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Original Research Article

Disposition kinetics, *in vitro* plasma protein binding and tissue residues of tilmicosin in healthy and experimentally (CRD) infected broiler chickens

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ABSTRACT

Background: Several studies assayed the pharmacokinetics of tilmicosin in broilers at a dosage of (25mg/kg.b.wt.). The aim of this study was to investigate the pharmacokinetics and tissue residues of tilmicosin following single and repeated oral administrations (25mg/kg.b.wt.) once daily for 5 consecutive days in healthy and experimentally *Mycoplasma gallisepticum* and *E. coli* infected broilers.
Methods: After oral administrations of tilmicosin (25 mg/kg.b.wt.) one ml blood was collected from the right wing vein and tissues samples for determination of tilmicosin concentrations and the disposition kinetics of it by the microbiological assay method using *Bacillus subtilis* (ATCC 6633) as a test organism.
Results: In this study, the plasma concentration time graph was characteristic of a two-compartments open model. Following a single oral administration, tilmicosin was rapidly absorbed in both healthy and experimentally infected broilers with an absorption half-life of ($t_{0.5(ab)}$) 0.45 and 0.52h, maximum serum concentration (C_{max}) was 1.06 and 0.69µg/ml at (t_{max}) about 2.56 and 2.81h, ($t_{0.5(el)}$) was 21.86 and 22.91h and (MRT) was 32.15 and 33.71h, respectively; indicating the slow elimination of tilmicosin in chickens. The *in-vitro* protein binding was 9.72±0.83%. Serum concentrations of tilmicosin following repeated oral administration once daily for five consecutive days, almost peaked 2h after each dose with lower significant values recorded in experimentally infected broiler chickens than in healthy ones.
Conclusions: This study showed that tilmicosin was cleared rapidly from tissues. The highest residue values were recorded in the lung followed by liver and kidneys while the lowest values were recorded in spleen, fat and thigh muscles. Five days for withdrawal period of tilmicosin suggested in broilers.

Keywords: Bioavailability, Broiler Chicken, *E. coli*, Kinetic, Mycoplasma, Tissue residues, Tilmicosin

INTRODUCTION

The macrolides are a class of antibiotics used to treat many different infections, and, in light of their excellent intracellular activity, they are especially important in the treatment of respiratory tract infections.[1] Macrolides, as a class of natural or semisynthetic products, express their antibacterial activity primarily by reversible binding to the bacterial 50S ribosomal subunits and by blocking nascent proteins progression through their exit tunnel in bacterial protein biosynthesis. Generally, macrolides are considered to be bacteriostatic, they may also be bactericidal at higher doses.[2]

Tilmicosin is one of the most important antimicrobial agents used for treatment and control of *Mycoplasma*

gallisepticum infection. Tilmicosin is a semi-synthetic broad-spectrum bacteriostatic antibiotic of macrolides group synthesized from tylosin for veterinary use only. It has an antibacterial spectrum that is predominantly effective against *Mycoplasma spp, Pasteurella spp*, and various Gram-positive organisms.[3]

Tilmicosin has been used extensively to treat respiratory disease in poultry.[4]

It accumulates in high concentrations in lung tissue in comparison with their plasma levels and it has a considerable concentration in macrophages, heterophyles, monocytes of the respiratory system in comparison with other wide spectrum antibiotics.[5,6]

The target of this study was to determine serum concentrations, kinetic profile as well as tissue residues of tilmicosin following a single oral (PO) and repeated oral administration of tilmicosin (25mg/kg.b.wt.) in healthy and experimentally *Mycoplasma gallisepticum and Escherichia coli* infected broiler chickens.

METHODS

Drug

Tilmicosin was obtained as an oral solution from ATCOPHARMA for pharmaceutical industries, Industrial Zone - Quisna - El-Menofia, Egypt, under a trade name (Tilmicoral 25% oral solution, 240ml). Each 100ml contain Tilmicosin phosphate 29.4gm Eq. to tilmicosin base 25gm.

