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PHARMACOKINETIC OF DANOFLOXACIN IN NEWCASTLE VACCINATED AND NON VACCINATED CHICKEN

(With 3 Tables and 2 Figures)

By

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حركية عقار الدانوفلوكساسين فى الدجاج المحصن بلقاح النيوكاسل والغير محصن

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أجرى هذا البحث على الدجاج المحصن بلقاح النيوكاسل وكذلك الغير محصن وذلك لدراسة حركية عقار الدانوفلوكساسين وكذلك الاتاحة الحيوية له بعد الحقن الوريدى والتجريع عن طريق الفم لمرة واحدة بجرعة ٥ مجم/كجم من وزن الجسم فى الدجاج. ولقد أظهرت النتائج التى تم الحصول عليها بعد الحقن الوريدى مرة واحدة بجرعة ٥ مجم/كجم من وزن الجسم سرعة انتشار (مرحلة ألفا) الدانوفلوكساسين بمعدل ٣,٧٥ لكل ساعة متبوعة ببطئ فى معدل الإخراج (Kel) له حيث أن معدل الإخراج كان ١,٤١ لكل ساعة وكانت فترة نصف العمر لإفراز الدواء ٥,٨ ساعة. إن حجم انتشار الدانوفلوكساسين فى الشق المركزى (vc) كان ١٩٣٨,٤ مللى/كجم وكان معدل انتقاله من الشق المركزى إلى الشق الطرفى (K12) أبطأ (٢,١١ لكل ساعة) من معدل انتقاله من الشق الطرفى إلى الشق المركزى (K21) حيث كان يساوى ٠,٣١١ لكل ساعة كما أن الدانوفلوكساسين يتم إخراجه كلياً من الجسم (Cl tot) بمعدل ٣,٩٤ مللى/كجم/دقيقة. إن حركية عقار الدانوفلوكساسين فى الدجاج المحصن بلقاح النيوكاسل وكذلك الغير محصن وبعد تناوله عن طريق الفم بجرعة ٥ مجم/كجم من وزن الجسم تميزت بزيادة تركيز (Cmax) الدانوفلوكساسين فى مصل الدجاج المحصن عنه فى الدجاج الغير محصن. وإن الإتاحة الحيوية له فى الدجاج الغير محصن هى ٢٨,٠٦%. ولقد لوحظ أن عقار الدانوفلوكساسن له تأثير تراكمى عند تناوله لمدة ٥ أيام متتالية وذلك من خلال مقارنة تركيز الدانوفلوكساسين فى مصل الدجاج المحصن والغير محصن بعد الجرعة الولى عن طريق الفم وتركيزه بعد الجرعات المتتالية الأخرى وعند تقدير متبقيات

الدانوفلوكساسين فى أجزاء جسم جسم الدجاج المذبوح سواء المحصن منه والغير محصن وجد أن هناك زيادة معنوية فى متبقيات الدانوفلوكساسين فى الدجاج المحصن عنه فى الدجاج الغير محصن ولقد لوحظ أن فترة السماح لذبح الدجاج المعالج بالدانوفلوكساسين يجب ألا تقل عن ٧٢ ساعة للتأكد من خلو أجزاء جسم الدجاج المذبوح من متبقيات الدانوفلوكساسين.

SUMMARY

The pharmacokinetics and bioavailability of danofloxacin were determined after single intravenous and oral administration of 5 mg/kg of body weight to healthy non vaccinated chicken. Data obtained were best described by a two compartment open model. The disposition kinetics following intravenous injection revealed a considerable rapid distribution phase (α-, 3.75 h^{-1}) followed by slower elimination phase (kel-, 1.41 h^{-1}) with a half-life ($t_{0.5\beta}$) of 5.80 h. The volume of distribution of the central compartment (Vc) was 1938.4 ml/kg. Danofloxacin was transferred from central to peripheral compartment (k_{12}) at slower arte (2.11 h^{-1}) than its passage form the peripheral to the central compartment (K_{21}) which equal to 0.311 h^{-1}. The drug was cleared by all processes (Cl_{tot}) at rate of 3.94 ml/kg/min. The disposition kinetics of danofloxacin following oral administration in non vaccinated and vaccinated chicken characterized by higher values in maximum serum concentration (C_{max}) in vaccinated than non vaccinated chicken. During repeated oral administration of danofloxacin a cumulative effects were recorded. Most of the pharmacokinetics parameters in vaccinated chicken were statistically changed when compared to non vaccinated ones. Tissue residues in slaughtered vaccinated chicken were significantly higher than that of non vaccinated ones. The drug completely disappeared form all tissues after 72 hours except spleen, breast and thigh muscles in which the drug disappeared after 48 hours following repeated oral administration.

