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The Influence of Different Routes of Administration on the pharmacokinetic aspects of Doxycycline in Turkey

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SUMMARY

The pharmacokinetic parameters and bioavailability of doxycycline were compared in four groups of six male turkeys each, after a single intravenous, oral, or intramuscular (thigh or pectoral muscle) routes at a dosage of 20 mg/kg b.wt. of doxycycline. HPLC with UV detection at 347 nm was used to estimate doxycycline concentrations. Following the intravenous injection, doxycycline obeyed a two-compartment open model, the distribution half-life time ($t_{1/2\alpha}$), the elimination half-life time($t_{1/2\beta}$), the body clearance (CL), and the volume of distribution (V_{ss}) were 0.235h, 10.49h, 0.132 mg/(µg/ml) and 2.00 L/Kg respectively. Following the extravascular administration, the maximal serum concentrations (C_{max}) of doxycycline in turkeys were 4.66 µg/ml, 6.17 µg/ml, and 5.61 µg/ml with time-to-peak concentration (T_{max}) of 2.80 h, 1.78 h, and 1.90 h and absolute bioavailability of 57.1%, 70.6% and 67.2% after oral, thigh, and pectoral muscle administration respectively. The MRT was 14.80 h, 18.48 h, 22.90 h, and 19.53 h after iv, oral, IMT, and IMP respectively. We recommend that the doxycycline should be injected into the thigh muscle in turkeys since it achieved high bioavailability and highest MRT, and longer $t_{1/2\beta}$.

INTRODUCTION

Tetracyclines are active against a wide range of bacteria, including Gram-positive and negative bacteria, chlamydias, rickettsias, mycoplasmas, and spirochaetes. They are bacteriostatic antibiotics that work by binding to the 30S ribosomal subunit of bacteria and interfering with protein synthesis in a time-dependent manner (Nguyen et al. 2014) by blocking the binding of aminoacylated tRNA to the ribosomal acceptor (A) site **(Chopra & Roberts, 2001).** Doxycycline, as hyclate salt, is presented as an intramuscular, intravenous injectable solution, as water-soluble or lacto-dispersible powders, tablets, and capsules. **(EMA 1997)**

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The pharmacokinetics of doxycycline have been established in various avian species including chickens (**Anadón et al. 1994; El-Gendi et al. 2010; Laczay et al. 2001; Soliman et al. 2015; Yang et al. 2016, 2018),** ostriches **(Abu-Basha et al. 2006),** ducks **(Bratoev et al. 2016)** and turkeys **(Santos et al. 1996 and Abo-EL-Sooud K. 2016).**

Doxycycline has a higher bioavailability and tissue penetration, a larger volume of distribution, and a longer elimination period than tetracycline. **(Papich and Riviere 2013).** It is chosen over other tetracyclines due to its superior absorption, high tissue concentrations, and lengthy persistence in animals that have been orally treated. **(Anadón et al. 1994),** This antibiotic is less harmful to patients with hepatic and renal impairment since it is largely eliminated into the feces via non-biliary pathways **(Andrade and Tulkens 2011; Plumb 2015).**

The route of administration of medications is determined not only by convenience but also by the drug's properties and pharmacokinetics (**Kim and De Jesus 2022).** Bioavailability studies are important in determining therapeutic efficacy and are required to register generic drug products according to the Food and Drug Administration (FDA) regulations **(Chen et al. 2001).** The rate and extent to which an active drug ingredient is absorbed and becomes available at the site of drug action are defined as bioavailability; and also, the fact that even within the same species, drug kinetics may differ depending on the route of administration or the drug formation **(Toutain et al. 2010).**

Turkeys (Meleagris gallopavo) are members of the Galliformes order (along with grouse, guinea fowl, and chachalacas), the Phasianidae family (along with pheasants, quail, peafowl, and jungle fowl), and the Meleagridinae subfamily **(Stangel 1992).**

In our Egyptian farms and from an economic point of view, it is important to determine the best route of drug administration that can achieve the maximum efficacy of the drug, especially when being used in heavy-weight species such as white turkey.

This research aims to investigate the best route of administration of doxycycline hyclate in turkeys by studying and comparing its pharmacokinetic parameters like distribution, elimination, and bioavailability after intravenous, oral, and intramuscular (thigh or pectoral) administration.

