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PHARMACOKINETICS AND TISSUE RESIDUES OF TYLVALOSIN IN NORMAL AND EXPERIMENTALLY *MYCOPLASMA GALLISEPTICUM* INFECTED BROILER CHICKENS

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ABSTRACT

The pharmacokinetic parameters of tylvalosin were studied following intravenous and oral (single & repeated) administrations in normal and experimentally *Mycoplasma gallisepticum* infected broiler chicken . Following a single intravenous injection of 25 mg tylvalosin /kg b.wt. in normal chicken, tylvalosin could be detected therapeutically for 24 hours post intravenous injection. The serum concentration – time curve of tylvalosin following intravenous injection showed that the drug obeyed a two compartments open model with elimination half- life ($t_{0.5(\beta)}$ = 7.01 ± 0.251h hours), volume of distribution (V_{dss} = 5.36 ± 0.115 L/kg) and total body clearance of the drug (CL_{tot} = 0.71±0.005 L/hr/kg). Following a single oral administration of 5 mg/kg body weight tylvalosin in normal chickens, the peak plasma concentration (C_{max}) was 1.36 ± 0.009 µg/ml was achieved at a maximum time (T_{max}) of 2.37± 0.023 hour . The oral bioavailability of tylvalosin in normal chicken was 44.28 ± 0.78%. Oral administration of 25 mg tylvalosin per kilogram body weight once daily for five consecutive days in normal and *Mycoplasma gallisepticum* infected chicken revealed a lower significant serum tylvalosin in *Mycoplasma gallisepticum* infected chickens compared with normal chickens.

KEYWORDS: Pharmacokinetics, tylvalosin, tissue residues, broiler chickens.

INTRODUCTION

Tylvalosin is a new macrolide antibiotic. It was previously known as (acetyl isovaleryl Tylosin). It derived from fermentation of factor A Tylosin with *Streptomyces thermotolerans*m, this fermentation results in the acetylation of the highly active 16-member lactone ring.[1] In poultry, oral tylvalosin is rapidly absorbed and widely distributed to tissues, reaching very high levels in intestinal phagocytic and epithelial cells. Its main metabolite,3- acetyltylosine is also microbiologically active.[2] Tylvalosin has antibacterial activity against Gram-positive (e.g. *Staphylococcus, Micrococcus, Microbacterium, Corynebacterium, Bacillus, Aerococcus, Arthrobacter and Streptococcus, Campylobacter, Enterococcus and Clostridia*) and some Gram negative organisms and against *mycoplasma* by way of inhibition of protein synthesis in the bacteria cell by reversibly binding to the 50S ribosome subunit. It was not active against most of the gram negative strains (including *Escherichia coli, Serratia, Klebsiella, Proteus, Salmonella, Shigella and Pseudomonas*), it is highly effective against a range of important diseases in many different veterinary species especially pigs and poultry.[3] Tylvalosin also indicated for prevention and treatment of *Mycoplasma hyosynoviae* and *Mycoplasma hyorhinis*is in Pigs.[4]

MATERIALS AND METHODS

Drug

Tylvalosin (formerly acetyl isovaleryl tylosin) is a new macrolide and derived from the fermentation of factor A tylosin with *Streptomyces thermotolerans*.[1] It was obtained as water soluble granules (Each 1 g contains 625 mg tylvalosin as tartrate) under the trade name of (Tylvamyco)®.It was manufactured by ATCO pharma for pharmaceutical industries, Quisna, Egypt. It is administrated in a dose of (25 mg/kg b.wt.) according to manufacturer.

Experimental birds

Thirty six apparently healthy broiler chickens of both sexes weighing from 1700-2000 g were used. Chickens were chosen randomly from a private poultry farm, Qalubia Governorate, Egypt, housed in hygienic floor system chambers and fed on balanced antimicrobial free ration obtained from Elfagr company for poultry ration formulation industries. Water was offered to chickens as ad-libitum. Chickens are kept under observation for two weeks before the start of experiments to ensure that their body fluids and tissues are free from drug residues.

Experimental design

The chickens were divided into 3 groups

Group (1)
It included 6 normal broiler chickens. Each chicken was injected intravenously with a single therapeutic dose of tylvalosin 25mg / kilogram body weight into the left wing vein.

