Disposition Kinetics and Tissue Residues of Florfenicol in Normal and *Salmonella Enteritidis* Infected Chickens

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Abstract: The pharmacokinetics of florfenicol was studied following intravenous and oral (single & repeated) administration. Florfenicol was assayed by high performance liquid chromatography method. Following a single intravenous injection of 30 mg/kg body weight of florfenicol in normal chickens, serum concentration-time curve was best described by two compartments model with elimination half-life ($t_{0.5(\beta)}$ = 6.38 hour), volume of distribution (V_{dss}= 5.42 ml/kg) and total clearance of the drug (Cl_{tot}= 0.003 l/kg/h). Following a single oral administration of 30 mg/kg body weight florfenicol in normal chickens, the peak serum concentration (C_{max}) was 4.83 µg/ml and was achieved at a maximum time (T_{max}) of 1.53 hour. The mean systemic bioavailability was 76.22 %. The serum concentrations of florfenicol following repeated oral administration of 30 mg/kg body weight once daily for five consecutive days in normal and experimentally *Salmonella enteritidis* infected chickens showed a lower significant value recorded in experimentally *Salmonella enteritidis* infected chickens than in normal ones. Florfenicol showed accumulative behavior in serum of chickens. Florfenicol was assayed in serum, heart, liver, lung, kidney, breast muscle, thigh muscle and skin after 24, 48, 72, 96, 120, 144 and 168 hours after the last dose following administration of 30 mg/kg body weight every 24 hours. Results of this study indicated that florfenicol was useful for treatment of *Salmonella enteritidis* infections in chickens.

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1. Introduction

Florfenicol is a structural analogue of thiamphenicol that belongs to amphenicol family, possessing a wide spectrum of activity against both Gram-negative and Gram-positive bacteria (Syriopoulou et al., 1981). Florfenicol was reported to have a greater activity than chloramphenicol and especially against Pasteurella, Salmonella, *E.coli* and *Staphylococcus aureus*. Florfenicol inhibits peptidyltransferase activity and affect microbial protein synthesis (Canon et al., 1990)

Thiamphenicol and florfenicol are different from chloramphenicol in that the para-nitro group attached to the benzene ring is replaced by a sulfomethyl group, that make florfenicol more safe, as the presence of para-nitro group in chloramphenicol prohibited its use for the treatment of food-producing animals as it induced 2 types of adverse toxic effect on bone marrow-derived cells (A dose-related reversible suppression on erythropoiesis due to inhibition of mitochondrial protein synthesis) (Breast, 1967) and a rare dose-independent idiosyncratic response resulting in aplastic anaemia (Yunis and Bloomberg, 1964), (Yunis, 1969) and (Yunis, 1973).In addition, replacement of –OH at C-3 site by fluorine atom florfenicol prevent the bacterial enzymatic acetylation at this site by Chloramphenicol Acetyltransferase (CAT) which present in resistant organisms (Sams, 1995).

Florfenicol firstly introduced in the markets as injectable solution for treatment of respiratory diseases in cattle and then it introduced in some countries as oral solution for the treatment of several poultry diseases.

Therefore, the aim of present work was undertaken to study the pharmacokinetic parameters of florfenicol after intravenous and oral administration in normal chickens. Also, the bioavailability of florfenicol was calculated after oral administration in normal chickens. Pharmacokinetic parameters and residues of florfenicol in chicken's tissues were studied in normal and *Salmonilla enteritidis* infected chickens.

2. Material and Methods

Drug

Florfenicol used in this study was 1. (Panflor ®) 10% oral solution. It was dispensed as 250 ml plastic vial in which each 1 ml of the solution contains 100 mg florfenicol, and was manufactured by Arabcomed for Marcyrl Animal Health, Egypt.

2. Nuflor ® 30% injectable solution, it was dispensed as 100 ml glass vial in which each 1ml of the solution contains 300 mg florfenicol (used for I/V injection) and was manufactured by Schering – Plough Animal Health, La Grindoliere, France.

