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Pharmacokinetics of Tylvalosin Alone or in Combination with Vitamin E in Broiler Chickens

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ABSTRACT

Few publications are describing the pharmacokinetics of tylvalosin (TVN) antibiotic, so the aims of this work were to study its pharmacokinetics with evaluation the effect of vitamin (vit) E on its kinetics after single and repeated oral administration in broiler chickens. The mean serum concentrations of the drug were markedly lower in tylvalosin alone when compared with tylvalosin pre-treated with vit E after single and repeated oral administration at the corresponding time intervals. The peak of serum concentration (C_{max}), absorption half-life ($t_{0.5ab}$) and elimination half-life ($t_{0.5\ el}$) were 2.11±0.3, 3.27±0.2 ug mL^{-1}, 0.94±0.04, 0.88±0.02 h and 1.61±0.05, 2.42±0.1, after single tylvalosin and tylvalosin-vit E, respectively. While after repeated dosing, the maximum serum levels were 5.01±0.13 and 5.9±0.1 ug mL^{-1} with pharmacokinetic parameters (C_{max}), ($t_{0.5ab}$) and ($t_{0.5\ el}$) 4.1±0.14, 5.67±0.4 ug mL^{-1}, 1.39±0.4, 0.86±0.07 h and 2.78±0.16, 3.05±0.3 h after repeated tylvalosin and tylvalosin-vit E, respectively. The combination of tylvalosin with vit E allows a prolongation of the dosage intervals in broiler for more 12 and 24 h after single and repeated dosing, respectively, indicated by longer elimination half-life and Mean Residence Time (MRT) of tylvalosin-vit E than tylvalosin alone after single and repeated administration which is very important for the dosage intervaland increasing the drug serum efficacy.

Key words: Tylvalosin, vit E, single, repeated, pharmacokinetics

INTRODUCTION

Poultry production excessively growing in the world. Poultry represents about 33% of the world meat consumption and is expected to increase by 2-3% per year in the world. Livestock production extremely affected by climate change; although the industry of poultry has a natural advantage over others livestock as its of low global warming potential. So, poultry meat and their other products are the most efficient animal protein. But, poultry production has been facing the critical gaps that need to be discovered by the institutions of research and the different studies (Mengesha, 2013) that's why we are choosing chickens as the experimental animal in this study.

Macrolides are group of antibiotics effective against mycoplasma, Gram positive and some Gram negative bacteria. Macrolide antibiotics have structurally the same compounds, that are classified as macrocyclic lactones with 12-20 carbon atoms in the lactone ring. On this lactone ring, several combinations of de-oxy sugars can be attached by glycosidic linkages (Watteyn *et al*., 2013).

Acetylisovaleryltylosin tartrate (aivlosin) is an antimicrobial of the macrolide group with antibacterial activity against Gram positive, some Gram negative organisms and mycoplasma and this drug used extensively in Latin America for treating mycoplasmosis, there are few publications describing its pharmacokinetics (Cerda *et al*., 2010). Tylvalosin antibiotic commonly used in poultry farms for the treatment of respiratory infections specially treatment of mycoplasmosis at the recommended dose 25 mg kg^{-1} for 3 days (Forrester *et al*., 2011) so studying its pharmacokinetics after oral administration in broiler chickens very important after single and repeated dosing alone or pre-treated with vit E.

The simultaneous administration of antibiotics and vitamins is routinely used besides; supplementation of antioxidants can be considered as the alternative method for chelation therapy (Al-Eryani *et al*., 2014). Vitamin E commonly used in poultry farms at vitamins deficiency and as immunostimulant that's why we are studying the experiment on vit E.

In poultry farms, the drug combinations are commonly used, in these farms drug interactions may occur. Theses interactions have been studied in chickens and may result either in diminished effects or drug potentiation (Becker, 2011).

So in our point of view, there were no previous studies concerning the combination of tylvalosin with vit E so the aims of this work was to explore the pharmacokinetic parameters of tylvalosin after single and multiple dosing and evaluates the possible effect if vitamin E (2 mg kg^{-1} b.wt.,) (as we first experiment this dose of vit E as powder form in the drinking water, water soluble form) changes the pharmacokinetics of tylvalosin (25 mg kg^{-1} b.wt.,) after single and repeated oral administration in broiler chickens.

MATERIALS AND METHODS

Chickens: The study was carried out on twenty four symptom-free healthy broiler chickens divided into four groups of both sexes with an average body weight from 1.4-2 kg and 42 days old. These birds were obtained from a special poultry farm in Beni-Suef Governorate. The chickens were fed on balanced commercial ration and water *ad-libitum*. They were kept under good hygienic conditions and left without treatment for 15 day before the experiment for acclimatization and ensuring complete clearance of any antibacterial drugs.