Birds

Fifty clinically healthy Hubbard broiler chickens of both sexes of 7 day of age were used in this investigation. Chickens were obtained from a private poultry farm. The chickens were housed in hygienic floor system chambers and were fed on a balanced antibiotics free ration obtained from five Stars Company for poultry ration formulation industries and water was offered to chickens as *ad-libitum.* The experiment was performed in accordance with the guidelines set by the Ethical Committee of Faculty of Veterinary Medicine, University of Sadat city, Egypt.

The chickens were divided into 4 groups:

Group 1

It included 6 healthy broiler chickens; each chicken was orally administered a single dose of tilmicosin 25mg/kg.b.wt. to determine the serum concentrations and pharmacokinetics of the drug.[7]

Group 2

Six broiler chickens were used in this group; each chicken was experimentally infected intratracheal (I/T) with 0.1ml aliquots of PPLO broth culture equal (100ul) containing ($1x10^6$CFU/ml of a pathogenic strain of *Mycoplasma gallisepticum*).[8]

After appearance of the respiratory clinical symptoms beginning from day 6 after infection and become intensive at 15th day post infection with *Mycoplasma gallisepticum*, each *Mycoplasma gallisepticum* infected bird was experimentally inoculated with 0.2ml of *E. coli* strain serotype (O111:H4) containing ($1x10^8$CFU/ml) intratracheally by using automatic micropipette.[9] After beginning of the symptoms; each infected bird was given tilmicosin orally at a dose rate of 25mg/kg.b.wt of once daily for five consecutive days to determine the serum concentrations and pharmacokinetics of the drug.

Group 3

It included 25 healthy broiler chickens. Each one was given orally with 25mg tilmicosin/kg.b.wt, once daily for five consecutive days to determine serum concentrations, pharmacokinetics, tissue distribution and residual contents of the drug.[7]

Group 4

It included 6 experimentally (*Mycoplasma gallisepticum* and *E. coli*) infected broiler chickens; each chicken was orally administered a single dose of tilmicosin 25mg/kg.b.wt. to determine the serum concentrations and pharmacokinetics of the drug.

Samples

Blood samples

One ml blood was collected from the right wing vein of each bird at 10, 20 and 30 minutes and 1, 2, 4, 8, 12 and 24 hours after oral administration. Blood samples following repeated oral administrations of tilmicosin in the healthy and experimentally infected chickens for 5 consecutive days were taken daily at 10, 20, 30 minutes, 1, 2, 4, 8, 12 and 24 hours. All blood samples were collected in sterilized centrifuged tubes and allowed to clot. Serum was separated by centrifugation at 3000 r.p.m for 10 minutes. Sera were kept frozen until assayed.

Tissue samples

Three chickens (from group 3) were randomly selected and slaughtered, 2 hours then at 1st,2nd,5th,7th,9th and 13th day after the last dose of drug administration. Tissues samples were taken from (liver, kidney, lung, spleen, fat and thigh muscle) and sera were collected from the slaughtered birds for drug assay.

Drug bioassay

Concentrations of tilmicosin in serum and tissue samples were determined by the microbiological method of

antibiotic using *Bacillus subtilis* (ATCC 6633) as a test organism for tilmicosin.[10]

Pharmacokinetic analysis

Serum concentrations of tilmicosin for each individual chicken after oral administration was subjected to a compartmental analysis using a nonlinear least-squares regression analysis with the help of a computerized curve-stripping program (R Strip; Micromath Scientific Software, Salt Lake City, UT, USA). For PO data, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC).[11]

Following PO administration, the serum concentration time relationship was best estimated as a two compartment open model system.[12]

The pharmacokinetic parameters were reported as mean ± SD. Data obtained throughout the study were analyzed using Students t-test.[13]

