aromatic P- nitro group was replaced with amethyl sulphonyl group. It is chemically [d (+)-threo-2-dichloroacetamido-1-(4-methyl sulphonylphenyl) propane -1, 3-diol] (Mengozi et al 2002). One reason for major interest in thiamphenicol is unlike chloramphenicol as it lacks the p nitro group, it does not induce irreversible bone marrow aplasia and aplastic anaemia (Li et al. 2002). It is generally recognized that thiamphenicol possess an essential bacteriostatic activity by binding to the 50S subunits of ribosomes to block peptidyl transferase, hence inhibiting the extension of peptide chain and synthesis of bacterial protein (Turton et al .2000 , Turton et al. 2002). It is a broad spectrum antibacterial act on Gram-negative and Gram-positive bacteria involved in upper and lower respiratory tract infections, evoked by most *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Moraxella catharralis* as well as anaerobes, (Mengozzi et al. 2002, Tullio et al. 2004).

Clinical pharmacology of thiamphenicol was investigated in sheep (Abdennebi and Stowe 1994) , beef and dairy cattle (Abdennebi et al .1994 b) , pre ruminant lambs and calves (Mengozzi et al. 2002) ,camels (Al Nazawi 2005) and in male goats (Bogazil and Tohamy 2015) .

2. Materials and methods

2.1. Drug

Thiamphenicol was used in this study under the trade name (Tirsan[®]), which is manufactured by FATRO S.P.A. Italy. The vial about 100 ml, each 1 ml of product contains 250 mg thiamphenicol base.

2.2. Experimental animals

Four clinically normal lactating baladi goats and four experimentally infected goats and were used 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 be 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 with thiamphenicol (30 mg/kg b.wt)

These goats were left for 15 days after the intravenous injection to insure complete excretion of thiamphenicol from bodies of goats. Then each goat was injected intramuscularly into the gluteus medius muscle with the same dose of thiamphenicol. The aim of in-

intramuscular injection to calculate the bioavailability of thiamphenicol in normal goats.

Group (2):

It included 4 normal post-partum lactating goats. Each goat was injected intramuscularly into the gluteus medius muscle with 30 mg/kg b.wt thiamphenicol once daily for five consecutive days.

Group (3):

It included 4 experimentally infected post-partum lactating goats with *Pasteurella multocida*, which was sub cultured according to Zamir –saad and Shafarin (2007) into blood agar at 37 °c for 24 hours then uniform sized colonies were selected and cultured into brain heart infusion broth and incubated for 16 hours at 37oc. The viable count was adjusted by Macferland tube to obtain concentration of 1×10^9 micro-organisms/ml. The infecting dose for each lactating goat was 1 ml subcutaneously in the dorsolateral side of the neck. The clinical symptoms of bacteraemia as fever and nasal discharge, appeared after 48-72 hours of injection with *Pasteurella multocida* suspension. Each goat was injected intramuscularly into the gluteus medius muscle with 30 mg/kg b.wt of thiamphenicol, 48 hours after experimental infection with *Pasteurella multocida* once daily for five consecutive days.

2.3. Collection of samples

2.3.1. Blood samples

Blood samples were collected from right jugular vein following a single intravenous injection of thiamphenicol in normal goats blood samples were collected after 5 min ,10 min, 0.25, 0.50, 1 , 2 , 4 , 8 , 12 and 24 hours of administration. Samples following the second, third, fourth and fifth intramuscular doses were collected before and 0.25, 0.50, 1, 2, 4, 8, 12 and 24 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 thiamphenicol and the second part was used for creatinine assay. All serum samples were stored at – 20°C until assay for thiamphenicol and creatinine.

2.3.2. 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 thiamphenicol (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 , 36 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 thiamphenicol, and the second part was used for creatinine assay. All urine samples were stored at - 20°C until assay for thiamphenicol. After the end of each experiment, the urinary bladder was irrigated with 15 milliliters potassium permanganate solution 1: 5000 as antiseptic agent.

2.3.3. Milk samples

The udder was completely evacuated before drug administration and milk samples were collected by hand stripping from both teats. Following injection of thiamphenicol (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 ,36 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 sample. 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 thiamphenicol.

2.3. Analytical procedure

2.3.1. Assay of thiamphenicol

Thiamphenicol was assayed in goat's serum, installed water and goat's milk by microbiological method using agar well diffusion method by using of *Bacillus Subtilis* ATCC (American type culture collection 6633) as tested microorganism, which was obtained from Microbiological Depart-

ment, Animal Health Institute, Doky, Giza, Egypt. According to (Arret et al. 1971)

2.3.2. Assay of samples

According to Grove and Randall (1955), 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.

2.4. Drug clearance

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

$$\text{Drug concentration in urine (} \mu\text{g/ml)} \times \text{Rate of diuresis (ml/min)}$$

Body weight (Kg)

Drug con

Drug concentration in serum ($\mu\text{g/ml}$) X

10

2.5. Assay of creatinine in serum and urine

Creatinine was assayed according to the method of Murray (1984) and performed by kit manufactured by Diamond diagnostics company, Egypt.

2.5.1. Creatinine clearance

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

$$\text{Creatinine concentration in urine (mg/L)} \times \text{Rate of diuresis (ml/min)}$$

Body weight (Kg)

$$\text{Creatinine concentration in serum (mg/L)} \times$$

10

2.6. Pharmacokinetic analysis

The pharmacokinetic parameters were calculated by using Winonlin, version 1.2 and other parameters according to Baggot (1978a & b)

2.7. Statistical Analysis

The data were calculated as mean \pm standard error. All statistical analysis were carried out according to Snedecor and Cochran (1980) using the scientific calculator CASIO fx 120.

3. Results

Following a single intravenous injection of 30 mg thiamphenicol /kg b.wt. in normal goats, thiamphenicol could be detected therapeutically for 24 hours post intravenous injection. The serum concentration – time curve of thiamphenicol following intravenous injection showed that the drug obeyed a two compartments open model (Figure 1). The disposition kinetics of thiamphenicol following a single intravenous, intramuscular injection were recorded in table (1).

Intramuscular injection of 30 mg thiamphenicol per kilogram body weight once daily for five consecutive days in normal and *Pasteurella multocida* infected goats revealed a lower significant serum thiamphenicol concentration in *Pasteurella multocida* infected goats compared with normal goats (Table 2). The pharmacokinetic parameters of thiamphenicol after repeated intramuscular injection in normal were compared to those in *Pasteurella multocida* infected goats (Table 3) and (Figure 2&3). From comparison, it's found that: marked significant decrease in ($k_1, K_{12}, K_{21}, T_{0.5(\alpha)}, T_{0.5(\beta)}, T_{max}$ and CL_{tot} in normal compared with infected goats, on the other hand a significant increase in C_{max}, AUC, C^0, B and β in normal compared with infected goats. The highest concentrations of thiamphenicol in milk were recorded 4 hours after each intramuscular dose (Table 4) with a significant lower value in *Pasteurella multocida* infected goats compared with normal goats. The calculated milk/serum concentrations ratios of thiamphenicol after repeated intramuscular injection (Table 5).

The amount of urine (ml/min) voided after repeated intramuscular injection of 30 mg/kg bwt. Once daily of thiamphenicol for five consecutive days in normal and experimentally *Pasteurella multocida* infected goats were recorded in table (6). The mean peak urine concentrations of thiamphenicol (Table 7) were reached 4 hours after each intramuscular dose with a lower significant concentration in *Pasteurella multocida* infected goats compared with normal goats. Urine/serum concentration ratios of thiamphenicol after repeated intramuscular injection in normal and experimentally *Pasteurella multocida* infected goats were calculated and illustrated in table (8). Creatinine clearance (ml/min/10 kglbwt.) expressing glomerular filtration rate from blood of goats was shown in a table (9). The rate of thiamphenicol clearance (ml/min/10 kglbwt.) from blood of goats was shown in a table (10). The ratio between thiamphenicol clearance and creatinine clearance was calculated and illustrated in a table (11). table (11).