MATERIALS And METHODS

Ethical Statement

This study was approved by the Research Committee of the Animal Health Research Institute and authorized by the Institutional Animal Care and Use Committee (ARC-IACUC)/ Agricultural Research Center (ARC/ AH/22/25).

Birds

This study used twenty-four apparently healthy male white turkeys aged seventy days and weighing 7.4 ± 0.57 kilograms on average. They were accommodated in a room with temperatures ranging between 22 and 25°C. They were fed a commercial diet free from antibiotics and given free access to water and ration for fifteen days for acclimatization with the environment and as a body clean-up period before starting the experiment

Drug

Doxycycline hyclate (Doxy 40 H.C.® doxycycline 40%) was obtained from ARAB-COMED Co. (Arab Company for Medical Products), Obour City, Industrial Area, Cairo, Egypt. The drug was analysed to verify the concentration of the active principle, according to (Mitić et al. 2008). In turkey, doxycycline was administered at the recommended dose of 20 mg/kg b.wt. **(EMA 2015).**

Chemical reagents

Methanol, acetonitrile, and acetic acid (HPLC grade) were purchased from Fisher Scientific, Leicestershire, United Kingdom. The mobile phase and diluted solutions were made with deionized water. The Doxycycline hyclate standard (purity of more than 98%) was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA).

Experimental design:

After the end of the body clean-up period, each male turkey was individually weighed to estimate the dose of doxycycline before its administration, and then a total of 24 male turkeys were divided into 4 groups as illustrated in Table (1) to start the current study.

Table 1. Grouping of experimental birds

Group number	Number of turkeys per each group	Drug	Dose	Route of administration
One	6, n=6	Doxycycline hyclate	20mg/kg b.wt Once daily	Intravenous
Two				Oral (into the crop using a thin plastic tube attached to a syringe)
Three				Intramuscular (thigh muscle)
Four				Intramuscular (pectoral muscle)

Sample collection:

Blood samples were collected from either the right- or left-wing vein before drug administration to assure that blood is free from antimicrobial and to establish the standard curve. Blood samples were collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours of i.v, oral, IMT, and IMP administration. Serum samples were obtained by centrifugation at 3000 RPM for ten minutes and serum samples were kept at -18 ^{O}C in screw-capped tubes till the quantification of doxycycline.

Chromatographic assay

High-performance liquid chromatography (HPLC) was utilized for determining doxycycline concentrations in serum.

Standard solutions:

According to the standard concentration, the standard was weighed to the nearest 0.01 g up to 10 mL with methanol to produce 1 mg/ml. This solution should be used at once for further standard curve concentration preparation.
Doxycycline calibration standards were prepared fresh daily at concentrations of 0.0156, 0.0313, 0.0625, 0.125, 0.250, 0.5, 1, 2, 5, 10, 20, 50, and 100 µg/ml in blank turkey serum. Doxycycline has been extracted according to the extraction steps that were mentioned as follows for kinetic analysis. A calibration curve was obtained by plotting the doxycycline peak areas versus known concentrations. The equation was calculated by the least-squares method using linear regression.

High-performance liquid chromatography device equipped with an Agilent Series 1260 quaternary pump, autosampler, Ultraviolet/ visual detector, and high-performance liquid chromatography chem-station software. The stationary phase was a reversed-phase C18 chromatographic column (4.6 mm, 250 mm, 5 µm), Thermo Co.

The chromatographic condition was as follows. The temperature in the used column was set to 10 degrees Celsius. A flow rate of 1 ml/ min and an Injection volume equal to 25 µl. Detection and quantitation were conducted at 347 nm. Estimation was integrated by the chem-station software of the HPLC. the mobile phase was Isocratic, and each one hundred -milliliters consisted of fifty-five-milliliter ace-

tic acid (5%), twenty-five-milliliters of acetonitrile, and twenty milliliters of methanol (Ruza et al. 2004).

Extraction method

Extraction procedure has been carried out as reported by **(Elshater et al. 2016),** briefly, two hundred microliters of a serum sample were mixed with two hundred microliters of acetonitrile. The mixture was vortexed for thirty seconds before being centrifuged for ten minutes at a speed of 12,857 Xg at a temperature of four degrees Celsius. Two hundred microliters of the supernatant were then evaporated in a nitrogen evaporator at forty degrees Celsius. The dried residues were reconstituted with two hundred microliters of mobile phase. A sample of twenty-five microliters of aliquot was injected into high-performance liquid chromatography.