Drugs

Tylvalosin (Aivlosin) (acetylisovaleryltylosin): White to off-white water-soluble powder as (tylvalosin tartrate) 625 mg g^{-1}. Aivlosin (ECO Animal Health, London, UK).

Vitamin E: White powder/α-tocopherol, water soluble powder, supplemented as α-tocopherol acetate powder 50% with target amount of 2 mg kg^{-1} b.wt., (trying to experiment this dose of vit E powder in the drinking water as water soluble powder). It was obtained kindly from Pharma Swede Pharmaceutical Company.

Experimental design

Single dose study: Twelve apparently healthy broiler chickens were divided into 2 groups, the first group administered tylvalosin 25 mg kg^{-1} b.wt., (Forrester *et al*., 2011), as a single oral dose and the second group were given vit E (2 mg kg^{-1} b.wt.) (firstly tested dose 2 h before starting TVN administration) then tylvalosin 25 mg kg^{-1} b.wt., had been given later (Forrester *et al*., 2011), as a single oral dose (intra-crop route). Blood samples (1 mL each) were collected from wing vein just

after 5, 10, 15, 30 min, 1, 2, 4, 6, 8, 12 and 24 h post administration. All blood samples were left to clot for 30 min, centrifuged at 3000 rpm for 15 min and the obtained clear sera were transferred to eppendorff's tubes and kept in deep freeze (-20°C) till assayed.

Multiple doses studies: This study was performed on the same single dose administered group, as (6 birds) had been given tylvalosin (25 mg kg^{-1} b.wt.) daily for another 3 consecutive days (intra-crop route) whereas, the other (6 birds) had been taken vit. E (2 mg kg^{-1} b.wt.) firstly 2 h before starting TVN administration then tylvalosin (25 mg kg^{-1}, b.wt.) daily for another 3 consecutive days (intra-crop route). In both groups the blood samples had been collected at the last day of drugs dosing (3rd day). Blood samples (1 mL each) had been taken from wing vein at 5, 10, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 48 and 72 h post-administrations. All blood samples were left to clot for 30 min, centrifuged at 3000 rpm for 15 min and the obtained clear sera were transferred to eppendorff's tubes and kept in deep freeze (-20°C) till assayed.

Analytical procedures: Tylvalosin samples in serum were determined by microbiological assay technique as a simple, give a realistic good results and has been become the most popular one used to examine the antimicrobial activity (Mayachiew *et al*., 2010) besides, the limit of quantification of the method was 0.05 ug mL^{-1} and the lower limit of detection was 0.015 so the tylvalosin serum concentration had been measured by microbiological assay using *Micrococcus luteus* (ATCC 9314) as test microorganism (Cerda *et al*., 2010). Standard curve of tylvalosin in healthy broiler chickens were linear over the range of 0.01-25 μg mL^{-1}. The diameter of the inhibition zones (mm) were linear when plotted against of concentration of tylvalosin (μg mL^{-1}) with correlation coefficient of 0.995 in normal chicken serum, 0.995 in distilled water. Estimation of protein binding tendency of tylvalosin was carried by the methods described in Abo El-Ela *et al*. (2014) by preparing a standard solution in distilled water and also in normal antibiotic free chicken's serum at concentrations of tylvalosin 0.01, 0.02, 0.04, 0.09, 0.1, 0.3 (reference concentration), 0.6, 1.75, 3.125, 6.25, 12.5 and 25 μg mL^{-1}. The difference in the diameter of inhibition between the solutions of the drugs in the distilled water (buffer) and that in serum of the chickens were used to calculate the percentage of protein binding of the tested antibacterial according to the Eq. 1 described in Abo El-Ela *et al*. (2014):

$$\text{Protein binding (\%)} = \frac{\text{Zone of inhibition in buffer-Zone of inhibition in serum}}{\text{Zone of inhibition in buffer}} \times 100 \quad (1)$$

Pharmacokinetic analysis of the data: Serum concentrations of tylvalosin versus time curve were generated and best fitted by the aid of computer poly-exponential curve stripping program (R strip computer programme). Data from each chicken was fitted individually and the pharmacokinetic variables were computed by the aid of the software programs, according to Abo El-Ela *et al*. (2014) as the hybrid rate constants of distribution and elimination phase (α and β), the first order absorption and elimination rate constants(K_{ab} and K_{el}) and corresponding extrapolated zero time intercepts (A and B), absorption, distribution and elimination half-lives $t_{0.5(ab)}$, $t_{0.5\,(el)}$, the area under the curve from zero to infinite time (AUC 0-œ), Mean Residence Time (MRT), maximum serum concentration (C_{max}) and time to be achieved (t_{max}) were calculated. The results were expressed as Mean±SE and the obtained data statistically analyzed using student"t test described in Abo El-Ela *et al*. (2014).