RESULTS

The mean serum tilmicosin concentrations in both healthy and experimentally infected broiler chickens following its single oral administration of (25mg/kg.b.wt.) are reported in Figure 1. The mean peak serum level in both healthy and experimentally infected broiler chickens (1.19 and 1.09µg/ml) achieved 2 hours post oral administration; and still detected in a concentration of (0.62and0.60µg/ml) at 24 hours, respectively. Tilmicosin could be distinguished in a therapeutic concentration for 24 h after oral administration. The pharmacokinetic parameters following a single oral administration of tilmicosin (25mg/kg.b.wt.) in both healthy and experimentally infected broiler chickens were outlined in Table 1. Tilmicosin reached its maximum serum concentrations (C_{max}) (1.06 and 0.69µg/ml) after 2.56 and 2.81h in both healthy and experimentally infected broiler chickens, respectively. Oral administration of tilmicosin (25mg/kg.b.wt.) once daily for five consecutive days in healthy and *M. gallisepticum and E. coli* infected broiler chickens revealed a significant decrease in tilmicosin serum concentration of *M. gallisepticum and E. coli* infected broilers than in healthy broilers (Figure 2, 3 and 4). The pharmacokinetic parameters of tilmicosin after repeated oral administration in healthy and experimentally *M. gallisepticum and E. coli* infected broiler chickens were tabulated in Table 2 and Table 3, respectively. Tilmicosin maximum serum concentrations (C_{max}) revealed significant decrease in experimentally infected broilers than healthy one from the 2nd day till 5th day of administration.

Table 1: Pharmacokinetic parameters of tilmicosin in healthy and experimentally infected broiler chickens after single oral administration of 25mg/kg.b.wt (N=6).

Parameter	Unit	Healthy (±SE)	Experimentally infected (±SE)
A	µg.ml^{-1}	1.07±0.006	0.98±0.006***
K_{ab}	h^{-1}	1.50±0.02	1.34±0.017***
$T_{0.5\ (ab)}$	H	0.45±0.007	0.52±0.006***
B	µg.ml^{-1}	1.17±0.006	1.10±0.003***
K_{el}	h^{-1}	0.03±0.001	0.03±0.001
$T_{0.5\ (el)}$	H	21.86±0.32	22.91±0.25*
C_{max}	µg.ml^{-1}	1.06±0.004	0.69±0.187
T_{max}	H	2.56±0.02	2.81±0.025***
$AUC_{(0\text{-}inf)}$	µg.h.ml^{-1}	38.68±0.42	37.77±0.31**
MRT	H	32.15±0.46	33.71±0.37*
IBD	H	57.18±0.09	56.06±0.05***