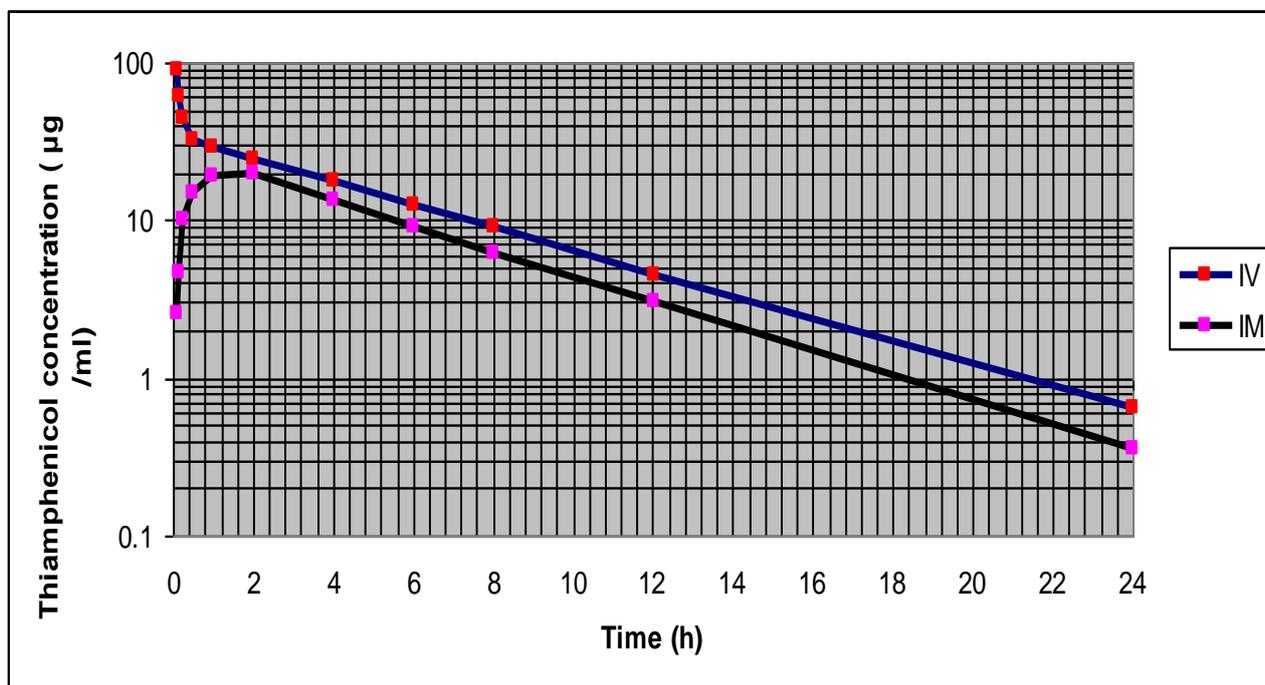


Fig. 1: Semilogarithmic Graph of Serum Concentrations of Thiamphenicol E (Mg/ MI) in Normal Goats Following A Single Intramuscular Injection (■—■) Previously Given the Same Dose by A Single Intravenous Injection (■—■) of 20 Mg Thiamphenicol /Kg.B.Wt (N=4).

Table 1: Pharmacokinetics Parameters of Thiamphenicol Following A Single Intravenous and Intramuscular Injection of 30 Mg/Kg B. Wt in Normal Goats (N=4)

Parameters	Unit	Intravenous $\bar{X} \pm S.E.$	Intramuscular $\bar{X} \pm S.E.$
C^0	$\mu\text{g/ml}$	149.59±0.0868	-----
A	$\mu\text{g/ml}$	115.63±0.882	71.25±0.837
α	h^{-1}	8.25±0.148	0.875±0.004
$t_{0.5T}$	h	0.084±0.148	0.791±0.003
T_{max}	h	-----	±0.0241.42
C_{max}	$\mu\text{g/ml}$	-----	4.6116.67±
K_{12}	h^{-1}	5.75±0.112	0.221±0.007
K_{21}	h^{-1}	2.06±0.036	0.560±0.002
V_{dss}	l/kg	0.785±0.003	-----
B	$\mu\text{g/ml}$	33.46±0.200	24.47±0.289
β	h^{-1}	0.167±0.003	0.172±0.001
$T_{0.5(\beta)}$	h	4.15±0.083	4.02±0.043
CL_{tot}	l/kg/h	0.002±0.0002	0.043±0.005
AUMC	$\mu\text{g/ml/h}$	1219.29±1.65	-----
MRT	h	5.65±0.030	-----
AUC	$\mu\text{g/ml/h}$	214.70±1.40	250.8±8.47
F	%	-----	66.63±0.813
K_{01}	h^{-1}	-----	1.11±0.016
$T_{0.5(k01)}$	h^{-1}	-----	0.625±0.009

C_0 : Drug concentration in the serum at zero time immediately after a single intravenous injection ($\mu\text{g} / \text{ml}$). A & B: Zero time plasma drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase ($\mu\text{g}/\text{ml}$). 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}). $T_{0.5}(\alpha)$: Distribution half – life (h). $t_{0.5}(\beta)$: Elimination half – life (h). K_{12} : First – order transfer rate constant for drug distribution from Central to peripheral compartment (h^{-1}). K_{21} : 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 $t = \alpha$ after administration of a single dose. F: Bioavailability. C_{max} : maximum drug concentration; T_{max} : time of maximum observed concentration in blood.

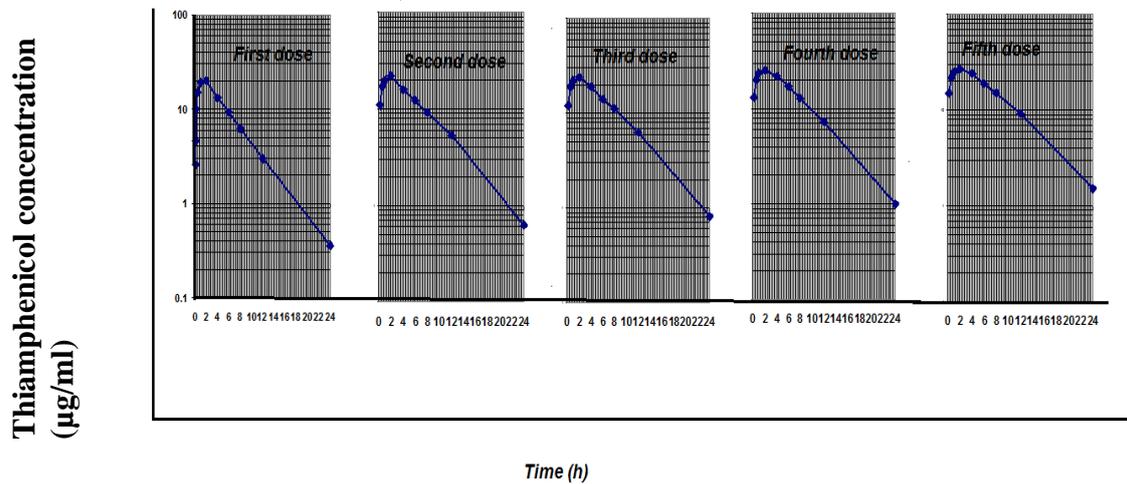


Fig. 2: Semilogarithmic Graph Depicting the Time Course of Thiamphenicol in Serum of Normal Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg.B.Wt. Once Daily for Five Consecutive Days. (N=4).

