

Pharmacokinetics, tissue residues and efficacy of D-Tylo50/25® (tylosin-doxycycline combination) in broiler chickens

Mohamed Aboubakr*, Mohamed Elbadawy

Department of Pharmacology,
Faculty of Veterinary Medicine,
Benha University, Egypt

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***Correspondence to:**

Dr. Mohamed Aboubakr,

Email:

mohamed.aboubakr@fvmt.bu.edu
u.eg

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ABSTRACT

Background: Pharmacokinetic study of a commercial tylosin-doxycycline combination product (D-Tylo50/25®) was conducted in broiler chickens following intravenous (IV) and oral (PO) administration at doses of 50 mg/kg b. wt. (tylosin) and 25 mg/kg b. wt. (doxycycline).

Methods: Serum drug concentrations were determined by a validated high performance liquid chromatography (HPLC) using UV detection.

Results: A rapid and nearly complete absorption of both drugs with a mean PO bioavailability of 89.16% (tylosin) and 94.30% (doxycycline), prolonged elimination half-lives, and high tissue penetration with steady state volume of distribution of 6.73L/kg (tylosin) and 5.51L/kg (doxycycline) were observed. Tissue residues were studied following oral administration of each drug alone for five consecutive days and blood and tissue samples were obtained for 10 days after the last dose. Residues of tylosin and doxycyclines showed that kidney, liver and lung contained highest drug residues and completely disappeared from those tissues at 5 and 6 days after the last oral dose, respectively. The efficacies of D-Tylo50/25® and other antibiotics (tiamulin and oxytetracycline) were investigated in broiler chicks experimentally infected by *Mycoplasma gallisepticum*.

Conclusions: The pharmacokinetics of both drugs was characterized by a rapid and complete absorption, extensive tissue distribution and slow elimination. D-Tylo50/25® is more effective than tiamulin and oxytetracycline against *Mycoplasma gallisepticum* infection in broilers.

Keywords: Chickens, Doxycycline, Efficacy, Pharmacokinetics, Residues, Tylosin

INTRODUCTION

Tylosin, is a macrolide antibiotic having bacteriostatic action against anaerobic bacteria, Gram-positive bacteria and mycoplasma.¹ Tylosin was indicated for treatment of respiratory disease caused by *Mycoplasma gallisepticum* and synoviae in chickens and infectious sinusitis in turkeys.² Tylosin is considered as a bacteriostatic time-dependent antibacterial agent that inhibits bacterial protein synthesis through reversible binding to the 50S subunit of the ribosome.³ Tylosin is still considered as one of the most effective antimicrobial agents against

different mycoplasmas species and has more activity against mycoplasma than bacteria.⁴

Doxycycline is a tetracycline derivative with a broad spectrum activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria: Spirochaete, Mycoplasma, Chlamydia and Rickettsia species.⁵ Doxycycline has some advantages over older tetracycline derivatives including higher lipid solubility, better bioavailability and tissue distribution, longer elimination half-life, and lower affinity for calcium ions.⁶

The rationale for a combination therapy with antimicrobial agents is the pharmacodynamic or

pharmacokinetic interactions, leading to improved efficacy or safety profiles, compared with the single components.⁷ Furthermore, combination therapy is considered an effective means of minimizing the emergence rate of bacterial resistance.

Mycoplasma gallisepticum (MG) infection is commonly known as chronic respiratory disease (CRD) in chickens and infection sinusitis in turkeys.⁸ MG infection causes significant economic losses to poultry industry throughout the world. Despite other control measures, antibiotic therapy remains the most economic method in controlling CRD infection.⁹ There is a variety of antibiotics available in the market but a little data are available regarding the efficacy of these antibiotics against the local isolates of the MG.

In this regard, the purpose of the present study was to determine the pharmacokinetic profile of a commercial tylosin-doxycycline combination product (D-Tylo50/25[®], ATCO Pharma Co, Egypt). Also, tissue residues following oral administration of D-Tylo50/25[®] for 5 consecutive days was investigated in broiler chickens. The efficacies of D-Tylo50/25[®] and other antibiotics (tiamulin and oxytetracycline) in broiler chicks infected by *Mycoplasma gallisepticum* were also evaluated.