Experimental Birds

Forty eight clinically normal Harbard chickens of 6 - 8 weeks age were used in this investigation. The mean weight of the used chickens was 1.53 kg. Chickens were obtained from poultry farms in El Giza governorate, Egypt. Chickens were feed balanced ration free from antibiotics for two weeks to ensure complete excretion of any drugs from their bodies. Water and feed were free from any antibacterial additives.

Experimental Design

The chickens were divided into 3 groups:

Group 1

It included 6 normal chickens. Each bird was injected intravenously into the left wing vein with 30 mg florfenicol /kg b.wt. These chickens were left for 15 days after the intravenous injection to ensure complete excretion of florfenicol from their bodies. Then each chicken were given 30 mg of florfenicol /kg b.wt orally to calculate bioavaibility of florfenicol in normal chickens.

Group 2

It included 21 chickens. Each bird was given 30 mg florfenicol /kg. b.wt, orally once daily for five consecutive days. Serum and tissue samples were taken for assaying drug residues after the last dose till disappearance of the drug from tissue.

Group 3

It included 21 chickens. Each bird was orally challenged with 1 ml of *Salmonella enteritidis* suspension (*S. enteritidis* strain of poultry origin was obtained from poultry department, animal health research institute- Dokki, Giza, Egypt) from a concentration of $1.3X10^8$ C.F.U/1ml according to (Ishola and Holt, 2008). After the appearance of the symptoms as diarrhea, lack of appetite and ruffled feathers, each chicken was given 30 mg florfenicol /kg b.wt. orally every 24 hours for five consecutive days. After that serum and tissue samples were taken for assaying of residues till disappearance of the drug from tissue.

Collection of Samples

Blood Samples

Blood samples were collected from either right or left wing vein following intravenous or oral administration in normal and experimentally infected chickens. Blood samples are collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 hours of administration in single study, and after 0.167,0.25, 0.50, 1, 2, 4, 8, 12 and 24 hours in the first, second, third, fourth and fifth day in repeated oral administration study in normal and experimentally *Salmonella enteritidis* infected chickens. Serum samples were separated by centrifugation and stored in plastic vials until assay of florfenicol.

Tissue Samples

Three chickens were slaughtered at the end of the fifth day of repeated oral administration of florfenicol in normal and experimentally *Salmonella enteritidis* infected chickens, Tissue samples from liver, kidney, lung, heart, breast muscle, thigh muscle, skin and blood were taken for assaying of residues of florfenicol at 24, 48, 72, 96, 120,144 and 168 hours after the last dose.

Analytical Procedures

Calibration Curve

The calibration curves of serum and tissues were prepared by using known concentrations from florfenicol standard stock solution diluted in blank chicken serum and deionized water respectively. The calibration curve in blank chicken serum and deionized water was obtained by plotting the florfenicol peak areas versus known corresponding florfenicol concentrations. The equation was calculated by the least-squares method using linear regression. The standard curve of florfenicol in chicken serum and deionized water was linear between 0.195 and 100 µg/ml; the value of the correlation coefficient (r) was > 0.99.

Analytical Method of Blood Samples

Florfenicol concentrations was assayed in serum samples by modified high performance liquid chromatographic method (Switala et al., 2007). An Agilent HPLC system were used for the separation and quantification of the drugs. The optimal mobile phase was established on mixture of acetonitrile and water (18:82) at a flow rate of 1 mL/min. The drugs were detected by UV absorption 224 nm.

Serum samples were separately extracted in ethylene acetate (1 mL: 2.5 mL). The tubes were rotated for 10 min and then centrifuged at 2000 g for 10 min as well. Then 2 mL of the organic layer was aspirated and evaporated under nitrogen. Each of the residues was dissolved in 0.375 mL of the solvent mixture of acetonitrile–water (1:2, v/v), vortexed, and then centrifuged at 19 000 g for 20 min at 4 °C. The supernatant was collected, filtered through a 0.45-µm nylon filter, and finally transferred to auto-sampler vials.