RESULTS

Single oral administration of tylvalosin alone or pre-treated with vit E (tylvalosin-vit E combination)

Effects of vit E on the disposition kinetics of tylvalosin after single oral administration: The mean serum concentrations of tylvalosin alone or in combination with vit E after single oral administration in healthy broiler chickens at different time intervals at a dose of 25 mg kg^{-1} b.wt., are shown in Table 1 and Fig. 1. The mean serum concentrations of the drug are markedly lower in single tylvalosin dosing broiler chickens as compared with tylvalosin-vit E at the corresponding time intervals. The maximum concentration of the drug in serum was 2.11 μg mL^{-1} in tylvalosin administration whereas 3.27 μg mL^{-1} in tylvalosin-vit E. The all pharmacokinetic parameters are recorded in Table 2 showed that the serum concentrations were higher after tylvalosin pre-treated with vit E when compared to the tylvalosin alone.

Repeated oral administration of tylvalosin alone or pre-treated with vit E (tylvalosin-vit E combination)

Effects of vit E on the disposition kinetics of tylvalosin after repeated oral administration: The mean serum concentrations of tylvalosin alone or in combination with vit E after repeated oral administration in healthy broiler chickens at different time intervals at a dose of 25 mg kg b.wt., (TVN) and 2 mg kg^{-1} b.wt., (vit E) are shown in Table 3 and Fig. 2. The mean serum concentrations of the drug were markedly lower in repeated tylvalosin alone as compared with tylvalosin-vit after repeated dosing at the corresponding time intervals. The maximum

Table 1: Mean serum concentrations of tylvalosin alone or in combination with vitamin E in healthy broiler chickens after single oral administration of 25 mg kg^{-1} tylvalosin and 2 mg kg^{-1} b.wt., (vit E) (N = 6)

	Mean±SE	
Time	Tylvalosin (μg mL^{-1})	Tylvalosin-vit E (μg mL^{-1})
15 min	0.05±0.02	0.23±0.0***
30 min	0.41±0.06	0.68±0.09**
1 h	1.45±0.42	1.75±0.14*
2 h	2.25±0.2	3.77±0.3***
4 h	1.55±0.2	2.55±0.09***
6 h	0.68±0.13	1.31±0.10***
8 h	0.33±0.08	0.67±0.07**
12 h	0.06±0.02	0.26±0.02***
24 h	-	0.07±0.06***

***,**,*Significant at $p \leq 0.001$, $p \leq 0.01$ and $p \leq 0.05$, respectively

Table 2: Pharmacokinetic parameters of tylvalosin alone or in combination with vit E in healthy broiler chickens following a single oral administration of 25 and 2 mg kg^{-1} b.wt., (vit E) (N = 6)

Kinetic parameters	Tylvalosin	Tylvalosin-vit E
A (μg mL^{-1})	8.60±2.2	7.6±1.05***
$K_{(ab)}$ (h^{-1})	0.69±0.01	0.78±0.02*
$t_{0.5\ ab}$ (h)	0.94±0.04	0.88±0.02*
B (μg mL^{-1})	8.80±2.3	7.8±1.04**
K_e (h^{-1})	0.40±0.01	0.28±0.01*
$t_{0.5\ el}$ (h)	1.61±0.05	2.42±0.1***
t_{max} (h)	2.03±0.06	2.18±0.07*
C_{max} (μg mL^{-1})	2.11±0.3	3.27±0.2***
AUC (μg h mL)	10.50±1.5	18.16±0.5***
MRT (h)	3.68±0.06	4.16±0.2**

k_{ab}: First-order absorption rate constant, K_{el}: Elimination rate constant, C_{max}: Maximum serum concentration, t_{max}: Time to peak serum concentration, $t_{0.5(ab)}$: Absorption half-life, $t_{0.5(el)}$: Elimination half-life, MRT: Mean residence time, AUC: Area under serum concentration time curve, ***,**,*Significant at $p \leq 0.001$, $p \leq 0.01$ and $p \leq 0.05$, respectively

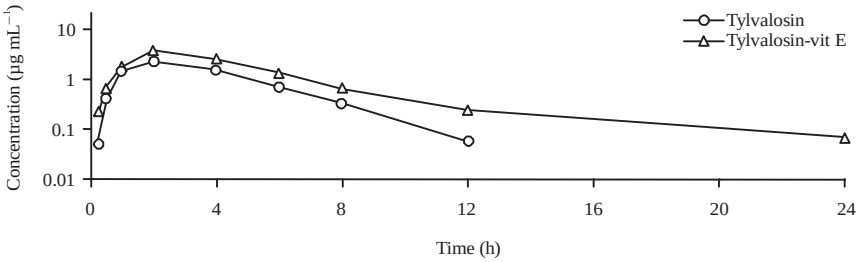

Fig. 1: Semilogarithmic plot depicting the time-course of tylvalosin and tylvalosin-vit E combination in serum after single oral administration of 2 mg kg^{-1} b.wt., (vit E) and 25 mg kg^{-1} b.wt., (TVN)