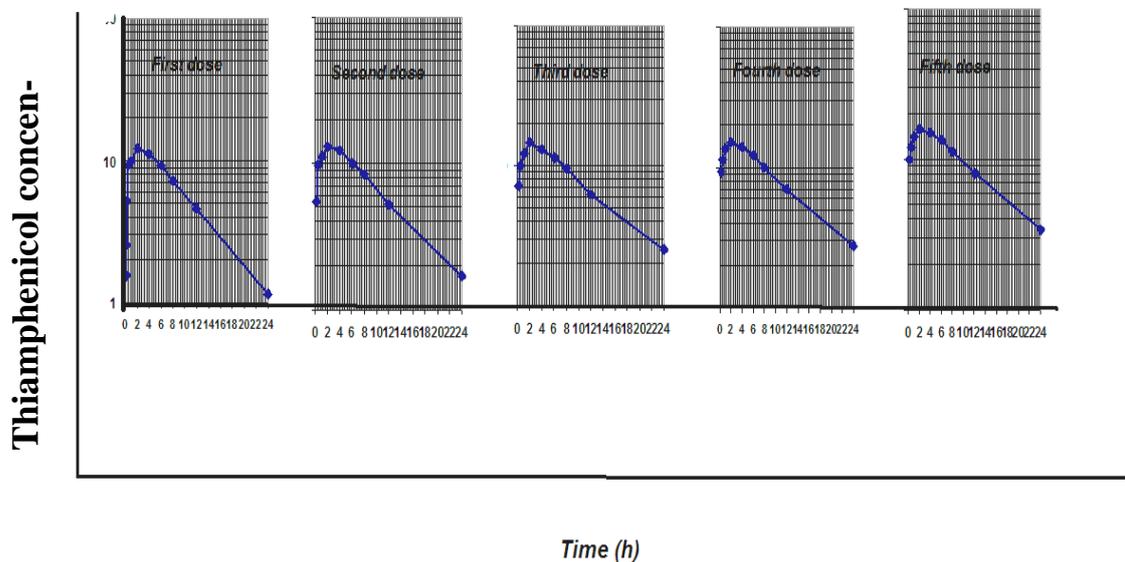


Fig. 3: Semilogarithmic Graph Depicting the Time Course of Thiamphenicol in Serum of Experimentally *Pastuerella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg.B.Wt. Once Daily for Five Consecutive Days. (N=4)

Table 2: Serum Concentrations of Thiamphenicol in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg.B.Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose									
	First		Second		Third		Fourth		Fifth	
	$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$	
	N	I	N	I	N	I	N	I	N	I
0.083	2.57±0.2 17	1.57±0.047 **	-----	-----	-----	-----	-----	-----	-----	-----
0.167	4.60±0.3 18	2.57±0.217 **	-----	-----	-----	-----	-----	-----	-----	-----
0.25	10.00±0. 408	5.25±0.433 ***	11.12±0. 657	5.50±0.204 ***	12.12±0. 718	7.25±0.144 ***	13.25±0. 322	9.25±0.322 ***	15.00±0.40 8	10.00±0.40 8***
0.50	15.00±0. 408	9.25±0.322 ***	17.00±0. 408	9.62±0.125	19.00±0. 707	10.00±0.40 8	20.00±0. 707	11.25±0.47 8	22.00±0.40 8	12.00±0.40 8
1	19.00±0. 408	10±0.408	20.00±0. 707	11.12±0.65 7	22.00±0. 408	12.12±0.71 8***	24.00±0. 707	13.50±0.20 4***	25.00±0.40 8	14.00±0.40 8***
2	20.00±0. 707	12.25±0.77 7***	22.00±0. 408	13.00±0.20 4	24.00±0. 707	14.75±0.47 8	25.00±0. 408	15.00±0.40 8	27.00±0.91 2	15.75±0.25 0
4	13.25±0. 322	11.12±0.62 7	16.00±0. 707	12.25±0.77 7*	19.00±0. 707	13.00±0.20 4	22.00±0. 408	14.00±0.40 8***	24.00±0.40 8	15.00±0.40 8
6	9.25±0.3 22	9.25±0.322	12.25±0. 777	10±0.408	14.00±0. 408	11.50±0.61 2	17.00±0. 408	12.25±0.77 7	19.00±0.70 7	13.50±0.20 4
8	6.25±0.4 33	7.25±0.144	9.25±0.3 22	8.37±0.314	11.12±0. 657	9.50±0.204	13.00±0. 408	10.00±0.40 8***	15.00±0.40 8	11.25±0.47 8***
12	3.00±0.4 08	4.60±0.318 **	5.25±0.4 33	5.25±0.433	6.25±0.4 33	6.25±0.433	7.25±0.1 44	7.00±0.353 ***	9.25±0.322	8.125±0.37 5
24	0.570±0. 010	1.15±0.017 ***	0.625±0. 032	1.70±0.020 ***	0.812±0. 042	2.53±0.074 ***	1.00±0.0 70	2.75±0.086 ***	1.52±0.047 ***	3.40±0.040 ***

* Between normal and *Pasteurella multocida* infected goats N= Normal I= infected *P< 0.05 **P<0.01 *** P<0.001

Table 3: Pharmacokinetic Parameters of Thiamphenicol (µg/ml) in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily or Five Consecutive Days (N=4)

