

## PHARMACOKINETICS AND BIOAVAILABILITY OF THIAMPHENICOL GLYCINATE HCL IN MALE GOATS

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### ABSTRACT

*The Pharmacokinetic profile of thiamphenicol glycinate HCl was studied in male goats following single intravenous and intramuscular administration of 30 mg kg<sup>-1</sup> b.wt. Thiamphenicol concentration in serum was determined by microbiological assay using Bacillus subtilis (ATCC 6633) as test organism. After intravenous injection the serum thiamphenicol concentration time course was found to obey two-compartment open model with distribution ( $t_{0.5(\alpha)}$ ) and elimination ( $t_{0.5(\beta)}$ ) half lives of  $0.06 \pm 0.003$  and  $1.20 \pm 0.163$  h., respectively. Total body clearance ( $Cl_B$ ) and steady state volume of distribution ( $Vd_{ss}$ ) were  $1.025 \pm 0.04$  L kg<sup>-1</sup> h<sup>-1</sup> and  $0.51 \pm 0.010$  L kg<sup>-1</sup>., respectively. After intramuscular administration the observed mean peak serum concentration ( $C_{max}$ ) was  $6.89 \pm 0.052$   $\mu\text{g ml}^{-1}$  achieved after maximum time ( $t_{max}$ ) of  $1.53 \pm 0.08$  hour post-injection. The systemic bioavailability after intramuscular was 87.61 % . The plasma protein binding percent was 13.3%.*

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## INTRODUCTION

Thiamphenicol is a derivative of chloramphenicol, in which the aromatic P- nitro group was replaced with a methylsulphonyl group. It is chemically [d(+)-threo-2-di-chloroacetamido-1-(4-methyl sulphonylphenyl) propane-1,3-diol] (*Kitamura et al., 1997; Drago et al.,2000;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 ,aplastic anaemia or grey syndrome in humans (*Li et al., 2002; Giguère, et al., 2013*).

It is generally recognized that TAP 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;2002*).

Thiamphenicol is 1–2 times less active than chloramphenicol, although of equal activity against *Haemophilus*, *B. fragilis*, and *streptococci*. Cross resistance with chloramphenicol is complete in bacteria that possess CATs. It is broad spectrum antibiotic includes both Gram-negative and Gram-positive bacteria involved in upper and lower respiratory tract infections, bacterial prostatitis, and sexually transmitted diseases evoked by most *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Moraxella catharralis*, and *Haemophilus influenzae*, as well as anaerobes (*Mengozi et al., 2002; Tullio et al., 2004*).

TAP, however, has been limited to oral administration because of its low water solubility. In order to develop parenteral formulation with improved water solubility, thiamphenicol glycinate (TG), the ester

prodrug of TAP, has been synthesized by esterificating the primary hydroxyl group with glycine. Unlike TAP, TG has high water solubility and can be readily developed for convenient parenteral formulation. TG is presumably cleaved by tissue esterase *in vivo* (**Drago et al., 2000**).

Unlike chloramphenicol, Thiamphenicol elimination is not affected by liver disease or by the use of other drugs metabolized in the liver. It is not eliminated by hepatic glucuronide conjugation but excreted unchanged in the urine. However, some studies in pigs indicate a low extent of TAP glucuronidation (**Uesugi et al.,1974; Emea, 1992;Castells et al., 2001**)).

The pharmacokinetic parameters of thiamphenicol follow allometric scaling, in that values for elimination half-life and volume of distribution increase with body size from mice through rats, rabbits, dogs, pigs, sheep and calves (**Castells et al., 2001**). Therapeutic concentrations are achieved in milk of lactating cows (**Abdennebi et al., 1994b**). There are numerous investigations of the pharmacokinetics of TAP after intravenous (i.v.) and intramuscularly (i.m.) administration in cattle (**Abdennebi et al., 1994b**), calves (**Gamez et al.,1992**), sheep (**Abdennebi et al., 1994a**), lambs (**Mengozzi et al.,1997**) lactating goats (**Lavy et al., 1991**), dogs (**Castells et al., 1997; Yang et al., 2011**) and pigs (**Castells et al., 1999**). The data obtained after oral (p.o.) administration of TAP in different animal species, including pigs (**Castells et al., 2000**) are inadequate, although it can be used orally to treat several bacterial infections (*Mycoplasma hyopneumoniae*, *Campylobacter fetus ssp. jejuni*, *Actinobacillus pleuropneumoniae* and others) in various animal species (**Vanhoof et al.,1980; Inamoto et al., 1994; Asawa et al., 1995**).Thiamphenicol has been widely used in many

countries and regions, for therapeutic purposes in clinical practice and veterinary medicine. It is approved for the treatment, control of respiratory and intestinal infections in cattle, poultry, recently, it has been adopted for the treatment of several infectious diseases in pigs, sheep and fin fish (*EMEA,1998 ;Turton et al., 2000; 2002*)).