Key words: *Pharmacokinetics, danofloxacin, newcastle, chicken.*

INTRODUCTION

Danofloxacin as a novel second generation of fluoroquinolones developed specifically for veterinary use (Giles *et al.*, 1991a). It is related structurally to nalidixic acid but has broader spectrum of antimicrobial activity and greater potency (Brander *et al.*, 1991).

Danofloxacin possesses a broad spectrum of activity against gram-negative bacteria, good *in vitro* efficacy, also has been demonstrated for gram-positive bacteria and mycoplasma (Takahashi *et al.*, 1990; Giles *et al.*, 1991; Migaki *et al.*, 1993 and Watts *et al.*, 1997).

Pharmacokinetic variables such as plasma concentration, half life, bioavailability, rate of elimination are important consideration for rational use of antimicrobial agents.

Kinetic evaluation of danofloxacin has been determined in cattle (Giles *et al.*, 1991a; Mann *et al.*, 1992 and Shem *et al.*, 1998), sheep (Mckeller *et al.*, 1998), goat (Atef *et al.*, 2001), pig (Lindecrona *et al.*, 2000) and broiler chicken (Knoll *et al.*, 1999). Limited information about the tissue distribution of danofloxacin in selected tissues and plasma of chicken were reported. The purposes of the study reported here were to evaluate the pharmacokinetic variable following intravenous and oral administration of 5 mg danofloxacin/kg b.wt. in non vaccinated and vaccinated chicken. Drug residues in non vaccinated and vaccinated chicken will be determined.

MATERIALS and METHODS

Danofloxacin: it was obtained as a 16.7% pharmaceutical preparation (Advocin®) from the Pfizer company, Egypt.

Newcastle virus vaccine: It is available as a vial, each contain 500 or 1000 doses of Lasota strain from Intervet International B.V. Boxmeer-Holand.

Chicken: Thirty-six clinically normal Hubbard chicken, 6 weeks-old (1.6 kg B. Wt.), chosen randomly form Quissina poultry farm, Egypt. Chicken were fed on a balanced ration free from antibiotic for 2 weeks to be sure complete clearance of any antibiotic residues.

Experimental design: The birds were allotted to 4 groups. Chicken of group 1 (5 chicken/group) were injected intravenously with 5 mg danofloxacin/kg body weight via the left wing vein. These chicken were left for 2 weeks to ensure complete excretion of the tested drug from their bodies. Then the tested chicken were administered orally with 5 mg danofloxacin /kg body weight. Chicken of group 2 (12 chicken/group) were administered orally with 5 mg danofloxacin /kg body weight three times daily for 5 consecutive days. The first 5 chicken of this group are those of the first group. Group 3, it included 12 chicken vaccinated with

Newcastle virus vaccine intraoculary and simultaneously administered with danofloxacin as mentioned for group 2. Chicken of group 4 (12 chicken/group) firstly were vaccinated intraocularly with New Castle disease virus vaccine and after 10 days from vaccination, when the titer of antibodies reach its maximum level, chicken were administered orally 5 mg danofloxacin/kg body weight 3 times daily for 5 consecutive days.

Blood samples were taken form the right wing vein of each bird after administration of danofloxacin at 5, 10, 15, 30 minutes, 1, 2, 4, 6, 8, 16 and 24 hours after a single intravenous or oral administration. Serum was separated after centrifugation and was stored frozen (-20°C) until analysed. Danofloxacin concentrations in the serum of chicken were measured. Three chicken from groups 2, 3 and 4 were slaughtered after the end of the fifth days of repeated oral administration of danofloxacin at 24, 48, 72 and 96 hours. Selected tissue specimen were obtained (brain, lung, heart, gizzard, kidney, liver, spleen, fat, skin, breast and thigh muscles). Samples were kept frozen (-20°C) until assayed for danofloxacin concentrations.

Drug assay: Danofloxacin was assayed in serum and tissues by microbiological method using *Staphylococcus aureus* as a test organism (Arret *et al.*, 1971 and Migliot and Dorigo, 1989).

Data analysis: The pharmacokinetic parameters were calculated according to Ritchel (1973) and Baggot (1978 a).

The obtained data were statistically calculated as mean and standard error (M ± S.E.) according to Berly and Lindgren (1990).