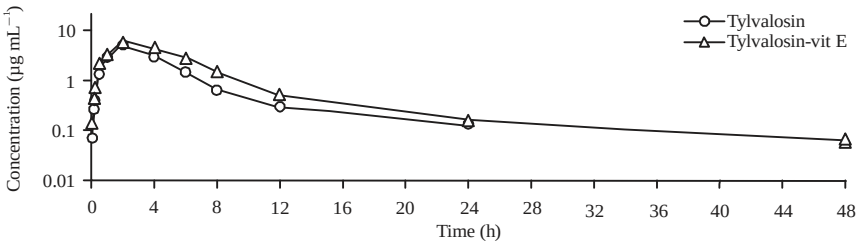

Fig. 2: Semilogarithmic plot depicting the time-course of tylvalosin and tylvalosin-vit E combination in serum after repeated oral administration of 2 mg kg^{-1} b.wt., (vit E) and 25 mg kg^{-1} b.wt., (TVN)

Table 3: Mean serum concentrations of tylvalosin alone or in combination with vitamin E in healthy broiler chickens after repeated oral administration of 25 mg kg^{-1} b.wt., tylvalosin and 2 mg kg^{-1} b.wt., (vit E) (N = 6)

	Mean±S.E	
Time	Tylvalosin (µg mL^{-1})	Tylvalosin-vit E (µg mL^{-1})
5 min	0.07±0.01	0.15±0.03***
10 min	0.28±0.02	0.44±0.06**
15 min	0.39±0.05	0.71±0.11***
30 min	1.28±0.26	2.21±0.1***
1 h	2.78±0.16	3.28±0.3***
2 h	5.01±0.13	5.90±0.1**
4 h	3.08±0.08	4.30±0.6***
6 h	1.46±0.28	2.80±0.4***
8 h	0.65±0.08	1.47±0.1***
12 h	0.29±0.04	0.51±0.06**
24 h	0.13±0.01	0.16±0.04*
48 h		0.06±0.01***

***,**,*Significant at $p \leq 0.001$, $p \leq 0.01$ and $p \leq 0.05$, respectively

concentration of the drug in serum was 4.1 µg mL^{-1} in tylvalosin alone whereas, 5.67 µg mL^{-1} in tylvalosin-vit E. The pharmacokinetic parameters are recorded in Table 4 showed that the serum concentrations were higher after tylvalosin in combination with vit E when compared to the tylvalosin alone.

Tylvalosin alone after single and repeated oral administration in broiler chickens: The mean serum concentrations of tylvalosin at different time intervals following single and repeated oral administration of 25 mg kg^{-1} b.wt., in 12 broiler chickens were presented in Table 5 and Fig. 3. The drug was firstly detected 0.05±0.02 and 0.07±0.01 µg mL^{-1} after 15 and 5 min and the

Table 4: Pharmacokinetic parameters of tylvalosin alone or in combination with vit E in healthy broiler chickens following repeated oral administration of 25 and 2 mg kg^{-1} b.wt., (N = 6)

Kinetic parameters	Tylvalosin	Tylvalosin-vit E
A (μg mL^{-1})	2.40±8.4	11.10±2.4***
$K_{(ab)}$ (h^{-1})	0.71±0.21	0.80±0.07*
$t_{0.5\ ab}$ (h)	1.39±0.4	0.86±0.07**
B (μg mL^{-1})	8.40±2.4	10.60±2.4***
K_{el} (h^{-1})	0.27±0.04	0.71±0.5**
$t_{0.5\ el}$ (h)	2.78±1.6	3.05±0.3***
t_{max} (h)	2.09±0.14	2.25±0.11*
C_{max} (μg mL^{-1})	4.10±0.14	5.67±0.4***
AUC (μg h mL)	23.09±1.14	36.40±2.7***
MRT (h)	4.28±0.2	4.80±0.12**

k_{ab}: First-order absorption rate constant, K_{el}: Elimination rate constant, C_{max}: Maximum serum concentration, t_{max}: Time to peak serum concentration, $t_{0.5(ab)}$: Absorption half-life, $t_{0.5(el)}$: Elimination half-life, MRT: Mean residence time, AUC: Area under serum concentration time curve, ***,**,*Significant at p≤0.001, p≤0.01 and p≤0.05, respectively

Table 5: Mean serum concentrations of tylvalosin in healthy broiler chickens following a single and repeated oral administration of 25 mg kg^{-1} b.wt., for 3 successive days (N = 6)