* P <0.05 ** P <0.01 *** P <0.005

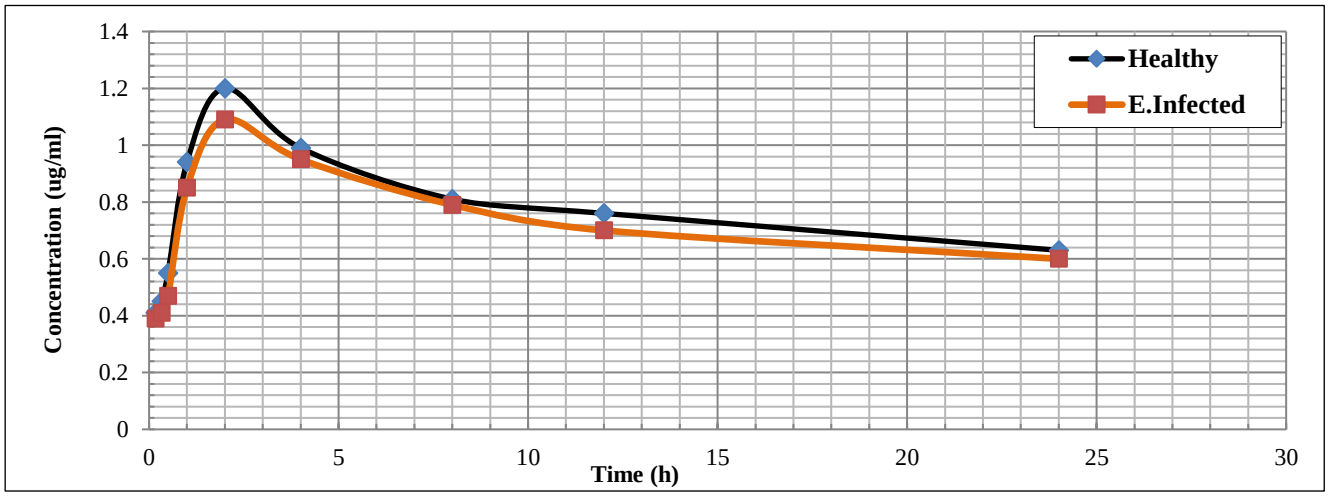

Figure 1: Semi-logarithmic graph depicting the time course of tilmicosin in serum of in both healthy and experimentally infected broiler chickens after a single oral dose of 25mg/kg.b.wt. (N=6).

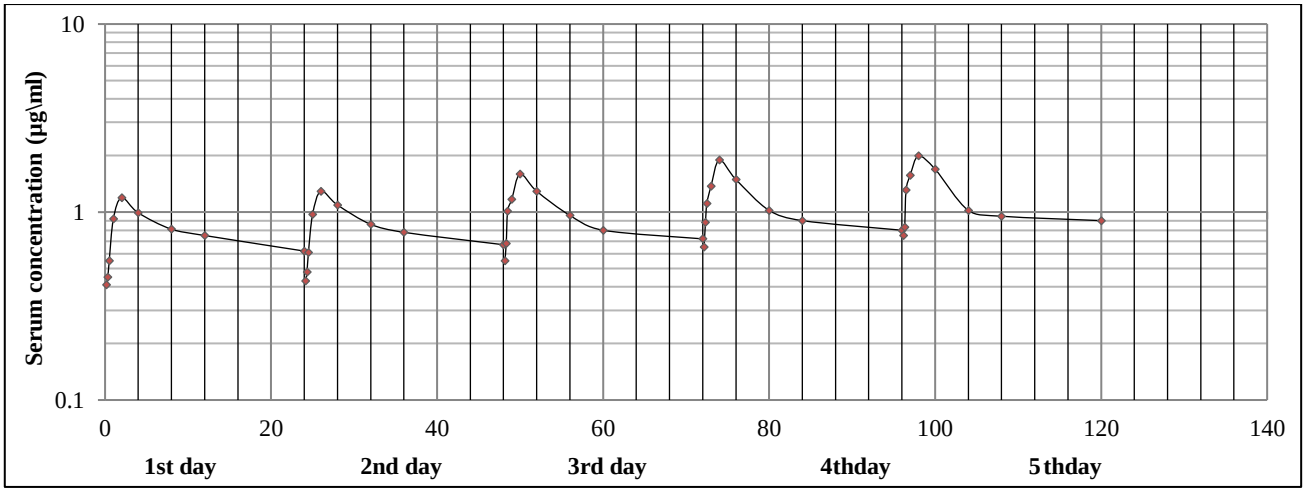

Figure 2: Semi-logarithmic graph depicting the time course of tilmicosin (µg/ml) in serum of healthy broiler chickens following repeated oral administration of 25mg/kg.b.wt. once daily for five consecutive days (N=6).