Thiamphenicol appears to be underutilized in the treatment of many infections caused by susceptible organisms due to lack of detailed dosage information and unavailable pharmacokinetic and clinical studies (*Giguère, et al., 2013*). Thus the aim of the present study was to determine the pharmacokinetic parameters and bioavailability of thiamphenicol in male goats in order to establish adequate dose regimen for potential clinical use in goat infections with susceptible organisms.

## MATERIAL AND METHODS

**Drug:** Thiamphenicol glycinate HCl (Thiamphenil<sup>®</sup>), The Nile Company For Pharmaceuticals and Chemical Industries). It was supplied as thiamphenicol glycinate HCl 0.9468 g as dry substance (Equivalent to 0.75g thiamphenicol).

**Animals:** Three healthy male goats weighing 13-17 kg b. wt (6 month old) were used. Animals were kept under good hygienic condition, feed on hay and concentrated mixture and water *ad-libitum*. Goats were not treated with antibiotics at least one month prior to the trial.

**Experimental design:** In cross over study with two weeks washout period, goats were administered thiamphenicol at a dose of 30 mg kg<sup>-1</sup> b. wt. according to *Castells et al., 2001*. Thiamphenicol was given by single intravenous (i.v.)(into the left jugular vein), and intramuscular

(i.m.) ( into the deep gluteal muscle of hindquarter). Blood samples (5 ml each) were collected from the right jugular vein just before drug administration and at 5, 10, 15, 30-minutes and 1, 2, 4, 6, 8, 12 and 24-hour post drug administration. The blood samples were left to clot at room temperature, then centrifuged at 3000 rpm for 15 minute to separate clear serum. Serum samples were stored at  $-20^{\circ}\text{C}$  until assayed. The obtained serum samples were used for determination of thiamphenicol concentration.

**Drug assay.** Thiamphenicol concentrations in serum samples were determined using the microbiological assay method described by *Arret et al., (1971)* using *Bacillus subtilis* (ATCC 6633) as a test organism. Standard curves were constructed using antibacterial-free sera collected from goats. Six wells, 8 mm in diameter were cut at equal distances in standard petri dishes containing 25 ml seeded agar. The wells were filled with 100  $\mu\text{l}$  of either the test samples or thiamphenicol standards. The plates were incubated at  $37^{\circ}\text{C}$  for 16-18 hours. The inhibition zone diameters were measured and the thiamphenicol concentrations in the test samples were calculated from the standard curve. The lower detectable limit of the thiamphenicol assay was  $0.048 \text{ ug ml}^{-1}$ . Semi-logarithmic plots of the inhibition zone diameter versus standard thiamphenicol concentrations in serum were linear with typical correlation coefficient of 0.998 (for the standard curve).

The extent of protein binding of thiamphenicol was determined *in vitro* using the method of *Craig and Suh, (1991)* with thiamphenicol concentrations of 100, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.195, 0.097 and  $0.048 \text{ ug ml}^{-1}$  in serum according to the following equation:

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$$\text{Protein binding \%} = \frac{\text{Zone of inhibition in buffer} - \text{Zone of inhibition in serum}}{\text{Zone of inhibition in buffer}} \times 100$$

### Pharmacokinetic analysis:

Serum concentrations of thiamphenicol for each individual goat after IV and IM administrations were subjected to a compartmental analysis using a nonlinear least-squares regression analysis with the help of a computerized curve-stripping program (RStrip; Micromath Scientific Software, Salt Lake City, UT, USA). For IV and IM data, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC) (*Yamaoka et al., 1978*). Following IV injection, the serum concentration-time relationship was best estimated as a two-compartment open model system (*Baggot, 1978*) according to the following bi-exponential equation:  $C_p^0 = Ae^{-\alpha t} + Be^{-\beta t}$