RESULTS

The serum concentrations of danofloxacin-time profiles following intravenous (i.v.) and post-oral (po) administrations of 5 mg/kg b.w. are shown in Figures (1 & 2).

Following i.v. injection, the serum concentration- time curve of danofloxacin showed that the drug obey the two compartment open model (Figure, 1A).

The disposition kinetic of danofloxacin following a single intravenous injection (Table, 1) revealed a considerable rapid distribution phase (α) equal to 3.75 ± 0.130 h^{-1} and $t_{0.5\ (\alpha)}$ of 0.190 ± 0.005 h. The volume of distribution of central compartment (Vc^1) of danofloxacin was 1983.4 ± 152.1 ml/kg whereas the total body distribution calculated by the extrapolation ($V_{d(\beta)}$), area ($V_{d(area)}$) and

steady-state (Vd_{ss}) methods were 1539.26 ± 403.39, 24024 ± 409.59, 15415.90 ± 530.41 ml/kg, respectively. The elimination rate constant (K_{13}) equal to 1.41 ± 0.52 h^{-1} and half-life ($t_{0.5}\beta$) value of 5.801 ± 0.22 h. Danofloxacin cleared by all clearance processes in the body (Cl_{tot}) at a rate of 3.94 ± 0.42 ml/kg/min.

The pharmacokinetic parameters following a single oral administration of danofloxacin are demonstrated in table (1). The results revealed that danofloxacin was absorbed with absorption rate constant (K_{ab}) equal 2.07 ± 0.097 h^{-1} and absorption half-life ($t_{0.5ab}$) of 0.339 ± 0.016 h. The maximum serum concentration (C_{max}) was 0.142 ± 0.014 µg/ml reached at about 1.23 ± 0.058 h (t_{max}).

Danofloxacin eliminated at a rate (Kel) equal to 0.229 ± 0.013 h^{-1} with half-life ($t_{0.5\beta}$) of 3.07 ± 0.20 h. The drug cleared by all clearance processes (Cl_{tot}) in the body at a fast rat equal to 63.93 ± 8.65 ml/kg/min. The mean systemic bioavailability after oral administration was 28.06 ± 0.881%.

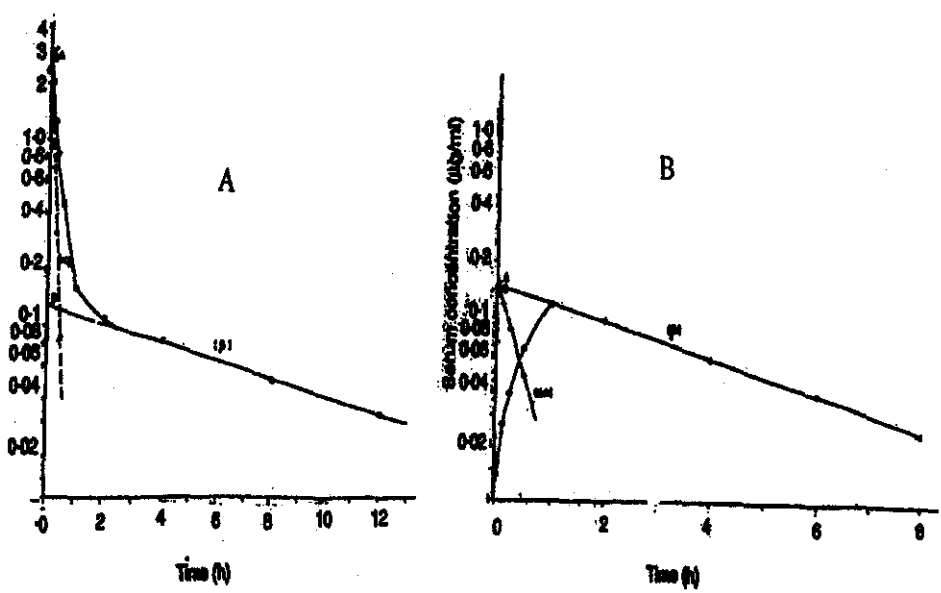

Fig. 1 : Semi logarithmic graph depicting the time course of danofloxacin in serum following a single intravenous (A) and a single oral (B) administration of 5 mg/kg b.wt. in non vaccinated chicken.

Table 1: Pharmacokinetic parameters of danofloxacin in serum following a single intravenous (iv) and oral (po) administration of 5 mg/kg b.wt. in non vaccinated chicken (n=5).