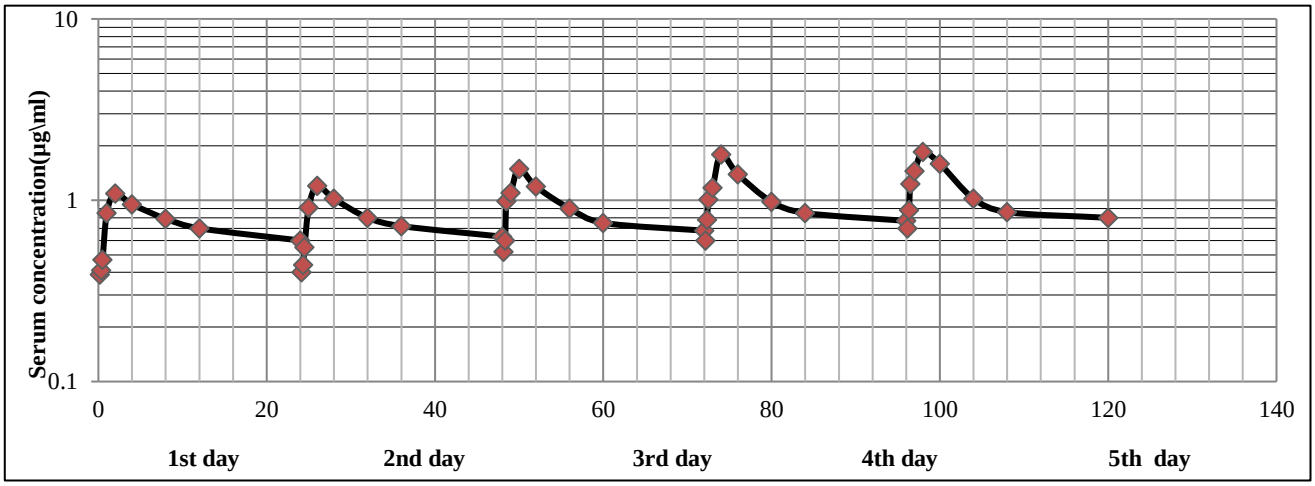

Figure 3: Semi-logarithmic graph depicting the time course of tilmicosin (µg/ml) in serum of experimentally *M. gallisepticum* and *E. coli* infected broiler chickens following repeated oral administration of 25mg/kg.b.wt. once daily for five consecutive days (N=6).

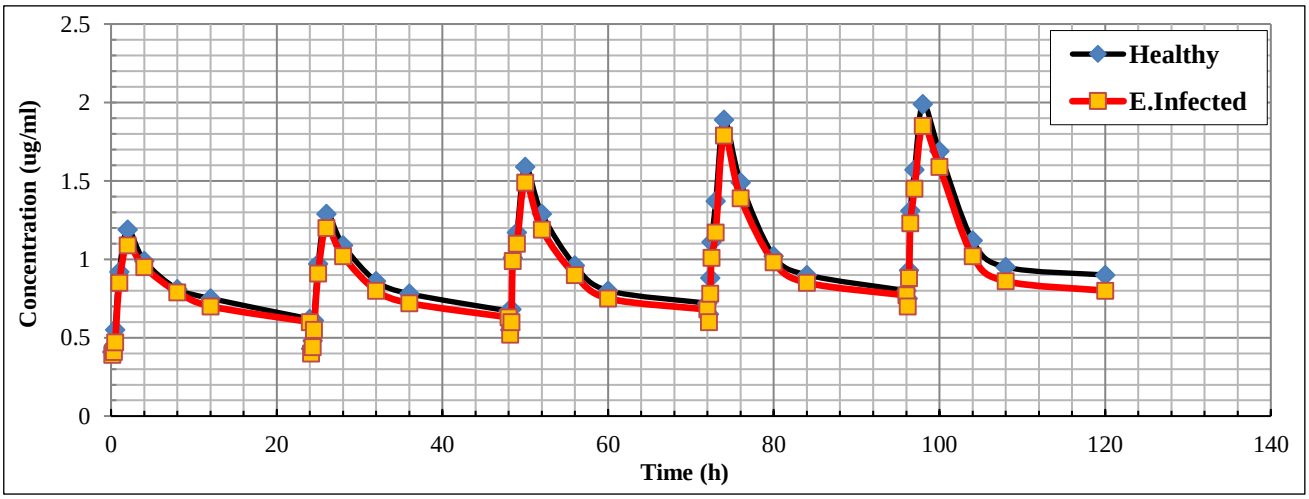

Figure 4: Semi-logarithmic graph depicting the time course of tilmicosin (µg/ml) in serum of healthy and experimentally *M. gallisepticum* and *E. coli* infected broiler chickens following repeated oral administration of 25mg/kg.b.wt. once daily for five consecutive days (N=6).