This method was validated according to **(USP 2021)** via the determination of method precision, recovery, linearity, and the limit of detection and quantification.

The method was precise, with high recovery (98-102%) and good linearity > (0.999) with low DL and QL for doxycycline; the detection limit was 0.48 microgram/milliliter and the quantification limit was 1.46 micrograms/milliliter, specificity and selectivity were illustrated in Figure 1 with the following retention time of 12.59 minutes.

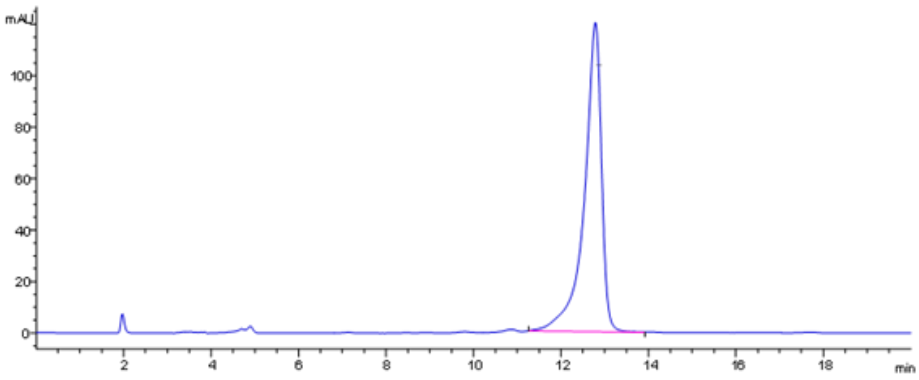

Figure 1: Chromatogram of doxycycline at a concentration of 50 µg/ml

Pharmacokinetic and statistical analysis

Data were expressed as mean ± SD, and the pharmacokinetic parameter was calculated by PK Solver: a Microsoft Excel add-in application, version 2 **(Zhang et al. 2010).** The data generated were subjected to statistical analysis employing one-way ANOVA with $P \leq 0.05$ as a level of significance. F % = ($AUC_{non\text{-}IV}/AUC_{IV}$) X 100 was the equation that has been used to calculate the bioavailability.

RESULTS

Throughout the investigation, doxycycline was well tolerated by all experimental birds, with no adverse medication reactions reported. The average serum concentration-time profiles of doxycycline after a single intravenous, oral, thigh muscle, and pectoral muscle administration were presented in Figure 2. No quantifiable concentration of doxycycline was shown in any sample collected before the drug was given. The average values of the calculated pharmacokinetic parameters were shown in Table 2.

respectively, till 24 hours in the serum samples in all the groups. The doxycycline in turkeys' serum in extravascular groups were detected after 15 minutes and 10 minutes of its administration in the oral group and intramuscular groups. At different time intervals, the doxycycline concentrations in the serum were lower after the oral and pectoral muscle route

as compared to that of the thigh muscle route.

The serum concentration-time profile of doxycycline after IV injection is fitted to an open two-compartment model (Figure 2).

Following intravenous (IV) injection, the elimination half-life ($T1/2_{\beta}$), the total body clearance (CL), and the volume of distribution (V_{ss}) were 10.49 h, 0.132 (mg)/(µg/ml)/h and 2.00 L/kg, respectively. k_{12} and k_{21} represented the micro-rate constants of doxycycline transfer between the central and peripheral compartments and were 1.41 and 1.48 h^{-1} in turkeys, respectively. This indicated very good drug distribution to the different tissues.

The MRT of doxycycline following intravenous injection was shorter than the average values obtained by extravascular routes, and there was also a statistical difference in the same parameter at $P \leq 0.05$ between extravascular administration groups.

The average value of the doxycycline concentration in the serum at zero time immediately after a single intravenous injection (C^0) is about four times the average C_{max} values obtained for all other extravascular administrations.

The mean serum concentration–time curves of doxycycline in turkeys following oral and IM routes are illustrated in Figure 2 and their corresponding pharmacokinetic parameters are presented in Table 2. A statistical difference at $P \leq 0.05$ was noticed between the maximum serum concentrations (C_{max}) of doxycycline in turkeys between different routes of extravascular administration.

C_{max} was 4.66, 6.17, and 5.61µg/ml with time to peak concentration (T_{max}) values of 2.80, 1.78, and 1.90 h for oral, thigh muscle, and pectoral muscle administration, respectively.