Parameters	Unit	Dose									
		First		Second		Third		Fourth		Fifth	
		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$		$\bar{X} \pm S. E.$	
	N	I	N	I	N	I	N	I	N	I	
C ₀	g/mlµ	45.55±0. .688	33.29±0. 042***	±0.150 55.82	40.01±0.2 67***	60.97±0. 215	34.42±0. 312***	57.59± 0.392	40.04±0. 282***	73.00±0. 823	36.95±0. 085***
A	g/mlµ	26.85± 0.244	15.53±0. 162***	27.42±0. 242	21.50±0.2 95***	23.68±0. 405	15.84±0. 202***	26.53± 0.267	18.62±0. 174***	34.07±0. 477	17.06±0. 156***
α	h ⁻¹	1.79±0. 014	1.042±0. 040***	2.05±0.0 26	0.564±0.0 14***	2.04±0.0 48	1.41±0.0 52***	2.40±0. 034	1.16±0.0 125***	2.60±0.0 67	1.27±0.0 15***
T _{0.5(α)}	H	0.387±0. .002	0.666±0. 025***	0.337±0. 004	1.23±0.03 1***	0.339±0. 008	0.493±0. 019***	0.288± 0.004	0.593±0. 0062***	0.266±0. 006	0.543±0. 006***
K ₁	h ⁻¹	1.25±0. 010	1.52±0.1 07*	1.27±0.0 15	1.57±0.07 9**	1.47±0.0 12	1.68±0.1 29	1.64±0. 025	2.45±0.2 03**	1.84±0.0 18	2.40±0.1 13**
T _{0.5(k1)}	H	0.554±0. .004	0.461±0. 030*	0.543±0. 006	0.441±0.0 21**	0.469±0. 003	0.418±0. 024	0.421± 0.006	0.288±0. 042*	0.376±0. 003	0.289±0. 014***
C _{max}	g/mlµ	20.99±0. .546	12.57±0. 511***	22.28±0. 196	13.56±0.2 95***	24.51±0. 281	14.91±0. 295***	25.59± 0.318	15.36±0. 089***	27.51±0. 171	16.41±0. 129***
T _{max}	H	1.45±0. 028	1.90±0.0 65	1.51±0.0 24	1.88±0.05 9**	1.52±0.0 16	1.84±0.0 87*	1.61±0. 013	1.48±0.0 87	1.74±0.0 19	1.51±0.0 62*
K ₁₂	h ⁻¹	0.170±0. .001	8.28±0.5 00***	0.318±0. 001	8.44±0.47 7***	0.284±0. 0017	8.51±0.3 94***	0.423± 0.004	8.61±0.0. 437***	0.319±0. 003	8.74±0.4 69***
K ₂₁	h ⁻¹	0.582±0. .001	8.95±0.1 16***	0.866±0. 002	10.19±0.0 64***	1.45±0.0 26	9.30±0.0 99***	2.34±0. 038	10.57±0. 072***	1.58±0.0 18	9.86±0.0 24***
K ₁₀	h ⁻¹	0.246±0. .001	1.52±0.0 03***	0.202±0. 002	0.149±0.0 03***	0.165±0. 002	0.153±0. 001***	0.127± 0.001	0.158±0. 003***	0.156±0. 001	0.125±0. 003***
T _{0.5(k10)}	h ⁻¹	2.81±0. 014	4.55±0.0 97***	3.42±0.0 41	4.65±0.11 0**	4.30±0.0 70	4.52±0.0 42*	5.42±0. 070	4.37±0.0 92***	4.43±0.0 45	5.52±0.1 74***
B	g/mlµ	27.98±0. .499	17.76±0. 153***	28.39±0. 333	18.51±0.2 00***	32.29±0. 420	18.58±0. 172***	31.05± 0.330	21.42±0. 242***	38.93±0. 391	19.88±0. 101***
β	h ⁻¹	0.174±0. .002	0.107±0. 009***	0.152±0. 002	0.0965±0. 0029***	0.129±0. 001	0.068±0. 0022***	0.103± 0.004	0.085±0. 003*	0.107±0. 001	0.079±0. 0025***
T _{0.5β}	H	3.98±0. 051	6.44±0.0 57***	4.54±0.0 59	7.20±0.22 5***	5.35±0.0 055	10.76±0. 868***	6.73±0. 300	8.19±0.3 16*	6.45±0.1 10	8.71±0.2 87***
CL _{tot}	L/kg/h	0.0016± 0.0001	0.218±0. 724	0.0013±0 .000008	0.194±0.5 06	0.0011± 0.00008	0.171±0. 303	0.0032 ±0.002	0.514±0. 272	0.0007± 0.00004	0.136±0. 214
AUC	g/ml/hµ	139.75± 1.09	133.60± 4.33	187.65±0 .970	149.23±4. 11***	221.32± 1.72	169.29±3 .16***	222.43 ±4.60	187.90±2 .96***	241.07± 4.09	208.02±3 .19***

* Between normal and *Pasteurella multocida* infected goats N= Normal I= infected *P< 0.05 **P<0.01 *** P<0.001

Table 4: Milk Concentrations of Thiamphenicol ($\mu\text{g}/\text{ml}$) In Normal and Experimentally *Pasteurella Multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg.B.Wt. Once Daily For Five Consecutive Days (N=4)

Time of administration (h)	Dose First (X \pm S. E.)		Second_ (X \pm S. E.)		Third_ (X \pm S. E.)		Fourth_ (X \pm S. E.)		Fifth_ (X \pm S. E.)	
	N	I	N	I	N	I	N	I	N	I
	0.50	-----	-----	1.57 \pm 0.0	1.49 \pm 0.00	2.25 \pm 0.3	1.75 \pm 0.144	3.25 \pm 0.4	2.50 \pm 0.204	3.30 \pm 0.0
1	3.25 \pm 0.400	2.67 \pm 0.394	4.125 \pm 0.314	3.17 \pm 0.118*	5.26 \pm 0.166	3.75 \pm 0.144*	6.35 \pm 0.155	4.50 \pm 0.204***	7.00 \pm 0.408	5.25 \pm 0.322*
2	5.26 \pm 0.166	4.23 \pm 0.423	5.87 \pm 0.426	4.60 \pm 0.368	6.35 \pm 0.155	4.99 \pm 0.002*	7.00 \pm 0.408	5.37 \pm 0.239	8.27 \pm 0.110	5.87 \pm 0.426**
4	10.00 \pm 0.408	9.25 \pm 0.250	12.00 \pm 0.408	10.00 \pm 0.408*	13.00 \pm 0.408	11.00 \pm 0.408	13.50 \pm 0.204	12.25 \pm 0.250	14.00 \pm 0.353	13.50 \pm 0.204
6	5.26 \pm 0.166	5.10 \pm 0.127	5.87 \pm 0.426	5.24 \pm 0.142	7.00 \pm 0.408	5.49 \pm 0.002*	8.27 \pm 0.110	5.87 \pm 0.125***	8.50 \pm 0.204	6.35 \pm 0.155***
8	3.30 \pm 0.400	3.10 \pm 0.057	4.125 \pm 0.314	3.55 \pm 0.165	5.26 \pm 0.166	4.00 \pm 0.204*	6.50 \pm 0.204	4.62 \pm 0.239	7.125 \pm 0.314	5.26 \pm 0.166**
12	1.57 \pm 0.047	1.49 \pm 0.002	2.125 \pm 0.314	1.75 \pm 0.142	3.25 \pm 0.400	2.37 \pm 0.239	3.30 \pm 0.027	3.37 \pm 0.239	4.25 \pm 0.322	4.125 \pm 0.314
24	0.800 \pm 0.020	0.75 \pm 0.020	1.35 \pm 0.155	1.025 \pm 0.062	1.95 \pm 0.064	1.42 \pm 0.075*	2.00 \pm 0.353	1.9 \pm 0.135	2.25 \pm 0.322	2.00 \pm 0.353

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P< 0.05 **P<0.01 *** P<0.001.

Table 5: Milk/Serum Concentrations Ratios of Thiamphenicol ($\mu\text{g}/\text{ml}$) in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First (X \pm S. E.)		Second_ (X \pm S. E.)		Third_ (X \pm S. E.)		Fourth_ (X \pm S. E.)		Fifth_ (X \pm S. E.)	
	N	I	N	I	N	I	N	I	N	I
	0.50	-----	-----	0.091 \pm 0.002	0.154 \pm 0.0018***	0.119 \pm 0.021	0.177 \pm 0.020	0.1621 \pm 0.021	0.225 \pm 0.027	0.153 \pm 0.003
1	0.175 \pm 0.033	0.217 \pm 0.073	0.207 \pm 0.018	0.289 \pm 0.023*	0.238 \pm 0.005	0.311 \pm 0.016**	0.264 \pm 0.000	0.333 \pm 0.013**	0.277 \pm 0.018	0.377 \pm 0.030**
2	0.262 \pm 0.009	0.354 \pm 0.054	0.264 \pm 0.015	0.353 \pm 0.024*	0.264 \pm 0.006	0.339 \pm 0.010***	0.279 \pm 0.014	0.358 \pm 0.014**	0.305 \pm 0.014	0.373 \pm 0.028
4	0.758 \pm 0.045	0.838 \pm 0.042	0.754 \pm 0.042	0.833 \pm 0.093	0.644 \pm 0.004	0.854 \pm 0.0321***	0.612 \pm 0.011	0.875 \pm 0.015***	0.582 \pm 0.002	0.902 \pm 0.032***
6	0.570 \pm 0.025	0.554 \pm 0.025	0.484 \pm 0.042	0.527 \pm 0.027	0.498 \pm 0.014	0.482 \pm 0.026	0.487 \pm 0.017	0.486 \pm 0.039	0.449 \pm 0.018	0.470 \pm 0.016
8	0.533 \pm 0.028	0.428 \pm 0.016	0.484 \pm 0.041	0.427 \pm 0.036	0.474 \pm 0.013	0.422 \pm 0.028	0.502 \pm 0.028	0.467 \pm 0.040	0.475 \pm 0.024	0.469 \pm 0.027
12	0.552 \pm 0.072	0.329 \pm 0.021	0.412 \pm 0.065	0.346 \pm 0.056	0.515 \pm 0.052	0.357 \pm 0.050	0.455 \pm 0.017	0.459 \pm 0.080	0.459 \pm 0.041	0.492 \pm 0.032
24	2.25 \pm 0.143	0.650 \pm 0.014	2.15 \pm 0.231	0.602 \pm 0.043***	2.40 \pm 0.074	0.561 \pm 0.024***	2.06 \pm 0.450	0.691 \pm 0.017*	1.46 \pm 0.185	0.585 \pm 0.046**