	Mean±SE	
Time	Single	Repeated
5 min	-	0.07±0.01***
10 min	-	0.28±0.02***
15 min	0.05±0.02	0.39±0.05***
30 min	0.41±0.06	1.28±0.26***
1 h	1.45±0.42	2.78±0.16***
2 h	2.25±0.2	5.01±0.13***
4 h	1.55±0.2	3.08±0.08***
6 h	0.68±0.13	1.46±0.28***
8 h	0.33±0.08	0.65±0.08***
12 h	0.06±0.02	0.29±0.04***
24 h	-	0.13±0.01***

***Significant at p≤0.001

Table 6: Pharmacokinetic parameters of tylvalosin in healthy broiler chickens following a single and repeated oral administration of 25 mg kg^{-1} b.wt., (N = 6)

Kinetic parameters	Single	Repeated
A (μg mL^{-1})	8.60±2.2	8.40±2.4*
$K_{(ab)}$ (h^{-1})	0.69±0.01	0.71±0.21*
$t_{0.5\ ab}$ (h)	0.94±0.04	1.39±0.4***
B (μg mL^{-1})	8.80±2.3	8.40±2.4*
K_{el} (h^{-1})	0.40±0.01	0.27±0.04*
$t_{0.5\ el}$ (h)	1.61±0.05	2.78±1.6***
t_{max} (h)	2.03±0.06	2.09±0.14*
C_{max} (μg mL^{-1})	2.11±0.3	4.10±0.14***
AUC μg.h.ml	10.50±1.5	23.09±1.14***
MRT (h)	3.68±0.06	4.280±0.2**

k_{ab}: First-order absorption rate constant, K_{el}: Elimination rate constant, C_{max}: Maximum serum concentration, t_{max}: Time to peak serum concentration, $t_{0.5(ab)}$: Absorption half-life, $t_{0.5(el)}$: Elimination half-life, MRT: Mean residence time, AUC: Area under serum concentration time curve, ***,**,*Significant at p≤0.001, p≤0.01 and p≤0.05, respectively

maximum serum level 2.25±0.2 and 5.01±0.13 μg mL^{-1} was reached at 2 h after single and repeated administration. The pharmacokinetic parameters are tabulated in Table 6. The peak concentration (C_{max}) was 2.11±0.3, 4.1±0.14 μg mL^{-1} and the calculated value of t_{max} was 2.03±0.06, 2.19±0.14 h, respectively. The absorption half-life ($t_{0.5ab}$) of 0.94±0.04, 1.39±0.4 h and eliminated with a mean half-life ($t_{0.5\ el}$) of 1.61±0.05, 2.78±0.16 h after single and repeated administration, respectively.

Tylvalosin pre-treated with vit E after single and repeated oral administration in broiler chickens: The mean serum concentrations of tylvalosin in combination with vit E at different time intervals following a single and repeated oral administration of 2 mg kg^{-1} b.wt.,

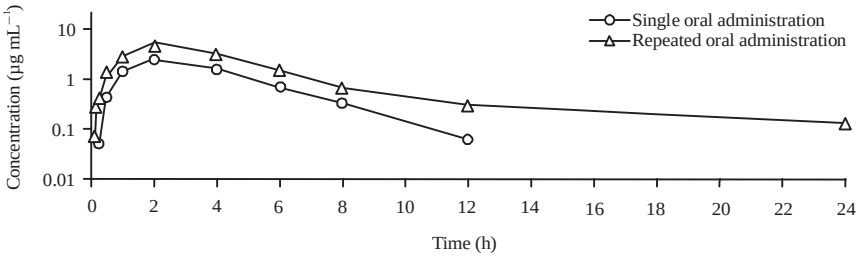

Fig. 3: Semilogarithmic plot depicting the time-course of tylvalosin in serum after single and repeated oral administration of 25 mg kg^{-1} b.wt.

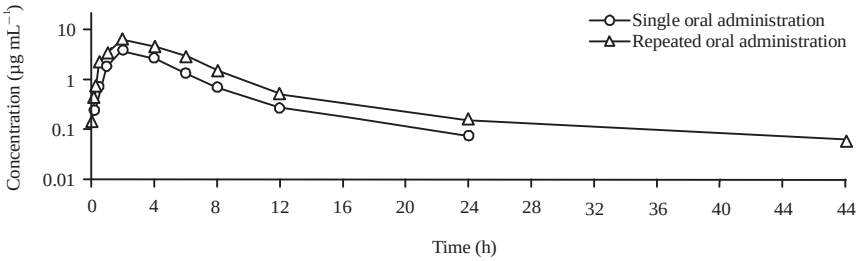

Fig. 4: Semilogarithmic plot depicting the time-course of tylvalosin-vit E combination in serum after single and repeated oral administration of 2 mg kg^{-1} b.wt., (vit E) and 25 mg kg^{-1} b.wt., (TVN)