The calculated absolute values of bioavailability after extravascular administrations were 57.1%, 70.6%, and 67.2%. after oral, thigh muscle injection, and pectoral muscle injection, respectively.

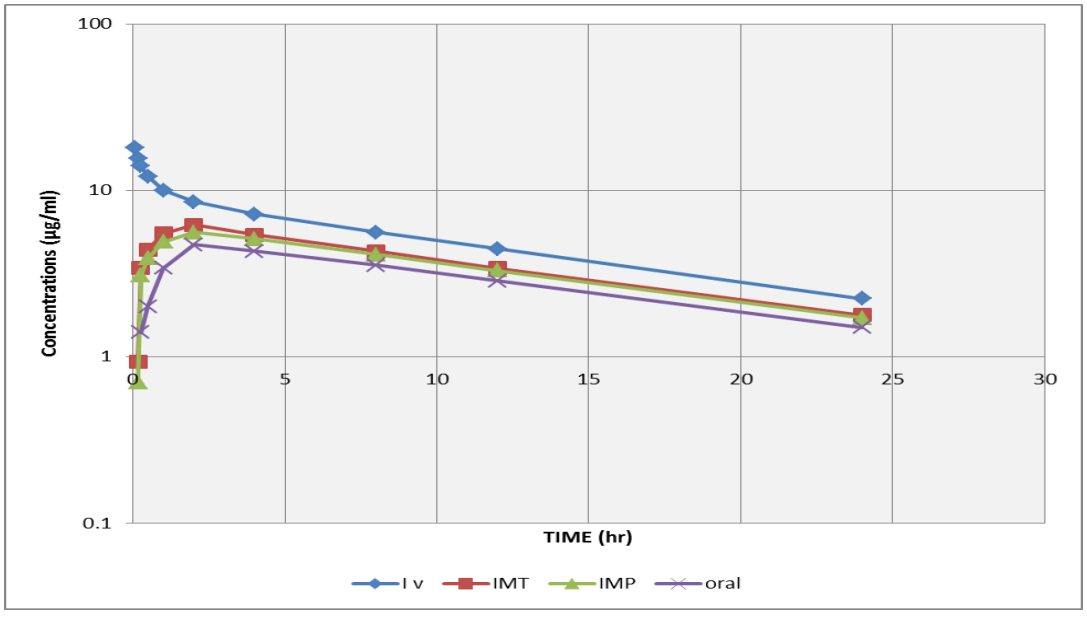

Fig. 2: Semilog. Graph depicting the time course of doxycycline in the serum of turkey after a single intravenous, oral, thigh muscle, and pectoral muscle dose of 20 mg/kg b.wt.

Table 2. Pharmacokinetic parameters (mean + SD) after a single intravenous (i.v.), oral, thigh, and pectoral muscle injection of doxycycline at a dose of 20 mg/kg b.wt (n=6) in male white turkeys (number equal to 6 in each group)

parameters	units	Intravenous route	Oral route	Intra-muscular route	
				Thigh muscle	Pectoral muscle
C^0	µg/ml	19.92±0.2			
α	1/h	2.96±0.14	0.62±0.02^c	1.14±0.03^a	1.09±0.1^b
β	1/h	0.066±0.001	0.054±0.002^a	0.05±0.001^b	0.053±0.001^a
K_a	1/h		0.70±0.023^c	1.32±0.01^a	1.28±0.04^b
k_{10}	1/h	0.132±0.002	0.084±0.002^a	0.069±0.001^b	0.070±0.001^{ab}
k_{12}	1/h	1.41±0.1	0.19±0.01^c	0.32±0.003^a	0.26±0.02^b
k_{21}	1/h	1.48±0.1	0.4±0.02^b	0.81±0.01^a	0.83±0.04^a
$t_{1/2\alpha}$	h	0.235±0.01	1.12±0.03^a	0.61±0.004^b	0.63±0.011^b
$t_{1/2\beta}$	h	10.49±0.2	12.84±0.3^b	13.80±0.35^a	13.13±0.4^b
$t_{1/2ka}$	h		0.99±0.032^a	0.52±0.02^b	0.54±0.1^b
V	L/Kg	1.00±0.01			
CL	(mg)/(µg/ml)/h	0.132±0.001			
V/F	(mg)/(µg/ml)		2.38±0.12^a	2.53±0.1^a	2.47±0.1^a
V_{ss}	L/Kg	2.00±0.02			
CL/F	(mg)/(µg/ml)/h		0.20±0.01^a	0.173±0.001^b	0.175±0.002^b
C_{max}	µg/ml		4.66±0.1^c	6.17±0.010^a	5.61±0.032^b
T_{max}	h		2.80±0.034^a	1.78±0.002^c	1.90±0.013^b
AUC $_{0-t}$	µg/ml*h	120.81±0.7	69±1.31^c	85.31±0.6^a	81. 19±0.8^b
AUC $_{0-inf}$	µg/ml*h	151.06±1.62	99.59±2.8^b	115.34±1.1^a	114.1±1.3^a
AUMC	µg/ml*h^2	2236.2±60.0	1841.25±155.9^c	2640±50.12^a	2228.94±82.3^b
MRT	h	14.80±0.3	18.48±1.3^c	22.90±0.41^a	19.53±0.5^b
F	%		57.1±1.1^c	70.6±0.5^a	67.2±0.6^b