METHODS

Drugs

Tylosin tartrate and doxycycline Hydrochloride were obtained as pure powder (99.4 and 98.5%, respectively) (Sigma Aldrich Chemical Co., St. Louis, USA) and were dissolved in sterilized water for IV injection. While D-Tylo50/25[®], ATCO Pharma Co, Egypt. D-Tylo50/25[®]; Each 100 gm contains: Tylosin tartrate 54.096 gm (eq. to 50 gm Tylosin base) and Doxycycline HCl 27.051 gm (eq. to 25 gm Doxycycline base). Tiamulin and oxytetracycline were obtained as pure powder (99%) from (Sigma Aldrich Chemical Co., St. Louis, USA). All reagents used for extraction and analysis were of analytical or high performance liquid chromatography (HPLC) grade.

Broiler chickens and experimental design

A total number of seventy clinically healthy Hubbard broiler chickens, approximately 5 weeks old and weighing 1.6-1.8 kg were used. The chickens were housed indoors in hygienic conditions, fed an antibacterial-free diet and given free access to water. The chickens were divided in two main experiments:

Pharmacokinetics study

Ten broiler chickens were individually weighed before drug administration and doses were calculated precisely. Each broiler chicken was injected IV with Tylosin50 mg+25 mg doxycycline standard/kg. b.wt. into the left

wing vein. Broiler chickens were left for 15 days to ensure complete excretion of drug combination from their bodies. Then each broiler chicken was administered the same dose PO (intra-crop) with D-Tylo50/25[®].

Tissue residue study

Sixty broiler chickens given D-Tylo50/25[®] at a dose of (50 mg tylosin+25 mg doxycycline /kg. b.wt.) equal to 1 gm of product/liter of drinking water once daily for five consecutive days. Six broiler chickens were slaughtered every day post last dose of D-Tylo50/25[®] for 10 days. Blood and tissue samples (liver, kidney, lung, heart and muscles) were taken and stored at -20°C pending assay.

Efficacy study

One day-old broilers chicks (n=200), free of *Mycoplasma gallisepticum* (MG) were randomly divided in to five groups designated as A, B, C, D and E comprising 40 birds each. At the age of one week, the birds in groups, A, B, C and D were inoculated with a virulent strain of MG intra-tracheally with 0.1 ml of the PPLO (Pleuro Pneumonia like organism) broth containing 1.2x10⁸ CFU/ml. All infected birds were examined daily for the development of clinical signs. The diseased birds in groups A were treated with D-Tylo50/25[®] which composed of 50 mg/kg (tylosin) and 25 mg/kg (doxycycline). Group B; was treated with tiamulin (25 mg/kg b.wt.). Group C; was treated with oxytetracycline (40 mg/kg b.wt.). All medications were given orally in drinking water for a period of 5 days. Group D; (infected and untreated) and group E; (uninfected and untreated) and groups D and E served as control groups. The birds were examined for 5 days post-medication for the clinical and pathological profile including mortality, morbidity and case-fatality.

Blood and tissue samples

Blood samples were obtained from the right wing vein (1 ml) and collected in test tubes immediately before and at 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours after a single intravenous or oral administration and blood samples were obtained also every day following the last dose of repeated oral administration. Samples were centrifuged at 3000 rpm for 10 minutes and the obtained sera were used for estimation of tylosin and doxycycline concentration. Blood and tissue samples (liver, kidney, lung, heart and muscles) were taken and stored at -20°C until assay. The serum and tissue samples were stored at -20°C until analysis, and the assay was performed within a week of obtainment.

Analytical procedure

The HPLC system (Shimadzu Corporation, Kyoto, Japan) consisted of a pump (LC-10AD), UV detector (SPD-6A), integrator (Chromatopac C-R7A plus) and auto injector. The mobile phase for doxycycline detection comprised of

acetonitrile: methanol: 0.15% trifluoroacetic acid (23: 25: 52 v/v/v). The mobile phase was filtered through 0.45 µm membrane and degassed. The mobile phase was eluted at a flow rate of 1.5 ml/min and detected at a UV wavelength of 347 nm. Tylosin was eluted with a mobile phase of 37% acetonitrile and 63% phosphate buffer (KH₂PO₄, pH adjusted to 2.4 by adding hydrochloric acid). The flow rate was adjusted at 1 ml/min and the wave length of the UV detector was set at 282 nm. The retention times of tylosin and doxycycline were approximately 7.1 and 15.4 min, respectively. No interfering peaks in all blank samples were noticed in the elution position of either drug.