Table 7: Mean serum concentrations of tylvalosin-vit E in healthy broiler chickens after single and repeated oral administration of 2 and 25 mg kg^{-1} b.wt., (N = 6)

	Mean±SE	
Time	Single	Repeated
5 min	-	0.15±0.03***
10 min	-	0.44±0.06***
15 min	0.23±0.0	0.71±0.11**
30 min	0.68±0.09	2.21±0.1***
1 h	1.75±0.14	3.28±0.3***
2 h	3.77±0.3	5.90±0.1***
4 h	2.55±0.09	4.30±0.6***
6 h	1.31±0.10	2.80±0.4***
8 h	0.67±0.07	1.47±0.1***
12 h	0.26±0.02	0.51±0.06***
24 h	0.07±0.06	0.16±0.04***
48 h	-	0.06±0.01***

***,**Significant at p≤0.001 and p≤0.01, respectively

(vit E) and 25 mg kg^{-1} b.wt., (TVN) in 12 broiler chickens were presented in Table 7 and Fig. 4. The drug was firstly detected 0.23±0.01 and 0.15±0.03 µg mL^{-1} after 15 and 5 min and the maximum serum level 3.77±0.3 and 5.9±0.1 µg mL^{-1} was reached at 2 h after the drug administration. The pharmacokinetic parameters of were tabulated in Table 8. The peak concentration (C_{max}) was 3.27±0.2 and 5.67±0.4 µg mL^{-1} and the calculated value of t_{max} was 2.18±0.07 and 2.25±0.11 h. The drug was absorbed from healthy broilers gut with absorption half-life ($t_{0.5ab}$) of 0.88±0.02 and 0.86±0.07 h and eliminated half-life ($t_{0.5el}$) of 2.42±0.1 and 3.05±0.3 h after single and repeated dosing, respectively.

Table 8: Pharmacokinetic parameters of tylvalosin-vit E in healthy broiler chickens following a single and repeated oral administration of 2 and 25 mg kg^{-1} b.wt., (N = 6)

Kinetic parameters	Single	Repeated
A (μg mL^{-1})	7.60±1.05	11.1±2.4***
$K_{(ab)}$ (h^{-1})	0.78±0.02	0.8±0.07*
$t_{0.5\ ab}$ (h)	0.88±0.02	0.86±0.07*
B (μg mL^{-1})	7.80±1.04	10.60±2.4***
K_{el} (h^{-1})	0.28±0.01	0.71±0.5**
$t_{0.5\ el}$ (h)	2.42±0.1	3.05±0.3***
t_{max} (h)	2.18±0.07	2.25±0.11*
C_{max} (μg mL^{-1})	3.27±0.2	5.67±0.4***
AUC (μg h mL)	18.16±0.5	36.40±2.7***
MRT (h)	4.16±0.2	4.80±0.12**

k_{ab}: First-order absorption rate constant, K_{el}: Elimination rate constant, C_{max}: Maximum serum concentration, t_{max}: Time to peak serum concentration, $t_{0.5(ab)}$: Absorption half-life, $t_{0.5(el)}$: Elimination half-life, MRT: Mean residence time, AUC: Area under serum concentration time curve, ***,**,*Significant at $p \leq 0.001$, $p \leq 0.01$ and $p \leq 0.05$, respectively

DISCUSSION

Tylvalosin commonly used in our poultry farms for treatments of mycoplasma and other respiratory diseases in poultry and swine. Few studies had been described the pharmacokinetics of tylvalosin in broiler chickens and there were no previous studies in our point of view had been studies the effects of vitamin E on the pharmacokinetics of tylvalosin after single and repeated oral administration so this work investigated to determine the effects of vit E on the disposition kinetics of tylvalosin.

Following a single oral administration of tylvalosin at s dose of 25 mg kg^{-1} b.wt. The drug has been detected in serum 15 min post administration (0.05 μg mL^{-1}). It was continued to increase gradually thereafter to reach its maximum concentration (C_{max}) 2.11 μg mL^{-1} at 2 h post administration and decreased gradually till reach its lower level (0.06 μg mL^{-1}) at 12 h. This result of (C_{max}) is similar to that reported in broiler chickens for tylvalosin at dose of 20 mg kg^{-1} b.wt., as (C_{max}) was (1.64 μg mL^{-1}) (Cerda *et al*., 2010) but differ from (Abo-El-Sooud *et al*., 2012a) about azithromycin (0.95 μg mL^{-1}) which might attributed also to dose variation and different in the chemical structure from tylvalosin and azithromycin. The t_{max} was 2.03 h, similar to that reported in broiler chickens for azithromycin (1.91 h) (Abo-El-Sooud *et al*., 2012b) but differ from tylvalosin (0.57 h) (Cerda *et al*., 2010), which might be attributed to presence of food in the crop, that would affect the crop movements, also according to the consistency of the feed, as the emptying of the crop can be complete in 3-20 h in addition; the presence of *Lactobacillus* ora in the crop almost 100% that has a major role in inactivation the macrolides (Cerda *et al*., 2010). The drug was rapidly absorbed after oral administration with an absorption half-life ($t_{0.5ab}$) 0.94 h. Our finding was similar to that reported for azithromycin in broiler chickens ($t_{0.5ab}$ 0.57 h) (Abo-El-Sooud *et al*., 2012a). All these knowledge confirmed that tylvalosin absorption rate markedly affected not only from species to another but also in the same species with individual variation (Cerda *et al*., 2010).