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P< 0.05 **P<0.01 *** P<0.001

Table 6: The Amount of Urine (ml/Min) Voided in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First (X \pm S. E.)		Second_ (X \pm S. E.)		Third_ (X \pm S. E.)		Fourth_ (X \pm S. E.)		Fifth_ (X \pm S. E.)	
	N	I	N	I	N	I	N	I	N	I
	0.50	0.423 \pm 0.037	0.408 \pm 0.034	0.474 \pm 0.016	0.458 \pm 0.016	0.508 \pm 0.028	0.491 \pm 0.020	0.616 \pm 0.021	0.616 \pm 0.021	0.733 \pm 0.036
1	0.547 \pm 0.017	0.554 \pm 0.019	0.617 \pm 0.045	0.579 \pm 0.029	0.629 \pm 0.071	0.674 \pm 0.080	0.683 \pm 0.037	0.704 \pm 0.071	0.791 \pm 0.053	0.807 \pm 0.063
2	0.614 \pm 0.018	0.645 \pm 0.026	0.679 \pm 0.022	0.6455 \pm 0.026	0.692 \pm 0.015	0.693 \pm 0.015	0.718 \pm 0.010	0.718 \pm 0.010	0.749 \pm 0.016	0.749 \pm 0.016
4	0.765 \pm 0.037	0.739 \pm 0.035	0.812 \pm 0.014	0.770 \pm 0.026	0.831 \pm 0.017	0.843 \pm 0.035	0.892 \pm 0.033	0.874 \pm 0.016	0.983 \pm 0.025	0.983 \pm 0.025
6	0.673 \pm 0.016	0.647 \pm 0.029	0.781 \pm 0.015	0.731 \pm 0.028	0.781 \pm 0.023	0.770 \pm 0.033	0.791 \pm 0.019	0.777 \pm 0.019	0.796 \pm 0.024	0.792 \pm 0.019
8	0.567 \pm 0.006	0.567 \pm 0.006	0.599 \pm 0.005	0.588 \pm 0.015	0.589 \pm 0.009	0.562 \pm 0.022	0.631 \pm 0.005	0.624 \pm 0.008	0.645 \pm 0.004	0.655 \pm 0.005
12	0.436 \pm 0.016	0.440 \pm 0.011	0.474 \pm 0.009	0.474 \pm 0.009	0.480 \pm 0.008	0.0451 \pm 0.013	0.487 \pm 0.014	0.482 \pm 0.015	0.548 \pm 0.007	0.655 \pm 0.004
24	0.367 \pm 0.008	0.369 \pm 0.007	0.450 \pm 0.016	0.242 \pm 0.011	0.433 \pm 0.003	0.383 \pm 0.007	0.443 \pm 0.003	0.440 \pm 0.002	0.552 \pm 0.029	0.531 \pm 0.042

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P< 0.05 **P<0.01 *** P<0.001

Table 7: Urine Concentrations of Thiamphenicol ($\mu\text{g}/\text{ML}$) in Normal and Experimentally *Pasteurella Multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First		Second_		Third_		Fourth_		Fifth_	
	(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)	
	N	I	N	I	N	I	N	I	N	I
0.50	111.50 \pm 2.59	90.00 \pm 1.73***	117.75 \pm 2.25	106.50 \pm 4.50	131.25 \pm 7.10	113.00 \pm 2.5*	138.75 \pm 3.75	115.50 \pm 2.59**	148.50 \pm 9.20	119.25 \pm 3.09*
1	131.25 \pm 7.18	102.00 \pm 5.19*	138.75 \pm 3.75	115.50 \pm 2.50	141.75 \pm 9.02	117.00 \pm 2.5*	162.00 \pm 6.92	123.75 \pm 3.75**	169.50 \pm 6.65	126.75 \pm 3.09**
2	163.50 \pm 7.88	113.25 \pm 2.25***	181.50 \pm 3.77	117.00 \pm 2.25***	186.00 \pm 3.46	125.25 \pm 3.54***	192.00 \pm 4.89	131.25 \pm 7.18***	198.00 \pm 3.46	138.75 \pm 3.75***
4	241.50 \pm 3.57	123.75 \pm 3.75***	249.75 \pm 7.48	131.25 \pm 7.18***	258.00 \pm 7.34	138.75 \pm 3.75***	265.5 \pm 8.61	146.25 \pm 3.75***	270.00 \pm 7.34	158.25 \pm 9.59***
6	78.00 \pm 1.73	72.00 \pm 1.73*	79.50 \pm 1.50	78.00 \pm 1.73	82.4 \pm 3.77	79.50 \pm 1.50	84.00 \pm 1.73	80.25 \pm 0.75	87.00 \pm 2.44	84.00 \pm 1.73
8	42.75 \pm 1.88	37.50 \pm 0.866*	48.00 \pm 2.24	42.75 \pm 1.88	49.50 \pm 1.50	48.00 \pm 4.42	54.00 \pm 2.44	54.00 \pm 2.44	58.50 \pm 2.87	57.00 \pm 1.73
12	19.50 \pm 2.87	17.25 \pm 1.43	21.00 \pm 2.12	18.00 \pm 1.73	23.4 \pm 1.36	19.50 \pm 2.87	24.15 \pm 1.10	22.50 \pm 1.50	25.50 \pm 0.866	24.15 \pm 1.10
24	5.85 \pm 1.13	4.20 \pm 0.173	8.1 \pm 0.714	5.85 \pm 1.13	9.30 \pm 0.173	6.75 \pm 0.75*	9.45 \pm 0.150	9.00 \pm 1.22	9.90 \pm 0.173	9.30 \pm 0.173*