Pharmacokinetics analysis

Serum concentrations of both tylosin and doxycycline combination versus time data were utilized for calculating various pharmacokinetic variables using compartmental and non-compartmental analysis using computerized program, WinNonline 4.1 (Pharsight, USA).

RESULTS

The pharmacokinetic parameters calculated for tylosin and doxycycline after single IV and PO administration are presented in Table 1 and Table 2, respectively. Semi-logarithmic plots of serum concentration versus time for tylosin and doxycycline were shown in Figure 1 and Figure 2, respectively.

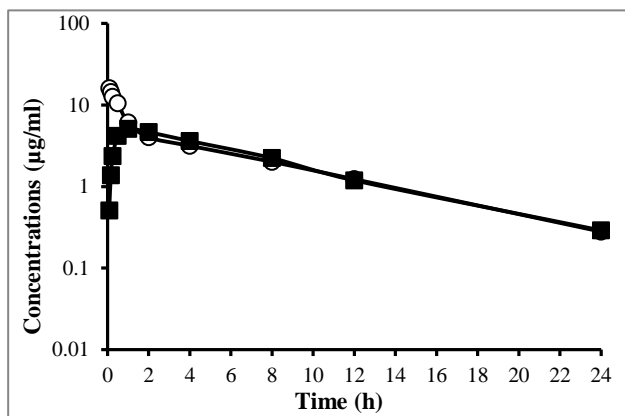


Figure 1: Semi-Logarithmic graph depicting the time-concentration of tylosin in serum of broiler chickens after a single IV (○) and PO (■) administration of 50 mg/kg b.wt. (n=10).

After IV injection, the total body clearance and steady state volume of distribution were 0.97 l/kg/hr and 6.73 l/kg for tylosin, and were 0.57 l/kg/hr and 5.51 l/kg for doxycycline, respectively. Mean peak serum concentrations (C_{max}) of 4.85µg/ml (tylosin) and 3.54µg/ml (doxycycline) were reached at 1.32 and 0.97hr, respectively after PO administration. The mean PO bioavailability was 89.16% for tylosin and 94.30% for

doxycycline. The mean terminal half-lives obtained after IV and PO injection were 5.62 and 5.55hr for tylosin and 7.62 and 8.97hr for doxycycline, respectively. Residues of tylosin and doxycyclines showed that liver, kidney and lung contained the highest tylosin and doxycycline residues and completely disappeared from those tissues at 5 and 6 days after the last oral dose, respectively and recorded in Table 3 and Table 4, respectively. The efficacies of D-Tylo50/25 and other antibiotics (tiamulin and oxytetracycline) in broiler chicks infected by *Mycoplasma gallisepticum* were determined in Table 5.

Table 1: Mean±SE serum pharmacokinetic parameters of tylosin in healthy chickens following IV and PO administration of 50 mg/kg b.wt. (n=10).

Parameter	Unit	IV	PO
α (k _{ab})	h ⁻¹	1.70 ± 0.11	2.27±0.02
t _{1/2α} (t _{1/2ab})	h	0.40 ± 0.02	0.30 ± 0.003
β (k _{el})	h ⁻¹	0.12 ± 0.003	0.21 ± 0.007
t _{1/2β} (t _{1/2el})	h	5.62 ± 0.21	5.55 ± 0.13
AUC	µg ml ⁻¹ h ⁻¹	51.2 ± 6.07	45.6 ± 5.18
AUMC	µg ml ⁻¹ h ⁻²	352.9±27.7	362.5±24.84
MRT	h	6.89±0.31	7.94±0.34
Vd _{ss}	l kg ⁻¹	6.73±0.36	—
Cl _{tot}	l kg ⁻¹ h ⁻¹	0.97±0.04	—
C _{max}	µg ml ⁻¹	—	4.85 ± 0.12
t _{max}	h	—	1.32 ± 0.05
F	%	—	89.2±6.02

α; β hybrid rate constant representing the slope of distribution and elimination phase after IV injection; Kab; Kelabsorbtion and elimination rate constant after PO administratin; t1/2(α) distribution half-life after IV injection; t1/2(ab) absorption half-life after po administration, respectively.; t1/2(β) elimination half-life after IV injection; t1/2(el) elimination half-life after PO administration; AUC area under concentration-time curve; AUMC area under moment curve; MRT mean residence time; Vdss volume of distribution at steady state; Cltot total body clearance. Cmax maximum serum concentration; Tmax time to peak serum concentration; F fraction of drug absorbed systemically after POadministration.