The drug has been eliminated with elimination half-life ($t_{0.5el}$) is 1.61 h. This result is similar to that reported in broiler chickens for tylvalosin 1.82 h (Cerda *et al*., 2010) but differ from (Abo-El-Sooud *et al*., 2012b) 31.50 h for azithromycin in broiler chickens which may attributed to that azithromycin was detected in the serum till 72 h but tylvalosin only till 12 h besides, the difference in chemical structure between tylvalosin and azithromycin as absence of actylisovaleryltylosin group in azithromycin and dose variation.

The *in vitro* protein binding tendency of tylvalosin in serum was 13.00%. Our result was lower than that reported for azithromycin in chickens 24.4% and for tulathromycin in rabbits (36%)

(Abo-El-Sooud *et al*., 2012a) and this difference may be attributed to different chemical structure, dose variation and species difference. This finding provides evidence that tylvalosin was not being extensively bound to serum protein in chickens and also it might explain the high diffusion of tylvalosin in tissues of chickens and high value of volume of distribution as reported by Zakeri-Milani *et al*. (2010) about macrolides distribution.

Concerning the effects of vit E on the tylvalosin pharmacokinetics following a single oral administration at a dose of 25 mg kg^{-1} b.wt., (TVN) and 2 mg kg^{-1} b.wt., (vit E) as this dose first experimented as vit E in the form of water soluble powder and dissolved in the drinking water and in our study at this dose vit E increase the drug efficacy as the drug was detected in serum 15 min post administration (0.23 μg mL^{-1}). It was continued to increase gradually thereafter to reach it's the maximum concentration (C_{max}) 3.77 μg mL^{-1} at 2 h post-administration and decrease gradually till reach its lower level (0.07 μg mL^{-1}) at 24 h. This result is higher than that reported for single tylvalosin administration alone C_{max} 2.11 μg mL^{-1}. This result explained on the increase of the absorption rates and serum accumulation of the drug after vit E combinations which lead to increase in the maximum serum concentration than tylvalosin administered alone and this indicated by the higher absorption rate constant (K_{ab}) 0.78 h^{-1} for drug combination with vit E than the values for the tylvalosin alone 0.69 h^{-1} this may be due to presence of vit E that help the absorption of the drug. The drug was rapidly absorbed with absorbed half-life $t_{0.5ab}$ 0.88 h, indicates that vit E may help more and rapid absorption of tylvalosin besides, increasing the absorption rate and serum concentration of tylvalosin that's may be due to binding of vit E with part of plasma proteins. In addition, vit E decrease the renal excretion on binding proteins through renal infiltration that's might bind with part of the drug leading also to increase its serum concentrations of vitamins help absorption of macrolides and increase its serum concentration as that reported by El-Hadjela *et al*. (2013) and increasing the therapeutic efficacy of tylvalosin after vit E treatment as informed by Goswami *et al*. (2011) about antioxidants when administered with antibiotics.

Vitamin E in combination with tylvalosin lead to more prolonged ($t_{0.5el}$) of 2.42 h in the body than single tylvalosin (1.61 h) alone leading to more prolonged effects of tylvalosin in the serum this increase might attributed to that the hepatoprotective effect of vit E (Attia *et al*., 2012; Uboh *et al*., 2012) so macrolides inhibition to liver microsomal enzymes would been decreased so their degradation by the liver from the body will be decreased so their serum concentration will increase. The combination of tylvalosin and vit E allows a prolongation of the dosage intervals in broiler for more than 12 h so this important combination allows the interval to be prolonged to 12 h. Tylvalosin eliminated at slower rate ($p<0.05$) when given with vit E than when given alone as indicated by long elimination half-life ($t_{0.5\,(el)}$) and residence time (MRT) in tylvalosin-vit E 2.42 and 4.16 h as compared to $t_{0.5el}$ 1.61 and 3.68 h for tylvalosin alone but the increasing in the serum concentrations of tylvalosin that's had been made by vit E increasing its efficacy but not reach to the level of toxicity as tylvalosin of wide safety margin and with low toxic level and has no signs of intolerance have been observed in poultry species at up to 150 mg tylvalosin per kilogram body weight per day for 5 days (EMEA., 2015).