Mean serum and tissues concentrations of tilmicosin (µg/ml or µg/gm) assayed microbiologically, in healthy broiler chickens following oral administration of 25mg/kg.b.wt. once daily for 5 consecutive days tabulated within Table 4. Lung had the highest concentration of tilmicosin followed by liver and kidney, while the lowest concentration was determined in spleen, fat and thigh muscle. Tilmicosin still detected in 5th day of administration at lung, liver, kidney, spleen and thigh muscles in a concentration of 15.20, 5.73, 3.44, 0.58 and 0.55µg/ml, respectively.

Table 2: Pharmacokinetic parameters of tilmicosin in healthy (H) broiler chickens after repeated oral administration of 25mg/kg.b.wt. for five consecutive days (n=6).

Days	1st day (1st dose)	2nd day (2nd dose)	3rd day (3rd dose)	4th day (4th dose)	5th day (5th dose)
Parameter	**(X±S.E.)**	**(X±S.E.)**	**(X±S.E.)**	**(X±S.E.)**	**(X±S.E.)**
A (µg/ml)	1.07±0.01	1.17±0.007	1.37 ±0.012	1.58±0.007	1.74 ±0.012
K_{ab} (h^{-1})	1.51±0.06	1.45±0.008	1.81±0.034	1.77±0.012	1.91±0.028
$T_{0.5\,(ab)}$ (h)	0.47±0.01	0.48±0.004	0.39±0.003	0.39±0.004	0.36±0.004
B (µg/ml)	1.17±0.01	1.27±0.004	1.54±0.004	1.81±0.004	1.98±0.007
K_{el} (h^{-1})	0.03±0.001	0.03±0.002	0.04±0.00	0.05±0.00	0.05±0.001
$T_{0.5\,(el)}$ (h)	21.30±0.36	20.49±0.29	16.38±0.24	14.81±0.14	14.73±0.20
C_{max} (µg/ml)	1.05±0.001	1.14±0.003	1.38±0.004	1.60±0.004	1.77±0.004
T_{max} (h)	2.59±0.01	2.59±0.012	2.08±0.006	2.02±0.009	1.92±0.011
AUC(µg/h/ml)	37.66±0.57	39.66±0.52	39.14±0.45	42.02±0.36	46.16±0.52
MRT (h)	31.37±0.52	30.19±0.42	24.13±0.34	21.85±0.21	21.7±0.28
IBD (h)	57.13±0.13	53.83±3.08	46.81±0.04	41.13±0.06	42.36±1.64

Table 3: Pharmacokinetic parameters of tilmicosin in experimentally *Mycoplasma gallisepticum* and *Escherichia coli* infected (E) broiler chickens during repeated oral administration of 25mg/kg.b.wt. for five consecutive days (n=6).

Days	1stday (1st dose)	2ndday (2nd dose)	3rdday (3rd dose)	4th day (4th dose)	5th day (5th dose)
Parameter	**(X±S.E.)**	**(X±S.E.)**	**(X±S.E.)**	**(X±S.E.)**	**(X±S.E.)**
A (µg/ml)	0.98 ±0.006	1.08±0.007	1.30±0.008	1.41±0.008	1.62±0.012
Kab (h^{-1})	1.34±0.017	1.43±0.005	1.92±0.02	1.55±0.02	1.83±0.014
$T0.5_{ab}$ (h)	0.52±0.006	0.48±0.002	0.36±0.003	0.45±0.003	0.38±0.003
B (µg/ml)	1.10±0.003	1.19±0.003	1.42±0.007	1.68±0.004	1.87±0.009
Kel (h^{-1})	0.03±0.001	0.03±0.001	0.04±0.001	0.04±0.001	0.05±0.001
$T0.5_{el}$ (h)	22.91±0.25	20.9±0.27	17.00±0.31	15.64±0.04	13.73±0.22
C_{max} (µg/ml)	0.69±0.187	1.06±0.002	1.28±0.003	1.48±0.003	1.65±0.005
T_{max} (h)	2.81±0.025	2.63±0.006	1.99 ±0.008	2.25±0.008	1.93±0.008
AUC(µg/h/ml)	37.77±0.31	37.86±0.42	37.69±0.54	41.09±0.09	40.81±0.42
MRT (h)	33.71±0.37	30.79±0.39	25.00±0.44	23.11±0.06	20.28±0.31
IBD (h)	56.06±0.05	57.54±0.04	45.7±0.07	48.20±0.04	39.90±0.06

Table 4: Mean serum and tissues concentrations of tilmicosin (µg/ml or µg/gm) assayed microbiologically, in healthy broiler chickens following oral administration of 25mg/kg.b. wt. once daily for 5 consecutive days (n = 3).