Parameters	Units	iv (n=5)	po (n = 5)
C°	µg/ml	2.59 ± 0.21	
A	µg/ml	2.45 ± 0.21	0.159 ± 0.01
A	h^{-1}	3.75 ± 0.13	
$T_{0.5\,(\alpha)}$	H	0.19 ± 0.005	
K_{ab}	h^{-1}		2.07 ± 0.097
$T_{0.5\,(ab)}$	H		0.339 ± 0.016
T_{max} (Calculated)	H		1.23 ± 0.058
(Observed)	H		1.006 ± 0.0388
C_{max} (Calculated)	µg/ml		0.142 ± 0.014
(Observed)	µg/ml		0.105 ± 0.044
B	µg/ml	0.131 ± 0.004	0.150 ± 0.013
B	h^{-1}	0.120 ± 0.004	
$T_{0.5\,(\beta)}$	H	5.80 ± 0.22	3.07 ± 0.203
Kel	h^{-1}		0.229 ± 0.013
K_{13}	h^{-1}	1.41 ± 0.52	
K_{12}	h^{-1}	2.11 ± 0.064	
K_{21}	h^{-1}	0.311 ± 0.021	
Vc^{1}	ml/kg	1983.4 ± 152.1	
Vd (β)	ml/kg	1539.26 ± 403.39	
$Vd_{(area)}$	ml/kg	24024 ± 409.59	
$Vd_{(ss)}$	ml/kg	15415.9 ± 530.41	
Cl_{total}	Ml/kg/min	3.94 ± 0.426	63.93 ± 8.65
AUC	µg/ml/h	2.25 ± 0.045	0.630 ± 0.049
Bioavailability	%		28.06 ± 0.881

Table 2: Comparison of pharmacokinetic parameters of danofloxacin following oral administration of 5 mg/kg b. wt., 3times daily for 5 consecutive days between non vaccinated (G2) and vaccinated (G3 & G4) chicken with Newcastle virus vaccine. (n = 12).