where  $C_p^0$  is the concentration of drug in the serum at time  $t$ ;  $A$  is the intercept of the distribution phase with the concentration axis expressed as  $\mu\text{g ml}^{-1}$ ;  $B$  is the intercept of the elimination phase with the concentration axis expressed as  $\mu\text{g ml}^{-1}$ ;  $\alpha$  is the distribution rate constant expressed in units of reciprocal time ( $\text{h}^{-1}$ );  $\beta$  is the elimination rate constant expressed in units of reciprocal time ( $\text{h}^{-1}$ ); and  $e$  is the base of natural logarithm. This program also calculated non compartmental parameters using the statistical moment theory (*Gibaldi and Perrier, 1982*). The terminal elimination half-life ( $t_{0.5(\text{el})}$ ) and absorption half-life ( $t_{0.5(\text{ab})}$ ) were calculated as  $\ln 2/K_{\text{el}}$  or  $\ln 2/K_{\text{ab}}$ , respectively, where  $K_{\text{el}}$  and  $K_{\text{ab}}$  are the elimination and absorption rate constants, respectively. The area under serum concentration-time curve (AUC) and area under the first moment curve (AUMC) were calculated by the method of

trapezoidal method. The mean residence time (MRT) and mean absorption time (MAT) were calculated as  $MRT = AUMC/AUC$  and  $MAT = MRT_{i.m} - MRT_{i.v}$ .

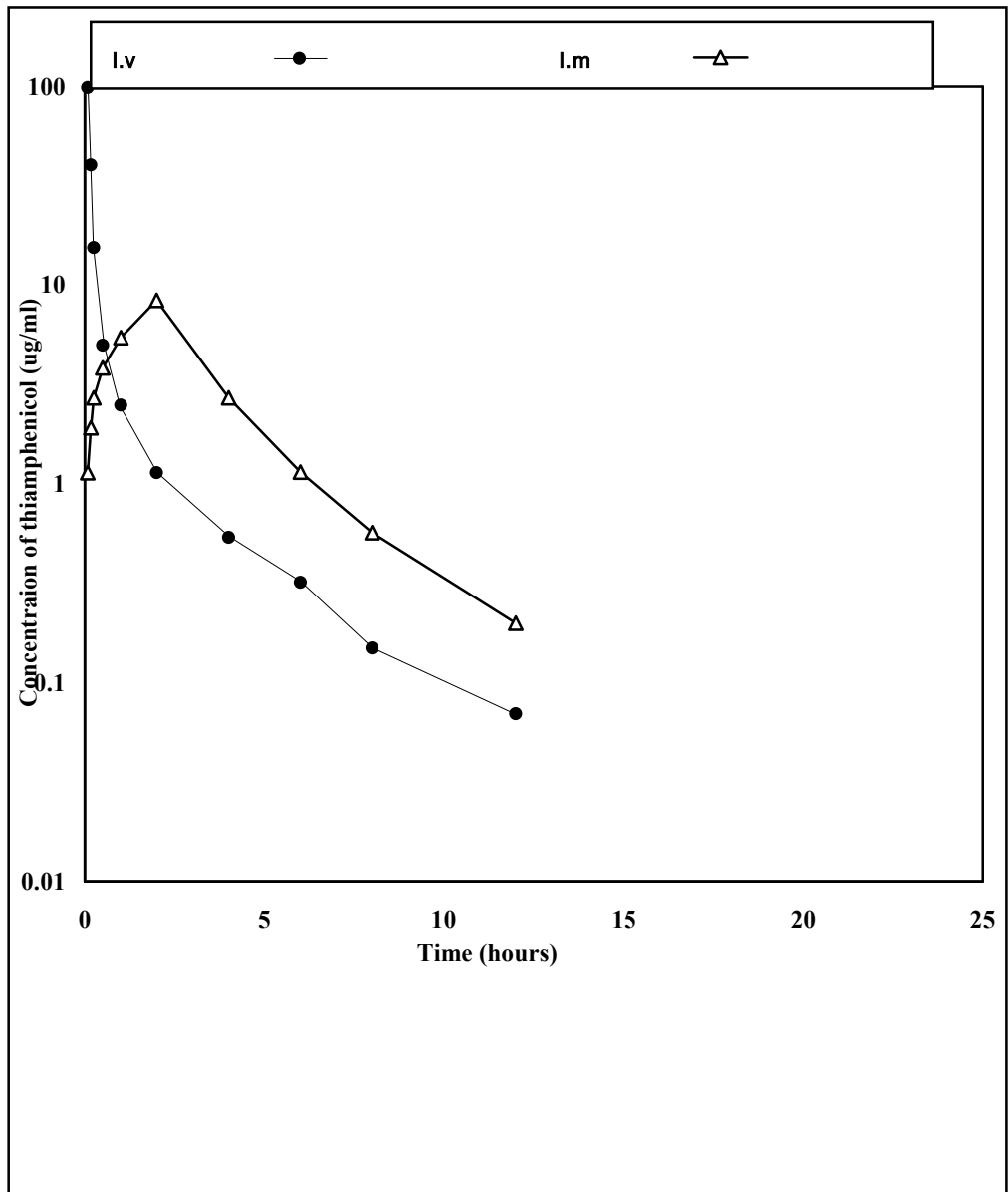
The total body clearance ( $Cl_B$ ) was calculated as  $Cl_B = Dose/AUC$  and the absolute bioavailability (F) as  $F = AUC_{i.m} / AUC_{i.v} \times 100$ .