These chickens were left for 15 days after the intravenous injection to ensure complete clearance of tylvalosin from their bodies. Then, each chicken was given orally a single therapeutic dose of tylvalosin 25mg / kilogram body.

The aim of this group was to calculate the pharmacokinetics bioavailability of tylvalosin in normal chickens.

Group (2)
It included 15 normal broiler chickens. Each chicken was given tylvalosin orally at dose rate of 25 mg/kilogram body weight, once daily for five consecutive days.

Three chickens were slaughtered 24, 48, 72, 96 and 120 hours after the last dose of tylvalosin administration.

Group (3)
It included 15 experimentally *Mycoplasma gallisepticum* infected broiler chickens. Each chicken was given tylvalosin orally at dose rate of 25 mg / kilogram body weight once daily for five consecutive days after the appearance of the clinical symptoms 48 hours after experimental infection with *Mycoplasma gallisepticum*.

Three chickens were slaughtered 24, 48, 72, 96 and 120 hours after the last dose of tylvalosin administration.

Collection of samples
Blood samples
About one milliliter of blood was taken from either right or left wing vein of chickens, following administration of the drug. Blood samples were collected. Blood samples were collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours of administration.

Blood samples following the second, third, fourth and fifth oral doses were collected at 0.167, 0.25, 0.50, 1, 2, 4,6, 8, 12 and 24 hours after oral administration of tylvalosin. The collected blood samples were allowed to clot and the serum was separated by centrifugation at 3000 r. p.m. for 15 minutes. All serum samples were stored at – 20°C until assay.

Tissue samples
After the end of the fifth day of repeated oral administration of tylvalosin in normal chicken, three chickens were slaughtered at 24, 48, 72, 96 and 120 hours.Tissue samples from blood, liver, kidney, spleen, heart, breast muscle, thigh muscle, fat, skin, gizzard and brain were taken from each slaughtered chicken for drug assay. Samples were frozen and stored at – 20°C until assayed.

Analytical procedure
Assay of Tylvalosin
Tylvalosin was assayed in chicken's serum and distilled water by microbiological method using agar well diffusion method by using *Bacillus subtillis* as tested microorganism, which was obtained from Microbiological Department, Animal Health Research Institute, Dokki, Giza, Egypt.

Assay of blood samples
Three plates were used for each sample. Six pores were made; three of them were filled with the reference concentration while the other three pores were filled with the serum samples in triplicate manner. The plates were incubated at 37°C for 18 hours then the diameter of inhibitory zones was measured. The diameter of inhibitory zones of samples was 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.

Assay of tissue samples
Two grams of tissue were homogenized by automatic homogenizer with 2ml of distilled water. Mixtures were centrifuged at 3000 r.p.m. for 10 minutes and the supernatant fluid of each sample was taken and directly assayed microbiologically for tylvalosin concentration.

Pharmacokinetic analysis
The pharmacokinetics parameters were calculated by Winnonlin program, version1.1 and 2.1 and other parameters according to.[5,6]

Statistical analysis
Data were expressed as mean ± S.E. The obtained data were statistically analyzed using Student *t*–test to express the differences between groups and pharmacokinetic parameters.[5]

RESULTS

Following a single intravenous injection of 25 mg tylvalosin / kg b.wt. in normal chickens, tylvalosin could be detected therapeutically for 24 hours post intravenous injection. The plasma concentration-time curve of tylvalosin following intravenous injection showed that the drug obeyed a two compartments open model. The disposition kinetics of tylvalosin following a single intravenous and oral administration were recorded in table (1) and showed in figure (1).

Oral administration of 25 mg tylvalosin /kg b.wt. once daily for five consecutive days in normal and *Mycoplasma gallisepticum* infected chickens revealed a lower significant plasma tylvalosin concentration at all-time sampling in *Mycoplasma gallisepticum* infected chickens than in normal chickens. The pharmacokinetic parameters of tylvalosin after repeated oral administration in normal chickens were compared to

those in *Mycoplasma gallisepticum* infected chickens (Table 2).