Time (day)		*First*			*Second*			*Third*			*Fourth*			*Fifth*		
Groups		*G2*	*G3*	*G4*	*G2*	*G3*	*G4*	*G2*	*G3*	*G4*	*G2*	*G3*	*G4*	*G2*	*G3*	*G4*
Parameters	Units															
A	µg/ml	0.157 ±0.012	0.119* ±0.009	0.230*** ±0.005	0.262 ±0.018	0.188** ±0.001	0.210* ±0.006	0.52 ±0.036	0.430* ±0.022	0.441* ±0.006	0.769 ±0.038	0.520*** ±0.019	0.7 ±0.013	1.7 ±0.087	0.910*** ±0.051	1.32*** ±0.032
K_{ab}	h^{-1}	2.06 ±0.095	1.47*** ±0.096	1.62*** ±0.042	1.86 ±0.086	1.06*** ±0.085	2.06 ±0.065	1.76 ±0.089	1.42** ±0.060	2.12** ±0.049	1.292 ±0.083	1.28 ±0.072	1.67** ±0.057	1.165 ±0.073	1.69*** ±0.083	1.07 ±0.018
$T_{0.5ab}$	H	0.336 ±0.015	0.471*** ±0.017	0.427*** ±0.013	0.373 ±0.018	0.654*** ±0.0139	0.337 ±0.011	0.394 ±0.016	0.477*** ±0.011	0.327** ±0.014	0.536 ±0.019	0.57 ±0.014	0.415*** ±0.007	0.595 ±0.015	0.411*** ±0.014	0.648** ±0.009
B	µg/ml	0.159 ±0.014	0.108 ±0.005	0.146 ±0.004	0.252 ±0.020	0.162*** ±0.001	0.228*** ±0.005	0.428 ±0.016	0.362** ±0.009	0.387 ±0.007	0.709 ±0.028	0.520*** ±0.012	0.68 ±0.008	1.297 ±0.060	0.850*** ±0.019	1.29 ±0.007
K_{el}	h^{-1}	0.227 ±0.014	0.400*** ±0.024	0.090*** ±0.002	0.224 ±0.012	0.763*** ±0.092	0.218 ±0.003	0.428 ±0.018	0.212* ±0.009	0.214 ±0.004	0.283 ±0.005	0.163*** ±0.007	0.274 ±0.009	0.262 ±0.013	0.213 ±0.915	0.247 ±0.006
$T_{0.5el}$	H	3.05 ±0.191	1.74** ±0.084	7.72*** ±0.192	3.094 ±0.180	0.909*** ±0.068	3.19 ±0.125	2.89 ±0.017	3.27*** ±0.095	3.24** ±0.110	2.45 ±0.116	4.27*** ±0.092	2.53 ±0.109	2.65 ±0.130	3.26*** ±0.098	2.81 ±0.110
C^0	µg/ml	0.316 ±0.030	0.227** ±0.009	0.376 ±0.008	0.514 ±0.027	0.350*** ±0.013	0.438** ±0.007	0.948 ±0.050	0.792*** ±0.029	0.828* ±0.016	1.478 ±0.056	1.04*** ±0.043	1.38 ±0.340	2.997 ±0.083	1.76*** ±0.093	2.60*** ±0.056
C_{max} *(calculated)*	µg/ml	0.14 ±0.013	0.14 ±0.006	0.312*** ±0.007	0.385 ±0.026	0.150*** ±0.057	0.336 ±0.007	0.692 ±0.540	0.57 ±0.035	0.64 ±0.009	1.22 ±0.073	0.770** ±0.043	0.700*** ±0.014	1.94 ±0.068	1.31*** ±0.073	1.68** ±0.057
(Observed)	µg/ml	0.118 ±0.008	0.086*** ±0.004	0.118 ±0.004	0.189 ±0.011	0.128*** ±0.006	0.181 ±0.006	0.324 ±0.019	0.285 ±0.008	0.315 ±0.006	0.56 ±0.026	0.420** ±0.042	0.52 ±0.009	0.98 ±0.057	0.632*** ±0.030	0.91 ±0.004
t_{max} *(calculated)*	H	1.2 ±0.530	1.22 ±0.043	1.89*** ±0.057	1.29 ±0.045	1.11** ±0.036	1.22 ±0.510	1.31 ±0.043	1.55** ±0.054	1.2 ±0.032	1.27 ±0.050	1.85*** ±0.068	1.3 ±0.027	1.45 ±0.057	1.4 ±0.062	1.78*** ±0.048
(Observed)	H	1.09 ±0.027	1.23** ±0.019	1.19 ±0.057	1.59 ±0.057	1.21*** ±0.026	1.091*** ±0.007	1.091 ±0.020	1.03* ±0.018	1.02 ±0.029	1.01 ±0.027	1.30*** ±0.035	1.21*** ±0.020	1.08 ±0.025	1.72*** ±0.079	1.37*** ±0.037
C_{max}	µg/ml	0.145 ±0.010	0.262*** ±0.0134	0.141 ±0.005	0.207 ±0.013	2.13*** ±0.010	0.23 ±0.008	0.361 ±0.011	0.289*** ±0.011	0.328* ±0.006	0.449 ±0.015	0.581** ±0.032	0.531 ±0.073	0.845 ±0.021	0.749 ±0.059	0.988** ±0.042
C_{min}	µg/ml	0.032 ±0.0035	0.017 ±0.007	0.082*** ±0.002	0.046 ±0.003	0.011*** ±0.0003	0.053* ±0.001	0.073 ±0.003	0.074 ±0.003	0.077 ±0.008	0.079 ±0.004	0.213*** ±0.011	0.085 ±0.002	0.89 ±0.007	0.184*** ±0.008	0.213*** ±0.013
$CL_{(tot)}$	Ml/kg/min	61.52 ±8.13	146.84*** ±7.05	83.33* ±2.92	83.33 ±5.99	83.33 ±5.46	41.48*** ±1.78	83.33 ±6.07	22.31*** ±0.848	21.54** ±0.862	80.02 ±7.31	13.06*** ±0.509	16.55*** ±0.762	69.57 ±5.09	10.09*** ±0.623	7.89*** ±0.363