Results were expressed as mean and standard error (S.E). Standard errors were calculated from the mean data according to *Snedecor and Cochran (1976)*.

## RESULTS

The mean serum concentrations time course of thiamphenicol after i.v. and i.m. administration are depicted in **figure(1)**. Pharmacokinetic parameters are showed in **table(1)**. After i.v. administration of 30 mg  $kg^{-1}$  b. wt., the thiamphenicol serum concentration time data obeys two-compartment open model. The distribution ( $t_{0.5(\alpha)}$ ) and elimination ( $t_{0.5(\beta)}$ ) half-lives were  $0.06 \pm 0.003$  and  $1.20 \pm 0.163$  h., respectively. Total body clearance ( $Cl_B$ ) and steady state volume of distribution ( $Vd_{ss}$ ) were  $1.025 \pm 0.04$  L  $kg^{-1} h^{-1}$  and  $0.51 \pm 0.010$  L  $kg^{-1}$ ., respectively and mean residence time was  $0.53 \pm 0.003$  h.

Thiamphenicol was rapidly absorbed after i.m. administration with absorption half life ( $t_{0.5(ab)}$ )  $0.83 \pm 0.02$  h. Peak serum concentration ( $C_{max}$ ) was  $6.89 \pm 0.052$   $\mu g$  ml<sup>-1</sup> achieved after maximum time ( $t_{max}$ ) of 1.53 hour post administration. The drug was slowly eliminated from blood after i.m. than i.v. administration. The systemic bioavailability after intramuscular administration was 87.61 % . The extent of the plasma protein binding was 13.3%.



**Fig. (1):** Semilogarithmic graph depicting the time-concentration of thiamphenicol in serum of male goats after a single intravenous and intramuscular injection of 30 mg/kg b.wt.



**Table (1):** Mean ( $\pm$  SE) Pharmacokinetic parameters of thiamphenicol following a single intravenous and intramuscular administration of 30 mg kg<sup>-1</sup> b.wt in male goats (n=3).

Parameter	Unit	I.V	Parameter	Unit	I.M
C <sub>p</sub> <sup>o</sup>	ug ml <sup>-1</sup>	259.00 $\pm$ 9.36	k <sub>ab</sub>	h <sup>-1</sup>	0.84 $\pm$ 0.17
A	ug ml <sup>-1</sup>	254.46 $\pm$ 7.51	K <sub>el</sub>	h <sup>-1</sup>	0.50 $\pm$ 0.02
B	ug ml <sup>-1</sup>	4.55 $\pm$ 0.2 3	t <sub>0.5(ab)</sub>	h	0.83 $\pm$ 0.02
$\alpha$	h <sup>-1</sup>	11.89 $\pm$ 0.566	t <sub>0.5(el)</sub>	h	1.37 $\pm$ 0.17
$\beta$	h <sup>-1</sup>	0.57 $\pm$ 0.038	C <sub>max</sub>	ug ml <sup>-1</sup>	6.89 $\pm$ 0.052
k <sub>21</sub>	h <sup>-1</sup>	0.77 $\pm$ 0.043	t <sub>max</sub>	h	1.53 $\pm$ 0.08
K <sub>el</sub>	h <sup>-1</sup>	8.84 $\pm$ 0.059	AUC	ug ml <sup>-1</sup> h <sup>-1</sup>	28.64 $\pm$ 2.07
k <sub>12</sub>	h <sup>-1</sup>	2.85 $\pm$ 0.184	MRT	h	3.11 $\pm$ 0.35
t <sub>0.5(<math>\alpha</math>)</sub>	h	0.06 $\pm$ 0.003	MAT	h	2.58 $\pm$ 0.10
t <sub>0.5(<math>\beta</math>)</sub>	h	1.20 $\pm$ 0.163	F	%	87.61 $\pm$ 5.11
MRT	h	0.53 $\pm$ 0.003			
AUC	ug ml <sup>-1</sup> h <sup>-1</sup>	32.69 $\pm$ 1.35			
V <sub>c</sub>	L kg <sup>-1</sup>	0.116 $\pm$ 0.007			
Vd <sub>ss</sub>	L kg <sup>-1</sup>	0.51 $\pm$ 0.047			
Cl <sub>B</sub>	L kg <sup>-1</sup> h <sup>-1</sup>	1.025 $\pm$ 0.04			