Table 2: Mean ± SE serum pharmacokinetic parameters of doxycycline in healthy chickens following IV and PO administration of 25 mg/kg b.wt. (n=10).

Parameter	Unit	IV	PO
α (k _{ab})	h ⁻¹	4.26 ± 0.19	3.61±0.09
t _{1/2α} (t _{1/2ab})	h	0.16± 0.01	0.19 ± 0.002
β (k _{el})	h ⁻¹	0.09 ± 0.002	0.07 ± 0.001
t _{1/2β} (t _{1/2el})	h	7.62 ± 0.22	8.97 ± 0.37
AUC	µg ml ⁻¹ h ⁻¹	43.4 ± 3.93	40.9 ± 4.07
AUMC	µg ml ⁻¹ h ⁻²	414.9±17.0	518.3±19.5
MRT	h	9.56±0.43	12.67±0.86
Vd _{ss}	l kg ⁻¹	5.51±0.17	—
Cl _{tot}	l kg ⁻¹ h ⁻¹	0.57±0.01	—
C _{max}	µg ml ⁻¹	—	3.54 ± 0.11
t _{max}	h	—	0.97 ± 0.02
F	%	—	94.3±6.83

Table 3: Tissue concentrations (Mean ± SE) of tylosin (µg/g) in healthy chickens during repeated oral administration of 50 mg/kg b.wt. once daily for 5 consecutive days (n=6).

Tissues	Days after last administration									
	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th
Heart	-	-	-	-	-	-	-	-	-	-
Lung	35.3±4.30	9.38±0.71	4.65±0.15	0.97±0.08	-	-	-	-	-	-
Liver	41.9± 5.07	12.9± 0.85	5.72± 0.19	1.13± 0.09	-	-	-	-	-	-
Kidney	47.0±5.92	14.5±0.73	6.39±0.23	1.78±0.11	-	-	-	-	-	-
Breast muscle	1.32±0.10	-	-	-	-	-	-	-	-	-
Thigh muscle	1.29±0.08	-	-	-	-	-	-	-	-	-

- Not detected

Table 4: Tissue concentrations (Mean ± SE) of doxycycline (µg/g) in healthy chickens during repeated oral administration of 25 mg/kg b.wt. once daily for 5 consecutive days (n=6).

Tissues	Days after last administration									
	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th
Heart	-	-	-	-	-	-	-	-	-	-
Lung	32.0±4.14	15.0±0.84	6.47±0.21	0.78±0.09	-	-	-	-	-	-
Liver	37.9±4.15	22.5±0.79	10.0±0.42	2.64±0.11	0.54±0.08	-	-	-	-	-
Kidney	42.8±4.73	27.4±2.58	11.6±0.43	3.81±0.08	0.89±0.10	-	-	-	-	-
Breast muscle	1.10±0.09	-	-	-	-	-	-	-	-	-
Thigh muscle	0.97±0.02	-	-	-	-	-	-	-	-	-

- Not detected

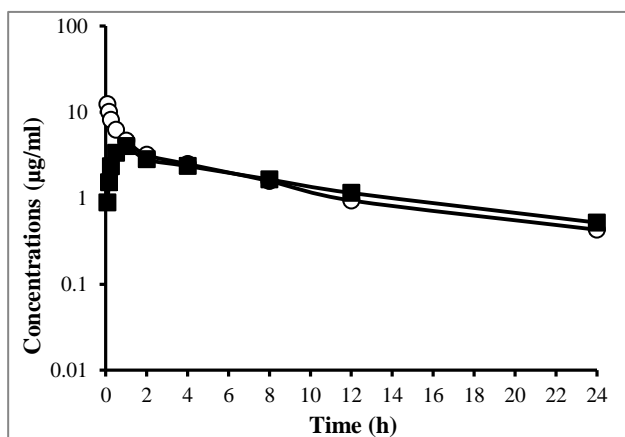


Figure 2: Semi-Logarithmic graph depicting the time-concentration of doxycycline in serum of broiler chickens after a single IV (○) and PO (■) administration of 25 mg/kg b.wt. (n=10).

DISCUSSION

After a single IV administration of tylosin (50 mg/kg b.wt.), it obeyed a two compartments-open model.⁴ The elimination half-life ($t_{1/2\beta}$) was 5.62 h, which was longer than those reported in sheep and goat (4.75 and 4.24 h, respectively, broiler chickens 0.52 h² and pigs 4.52 h.^{10,11} This dissimilarity may be attributable to differences in the administered dose.