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P<0.05 **P<0.01 *** P<0.001**Table 8:** Urine/Serum Concentrations Ratios of Thiamphenicol ($\mu\text{g}/\text{ML}$) in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg.B.Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First		Second_		Third_		Fourth_		Fifth_	
	(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)	
	N	I	N	I	N	I	N	I	N	I
0.50	7.72 \pm 0.326	9.78 \pm 0.517*	6.94 \pm 0.280	11.06 \pm 0.448***	6.93 \pm 0.464	11.35 \pm 0.327***	6.98 \pm 0.456	10.31 \pm 0.427**	6.75 \pm 0.470	9.98 \pm 0.517**
1	7.07 \pm 0.692	10.20 \pm 0.370**	6.95 \pm 0.234	10.48 \pm 0.644**	6.92 \pm 0.222	10.48 \pm 0.647**	6.74 \pm 0.173	9.17 \pm 0.307***	6.71 \pm 0.236	9.08 \pm 0.448**
2	8.18 \pm 0.385	9.35 \pm 0.617	8.24 \pm 0.039	8.64 \pm 1.79	7.76 \pm 0.214	8.50 \pm 0.206**	7.69 \pm 0.322	8.78 \pm 0.618	7.34 \pm 0.134	8.80 \pm 0.224**
4	18.27 \pm 0.685	11.27 \pm 0.908***	15.75 \pm 1.19	10.96 \pm 1.11*	13.60 \pm 0.369	10.66 \pm 0.177***	12.07 \pm 0.441	10.48 \pm 0.417*	11.25 \pm 0.171	10.58 \pm 0.748
6	8.46 \pm 0.414	8.45 \pm 0.717	6.55 \pm 0.33	7.85 \pm 0.464	5.92 \pm 0.447	7.81 \pm 0.186*	4.94 \pm 0.085	6.64 \pm 0.488*	4.58 \pm 0.139	6.22 \pm 0.155***
8	6.14 \pm 0.510	5.17 \pm 0.157	5.17 \pm 0.380	5.12 \pm 0.289	4.48 \pm 0.195	5.08 \pm 0.555	4.155 \pm 0.171	5.40 \pm 0.216**	3.91 \pm 0.267	5.08 \pm 0.220**
12	6.56 \pm 0.543	3.80 \pm 0.407*	4.04 \pm 0.391	3.57 \pm 0.628	3.82 \pm 0.26	3.08 \pm 0.275	3.32 \pm 0.15	3.22 \pm 0.193	2.76 \pm 0.161	2.89 \pm 0.170
24	16.37 \pm 3.21	3.64 \pm 0.168*	13.21 \pm 1.70	3.42 \pm 0.639*	11.51 \pm 0.468	2.62 \pm 0.193**	9.60 \pm 0.744	3.24 \pm 0.377***	6.50 \pm 0.1999	3.73 \pm 0.036***

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P<0.05 **P<0.01 *** P<0.001**Table 9:** Creatinine Clearance (ML/Min/10kg.B.Wt) of Thiamphenicol in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First		Second_		Third_		Fourth_		Fifth_	
	(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)		(X \pm S. E.)	
	N	I	N	I	N	I	N	I	N	I
0.50	8.46 \pm 1.22	8.86 \pm 1.18	9.93 \pm 1.59	10.64 \pm 1.81	11.58 \pm 1.36	13.08 \pm 1.19	15.37 \pm 1.03	17.13 \pm 0.816	17.69 \pm 2.21	18.21 \pm 2.32
1	12.96 \pm 2.60	19.02 \pm 2.64	15.88 \pm 5.88	15.26 \pm 3.44	15.79 \pm 3.75	19.10 \pm 4.59	15.79 \pm 3.88	20.55 \pm 4.66	19.25 \pm 2.26	20.02 \pm 1.89
2	10.06 \pm 11.09	10.43 \pm 0.701	10.29 \pm 1.20	10.43 \pm 0.576	11.15 \pm 0.992	13.16 \pm 1.37	19.88 \pm 4.69	14.55 \pm 1.76	12.86 \pm 1.20	13.55 \pm 1.35
4	29.87 \pm 6.25	28.54 \pm 4.97	24.07 \pm 5.12	31.87 \pm 6.10	31.24 \pm 5.34	37.16 \pm 7.60	26.79 \pm 4.80	34.89 \pm 4.96	34.22 \pm 5.12	36.54 \pm 5.45
6	16.34 \pm 4.22	18.19 \pm 7.47	19.47 \pm 4.88	19.85 \pm 5.62	18.79 \pm 5.04	17.95 \pm 2.86	19.30 \pm 3.93	19.56 \pm 4.71	17.10 \pm 5.21	20.03 \pm 5.07
8	16.79 \pm 2.67	17.98 \pm 3.25	15.99 \pm 1.78	16.18 \pm 0.326	17.22 \pm 1.19	17.19 \pm 1.06	17.21 \pm 0.435	19.30 \pm 1.43	17.57 \pm 1.49	18.81 \pm 1.68
12	14.34 \pm 0.573	14.07 \pm 0.56	13.39 \pm 0.525	15.38 \pm 0.484**	14.12 \pm 0.400	14.77 \pm 0.114	12.45 \pm 1.51	15.25 \pm 1.12	15.54 \pm 0.839	16.31 \pm 0.895
24	12.47 \pm 0.997	12.36 \pm 1.02	14.52 \pm 1.06	14.19 \pm 1.09	12.43 \pm 0.830	14.28 \pm 1.61	11.96 \pm 1.009	14.65 \pm 0.729	16.26 \pm 1.04	17.00 \pm 1.68

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P<0.05 **P<0.01 *** P<0.001

Table 10: Thiamphenicol Clearance (ML/Min/10kg. B. Wt) in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First		Second		Third		Fourth		Fifth	
	(X±S. E.)		(X±S. E.)		(X±S. E.)		(X±S. E.)		(X±S. E.)	
	N	I	N	I	N	I	N	I	N	I
0.50	1.17±0.128	1.60±0.137	1.20±0.125	2.04±0.050**	1.27±0.137	2.26±0.166*	1.58±0.163	2.56±0.121*	1.80±0.217	2.94±0.125*
1	1.44±0.138	2.30±0.215*	1.55±0.176	2.46±0.225*	1.61±0.304	2.67±0.327	1.65±0.092	2.59±0.215*	1.93±0.158	2.76±0.140*
2	1.91±0.122	2.455±0.242	2.02±0.114	2.36±0.098	1.94±0.097	2.38±0.089*	2.00±0.163	2.40±0.201	1.99±0.107	2.81±0.148*
4	5.21±0.346	3.41±0.458*	4.61±0.314	3.21±0.115*	4.07±0.075	3.68±0.214	3.89±0.219	3.47±0.346	4.00±0.163	4.09±0.328
6	2.27±0.144	2.24±0.240	1.86±0.161	2.36±0.152	1.66±0.099	2.18±0.203	1.41±0.055	2.08±0.151*	1.33±0.070	1.99±0.050**
8	1.31±0.134	1.19±0.077	1.11±0.048	1.2±0.033	0.962±0.088	0.952±0.330	0.906±0.048	1.36±0.063*	0.913±0.074	1.34±0.016*
12	1.09±0.090	0.688±0.095*	0.697±0.081	0.561±0.075	0.665±0.078	0.687±0.105	0.681±0.069	0.626±0.019	0.547±0.028	0.651±0.052
24	2.50±0.621	0.149±0.005**	2.14±0.302	0.172±0.009***	1.80±0.094	0.152±0.014***	1.54±0.150	0.178±0.003***	1.29±0.064	0.214±0.013***

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P<0.05 **P<0.01 *** P<0.001

Table 11: Thiamphenicol Clearance /Creatinine Clearance in Normal and Experimentally *Pasteurella multocida* Infected Goats Following Repeated Intramuscular Injection of 30 Mg Thiamphenicol /Kg. B. Wt. Once Daily for Five Consecutive Days (N=4)