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

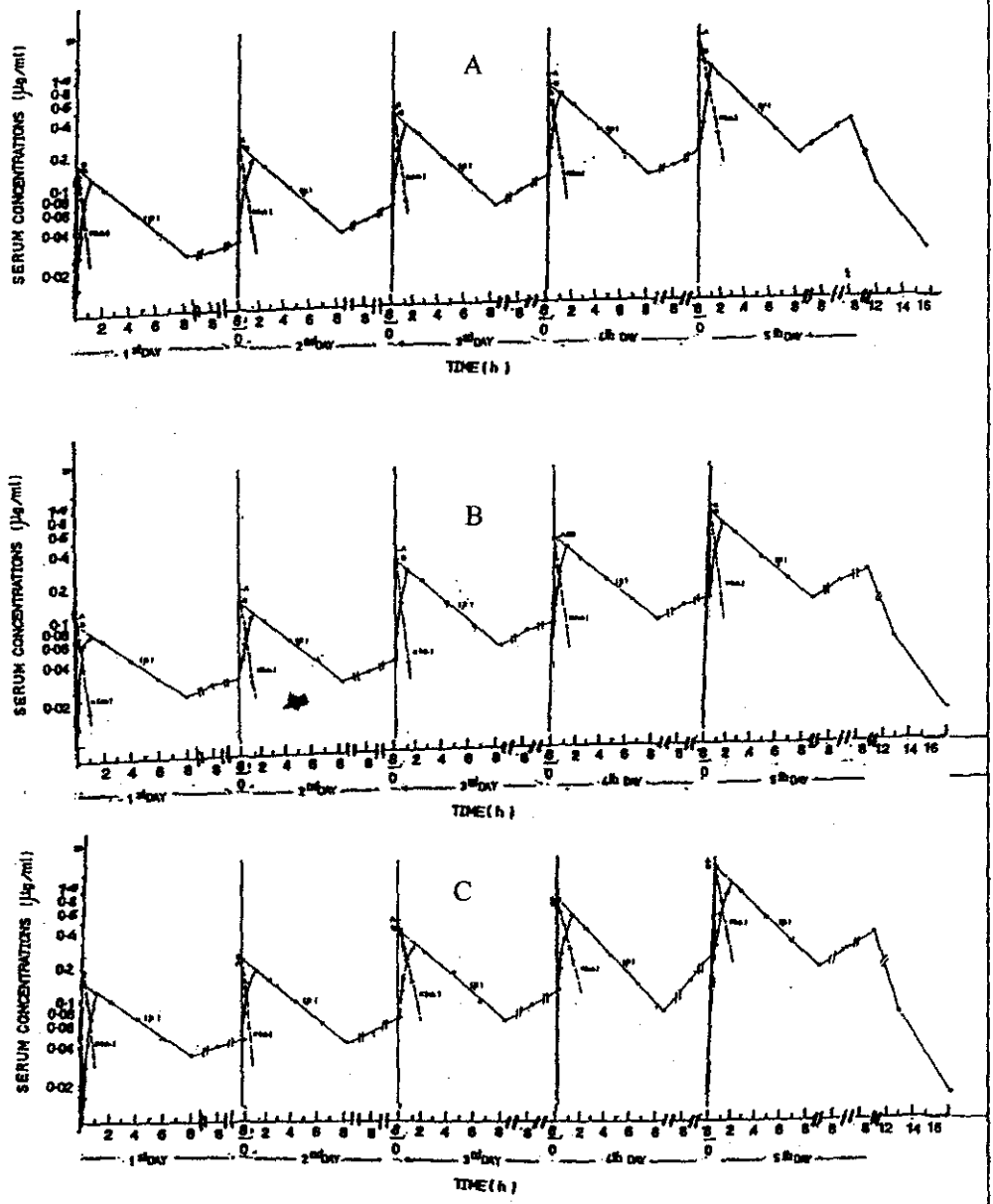

Fig. 2 : Semi logarithmic graph depicting the time course of danofloxacin in serum following repeated oral administration of 5 mg/kg b.wt. in non vaccinated (A), simultaneously vaccinated (B) and 10 days after vaccination (C).

Table 3 : Tissue concentrations of danofloxacin following oral administration of 5 mg/kg b. wt., 3 times daily for 5 consecutive days in non vaccinated (G2) and vaccinated (G3 & G4) chicken with Newcastle virus vaccine intraocularly. (n =3).