Values are the mean ±SD (n = 6). Means with different superscript small letters are significantly different between groups in the same row at P≤ 0.05 using one-way ANOVA test.

C°, drug concentration in the serum at zero time immediately after a single intravenous injection**; α and β,** Hybrid rate constants of the biphasic intravenous disposition curve, values of α and β are related to the slopes of the distribution and the elimination phases respectively**; K_a,** absorption rate constant**; K_{10},** elimination rate constant**; K_{12},** transfer rate constant for drug distribution from the central to the peripheral compartment**; K_{21},** transfer rate constant for drug distribution from the peripheral to the central compartment; **$t_{0.5(\alpha)}$,** distribution half-life**; $t_{1/2\beta}$,** elimination half-life**; $t_{1/2ka}$,** absorption half-life**; V/F, is** apparent volume of distribution**; V_{ss}, is** The apparent volume of distribution, which was calculated by the steady-state method**. CL/F,** total clearance of the drug from the serum**; C_{max}, is the** maximum serum concentration of the drug in blood after extravascular administration**; t_{max},** the time at which the maximum concentration of the drug was reached after extravascular administration**; AUC,** Total area under the serum drug concentration versus time curve from t = 0 to t = α after administration of a single dose**; AUMC, the** area under the first moment of the concentration-time curve from zero up to ∞**; MRT,** mean residence time; **F,** the bioavailability of the drug.

DISCUSSION

Antimicrobial agents are extremely important in the poultry farming sector as they are used for either preventative or therapeutic purposes **(Watteyn et al. 2013).** Doxycycline is a semi-synthetic bacteriostatic tetracycline with a broad spectrum of antibacterial activity against Gram-negative and Gram-positive aerobic and anaerobic bacteria, Rickettsiae, Chlamydiae, Mycoplasmas, and some protozoa **(Jha et al. 1989; Prats et al. 2005).** In the current study, the pharmacokinetic parameters of doxycycline were inspected in apparently healthy male turkeys, after being given through four different routes of administration (intravenous, oral, thigh muscle injection, and pectoral muscle injection) at a dose of 20 mg/kg b.wt.

The serum concentration-time profile after IV injection was best described by a two-compartment open model; it was widely distributed throughout the body in a short period. The V_{ss} in our study (2.00 L/kg) was in agreement with the previous mean value reported in male native Baladi breed turkeys (2.39 L/kg) **(Abo EL-Sooud et al. 2016),** but it was higher than the value that has been reported for chickens (0.11 L/kg)**(Anadón et al. 1994),** ostrich (0.86 L/kg) (**Abu-Basha et al. 2006),** and geese (0.58 L/kg)(**Sartini et al. 2021),** and it was lower than the mean value reported in ducks (2.80 L/kg) **(Bratoev et al. 2016),** and chickens (5.05 L/kg) (**Soliman et al. 2015**) by using the same administration route. The diversity in the V_{ss} may be explained by differences in bird species, body size, differing patterns of blood protein-binding, estimation method, dose provided, or variances in drug disposition **(Ismail and El-Kattan 2009; Toutain et al. 2010; Houben et al. 2016 and Csiko et al. 2018).**

The values of the volume of distribution and the micro-rate constants of drug transfer between the central and peripheral compartments (k_{12}) suggested very good drug distribution in different tissues and body fluids. With the high lipophilic nature of doxycycline, it would be expected to be distributed widely in fat-containing tissues. The body clearance was (0.132 mg/(μg/ml)/h) similar to that was reported in ostriches (0.15 L/h.kg) **(Abu Basha et al. 2006),** laying hens (0.10 L/h.kg) **(Yang et al. 2016)** and younger turkeys (0.11 L/h.kg) **(Santos et al. 1996)** but lower than that reported in male native Baladi breed turkeys (0.55 L/h.kg) **(Abo EL-Sooud et al. 2016) and ducks (0.40 L/h.kg) (Bratoev et al. 2016).** The difference in the pharmacokinetics parameters among poultry is somewhat common and may be due to the inter-species variation, the used assay methods, times of blood samplings, health conditions, and birds' age.