Tissue samples from lung, liver, kidney, spleen, heart, breast muscle, thigh muscle, skin and fats were taken for assaying of residues of tylvalosin at 24, 48, 72, 96 and 120 hours after the last oral dose of 25 mg/kg b.wt. from normal chickens were compared to those in *Mycoplasma gallisepticum* infected chickens (Table 3).

Table 1: Pharmacokinetic parameters of tylvalosin following a single intravenous and oral adminstration of 25mg/kg b.wt. in normal chickens (n=6).

Parameter	Unit	Intravenous	Oral
C^0	µg/ml	19.90 ± 0.015	--------
A	µg/ml	16.59 ± 0.008	--------
α	h^{-1}	2.83 ± 0.009	--------
$t_{0.5(\alpha)}$	H	0.245 ± 0.008	--------
K_{12}	h^{-1}	1.76 ± 0.005	--------
K_{21}	h^{-1}	0.58 ± 0.004	--------
V_{dss}	ml/kg	5.36 ± 0.115	--------
CL_{tot}	L/hr/kg	0.710 ± 0.005	--------
B	µg/ml	3.30 ± 0.014	--------
β	h^{-1}	0.01 ± 0.004	--------
$t_{0.5(\beta)}$	H	7.01 ± 0.25	6.84 ± 0.199
AUC	hr/µg/mL	35.20 ± 0.249	15.765 ± 0.272
AUMC	hr/h/µg/ml	266.034 ± 9.225	161.08 ± 7.340
MRT	H	7.55 ± 0.212	10.19 ± 0.302
K_{ab}	h^{-1}	--------	0.979 ± 0.019
K_{el}	h^{-1}	--------	0.102 ± 0.003
$t_{0.5(ab)}$	H	--------	0.709 ± 0.019
T_{max}	H	--------	2.37 ± 0.023
C_{max}	µg/ml	--------	1.36 ± 0.009
MAT	H	--------	2.64 ± 0.326

A, B and C Zero time plasma drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (µg/ml); α & β, Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h^{-1}); AUC, Total area under the plasma drug concentration versus time curve from t = 0 to t = α after administration of a single dose; C°, Drug concentration in the plasma at zero time immediately after a single intravenous injection (µg/ml); C_{max}, Maximum plasma concentration of drug in blood after extra vascular administration (µg/ml); Cl_{tot}, The total clearance of a drug, which represents the sum of all clearance processes in the body (ml/kg /min); 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}); $t_{0.5(\alpha)}$, Distribution half - life (h); $t_{0.5(\beta)}$, Elimination half - life ; t_{max}, The time at which the maximum concentration of drug was reached after extravascular administration (h); V_{dss}, The apparent volume of distribution which was calculated by Steady - state method (ml/kg).

Table 2: Pharmacokinetic parameters of tylvalosin in normal (N) and experimentally *Mycoplasma gallisepticum* infected chickens (I) during repeated oral administration of 25 mg/kg b.wt. once daily for 5 consecutive days (n=6).