Tissues	Time of slaughter after the last dose					
	2h	**1st day**	**2nd day**	**5th day**	**7th day**	**9th day**
Serum	2.00± 0.29	1.23±0.14	0.91±0.078	-----	------	-----
Liver	19.20±0.00	13.87±2.91	10.53±1.33	5.73±0.67	-----	-----
Kidney	13.20±0.00	10.53±1.33	8.30±0.93	3.44±0.48	-----	-----
Lung	30.67±0.67	25.06±2.93	17.20±2.00	15.20±2.00	-----	-----
Spleen	6.24±0.53	3.55±0.26	1.6±0.08	0.58 ±0.04	-----	-----
Fat	5.73±0.67	4.16±0.24	3.20±0.24	-----	-----	-----
Thigh muscle	5.73±0.67	3.92±0.48	3.20±0.24	0.55±0.03	-----	-----

----- Undetectable

DISCUSSION

The current study was mainly designed to investigate and provide an overview of the pharmacokinetics of tilmicosin oral solution following single oral administration in healthy and experimentally *M. gallisepticum* and *E. coli* infected broiler chickens. Also, to investigate the pharmacokinetics as well as serum and tissue residues of tilmicosin following repeated oral administrations in healthy and experimentally *M. gallisepticum* and *E. coli* infected broiler chickens to determine the withdrawal time in healthy broiler chickens. In a preliminary study, i.v. administration of tilmicosin in chickens at a dose of 25mg/kg body weight caused considerable adverse cardiovascular effect and death (our unpublished data). For this reason, the PK of the drug after IV administration, the absolute bioavailability and the apparent volume of distribution values of tilmicosin after oral administration was not determined in this study. These results are in consistent with the results following a single oral administration of tilmicosin at a dose of 25mg/kg.b.wt., the drug has been detected in serum 10 min post administration (0.41µg/ml).[14]

In healthy broiler chickens tilmicosin was continued to increase gradually thereafter to reach its maximum serum concentration (Cmax) (1.06µg/ml) at 2 h post administration and decreased gradually till reach its lower level (0.63µg/ml) at 24 hours. This result of (Cmax) is similar to that reported for tilmicosin in fowl 1.28µg/ml, tylosin in broiler chickens 1.2µg/ml, tilmicosin in broilers 1.297µg/ml, tilmicosin in chicken 1.11µg/ml.[15-17]

Tilmicosin reached its maximum time (tmax) at about (2.56 h). This result was in consistent with those recorded for tilmicosin in rabbit 2 h, tylosin in broiler chickens (2.36 and 2.30h and tylvalosin in broiler chicken (2.03h).[18-20]

Following a single oral administration of 25mg/kg.b.wt., the drug was rapidly absorbed with a short absorption half-life ($T_{0.5(ab)}$) of 0.45±0.007 h. Our finding was similar to that reported for azithromycin in broiler chickens (0.57 h) and tilmicosin in lactating goat (0.47 h).[21,22]

Moreover, this result was shorter than those recorded for tilmicosin in broilers (0.948 and 0.757h), tilmicosin in chicken (0.66h) but longer than tylvalosin in turkeys (0.283h).[17,23,24]

Macrolides absorption rate is markedly affected not only from species to another but also in the same species with individual variation.[25]

The drug was slowly eliminated following single oral administration with elimination half-life ($T_{0.5(el)}$) of 21.86±0.32 h. which may attributed to that tilmicosin was detected in the serum till 24 h. The obtained result is similar to those reported for tilmicosin in swine 20.66h and tylosin in cow (20.46 h).[26,27]