Our results showed a higher serum level of doxycycline after intramuscular injection than after oral administration. Similar findings were mentioned previously in turkeys by **(Abo EL-Sooud et al. 2016)** and in ducks by **(Abu Basha et al. 2006).**

Following extravascular administration, doxycycline was significantly more rapidly absorbed from the thigh muscle than from the oral and pectoral muscles, respectively, as reflected by the values of K_a . This may be attributed to many factors that may affect the absorption of orally administered doxycycline such as the presence of food in the GIT, which results in many physiological changes such as fluctuations in gastric and intestinal PH, a delay in gastric emptying, an increased bile secretion, and an increased splenic and hepatic blood flow **(Lisa and Harvey 2020).** The strong lipophilic nature of doxycycline, fat infiltration of the pectoral muscle, and decreased local blood flow at the pectoral muscle injection site may explain the significantly lower K_a values after pectoral muscle injection in comparison with thigh injection **(Tuttle 1977).**

The reported absorption rate constant (k_a) in this study, $0.70h^{-1}$, $1.32h^{-1}$, and $1.28h^{-1}$ for oral, thigh muscle, and pectoral muscle, respectively, were similar to those previously reported in turkeys after oral and pectoral muscle administration of doxycycline at 20 mg/kg body weight ($0.79h^{-1}$ and $1.52h^{-}1$) **(Abo EL-Sooud et al. 2016)** and in chickens after oral administration of doxycycline at 10 mg/kg body weight ($0.62\ h^{-1}$) **(Laczay et al. 2001),**

while our result for k_a after oral administration was higher than that previously reported in 2 days chicks after oral administration of doxycycline at 20 mg/kg body weight (0.27 h^{-1}) **(Gutierrez et al. 2012),** these differences may be attributed to different species, age and the variation of the administered doxycycline doses.

AUC is an important pharmacokinetic term that is used to describe and quantify aspects of the serum concentration-time profile of an administered drug. In our study, the AUC after thigh injection was significantly larger than the AUC after pectoral injection and oral administration, which is due to the amount of doxycycline that entered the central compartment via thigh injection being significantly greater than the amount reached via the other two routes of administration which may be attributed to a higher amount of blood supply to the thigh muscle. This result was consistent with previous findings in healthy turkeys (**Abo EL-Sooud et al. 2016).**

The C_{max} value obtained for oral administration (4.66 µg/ml) was similar to that reported in normal broilers following oral administration (4.65 µg/ml) **(Soliman et al. 2015)** and (4.5 µg/ml) **(El-Gendi et al. 2010)** after the single dose of 20 mg/kg b.wt., healthy young turkey (4.9 µg/ml) **(Santos et al. 1996)** after a dose of 25 mg/ml. our results were higher than those reported in healthy Baladi turkey (3.14 µg/ml) (**Abo EL-Sooud et al. 2016)** after the single dose of 20 mg/kg b. wt. , healthy ducks (0.7µg/ml) **(Bratoev et al. 2016)** after the single dose of 15 mg/kg b. wt., healthy chickens (3.07 µg/ml) **(Laczay et al 2000**) after the single dose of 10 mg/kg b. wt. and healthy ostrich (0.30 µg/ml**) (Abu-Basha et al. 2006)** after the single dose of 15 mg/kg b. wt. The C_{max} in the present results were lower than the previously reported values in healthy chickens (5.4 µg/ml) **(Hantash et al., 2008)** and (5.65 µg/ml) **(Yang et al. 2018)** after the single oral dose of 20 mg/kg b. wt.