Analytical Method of Tissue Samples

The tissue sample was sheared, and thereafter 1 g of ground tissue was weighed into a 40 ml centrifuge tube. Volume of 500 µl of water was added. Ethyl acetate (4 ml) was added, and the mixture was homogenized with disperser for 10 s at 16,000 r / min. After centrifugation for 15 min at 4000 r/min, the supernatant was removed and transferred to a 15 ml

glass-stoppered centrifuge tube. The extraction step was repeated. The combined ethyl acetate extract was then evaporated to dryness at 60 ℃ under a gentle stream of nitrogen. The residue was dissolved in 1 ml of mobile phase solution and 0.5 ml hexane, and then was whirlimixed. After centrifugation for 20 min at 16,000 r/min, the hexane layer was discharged. The water-based phase was filtered through a nylon centrifuge filter (0.2 µm). Aliquots of 20 µl were injected on the HPLC column.

The analyses were performed on a HPLC system at 223 nm. The mobile phase of acetonitrile–water (25:75, v/v) was filtered through a 0.45 µm Millipore filter and degassed using sonication (5 min). The flow rate was 1.0 ml/min. The column was operated at 20 ℃. (Feng et al., 2008)

Pharmacokinetic Analysis

The pharmacokinetic parameters were calculated by winnonlin program, version 1.2. and other parameters were calculated according to (Baggot, 1978a) and (Baggot, 1978b)

Statistical Analysis

Data were expressed as mean ± S.E. The obtained data were statistically analyzed using student t-test (Snedecor and Cochran, 1980) to express the differences between groups and pharmacokinetic parameters.

3. Results

Following a single intravenous injection of 30 mg/kg b.wt. in normal chickens, florfenicol could be detected therapeutically for 24 hours post intravenous injection. The serum concentration-time curve of florfenicol following intravenous injection showed that the drug obeyed a 2 compartment model. Serum concentrations of florfenicol (µg/ml) following a single intravenous and oral administration were showed in figure (1) and the disposition kinetics of florfenicol following a single intravenous and oral administration were recorded in table (1).

Serum concentrations of florfenicol (µg/ml) in normal and *Salmonella enteritidis* infected chickens following a repeated oral administration of 30 mg/kg b.wt. are shown in figure (2).

Oral administration of 30 mg/kg.b.wt every 24 hours for five consecutive days in normal and *Salmonella enteritidis* infected chickens revealed a lower significant serum florfenicol concentration at all-time sampling in *Salmonella enteritidis* infected chickens than in normal chickens. The pharmacokinetic parameters of florfenicol after repeated oral administration in normal chickens were compared to those in *Salmonella entretidis* infected chickens (Table 2).

Tissue samples from liver, kidney, lung, heart, breast muscle, thigh muscle, skin and blood were taken for assaying of residues of florfenicol at 24, 48, 72, 96, 120, 144 and 168 hours after the last oral administration of 30 mg/kg.b.wt from normal chickens were compared to those in *Salmonella entretidis* infected chickens (Table 3).