Time (h)	24			48			72		
Group / organs	G2	G3	G4	G2	G3	G4	G2	G3	G4
Brain	0.030 ±0002	0.032*** ±0.0001	0.036*** ±0.0002	0.020 ±0.0003	0.021* ±0.0001	0.021* ±0.0002	0.010 ±0.0001	0.011 ±0.000 1	0.012*** ± 0.0001
Lung	0.057 ±0.0005	0.059** ±0.0005	0.070*** 0.001	0.031 ±0.0002	0.032 ±0.0009	0.038*** 0.0005	0.014 ±0.0001	0.025*** ±0.0002	0.017*** 0.0001
Heart	0.031 ±0.0002	0.041*** ±0.0003	0.041*** ±0.0003	0.019 ±0.0001	0.025*** ±0.0001	0.025*** ±0.0001	0.010 ±0.0001	0.013*** ±0.0002	0.012 ±0.0001
Gizzard	0.033 ±0.0001	0.038*** ±0.0003	0.047*** ±0.0008	0.019 ±0.0002	0.022*** ±0.0001	0.026*** ±0.0002	0.010 ±0.0001	0.0011 ±0.0001	0.012*** ±0.0001
Liver	0.082 ±0.0006	0.097*** ±0.0007	0.13*** ±0.001	0.044 ±0.0003	0.059*** ±0.0005	0.077*** ±0.0008	0.017 ±0.0002	0.025*** ±0.0002	0.027*** 0.0001
Spleen	0.020 ±0.0003	0.030*** ±0.0001	0.030*** ±0.0001	0.011 ±0.0002	0.015*** 0.0001	0.015*** ±0.0002	———	———	———
Kidney	0.044 ±0.0002	0.052*** ±0.0001	0.062*** ±0.0001	0.028 ±0.0005	0.025** ±0.0002	0.030* ±0.0001	0.012 ±0.0002	0.013* ±0.0002	0.015*** ±0.0002
Fat	0.030 ±0.0001	0.031** ±0.0002	0.038*** ±0.0005	0.020 ±0.0001	0.021 ±0.0001	0.027*** ±0.0001	0.013 ±0.0001	0.014** ±0.0001	0.019*** ±0.0001
Breast muscle	0.031 ±0.0002	0.038*** ±0.0003	0.037*** ±0.0004	0.019 ±0.0002	0.022*** ±0.0001	0.025*** ±0.0001	———	0.011 ±0.0001	0.012 ±0.0001
Thigh muscle	0.040 ±0.0007	0.041 ±00003	0.052*** ±0.0001	0.023 ±0 0005	0.025* ±0.0001	0.029*** ±0.0003	—	0.013 ±0.0001	0.015 ±0.0002
Skin	0.030 ±0.0001	0.031** ±0.0002	0.038*** ±0.0005	0.019 ±0.0001	0.021*** ±0.0001	0.027*** ±0.0001	0.010 ±0.0001	0.012 ±0.0001	0.019*** ±0.0001

*P< 0.05 ** P< 0.01 **** P< 0.001

The comparison of pharmacokinetic parameters of danofloxacin following repeated oral administrations between non vaccinated (G2) and vaccinated (G3 & G4) chicken revealed statistically significant difference between non-vaccinated and vaccinated chicken (Table, 2).

Tissue danofloxacin concentrations in slaughtered non vaccinated (G-2) and vaccinated (G3 and G4) chicken following repeated oral administration of 5 mg danofloxacin /kg b.wt. 3 times daily for 5 consecutive days were tabulated in table (3) There were a high significant increase in tissue residues in G-3 and G-4 when compared with G-2.

DISCUSSION

It is essential for the treatment of bacterial infection that the concentration of antibacterial drugs at the site of infection must be adequate. The kinetic behavior of the drug in blood is usually taken to indicate its distribution in the body.

In the present study, a single intravenous injection of 5mg danofloxacin/kg b.wt. in non vaccinated chicken showed that the serum concentration time curve of danofloxacin obeyed a two-compartment open model. Similar result were obtained by Giles *et al.* (1991a) and Atef *ei al.* (2001) following intravenous injection of danofloxacin in cattle and goats, respectively. Meanwhile, Friis (1993) elaborated the experimental data in calves after intravenous injection of danofloxacin according to three compartments open model. These variation are often related to species difference between chicken and ruminants.

The mean values of K_{12} ($2.11 \pm 0.064\ h^{-1}$) were higher than K_{21} ($0.311 \pm 0.021\ h^{-1}$) which indicated higher transfers of danofloxacin form central to peripheral compartment. Lindecrona *et al.* (2000) and Atef *et al.* (2001) found that danofloxacin persisted in central compartment. These differences might be attributed to specific variation between chicken and animals, method used and healthy status of each subject (El-Sayed *et al.*, 1989).

The short distribution half-life ($t_{0.5\alpha}$) obtained by Mckellar *et al.* (1998) in sheep (0.18 h) and Atef *et al.* (2001) in goats (0.17 h) confirm our results in chicken (0.19 h). This short period of distribution half-life might be attributed to the intracellular binding feature of quinolones (Mckeller *et al.*, 1998).