Moreover, this value was longer than erythromycin in broiler chicken (4.1h), erythromycin in broiler chickens (2.01 and 1.90h), tylvalosin in broiler chickens (1.82h).[28-30]

On the other hand, this value was shorter than tilmicosin in fowl (30.18h), tilmicosin in broilers (24.18±3.946 and 29.041h), tilmicosin in chicken (36.34h), and tilmicosin in broiler chickens (32.36h).[15,17,23,30]

These existing differences are relatively common and are frequently attributed to inter-species variation, assay methods used, dose of drug, chemical form and structure of drug, amount of time between blood sampling and/or the health status, live body weight, age of the animal, climatic or other conditions related to experimental designs.[31]

In this study, the *in vitro* protein binding of tilmicosin to broiler chickens serum was 9.72±0.83%. This finding provides evidence that tilmicosin is slightly bound to serum protein in chicken and it might explain the high diffusion of tilmicosin in tissues of broiler chickens and high value of the volume of distribution.[32]

The protein binding percent in this study was nearly consistent with those reported for tilmicosin in ewes 16.8%, tylvalosin in broiler chicken 13.00% and tylvalosin in Turkeys 12.33%.[20,24,33]

The relative higher serum concentrations of tilmicosin after repeated doses compared to the first dose indicated the accumulation of tilmicosin in serum during multiple dosing at 24 hours intervals for five consecutive days. Similar results about macrolides accumulation tendency had been reported for tylvalosin in broiler chicken and azithromycin and erythromycin.[20,32]

The obtained serum levels of tilmicosin in *M. gallisepticum* and *E. coli* infected broiler chickens were significantly lower than those in healthy ones following repeated oral administrations. These lower serum concentrations in experimentally *Mycoplasma gallisepticum and Escherichia coli* infected broiler chickens might be attributed the higher penetrating power of the drug to the diseased tissues.[34]

Tilmicosin has good tissue penetration and reaches high concentration and accumulates in the lungs of rats than serum and infection/inflammation further improve its tissue penetration.[35]

In this experiment, the obtained results of serum and tissue residues of tilmicosin in slaughtered healthy chickens following its repeated oral administrations (25mg/kg.b.wt once daily for 5 consecutive days) revealed a good spread distribution of tilmicosin in serum and all other tested tissues (lung, liver, kidney, spleen, fat and thigh muscle). Lung had the highest concentration of tilmicosin followed by liver and kidney, while the lowest concentration was

determined in spleen, fat and thigh muscle. This suggests that lung should be the target tissue for tilmicosin residues in broiler chickens. Similar findings were previously reported for tilmicosin in fowl, tylosin in calves, tilmicosin in broiler chickens, Spiramycine in chicken, and tylosin in broiler chickens.[15,36-39]

The withdrawal period for tilmicosin in this study is suspected to be more than five days. The obtained results were similar to those recorded after oral administration of tilmicosin in broiler chickens at 25mg/kg.b.wt. for 5 days; withdrawal period of about 4 days, oral administration of spiramycin in broiler chickens at 2mg/kg.b.wt. for 3 days; withdrawal period of about 5 days, and after oral administration of tylosin in broiler chickens at 50 mg/kg b.wt. for 5 days, withdrawal period of about 6 days.[7,38,39]

On the other hand, the obtained result was shorter than that recorded after oral administration of tilmicosin to broiler chicken at 37.5 and 75.0mg/L for 5 days, a pre-slaughter withdrawal time of more than 9 days is needed to ensure that the drug is eliminated from the tissues.[37]

CONCLUSION

Oral administration of tilmicosin at a dose of 25mg/kg.b.w. seems to be a suitable therapeutic dose in broiler chickens. However, repeated doses are necessary to maintain tilmicosin serum concentrations above the MIC for most susceptible microorganisms. Tilmicosin is highly efficacious against susceptible micro-organisms in broiler chickens. Chicken must not be slaughtered before 5 days of stopping tilmicosin administration.

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