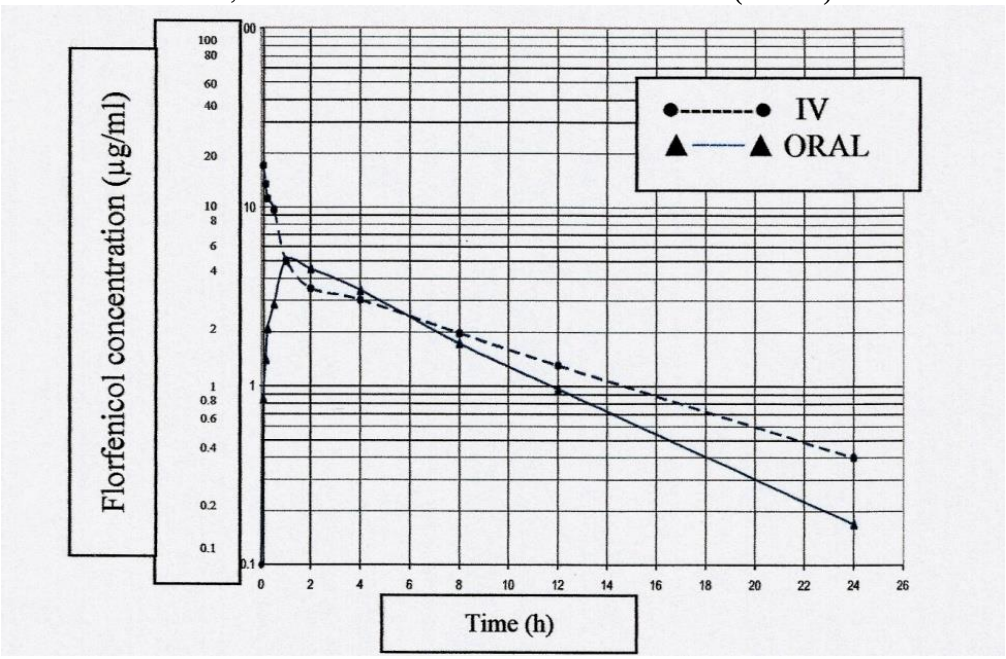

Figure 1. Semi logarithmic plots of serum of florfenicol concentrations in normal chicken following a single oral administration of 30 mg/kg b.wt. (▲−−−▲) in chicken previously given the same dose by a single intravenous injection (●------●) (n=6).

Table 1. Pharmacokinetic parameters of florfenicol following a single intravenous and oral administration of 30 mg / Kg b.wt. in normal chickens (n=6).

Parameter	Unit	Intravenous ($\bar{x}$ + SE)	Oral ($\bar{x}$ + SE)
Body weight	kg	1.53 ± 0.016	1.850 ± 0.0013
C°	µg/ml	18.9 ± 0.129	14.38 ± 0.176
A	µg/ml	14.46 ± 0.119	7.67 ± 0.136
α	h^{-1}	2.49 ± 0.016	3.87 ± 0.009
$t_{0.5\,\alpha}$	h	0.279 ± 0.002	0.177 ± 0.002
B	µg/ml	4.42 ± 0.015	6.71 ± 0.045
β	h^{-1}	0.110 ± 0.006	0.154 ± 0.002
$t_{0.5\,\beta}$	h	6.38 ± 0.343	4.50 ± 0.055
K_{12}	h^{-1}	1.54 ± 0.014	0.331 ± 0.001
K_{21}	h^{-1}	0.65 ± 0.008	0.526 ± 0.001
V_{dss}	ml/kg	5.42 ±0.060	----------
Cl_{tot}	l/kg/h	0.003 ±0.0002	5.36 ± 0.064
AUMC	µg.h2/ml	424.7 ± 1.64	----------
MRT	h	8.72 ± 0.022	----------
T_{max} (calc.)	h	----------	1.53 ± 0.008
C_{max} (calc.)	µg/ml	----------	4.83 ± 0.032
AUC	µg /ml/h	48.54 ± 0.259	37.00 ± 0.351

A, B Zero time serum drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (µg/ml); α & β, Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h^{-1}); AUC, Total area under the serum drug concentration versus time curve from t = 0 to t = α after administration of a single dose; C°, Drug concentration in the serum at zero time immediately after a single intravenous injection (µg/ml); C_{max}, Maximum serum concentration of drug in blood after extra vascular administration (µg/ml); Cl_{tot}, The total clearance of a drug, which represents the sum of all clearance processes in the body (ml/kg /min); K_{12}, First – order transfer rate constant for drug distribution from central to peripheral compartment (h^{-1}); K_{21}, First order transfer rate constant for drug distribution from peripheral to central compartment (h^{-1}); K_{13}, First - order elimination rate constant for disappearance of drug from central compartment (h^{-1}); $t_{0.5(\alpha)}$, Distribution half - life (h); $t_{0.5(\beta)}$, Elimination half - life; t_{max}, The time at which the maximum concentration of drug was reached after extravascular administration (h); V_{1c}, The apparent volume of central compartment (ml/kg); $V_{d(B)}$, The apparent volume of distribution Which calculated by extrapolation method (ml/kg); $V_{d(area)}$, The apparent volume of distribution which was calculated by the area method (ml/kg); V_{dss}, The apparent volume of distribution which was calculated by Steady - state method (ml/kg).