The volume of distribution at steady state (Vdss) was 15415.9 ml/kg/min which is higher than that obtained by Mckellar *et al.* (1998)

in sheep and Atef *et al.* (2001) in goats. This variation often related to species differences. Apley and Upson (1993 b) stated that extensive tissue penetration was suggested by a high steady state volume of distribution.

The elimination half-life ($t_{0.5\beta}$) valued 5.80 ± 0.22 h with elimation rate constant (Kel) 1.41 ± 0.052 h^{-1}. This result was nearly parallel to that obtained by Apley and Upson (1993b) and Friis (1993) in calves (6.26 h and 7.4 h), respectively. Apley *et al.* 1992[3] and Mckellar *et al.* (1998) reported low value of $t_{0.5\beta}$ in calves (2.27 h) and in sheep (3.35 h), respectively. This variation might be attributed to method used, healthy status of animal and specific interspecies variation (El-Sayed *et al.*, 1989).

The mean values of total body clearance (Cl_{tot}) of danofloxacin following intravenous injection was 3.94 ± 0.426 ml/kg/min. This result was slightly higher than that reported by Mckellar *et al.* (1998) and Tuhami (1998) in sheep (2.5 ml/kg/min.) and in cattle (1.4 ml/kg/min.), respectively. This variation may be attributed to anatomical and physiological differences between chicken and ruminants.

The pharamacokientic profile of danofloxacin following single and repeated oral administration of 5 mg /kg b.wt. 3 times daily for 5 consecutive days in non vaccinated and vaccinated chicken were studied. The obtained results revealed that the drug reach its maximum concentration (0.116 ± 0.0098 µg/ml) one hour post-administration and persisted till 8 hours with concentration above the MIC (0.020 µg/ml) (Mckellar *et al.*, 1998).

The absorption rate constant (Kab) was significantly higher in vaccinated than in non vaccinated chicken. This might be attributed to the immune status of vaccinated chicken as mentioned by Danielova and Ambartsumian (1976). The calculated maximum serum concentration (C_{max}) of danofloxacin was significantly decreased meanwhile the time needed to reach it (t_{max}) increased significantly in vaccinated than in non vaccinated chicken. Viral infection in experimentally infected chicken induce considerable decrease in serum total protein, albumin and gamma globulin (Kraezkowski, 1964). Depending on this fact danofloxacin blood levels increased in vaccinated than in non vaccinated chicken. Similar results were reported by Knoll *et al.* (1999) in broiler chicken. Danofloxacin was cleared by all clearance processes (Cl_{tot}) at a faster rate in vaccinated than in non vaccinated chicken. This might be attributed to the immunogenesis of lymphoreticular cells occurred (Danielova and Ambartsumian, 1976). The obtained results revealed that

the bioavailability percent 28.06 ± 0.881 in non vaccinated chicken which was lower than that reported by Knoll *et al.* (1999) in broiler chicken and Atef *et al.* (2001) in goat. This difference might be attributed to method used, healthy status and species variation.

The obtained results revealed that a significant increase at most time of serum danofloxacin concentrations in vaccinated than in non vaccinated chicken. This phenomena was confirmed by the study of Danielova and Ambartsumian (1976) who found an increase in oxytetracycline level in immunized rabbits with dry brucellosis vaccine. Danofloxacin serum concentrations in non vaccinated as well as in vaccinated chicken were significantly increased during multiple dosage regimen in comparison with that of the first day. These observation indicated that danofloxacin has a cummulative effects.

In regarding to the tissue residues of danofloxacin, the obtained results indicated that administration of 5 mg/kg b.wt. for 5 consecutive days induce a significant increase of tissue residues in vaccinated than in non-vaccinated chicken. This might be attributed to a marked decrease of serum total protein and albumin fraction in vaccinated chicken (Kraezkowski, 1964). These results were nearly consistent with that reported by Nakamura (1995) who found that danofloxacin was effective and safe in bird and disappeared from edible tissues after appropriate time. Abdel Aziz *et al.* (1997) reported that enrofloxacin was completely disappeared from all tissues after three days following repeated oral administration.

In conclusion the immune status altered the pharamacokientic patterns of danofloxacin in vaccinated chicken where the serum level as well as the distribution of the drug increased in vaccinated chicken. Moreover, significant increase of the rate of absorption form the site of administration. This might be increased the efficacy of the antibacterial activity of danofloxacin. So, we concluded that danofloxacin was recommended during vaccination program from the kinetic point of view after putting in consideration its effect on the immune status.

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