C<sub>p</sub><sup>o</sup> Thiamphenicol concentration at zero time (immediately after single i.v injection); **A**, **B** zero-time intercepts of the biphasic disposition curve;  $\alpha$ ,  $\beta$  hybrid rate constants representing the slopes of distribution and elimination phases, respectively; k<sub>12</sub> first-order constant for transfer from central to peripheral compartment; k<sub>21</sub> first-order constant for transfer from peripheral to central compartment; K<sub>el</sub> elimination rate constant; t<sub>0.5( $\alpha$ )</sub> distribution half-life; t<sub>0.5( $\beta$ )</sub> elimination half-life; **MRT** mean residence time; **AUC** area under serum concentration-time curve; **V<sub>c</sub>** volume of the central compartment; **Vd<sub>ss</sub>** volume of distribution at steady state; **Cl<sub>B</sub>** total body clearance. k<sub>ab</sub> first-order absorption rate constant; C<sub>max</sub> maximum serum concentration; t<sub>max</sub> time to peak serum concentration; t<sub>0.5(ab)</sub> absorption half-life; t<sub>0.5(el)</sub> elimination half-life; **MAT** mean absorption time; **F** fraction of drug absorbed systemically after i.m.

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## DISCUSSION

The present work was designed to study pharmacokinetic parameters of thiamphenicol in male goats after the single intravenous (i.v.) and intramuscular (i.m.) administration of 30 mg kg<sup>-1</sup> b.wt .The thiamphenicol serum concentration was determined using microbiological assay.

Thiamphenicol concentration time course in serum of male goats after the single i.v. dose of 30 mg kg<sup>-1</sup> b.wt. was best fitted using a two-compartment open model. Our findings are similar to those reported in lactating goats , veal calves. ,dairy cows, pig, sheep ,camel and beagle dog, (*Lavy et al., 1991; Gamez et al., 1992;Mestorino et al., 1993; Haritova et al., 2002 ; Al-Nazawi ,2005 and Yang et al.,2011*).

The initial distribution phase was rapid with distribution half life ( $t_{0.5(\alpha)}$ ) of 0.06 h. similar to findings recorded for thiamphenicol in lactating cattle 0.1 h (*Mestorino et al., 1993*) beagle dog 0.069 h (*Yang et al.,2011*), and slightly shorter than sheep 0.151 and camel 0.165 h (*Al-Nazawi, 2005*).

The mean elimination half-life ( $t_{0.5(\beta)}$ ) was 1.20 h., which is similar to findings reported in other studies as in pig 1.2 h. (*Castells et al.,2001*), sheep 1.5 h. (*Al-Nazawi ,2005;*) and dog 1. 17 h. (*Yang et al.,2011*), nearly similar to that reported in lactating cattle 1.6±0. h. (*Mestorino et al., 1993*), dairy cattle 1.75h. (*Abdennebi et al., 1994b*), dog 1.7 h. and rabbit 1.8 h (*Castells et al.,2001*) and also, lower than values in calf 2.4 h. (*Castells et al.,2001*) and camel 2.1 h. (*Al-Nazawi, 2005*). This variation may be due to species difference.

The mean body clearance ( $Cl_B$ ) of  $1.025 + 0.04 \text{ L kg}^{-1} \text{ h}^{-1}$  was larger than those reported in lactating cattle  $0.234 \text{ L kg}^{-1} \text{ h}$  (*Mestorino et al., 1993*), camel  $0.318 \text{ L kg}^{-1} \text{ h}$ , sheep  $0.36 \text{ L kg}^{-1} \text{ h}$  (*Al-Nazawi, 2005*), beagle dogs  $0.076 \text{ L kg}^{-1} \text{ h}^{-1}$  (*Yang et al., 2011*) and smaller than those reported in rabbit 2.1, calf 19.608, dog 5.28, pig 21.9, sheep  $26.928 \text{ L kg}^{-1} \text{ h}^{-1}$  (*Castells et al., 2001*). An allometric relationship exists for physiological functions in particular hepatic blood flow, correlated with body weight across different species (*Adolph, 1949*). By applying principles of allometry to pharmacokinetic parameters (*Riviere et al., 1997*), the finding of larger clearance for the species with the smaller body weight may be expected. The shorter elimination half-life might be attributed to higher glucuronyl transferase activity in goats (*Short et al., 1988*).