Paramater	Unit	1st dose		2nd dose		3rddose		4th dose		5th dose	
		N_ (X±S.E.)	I_ (X±S.E.)	N_ (X±S.E.)	I_ (X±S.E.)	N_ (X±S.E.)	I_ (X±S.E.)	N_ (X±S.E.)	I_ (X±S.E.)	N_ (X±S.E.)	I_ (X±S.E.)
K_{ab}	h^{-1}	1.08 ± 0.022	1.15 ± 0.038	1.181 ± 0.026	1.35 ± 0.041**	1.58 ± 0.041	1.74 ± 0.031*	1.80 ± 0.013	1.80 ± 0.026	2.33 ± 0.030	1.99 ± 0.048***
$t_{0.5(ab)}$	H	0.642 ± 0.013	0.606 ± 0.020	0.588 ± 0.013	0.52 ± 0.016**	0.441 ± 0.011	0.399 ± 0.007*	0.386 ± 0.003	0.386 ± 0.006	0.297 ± 0.004	0.348 ± 0.008***
K_{el}	h^{-1}	0.074 ± 0.003	0.065 ± 0.003*	0.060 ± 0.003	0.049 ± 0.002**	0.046 ± 0.001	0.045 ± 0.001	0.043 ± 0.001	0.044 ± 0.001	0.028 ± 0.001	0.039 ± 0.002**
$t_{0.5(el)}$	H	9.43 ± 0.437	10.81 ± 0.425*	11.65 ± 0.506	14.24 ± 0.499**	15.28 ± 0.433	15.35 ± 0.345	16.05 ± 0.407	15.72 ± 0.417	24.88 ± 1.009	18.21 ± 1.007**
T_{max}	H	2.51 ± 0.016	2.43 ± 0.031*	2.53 ± 0.019	2.33 ± 0.043**	2.17 ± 0.040	2.06 ± 0.025*	2.04 ± 0.010	2.03 ± 0.019	1.84 ± 0.012	1.90 ± 0.026*
C_{max}	µg/ml	1.21 ± 0.008	0.925 ± 0.005***	1.40 ± 0.006	1.07 ± 0.012***	1.55 ± 0.005	1.23 ± 0.007***	1.65 ± 0.005	1.41 ± 0.004***	1.70 ± 0.008	1.55 ± 0.009***
AUC	hr/µg /ml	18.72 ± 0.378	15.31 ± 0.349***	25.89 ± 0.702	21.77 ± 0.314***	34.52 ± 0.597	27.95 ± 0.540***	39.43 ± 0.582	33.06 ± 0.408***	60.25 ± 1.79	39.99 ± 1. 13***
AUMC	hr/hr/ µg/ml	258.48 ± 14.77	242.79 ± 12.961	443.83 ± 30.12	443.51 ± 16.44	759.87 ± 32.08	619.57 ± 26.82**	916.11 ± 34.78	750.63 ± 25.741**	2171.55 ± 151.97	1052.01 ± 80.53***
MRT	H	13.76 ± 0.528	15.80 ± 0.501*	17.05 ± 0.715	20.35 ± 0.572**	21.97 ± 0.558	22.12 ± 0.554	23.19 ± 0.564	22.67 ± 0.50	35.83 ± 1.44	26.13 ± 1.27***

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

Table 3: Tissue concentrations of tylvalosin (µg/ml) in normal (N) and experimentally *Mycoplasma gallisepticum* infected chickens (I) during repeated oral administration of 25 mg/kg b.wt. once daily for 5 consecutive days (n=3).

Tissue	After 24 h		After 48 h		After 72 h		After 96 h		After 120 h	
	N_ (X ± S.E.)	I_ (X ± S.E.)	N_ (X ± S.E.)	I_ (X ± S.E.)	N_ (X ± S.E.)	I_ (X ± S.E.)	N_ (X ± S.E.)	I_ (X ± S.E.)	N_ (X ± S.E.)	I_ (X ± S.E.)
Liver	8.82±0.33	3.86±0.27	5.76±0.18	1.53±0.09	3.98±0.11	0.42±0.09	1.02±0.08	---	---	---
Lung	24 22.14±0.18	16.32±0.21	24 17.14±0.08	9.92±0.14	24 8.24±0.03	3.62±0.12	24 3.04±0.08	0.62±0.01	24 0.19±0.003	---
Spleen	2.64±0.28	1.24±0.07	1.42±0.09	0.31±0.05	0.62±0.13	0.15±0.03	0.19±0.01	---	---	---
Kidney	5.44±0.38	3.14±0.17	3.12±0.11	1.81±0.06	1.09±0.12	0.37±0.03	0.47±0.01	---	---	---
Fat	3.26±0.01	1.21±0.02	1.55±0.09	0.27±0.03	---	---	---	---	---	---
Breast muscle	3.36±0.11	1.31±0.05	1.68±0.07	0.34±0.01	0.68±0.03	---	---	---	---	---
Thigh muscle	3.14±0.12	1.36±0.03	1.62±0.04	0.31±0.02	0.53±0.01	---	---	---	---	---