The mean C_{max} values obtained from our study for thigh and pectoral muscle injection, (6.17µg/ml) and (5.61 µg/ml), respectively, were higher than the values reported by using the pectoral muscle injection and the same dose in black Baladi turkey (4.38 µg/ml) (Abo **EL-Sooud et al. 2016),** and in ostrich (1.35 µg/ml) **(Abu-Basha et al 2006)** after using iliotrochanteric muscle injection and a different dose of doxycycline, The observed variations could be due to breed or species differences in drug management **(Toutain et al. 2010),** variation in the administered dose **(Houben et al. 2016).**

Absolute bioavailability (F %) is a critical pharmacokinetic parameter that indicates the rate and degree to which a drug's given dosage will enter systemic blood circulation **(Toutain et al. 2010).**

In our study, the F % of doxycycline after intramuscular routes (thigh muscle and pectoral muscle) were 70.6 and 67.2 respectively higher than that reported after oral routes (57.1). These results agreed with what has been reported in black Baladi turkey by **(Abo EL-Sooud et al. 2016)** and may be attributed to the fact that the doxycycline makes complexes with metal ions such as calcium, magnesium, and iron that reduce its bioavailability from the gastrointestinal tract **(Kucers et al. 1997).**

In the present study, the distribution constant rate **α** in the thigh muscle group (1.14 h^{-1}) was significantly higher than that of the oral and pectoral muscle groups (0.62 h^{-1} and 1.09 h^{-1}) respectively**.** These results were also supported by a significantly shorter distribution half-life $\mathbf{t_{0.5\alpha}}$ in intramuscular groups (0.61h and 0.63h for the thigh and pectoral muscle groups, respectively) when compared with an oral group (1.12h) which indicated that the drug was more rapidly distributed in the thigh muscle group than the oral and pectoral groups.

In the current study, the α and $\mathbf{t_{0.5\alpha}}$ were similar to that which has been mentioned before in black Baladi turkey by **(Abo EL-Sooud et al. 2016)** who discovered a higher distribution constant rate α (1.52h^{-1}) and a shorter distribution half-life $t_{0.5\alpha}$ (0.45h) after intramuscu-

lar injection than after oral administration (0.79 h^{-1} and 0.88h).

Body clearance is a kinetic parameter showing the body's total ability to remove a medicine **(Houben et al. 2016)** and it is widely recognized as the most essential pharmacokinetic parameter associated with elimination processes **(Toutain and Bousquet-Mélou 2004).**

The mean total clearance of the drug from the serum obtained in this study after oral administration [0.20 (mg)/(µg/ml)/h] was significantly higher than that after intramuscular injections [0.173 and 0.175 (mg)/(µg/ml)/h for IMT and IMP respectively]. These results, side by side with a higher elimination rate constant (β) and a shorter elimination half-life ($t_{1/2\beta}$) for oral administration than the intramuscular injection, indicate a rapid elimination of the drug after oral administration.

Our results revealed that the (CL/F) ratio was slightly similar to that reported in chicken (0.23 L/kg/h) after the oral route **(Hantash et al. 2008)** and (0.229 L/kg/h, **Yang et al. 2018).** The (CL/F) ratio was lower than the values that were reported in ostrich, (12.14 L/kg/h) and (40.19) after the im and oral routes, respectively, **(Abu-Basha et al. 2006),** and higher than the value that was reported in chickens (0.040 L/kg/h), **(Anadon et al. 1994).**

The variations in clearance seen may be caused by a variety of factors, including bird species, body size, protein binding, the amount of the delivered drug, or variances in drug disposition. **(Ismail and El-Kattan 2009; Toutain et al. 2010; Houben et al. 2016 and Csiko et al. 2018).**

The obtained average values of $t_{1/2\beta}$ in this study following oral, thigh muscle injection, and pectoral muscle injection (12.84 h, 13.8 h, and 13.13 h respectively) were higher than the previous values reported for oral and IM in turkeys (4.45h and 5.7h, **Abo EL-Sooud et al. 2016).** The differences in body weight between the turkeys utilized in both trials could be one cause. Furthermore, an age-dependent increment in body weight was found to have a considerable influence on pharmacokinetic and hemodynamic parameter variability within the same species of birds.

CONCLUSION

We concluded that the pharmacokinetic parameters of doxycycline are influenced by the route of administration of the drug, there was a preference for the intramuscular routes over the oral route, and in the intramuscular routes, there was a preference for the thigh muscle injection over the pectoral muscle injection. So we recommend that the doxycycline should be injected into the thigh muscle in turkeys since it achieved the best kinetic parameters and assures the best marketing quality of the turkey carcass and meat.

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