Table 5: Comparative efficacies of D-Tylo50/25®, tiamulin and oxytetracycline in broiler chicks with CRD.

Group	Morbidity		Mortality		Case Fatality	
	No.	%	No.	%	No.	%
A	35	87.5	0	0	0	0
B	37	92.5	1	2.5	1	2.7
C	36	90	2	5	2	5.55
D	39	97.5	4	10	4	10.3
E	0	0	0	0	0	0

A=infected and treated with D-Tylo50/25;
 B=infected and treated with Tiamulin;
 C=infected and treated with Oxytetracycline;
 D=infected and non-treated (Control);
 E=non-infected and non-treated (Control).

The disposition kinetics of tylosin following oral administration of 50 mg tylosin/kg.b.wt. revealed that the maximum blood concentration (C_{max}) were 4.85 µg/ml and attained at (t_{max}) of 1.32 hours and was eliminated with half-life ($t_{1/2el}$) equal to 5.55 hours. These results are consistent with those recorded in cows and some avian species.^{12,13} The mean systemic bioavailability of tylosin following oral administration was 89.16%, which higher than those reported in broiler chickens 30%.² Tylosin had good absorption from the GIT and no enteric coating is required to maintain the stability of the compound in the stomach. It is widely distributed, metabolized by the liver and excreted via the bile and feces.^{14,2}

Tissue residues of tylosin in slaughtered chickens following repeated oral administrations of 50 mg tylosin/kg.b.wt once daily for 5 consecutive days revealed a wide spread distribution of tylosin in lung, liver, kidney, muscles. Liver, kidney and lung contained the highest drug residues. Tylosin was completely cleared from blood and all tissues at 5 days (120 hours) after the last dose. These data were consistent with those reported by.¹⁵ Tylosin is widely distributed in the body, which attains higher concentration at the tissue compared to that at the plasma and has low binding to plasma.¹⁶ Tylosin is concentrated in tissues including lungs at levels between 3 to 5 times greater than those detected in plasma.^{2,1}

Doxycycline after IV administration obeyed a two compartments-open model.¹⁷ The pharmacokinetics of doxycycline were studied in chickens following different routes of administrations.¹⁸⁻²⁰ Doxycycline was eliminated with half-life ($t_{1/2\beta}$) equal to 7.62 h. The long $t_{1/2\beta}$ is a clear characteristic of doxycycline in different species, which range from 4.2 to 16.6 h.^{18,19,21} High volume of distribution (5.51 L/kg) and a low total body clearance (0.57 L/kg/h) indicates that doxycycline is rapidly absorbed, widely distributed and slowly eliminated in body of chickens as reported by.¹⁸⁻²⁰ Following oral administration, of doxycycline, elimination half-life ($t_{1/2el}$) was 8.97 h. This value varies with age of chickens between 10 and 12 h.^{22,23} However, these values are notably different from the $t_{1/2el}$ values of 3.64 to 4.75 h reported in chickens.^{4,18,24} The oral bioavailability of doxycycline in this study was 94.30%, indicated a good absorption from GIT. This result was higher than doxycycline in broiler chickens.¹⁹ Tissue residues of doxycycline in slaughtered chickens following repeated oral administrations of 25 mg/kg b.wt once daily for 5 consecutive days revealed that, liver, kidney and lung contained the highest drug residues while the lowest drug residue was in the plasma. Doxycycline was completely cleared from the plasma and all tissues on day 6 (144 hrs) after the last dose.²⁵

D-Tylo50/25[®] is more effective than tiamulin and oxytetracycline against *Mycoplasma gallisepticum* infection in broilers. The study is in agreement with who evaluated efficacy of Tiamulin, Tylosin, Spiramycin, oxytetracycline and dihydrostreptomycin at different dosages to layer hens naturally infected with *Mycoplasma gallisepticum*.²⁶ The cure rate was significantly higher in treated hens than in untreated hens, as early as one day after treatment.

CONCLUSION

After IV and PO administration of the doxycycline-tylosin combination to broiler chickens, no adverse effects were observed. The pharmacokinetics of both drugs was characterized by a rapid and complete absorption, extensive tissue distribution and slow elimination. D-Tylo50/25[®] is more effective than

tiamulin and oxytetracycline against *Mycoplasma gallisepticum* infection in broilers.

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