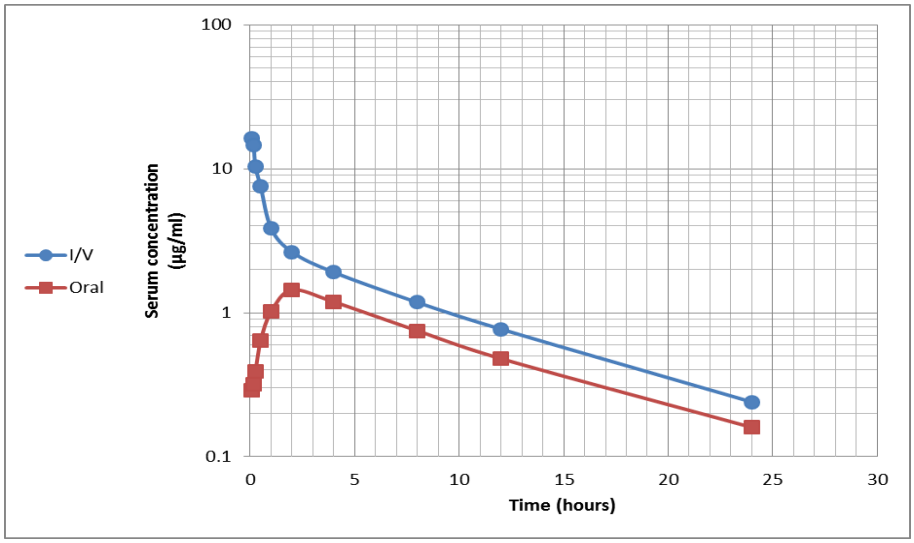
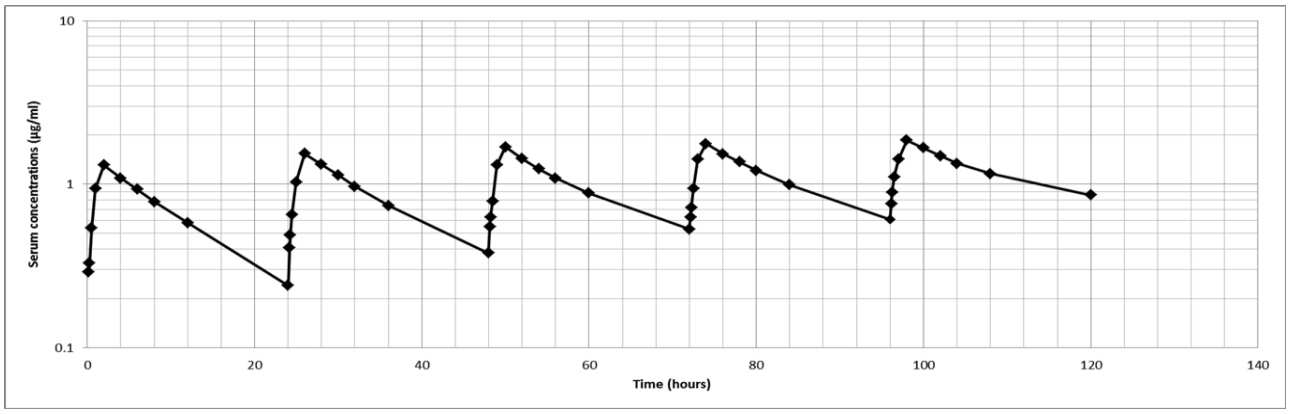


Figure (1): Semilogarthmic graph depicting the time course of tylvalosin (µg/ml) following a single oral administration of 25mg/kg b.wt in normal broiler chickens previously given the same dose by a single intravenous bolus injection (n=6).



Figure(2): Semi logarithmic graph depicting the time course of tylvalosin (µg/ml) in serum following a single oral administration of 25mg/kg b.wt once daily for 5 consecutive days in normal chickens (n=6).