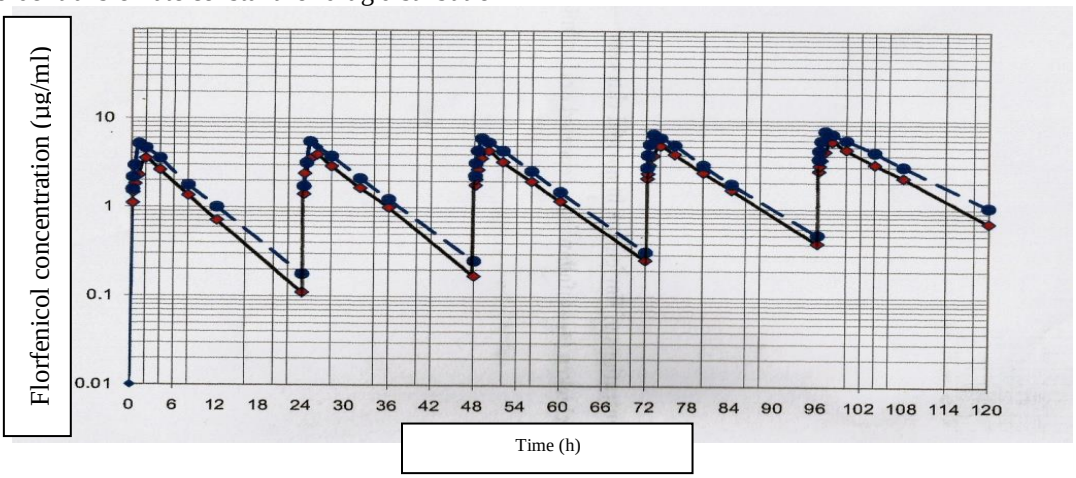

Figure 2. Semi logarithmic plots of serum concentrations of florfenicol in normal chicken (•---•) and in experimentally *salmonella enteritidis* infected chicken (♦—♦) following a repeated oral administration of 30 mg/kg b.wt. (n=6).

Table 2. Pharmacokinetic parameters of florfenicol in normal (N) and experimentally *Salmonella enteritidis* infected chickens (I) during repeated oral administration of 30 mg/kg. b.wt. once daily for five consecutive days (n=6).