Time of administration (h)	Dose First		Second		Third		Fourth		Fifth	
	(X±S. E.)		(X±S. E.)		(X±S. E.)		(X±S. E.)		(X±S. E.)	
	N	I	N	I	N	I	N	I	N	I
0.50	0.159±0.050	0.220±0.071	0.142±0.046	0.219±0.055	0.110±0.006	0.176±0.019*	0.113±0.011	0.150±0.009*	0.103±0.010	0.171±0.029
1	0.124±0.022	0.123±0.006	0.093±0.027	0.183±0.038	0.109±0.016	0.165±0.044	0.120±0.023	0.336±0.183	0.104±0.014	0.140±0.012
2	0.195±0.018	0.236±0.026	0.202±0.014	0.227±0.013	0.176±0.009	0.183±0.015	0.131±0.022	0.177±0.021	0.366±0.208	0.211±0.015
4	0.194±0.062	0.137±0.040	0.223±0.054	0.112±0.021	0.145±0.030	0.115±0.029	0.219±0.061	0.113±0.034	0.128±0.027	0.123±0.027
6	0.166±0.037	0.170±0.040	0.102±0.219	0.142±0.028	0.103±0.018	0.128±0.015	0.070±0.023	0.122±0.022	0.126±0.059	0.119±0.028
8	0.082±0.014	0.056±0.017	0.615±0.009	0.075±0.004***	0.056±0.005	0.057±0.019	0.044±0.005	0.186±0.115	0.505±0.001	0.072±0.0049***
12	0.077±0.008	0.053±0.0025	0.067±0.012	0.044±0.007	0.046±0.005	0.046±0.007	0.041±0.004	0.041±0.032	0.034±0.003	0.039±0.005
24	0.197±0.038	0.011±0.011**	0.143±0.025	0.011±0.047*	0.148±0.013	0.012±0.019***	0.124±0.003	0.011±0.0005***	0.084±0.004	0.012±4.78

* Between normal and *Pasteurella multocida* infected goats. N= Normal I= infected *P<0.05 **P<0.01 *** P<0.001

4. Discussion

Following a single intravenous injection of 30 mg thiamphenicol/kg.b.wt. in normal goats, the drug showed high serum level ($90 \pm 0.707 \mu\text{g/ml}$) at 5 minutes post-injection, then its concentration was decreased gradually till reached its minimum level ($0.645 \pm 0.033 \mu\text{g/ml}$) at 24hours post-injection.

In the present investigation, the intravenous injection of 30 mg thiamphenicol / 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 thiamphenicol in pre-ruminant labs and calves (Mengozzi et al .2002), male goats (Bogazil and Tohamy 2015). Also this phenomenon is in agreement with those reported for other amphenicols as choloramphenicol in calves (Watson and Black 1986), florfenicol in pigs (Jianzhong et al. 2003), healthy foal (Tohamy and Radi 2008). On contrast this result isn't agreed with that reported for florfenicol in healthy sheep, Jianzhong et al. 2004), cattle (Lobell et al 2008) as reported by three compartment. Thiamphenicol was distributed after intravenous injection with a distribution phase (α) equal to 8.25per hour with a short distribution half - life [$t_{0.5(\alpha)}$] equal to 0.084 hour. The shorter distribution half-life of thiamphenicol in goats suggested the rapid distribution of the drug in body tissue and fluid and that nearly similar to that

recorded for cholramphenicol in healthy skotored goats (0.08 h) (Etuk et al. 2005) , and nearly similar to that reported for thiamphenicol in neagle blog (0.069 h) (Yang et al 2011), in male goats (0.06 h) (Bogazil and Tohamy 2015). On the other hand, this result is slightly shorter than that reported for thiamphenicol in sheep, camel (0.151h) and (0.165h) (Al Nazawi 2005) ,florfenicol in healthy foal (0.194 h) (Tahamy and Radi 2008) .

The rapid distribution of thiamphenicol in goats is supported by high rate constant of transfer of the drug from central to peripheral compartment [$K_{12} = 5.75 \text{ h}^{-1}$] as compared to the rate constant of transfer of the drug from peripheral to central compartment [$K_{21}=2.06 \text{ h}^{-1}$]. This value is higher than those recorded for thiamphenicol in lambs and calves ($K_{12} = 0.80, 0.29 \text{ h}^{-1}$ and $K_{21}=0.54, 0.23 \text{ h}^{-1}$) (Mengozzi et al. 2002), for florfenicol in broiler chicken ($K_{12} = 2.5 \text{ h}^{-1}$ and $K_{21}=0.85 \text{ h}^{-1}$) (El Banna and El Zorba 2011).

The apparent volume of distribution of thiamphenicol at steady state (V_{dss}) is an accurate indication for the diffusion of the drug into the body tissue (Gilman et al 1980). Thiamphenicol showed V_{dss} of 0.785 L/Kg, this value is nearly similar to those recorded for thiamphenicol in sheep (0.68 L/kg) (Al Nazawi 2005) and in male goats (0.51 L/kg) (Bogazil and Tohamy 2015). Thiamphenicol showed smaller V_{dss} in comparison to those in lactating cattle (1.22 L/kg) (Mestorino et al 1993) ,dairy cattle (0.9 l/kg) (Abdennabi et al 1994 b) ,camel (0.97 L/kg) (Al Nazawi 2005) .On the other hand, thiamphenicol in lactating goats in this study

showed larger V_{dss} compared to those reported in beagle dogs (0.264 L/kg) (Yang et al 2011).

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 (Baggot, 1977). The apparent volume of distribution in the present study indicated moderate tissue penetrating power.

Thiamphenicol is eliminated in the current study following a single intravenous injection with elimination half-life [$t_{0.5(\beta)}$] equal to 4.15h. This observation is nearly agreed with the data recorded for chloramphenicol in sheep (3.24 h) (Mestorino and Errecalde 1998), thiamphenicol in calves and lambs (3.50 and 3.76 h) (Mengozzi et al 2002). On contrast, this value was longer than those reported for thiamphenicol in pigs (1.2 h) (Castells et al 2001), sheep (1.2 h) (Al Nazawi 2005), dog (1.17h) (Yang et al 2011) and male goats (1.2h) (Bogazil and Tohamy 2015). On contrast, this value is shorter than those recorded for florfenicol in sheep (18.83 h) (Jianzhong et al 2004) and healthy foal (7.20 h) (Tohamy and Radi 2008).

The rate of total body clearance of thiamphenicol following a single intravenous injection is 0.002 L/kg/h, this value is lower than that reported for thiamphenicol in lambs and calves (0.40 and 0.58 L/kg/h) (Mengozzi et al 2002), in male goats (0.51 L/kg/h) (Bogazil and Tohamy 2015). Also it lower than those reported for other amphenicols as that reported for florfenicol in egyptian goats (3.306 L/kg/h) (Atef et al 2000), in camel, sheep and goats (0.33, 0.30 and 0.27 L/kg/h) (Ali et al 2003), in rabbit (0.34 L/kg/h) (Abd El Aty et al 2004) in healthy sheep (0.26 L/kg/h) (Jianzhong et al 2004), in pigs (0.23 L/kg/h) (Jianzhong et al 2006) and in healthy broiler chicken (0.38 L/kg/h) (El Banna and EL Zorba 2011).

The variation in total body clearance might be attributed to specific interspecies variation, handling of the drug, method used, healthy status of the animals (Baggot, 1980).

The difference between values calculated for pharmacokinetic parameters may be attributed to animal species, the drug formulation employed, the age, the size or sex of the animal or even inter individual variation and also due to method of analysis of the drug (Hadded et al.1985).

Following a single intramuscular injection of 30 mg thiamphenicol/kg bwt. In normal goats, the drug reached its peak serum concentrations after two hour of injection with a value of (20 μ g/ml). Thiamphenicol could be detected in serum in a therapeutic level (0.357 μ g/ml) at 24 hours post-injection. The reported peak serum concentrations nearly similar to those reported for thiamphenicol in sheep (19.50 μ g/ml) (Abdennabi and Stowe 1994), camel (18.5 μ g/ml) (Al Nazawi 2005). On contrast this result is higher than that recorded for chloramphenicol in sheep (15.75 μ g/ml) (Mestorino and Errecalde 1998). Otherwise, it is lower than that reported for thiamphenicol in lactating cattle (30.90 μ g/ml) (Mestorino et al 1993).