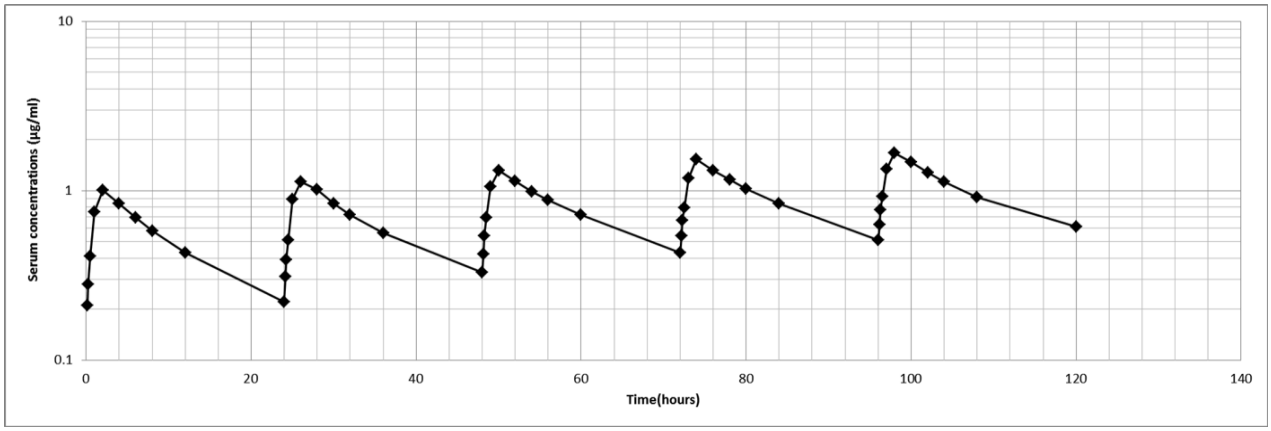


Figure (3): Semi logarithmic graph depicting the time course of tylvalosin (µg/ml) in serum following a single oral administration of 25mg/kg b.wt once daily for 5 consecutive days in experimentally *Mycoplasma gallisepticum* infected chickens (n=6).

DISCUSSION

In the present investigation intravenous injection of 25mg of tylvalosin/kg b. wt. in normal chickens showed that the disposition best fitted a two compartments open model. The obtained results were consistent with those reported for The obtained results were consistent with those reported for tylvalosin in broiler chickens by [7]&[8] and for tylvalosin in turkey by.[9]

The V_{dss} is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions.[10]

In the current study, the Vd_{ss} for tylvalosin was 5.36 ± 0.115 L/kg suggesting higher penetration through biological membranes and tissue distribution after intravenous administration in broiler chickens. This value was nearly similar to those recorded for tylosin in broiler chickens (6 L/ kg).[11]

The obtained value was higher than the data recorded for tylosin in broiler chickens (0.69 L/kg),[12] tylvalosin in turkeys (1.155 ± 0.183 l/kg).[9] and for tylvalosin in broiler chickens (3.802±0.148 l/kg) [13]. These findings were consisted with those reported by,[14] who found that the difference in kinetic parameters was referred to the changes in chemical structure of tylvalosin than tylosin.

Tylvalosin was transferred from central to peripheral compartment at a higher rate (K_{12} =1.761 ± 0.005h^{-1}) than its passage from peripheral compartment to central compartment (K_{21} = 0.576 ± 0.004h^{-1}). These values were nearly similar to that reported for tylvalosin in broiler chickens (K_{12} = 2.554±0.170h^{-1}) and (K_{21} = 1.920±0.051) by **[13]**.

Tylvalosin was eliminated at slow rate elimination half-life [$t_{0.5(\beta)}$] equal to 7.01 ± 0.251h. This result was nearly similar those reported for erythromycin in broiler chickens (5.3 h),[15] for tylvalosin in broiler chickens (6.666±0.285h) [13] and for tylosin in broiler chickens (7.29 h),[11]

The obtained elimination half-life was longer than those reported for tylosin in broiler chickens (0.52 h),[12] tylvalosin in laying hens (0.61±0.56h).[16] and for tylvalosin in turkeys (0.788±0.107 h).[9] Such differences are relatively common and frequently related to inter-species variations assay methods used, the time between blood samplings, and/or the health status and age of the animals.[17]

The rate of total body clearance [CL_{tot}] of tylvalosin following intravenous injection was 0.71±0.005 L/kg/hr. This value was close to values recorded for tylvalosin in broiler chickens (0.953±0.040 L/Kg/hr).[13]

On the other hand, the obtained result of the rate of total body clearance [CL_{tot}] was lower than those reported for erythromycin in lactating ewes (1.29 ± 0.121 L/h/kg),[18] for tylvalosin in laying hens (4.37±0.051 L/h/kg) [16] and for tylvalosin in turkeys (1.489 ± 0.143L/kg/h).[9]

Following a single oral administration of 25mg tylvalosin /kg b.wt. the drug is detected in serum five minutes post administration (0.29±0.01), the concentration was continued to increase to reach maximum concentration (C_{max}) of (1.36 ± 0.009 µg/ml) at (t_{max}) (2.37± 0.023 h) and could be detected in serum (0.16 ± 0.011µg/ml) at 24 hours post administration.