The volume of distribution at steady state ( $V_{d_{ss}}$ ) is an accurate indication for the diffusion of the drug in the body tissues (*Gilman et al., 1980; Galinsky and Svensson, 1995*). Thiamphenicol showed  $V_{d_{ss}}$  of  $0.51 + 0.047 \text{ L kg}^{-1}$ , in male goats, which is similar to that in sheep  $0.68 \text{ L kg}^{-1}$  (*Al-Nazawi, 2005*). Thiamphenicol showed smaller  $V_{d_{ss}}$  compared to those in dairy cattle  $0.9 \text{ L kg}^{-1}$  (*Abdennebi et al., 1994,b*), sheep  $1.0 \text{ L kg}^{-1}$  (*Abdennebi et al., 1994a*), lactating cattle  $1.220 \text{ L kg}^{-1}$  (*Mestorino et al., 1993*), rabbit 3.5, calf 63, dog 11, pig 16.5, sheep  $46.2 \text{ L kg}^{-1}$  (*Castells et al., 2001*), camel ( $0.97 \text{ L kg}^{-1}$ ) (*Al-Nazawi, 2005*). On the other hand, Thiamphenicol in male goats showed larger  $V_{d_{ss}}$  compared to those in beagle dogs ( $0.264 \text{ L kg}^{-1}$ ) (*Yang et al., 2011*). This may be due to individual, anatomical or physiological variations between the different individuals and species.

Thiamphenicol was absorbed following the i.m. administration with an absorption half-life ( $t_{0.5(ab)}$ )  $0.83 \pm 0.06$  h. compared to those reported in sheep 0.08 h (**Abdennebi and Stowe, 1994**) and 0.07 h in dairy cattle (**Mestorino et al., 1993**). Elimination half-life( $t_{0.5(el)}$ )  $1.37 \pm 0.17$  h This result is similar to findings reported in sheep 1.5 h (**Abdennebi and Stowe, 1994**), but shorter than findings reported in dairy cattle 2.2h (**Mestorino et al., 1993**).

The mean peak plasma concentration ( $C_{max}$ ) of Thiamphenicol was  $6.89 \pm 0.03 \mu\text{g ml}^{-1}$  achieved at ( $t_{max}$ )  $1.53 \pm 0.08$  h. post-injection. Our finding is lower and longer than the values reported in lactating cows  $C_{max}$   $30.9 \mu\text{g ml}^{-1}$  and  $t_{max}$  23 min in dairy cattle (**Mestorino et al., 1993**). The differences in kinetic parameters are relatively common and are frequently related to interspecies variation, assay method used, extent of blood sampling and the health status of the animals (**Haddad et al., 1985**).

The systemic bioavailability (F) of thiamphenicol in male goats after i.m. injection was  $87.61 \pm 5.11\%$ . This value was similar to that is recorded in veal calves 85 % (**Ashraf, 1989**) sheep 87.5 % (**Abdennebi and Stowe, 1994**), dairy cattle 84% (**Abdennebi et al., 1994,b**) and slightly lower than that in lactating cattle 100% (**Mestorino et al., 1993**). Variability in absorption from the i.m. site might be due to differences in regional blood flow in the different muscle tissue sites which is the major determinant.

*In vitro* protein binding percentage of thiamphenicol in serum of male goats was  $13.30 \pm 0.164 \%$ . This value was similar to its value in beagle dogs lowest than 10 % (**Yang et al.,2011**). This finding indicates that the drug is moderately low bound to serum proteins

Previous studies showed that thiamphenicol concentration in tissues was similar to that found in plasma (*Cambiers et al., 1970*). The minimum inhibitory concentrations (MIC<sub>s</sub>) against most of thiamphenicol sensitive bacteria have been reported as 0.5 ug/ml (*Sutter and Finegold. 1976*), the mean serum concentration remain over the MIC for 8 hours after i.m. administration.

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