The calculated maximum serum concentration (C_{max}) is (16.67 μ g/ml) at maximum time (t_{max}) is equal to 1.42 of hours. The reported maximum serum concentration (C_{max}) is higher than those reported for thiamphenicol in lambs and calves (5.20 and 3.51 μ g/ml) (Mengozzi et al 2002), in male goats (6.89 μ g/ml) (Bogazil and Tohamy 2015). Also it is higher than those reported for other amphenicols as that reported for florfenicol in pigs (4 μ g/ml) (Jianzhong et al 2003), healthy foal (4.709 μ g/ml) (Tohamy and Radi 2008), in goats (3.07 μ g/ml) (Verma et al 2009), in broiler chicken (6.8 μ g/ml) (El Banna and El Zorba 2011) and in dogs (3.05 μ g/ml) (Birdane and Birdane 2015). On the other hand, the result was lower than that reported by Abd El Aty et al (2004) who detected the maximum serum concentration (C_{max}) of florfenicol in rabbits after intramuscular administration with a value of (21.65 μ g/ml).

The reported [t_{max}] is nearly similar to that reported for florfenicol in pigs (1.00 h) (Jianzhong et al 2006). On contrast, it is longer than those reported for thiamphenicol in sheep (0.37 h) (Abdennebi and Stowe 1994) and for chloramphenicol in sheep (10.00 min) (Wesongah et al 2009).

The elimination half life [$t_{0.5(\beta)}$] following a single intramuscular administration was 4.02 hours. This value is nearly similar to that recorded for florfenicol in pigs (3.91 hours) (Jianzhong et al 2003). On contrast, this result is longer than that reported for thiamphenicol in sheep (1.51 hours) (Abdennebi and Stowe 1994). On the other hand, this result is shorter than those reported for chloramphenicol in sheep (5.75 hours) (Mestorino and Errecalde 1998), for florfenicol in sheep (18.71 hours) (Jianzhong et al 2004), and in pigs (17.2 hours) (Jianzhong et al 2006).

The rate of total body clearance of thiamphenicol following a single intramuscular injection is 0.0016 L/kg/h. This value was lower than that reported for chloramphenicol in cattle (0.128 L/kg/h) (Sanders et al 1988). For florfenicol in sheep (0.25 L/kg/h) (Jianzhong et al 2004).

Bioavailability is the fraction of the drug administered by non vascular route that gains access to the systemic circulation. The obtained result revealed that the calculated systemic bioavailability percent was 66.63%. It is nearly equal to those recorded for chloramphenicol in sheep (65%, Mestorino and Errecalde 1998),

florfenicol in egyptian goats (65.71%) (Atef et al 2000), and for florfenicol in sheep (65.82%) (Ali et al 2003). On contrast, it is higher than those recorded for thiamphenicol in rabbit (16.2%) (Aldana et al 1992), preruminant calf (62%) (Intorre et al 1997), lambs and calves (60%) for both species, (Mengozzi et al 2002), and for florfenicol in dogs (44.70%) (Birdane and Birdane 2015). Also it is higher than that reported for other amphenicols as those reported for chloramphenicol in cattle (19.1%) (Sanders et al 1988) and for florfenicol in diseased broiler chicken (55%) (El Banna and El Zorba 2011). On the other hand, this value is lower than those reported for thiamphenicol in beef and dairy cattle (84%) (Abdennabi et al 1994 b), male goats (87.61%) (Bogazil and Tohamy 2015), and also lower than those reported for other amphenicols as that reported for florfenicol in rabbit (88.25%) (Abd El Aty et al 2004), pigs (96.9%) (Jianzhong et al 2006), in healthy foal (73.48%) (Tohamy and Radi 2008), goats (87.64%) (Verma et al 2009), broiler chicken (71.5%) (El Banna and El Zorba 2011), and for chloramphenicol in Sokoto red goats (80%) (Etuk et al 2005).

Repeated intramuscular administration of thiamphenicol in normal and *Pasteurella multocida* infected goats once daily for 5 consecutive days revealed that the drug could be detected in a therapeutic level for 24 hours following repeated intramuscular administrations and exceeded the minimum inhibitory concentration (MIC_{90}) of thiamphenicol (0.3 μ g/ml).

The relative higher serum concentrations of thiamphenicol after the last dose compared to the first doses indicated the accumulation of thiamphenicol in blood during multiple dosing at 24 hours intervals for five consecutive days. These observations agreed with data reported by Lohani et al (2010), who found that increase in the mean plasma concentration of following the oral administration of florfenicol in chicken given a daily dose of 30 mg/kg b.wt for five consecutive days. The study showed that the blood concentrations of thiamphenicol in *Pasteurella multocida* infected goats are significantly lower than those in normal goats following repeated intramuscular injection. These lower blood concentrations in *Pasteurella multocida* infected goats might be attributed to the higher penetrating power of thiamphenicol to the diseased tissues (Baggot, 1980). This phenomenon is similar to data recorded by El banna and El Zorba (2011), who found that the maximum plasma concentration of florfenicol detected in control healthy broiler chicken was higher than that detected in infected bird. On contrast this result is differ than that recorded by Perez et al (2015) who showed that intravenous administration of *E. coli* lipopolysaccharide in sheep produce higher plasma concentrations of florfenicol due to decrease in the total body clearance of the drug.

In this study, the total body clearance (CL_{tot}) in normal goats are lower than in *Pasteurella multocida* infected goats. This result supported by Abdulgafar et al. (2011) and Etuk and Onyeyili, (2006), 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 (Perez et al 2015) who observed that the clearance of florfenicol was significantly reduced in Ecoli infected sheep than in non infected animals.

The highest concentrations of thiamphenicol in milk are recorded 4 hours after each intramuscular injection with significant lower values in *Pasteurella multocida* infected goats than in normal goats. This might be attributed to accumulation of drug in the inflamed tissues (Baggot, 1980). This result is similar to those reported by El-sayed et al, (1989) and (1994) who found that milk concentrations of gentamicin and cephradine were significantly lower in infected goats and cattle than in normal ones, respectively.

From the obtained results, the dose of thiamphenicol used in the present study induced therapeutically concentrations in milk. These concentrations suggested that, thiamphenicol would be efficacious in treatment of mastitis caused by sensitive organisms in lactating goats at dose 30 mg /kg bwt. daily for 3-5 days.

The mean peak urine concentrations of thiamphenicol were reached 4 hours after each intramuscular injection. The lower urine thiamphenicol concentrations in *Pasteurella multocida* infected goats than in normal goats might be attributed to the accumulation of the drug in the inflamed tissues (Baggot, 1980).

The ratio between thiamphenicol clearance and creatinine clearance revealed a significant lower ratio in *Pasteurella multocida* infected goats than in normal goats at different time of sampling. This indicates that glomerular filtration seemed to be the main pathway of thiamphenicol elimination. This observation supported by (El-Sayed et al 1994) 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 filtration seemed to be the main pathway of cephradine elimination with a limited rate of tubular reabsorption

5. Conclusion

The intramuscular bioavailability of thiamphenicol in normal goats was 66.63 %. This value referred a better absorption of thiamphenicol from its site of intramuscular administration. The high milk concentrations of thiamphenicol e in lactating goats after repeated intramuscular administrations, suggested that thiamphenicol could be used for treatment of infection caused by sensitive microorganisms to thiamphenicol in lactating goats. The high concentrations of thiamphenicol in urine after repeated intramuscular administrations, suggested that thiamphenicol is a suitable antimicrobial for treatment of urinary tract infections caused by microorganisms sensitive to thiamphenicol in goats.

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