Parameter	unit	First day		Second day		Third day		Fourth day		Fifth day	
		N	I	N	I	N	I	N	I	N	I
C°	µg/ml	13.42 ± 0.070	9.41 ± 0.245***	12.55± 0.009	9.85 ± 0.276***	10.24± 0.044	9.91 ± 0.277	11.9 ± 0.013	11.82 ± 0.307	13.2 ± 0.018	12.07 ± 0.326**
A	µg/ml	7.21 ± 0.053	4.55 ± 0.141***	6.75 ± 0.005	4.62± 0.116***	2.82 ± 0.008	4.15 ± 0.109***	3.44 ± 0.007	5.23 ± .141***	4.40 ± 0.010	5.09 ± 0.137***
α	h^{-1}	0.191 ± 0.001	1.66 ± 0.043***	0.853± 0.0006	1.04 ± 0.027***	1.35 ± 0.006	1.18 ± 0.033***	1.14 ± 0.003	0.924 ± 0.025***	1.03 ± 0.008	0.980 ± 0.026
$t_{0.5(\alpha)}$	h	3.62 ± 0.022	0.418 ± 0.012***	0.812± 0.0006	0.666 ± 0.017***	0.513± 0.002	0.589 ± .016***	0.606 ± 0.002	0.750 ± 0.020***	0.676 ± 0.005	0.707 ± 0.018
$K_{ab.}$	h^{-1}	1.60 ± 0.010	4.44 ± 0.107***	1.93 ± 0.009	4.15 ± 0.108***	2.08 ± 0.007	4.72 ± 0.132***	2.72 ± 0.007	3.70 ± 0.096***	3.03 ± 0.019	3.92 ± 0.105***
$t_{0.5(ab.)}$	h	0.433 ± 0.003	0.156 ± 0.004***	0.359± 0.002	0.167 ± 0.004***	0.334± 0.001	0.147 ± 0.004***	0.255 ± 0.0007	0.187 ± 0.005***	0.228 ± 0.001	0.177 ± 0.005***
K_{12}	h^{-1}	0.060 ± 0.001	0.199 ± 0.005***	0.021± 0.0006	0.175 ± 0.005***	0.136 0.001	0.363 ± 0.006***	0.080 ± 0.0008	0.273 ± 0.007***	0.127 ± 0.0008	0.310 ± 0.007***
K_{21}	h^{-1}	0.016 ± 0.0004	0.820 ± 0.021***	0.347± 0.0006	0.828 ± 0.022***	1.22 ± 0.006	0.740 ± 0.019***	0.060 ± 0.0008	0.570 ± 0.016***	0.117 ± 0.001	0.609 ± 0.017***
T_{max}	h	1.522 ± 0.009	1.53 ± 0.038	1.45 ± 0.006	1.68 ± 0.047***	1.28 ± 0.009	1.83 ± 0.048***	1.22 ± 0.005	2.03 ± 0.055***	1.35 ± 0.005	2.21 ± 0.057***
C_{max}	h	4.89 ± 0.007	3.82 ± 0.099***	5.23 ± 0.007	4.23 ± 0.123***	6.04 ± 0.037	4.64 ± 0.116***	6.79 ± 0.006	5.17 ± 0.114***	8.12 ± 0.009	5.64 ± 0.197***
B	µg/ml	6.19 ± 0.011	4.86 ± 0.131***	5.80 ± 0.007	5.23 ± 0.146**	7.42 ± 0.048	5.76 ± 0.150***	8.42 ± 0.015	6.59 ± 0.178***	8.79 ± 0.013	6.98 ± 0.188***
β	h^{-1}	0.158 ± 0.001	0.159 ± 0.004	0.128± 0.001	0.143 ± 0.004**	0.131± 0.001	0.127 ± 0.003***	0.138 ± 0.0006	0.124 ± 0.003**	0.146 ± 0.0004	0.100 ± 0.003***
$t_{0.5\beta}$	h	4.39 ± 0.019	4.36 ± 0.122	5.40 ± 0.035	4.84± 0.126**	5.30 ± 0.041	5.47 ± 0.137	5.02 ± 0.020	5.57 ± 0.137**	4.10 ± 0.663	6.95 ± 0.191**
Cl_{tot}	L/kg/h	5.88 ± 0.050	8.45 ± 0.220***	5.11 ± 0.034	7.26 ± 0.189***	6.46 ± 0.021	6.41 ± 0.160	5.82 ± 0.025	5.25 ± 0.139**	5.51 ± 0.019	4.23 ± 0.143***
AUC	µg /ml/h	52.5 ± 0.741	29.91 ± 0.837***	44.5 ± 0.016	35.37 ± 0.990***	53.3 ± 0.161	47.82 ± 1.29	66.2 ± 0.179	53.87 ± 1.15***	73.2 ± 0.288	69.17 ± 1.32*

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

Table 3. Serum (µg/ml) and tissue (µg/g) concentrations of florfenicol in normal (N) and experimentally *Salmonella enteritidis* infected chickens (I) during repeated oral administration of 30 mg /kg.b.wt. once daily for five consecutive days (n=3).