On these bases, it was suggested that oral administration of 25 mg tylvalosin /kg b.wt. with 24 hours intervals should be adequate for control of avian bacterial diseases. The obtained maximum concentration (C_{max}) was nearly consistent with those reported for tylosin in broiler chickens (C_{max} = 1.2 µg/ml) [12], tylvalosin in broiler chickens (C_{max} = 1.226 µg/ml),[13] tylvalosin in broiler chickens (1.64 µg/ml) [19] and for tilmicosin in broiler chickens (1.25 ± 0.09 µg/ml).[20]

On the other hand the obtained C_{max} was higher than value recorded for tylvalosin in laying hens (0.22±0.052µg/ml) [16]. In contrast the obtained C_{max} was lower than value recorded for erythromycin (6.9 µg/ml),[18] for tylvalosin in broiler chickens (2.11±0.3 µg/ml),[8] and for tylosin in broiler chickens (3.40µg/ml).[11]

The systemic bioavailability of tylvalosin in normal chickens, which estimated the rate and extent of the dose entered the systemic circulation after oral administration was 44.28 ± 0.78%. This value was nearly close to those recorded for tylosin in broiler chickens (F=40.56 %).[21] and for tylvalosin in broiler chickens (F= 48.39 %).[13]

This value was higher than the bioavailabilities recorded for tylvalosin in turkey (F=33.84%).[9] On the other hand the obtained value was lower than the bioavailabilities reported for tylvalosin in laying hens (F= 60.26±4.72%).[16]

In this study findings indicated that tylvalosin could be detected in a therapeutic level for 24 hours in serum following repeated oral administrations. These concentrations were higher than MICs for tylvalosin (MIC_{50} and MIC_{90} of 0.016 and 0.06 mg/ml) respectively.[22]

The study showed that the blood concentrations of tylvalosin in *Mycoplasma gallisepticum* infected chickens were significantly lower than those in normal chickens following repeated oral administrations. These lower blood concentrations in infected broiler chickens might be attributed to a higher penetration of the tylvalosin to diseased tissues.[23,24,25] Furthermore, inflammation decreased the protein bending tendency due to hyperproteinemia lead to lowering of serum concentration of administrated drugs.[23,26]

Repeated oral administration of 25 mg tylvalosin /kg b.wt once daily for five consecutive days in normal and experimentally *Mycoplasma gallisepticum* infected chickens revealed that the drug was distributed in serum, and tested tissues (lung, liver, kidney, spleen, fat, breast and thigh muscles). Lung, liver and kidneys had the highest concentration of tylvalosin. These findings came in aggrement with the results previously reported for

tylvalosin in pigs by,[27] tylvalosin in broiler chickens by,[13] for tylosin in broiler chickens by,[11] and for tilmicosin in broiler chickens.[20]

The withdrawal period in this study was suspected to be five days. The obtained results were similar to those reported after oral administration of tilmicosin in broiler chickens at 25mg/kg b.wt. for five days, withdrawal period of about six days.[20]

This result was shorter than the result obtained for tylvalosin in broiler chickens by **[13]** who reported that a withdrawal time of a period of 8- 10 days for liver and muscles was considered acceptable.

On the other hand, the obtained result was longer than that recorded for tylvalosin in pigs, chickens and pheasants, a withdrawal period of 2 days for meat and offal was considered acceptable.[27]

CONCLUSION

The oral bioavailability of tylvalosin was 44.28 ± 0.78%.This value referred a good absorption of tylvalosin from its site of oral administration. Repeated oral administrations of tylvalosin (25 mg/kg b.wt.) once daily for five consecutive days would provide an effective concentration against *Mycoplasma gallisepticum* in broiler chickens. The highest concentration of tylvalosin in lung and kidney tissues suggested that tylvalosin is suitable for treatment of urinary tract and respiratory tract infection respectively. Treated chickens must not be slaughtered before 5 days from last dose of repeated administration of tylvalosin to withdraw the drug residues from all tissues of treated chickens.

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