Following repeated oral administration, tylvalosin reaches its maximum serum concentration 5.01 μg mL^{-1}, which is higher than the single dosing of tylvalosin alone 2.11 μg mL^{-1}. This result explained on accumulation tendency of the drug after repeated dosing proved in the present study, similar results about macrolides accumulation tendency had been reported for azithromycin and erythromycin (Zakeri-Milani *et al*., 2010). The increase in the observed maximum serum concentration was 5.01 μg mL^{-1} after repeated dose than the single dosing 2.25 μg mL^{-1} as the

kinetic parameter of C_{max} was 4.11 μg mL^{-1} after repeated dosing (higher than single one 2.11 μg mL^{-1}) the increase in the absorption rates and serum accumulation of the drug after repeated dosing than single one indicated by the low absorption rate constant (k_{ab}) 0.69 h^{-1} and absorption half-life ($t_{0.5ab}$) 0.94 h in single dosing as compared to 0.71 h^{-1} and 1.39 h in repeated dosing, respectively and slowly eliminated with an elimination half-life ($t_{0.5el}$) of 2.78 h which is also higher than that of single dose administration 1.61 h. This indicates the slow and extensive accumulation of tylvalosin in serum as reported about azithromycin and erythromycin (Zakeri-Milani *et al*., 2010). Also, its concentration increased after repeated administration which indicates the serum accumulation of part of the drug after its administration. In addition, several macrolide antibiotics are known to be mechanism-based inhibitors of microsomal liver enzymes responsible for macrolides degradation specially CYP3A and the degree of inhibition of CYP3A varies among the macrolides (Wang *et al*., 2011) so, increasing the serum concentration after repeated dosing lead to more liver enzyme inhibition and prolonged ($t_{0.5el}$) of 2.78 h in the body than single dose administration. Tylvalosin has long elimination half-life ($t_{0.5\ (el)}$) and residence time (MRT) in repeated dosing 2.78 and 4.28 h compared to 1.61 and 3.68 h in the single dose administration which indicates prolongation the duration of action of the drug efficacy but not reach to the toxic level (EMEA., 2015) in the serum for more 12 h after repeated administration.

While after repeated oral administration of tylvalosin in combination with vit E the drug reach its maximum concentration (C_{max}) 5.9 μg mL^{-1} and decrease gradually till reach its lower level (0.06 μg mL^{-1}) at 48 h. This result (C_{max}) was higher than single dose administration of tylvalosin-vit E combination which indicates serum accumulation of part of the drug in the serum with help of the role of vitamins in increasing the serum concentrations of antibiotics (El-Hadjela *et al*., 2013). This result explained on that increasing the absorption rates and serum accumulation of the drug after vit E combination with repeated dosing leading to an increase in the maximum serum concentration than the single dose administration of tylvalosin-vit E one indicated by absorption half-life ($t_{0.5ab}$) after repeated dosing 0.86 h was slightly lower than tylvalosin-vit E single administration 0.88 h. Vitamin E help rapid absorption of the drug. The drug is rapidly absorbed with absorption half-life ($t_{0.5ab}$) 0.86 h which is slightly lower than the result reported for single tylvalosin-vit E administration 0.88 h.

Vitamin E in combination with tylvalosin after repeated administration leads to more prolonged ($t_{0.5el}$) of 3.05 h than single tylvalosin-vit E 2.42 h alone leading to more prolonged the effect of tylvalosin in the serum that's might attributed to the hepatoprotective effect of vit E (Attia *et al*., 2012; Uboh *et al*., 2012) and the accumulation of a part of the drug in the serum besides the vit E effects on plasma protein excretion. Tylvalosin eliminated at slower rate ($p<0.05$) when given with vit E after repeated dosing than given single dose indicated by long elimination half-life ($t_{0.5el}$) and residence time (MRT) in vit E-tylvalosin combination (repeated dosing) 3.05 and 4.8 h as compared to 2.42 and 4.16 h in the single dose administration of tylvalosin-vit E. The combination of tylvalosin and vit E with repeated dosing allows a prolongation of the dosage intervals in broiler for 24 h so this important combination allows the interval to be prolonged to more one day of the drug to be effective.

CONCLUSION

In conclusion, combination of tylvalosin and vit E with repeated dosing allows a prolongation of the dosage intervals in broiler for 24 h so this important combination allows the interval to be prolonged to more one day of the drug to be serum concentration and efficacy (but not toxicity) which is very important for dosage interval and drug serum efficacy.

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