Time / Tissue	After 24 hours		After 48 hours		After 72 hours		After 96 hours		After 120 hours		After 144 hours	
	N	I	N	I	N	I	N	I	N	I	N	I
Blood (µg/ml)	0.97 ± 0.017	0.600 ± 0.029	--------	------	———	----------	———	--------	———	--------	———	--------
Liver (µg/gm)	12.1 ± 0.088	10.9 ± 0.115	7.80 ± 0.086	6.70 ± 0.088	3.50 ± 0.032	2.40 ± 0.073	1.20 ± 0.086	0.900 ± 0.044	0.800 ± 0.031	0.300± 0.058	0.390 ± 0.021	---------
Kidney (µg/gm)	11.7 ± 0.436	10.00 ± 0.088	6.30 ± 0.173	5.10 ± 0.060	2.70 ± 0.058	1.50 ± 0.058	1.40 ± 0.023	1.00 ± 0.073	1.10 ± 0.017	0.420± 0.060	0.500 ± 0.029	------
Heart (µg/gm)	7.40 ± 0.208	6.30 ± 0.116	4.10± 0.058	3.00± 0.060	1.90± 0.087	0.9 00± 0.057	0.650± 0.029	0.400 ± 0.052	0.250 ± 0.032	--------	———	------
Lung (µg/gm)	5.70 ± 0.120	4.60 ± 0.081	2.30 ± 0.017	1.50 ± 0.087	1.00 ± 0.050	0.700 ± 0.032	0.700 ± 0.026	0.350 ± 0.029	0.290 ± 0.012	--------	———	------
Breast M. (µg/gm)	1.10± 0.040	0.800 ± 0.040	0.800± 0.032	0.600± 0.032	0.500± 0.036	0.300 ± 0.036	0.300± 0.030	----------	———	--------	———	---------
Skin (µg/gm)	0.700± 0.036	0.500 ± 0.062	0.50 ± 0.040	0.250± 0.029	0.20 ± 0.010	----------	———	----------	———	--------	———	--------
Thigh M. (µg/gm)	0.900± 0.046	0.600 ± 0.028	0.700± 0.036	0.40 ± 0.040	0.550± 0.012	0.250 ± 0.017	0.250 ± 0.021	---------	———	--------	———	---------

4. Discussions

In the present investigation intravenous injection of 30 mg of florfenicol /kg B.wt. in normal chickens showed that the disposition best fitted a two compartment open model. The obtained result is in agreement with the result previously recorded in broiler chickens (Afifi and Abo El-Sooud, 1997), ducks (El-Banna, 1998) and turkeys (Switala et al., 2007) but inconsistent with what has been recorded in rabbit (Koc et al., 2009) where the results showed that the disposition best fitted a one compartment open model.

The elimination half-life ($t_{o.5\beta}$) in the present study of 6.38 h was higher than values recorded in broiler chickens (2.88 h) (Afifi and Abo El-Sooud, 1997), turkeys (2.37 h) (Switala et al., 2007) but shorter than values recorded in ducks (El-Banna, 1998).

The V_{dss} is the volume of distribution at steady state and total body clearance (CI_{tot}) were 5.11 L/Kg and 26.86 ml / kg / min respectively in broilers (Afifi and Abo El-Sooud, 1997) and 1.06 L/kg and 0.32 L/Kg/h respectively in turkeys (Switala et al., 2007) as compared with 5.42 L/Kg and 0.003 L/Kg/h respectively for healthy broilers in the present investigation.

Florfenicol was transferred from central to peripheral compartment at a faster rate $k_{12} = 1.54\ h^{-1}$ than its passage from peripheral compartment to central compartment $k_{21}=0.65\ h^{-1}$, these values were similar to that reported for florfenicol in chickens ($k_{12}=2.5\ h^{-1}$ and $k_{21}=0.85\ h^{-1}$). (El-Banna and El-Zorba, 2011).

Following a single oral administration of 30 mg florfenicol /kg b.wt., the drug reached its maximum serum concentration after 1.53 h of administration. florfenicol could be detected in serum in a therapeutic level (0.17 µg/ml) at 24 hours. The mean peak serum concentration of florfenicol (C_{max}) was (4.83 µg/ml).this value was similar to those recorded for florfenicol in normal chickens (4.5 µg/ml) (Ismail and El-Kattan, 2009) which have been given injectable formulation and normal chickens (5.82 µg/ml) (Shen et al., 2003) which have been given oral formulation. On contrast, the obtained results were lower than those reported for turkey (12.25 µg/ml) (Switala et al., 2007) and rabbits (15.14 µg/ml) (Abd El Aty et al., 2004) which have been given oral formulation and higher than pigeons (2.9 µg/ml) (Ismail and El-Kattan, 2009), quails (2.1 µg/ml) (Ismail and El-Kattan, 2009) and ducks (2.99 µg/ml) (El-Banna, 1998) which have been given injectable formulations. The T_{max} was (1.53 h) which is similar to those reported in chickens (1.4 h) (El-Banna and El-Zorba, 2011) and (1.35 h) (Shen et al., 2003) which have been given oral formulation and also similar to pigeons (1.5 h) (Ismail and El-Kattan, 2009) and quails (1.5 h) (Ismail and El-Kattan, 2009) which have been given injectable formulation. On contrast, the obtained result was shorter than those reported for turkey (2 h) (Switala et al., 2007) which have been given oral formulation. Also the recorded result for T_{max} was longer than those reported for ducks (1.15 h) (El-Banna, 1998) which have been given lnjectable formulation and rabbits (0.5 h) (Abd El Aty et al., 2004) which have been given oral formulation. These variations might be attributed to anatomical differences between species, healthy status, the dose administered and the route of administration in each case.

The systemic bioavailability of florfenicol in normal chickens was (76.22%) in present study. This value referred to a good absorption of florfenicol after oral administration. This value was lower than that recorded for turkey (81.73%) (Switala et al., 2007), higher than that recorded for rabbit (50.79%) (Abd El Aty et al., 2004) and also it was similar to those recorded for chickens (71%) (Shen et al., 2002) and (71.5%) (El-Banna and El-Zorba, 2011) respectively.

The obtained result showed significantly lower serum concentrations of florfenicol in diseased broilers as compared with healthy ones following the drug administration at different time intervals. This observation could be attributed to a more rapid extravascular distribution and the higher penetrating power of florfenicol to the diseased tissue. The phenomenon of rapid and wide distribution of antimicrobial drugs in diseased tissues has been previously reported in chickens (Atef et al., 1991) and in mammals (Ladefoged, 1979) and (Baggot, 1980).

The minimum inhibitory concentration of florfenicol for *Salmonella enteritidis* is 0.09 µg/ml (El-Shafei and Eladl, 2014). The obtained results revealed that the florfenicol serum concentrations after intravenous and oral injection were 0.4 µg / ml and 0.17 µg/ml respectively which were higher than MIC for 24 h, So florfenicol should be given once a day at 30 mg / kg. b.wt. to maintain its therapeutic concentration in serum.

Repeated oral administration of 30 mg florfenicol /kg b.wt every 24 hours for five consecutive days in normal and experimentally *Salmonella enteritidis* infected chickens revealed that the drug could be detected only in blood till 24hours post last dose, muscles (breast & thigh muscles) till 96 hours post last dose, skin till 72 hours post last dose, heart and lung till 120 hours post last dose and till 144 hours post last administration in liver and kidney. Results showed that liver and kidney contained the highest drug concentrations (12.1, 11.7 µg/g respectively) while the lowest drug concentrations was found in thigh muscle and skin (0.9, 0.7 µg/g respectively). This result agreed with that recorded for

florfenicol in chickens (El-Banna and El-Zorba, 2011) who found that the highest concentration was in liver, kidney and also slightly agreed with that recorded for florfenicol in duck (El-Banna, 1998). The present finding revealed that the drug was detected also in the liver and kidney of diseased birds only on the 5th day after treatment cease and also revealed that a higher florfenicol concentrations in liver, kidney and lung than the concurrent serum concentrations, indicating that the penetration of florfenicol into these tissues was good and that florfenicol may be an excellent drug for treating respiratory and urinary tract infections caused by susceptible organisms.

5. Conclusion

The oral bioavailability of florfenicol is good, so it is recommended to be used against *Salmonella enteritidis* infection. Repeated oral administrations of florfenicol (30 mg/kg b.wt.) once daily for five consecutive days would provide an effective concentration against *Salmonella enteritidis* in broiler chickens. Treated chickens must not be slaughtered before 7 days from last dose of repeated administration of florfenicol to withdraw the drug residues from all tissues of treated chickens.

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