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PHARMACOKINETIC OF FOSFOMYCIN IN HEALTHY AND ESCHERICHIA COLI INFECTED BROILER CHICKEN

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SUMMARY

In the present work, the pharmacokinetic parameters of fosfomycin after intravenous and oral administration in normal and experimentally infected chicken were studied in fourty clinically normal Habard chickens (9 normal and 5 experimentally infected chicken). Chickens were divided into 3 groups. The bioavailability of fosfomycin was calculated in normal chicken. The disposition kinetics as well as the tissue residues after repeated administration of fosfomycin once daily for five consecutive days in normal and experimentally infected chicken were studied. Following a single intravenous injection of 80 mg fosfomycin/kg b.wt. in normal chickens, the drug could be detected therapeutically till 24 hours post intravenous injection with value equal to 2.03 µg/ml. The serum concentration time curve of fosfomycin following intravenous injection showed that the drug obayed a first order two-compartments open model. Fosfomycin after intravenous dose revealed a rapid distribution phase (α =0.567h^{-1}) with a distribution half-life ($t_{0.5(\alpha)}$) of 1.23h. The apparent volume of distribution by steady-state method (ml/kg), [$V_{(dss)}$] method was 1.63l/kg. Fosfomycin was transferred from central to peripheral compartment [K_{12}] at slower rate (0.169 h^{-1}) than its passage from peripheral to central compartment [K_{21}] (0.1783 h^{-1}). Fosfomycin was decreased after intravenous injection with a half-life [$t_{0.5(\beta)}$] value of 7.06 hours and cleared by all clearance processes in the body at a rate of 0.26 l/kg/h.

Following a single oral administration of 80 mg fosfomycin /kg.b.wt. in normal chickens, the drug reached its maximum serum concentrations after 2 hours of injection with value equal to 28.50 µg/ml. Fosfomycin could be detected in a therapeutic concentration 12 hours post oral dose with value equal to 2.75 µg/ml. The pharmacokinetics parameter revealed that the maximum serum concentration (C_{max}) was 25.59 µg/ml reached at maximum time (T_{max}) at about 2.05h, the absorption half-life [$t_{0.5(ab)}$] was 0.31 hours, the elimination half-life $t_{0.5(\beta)}$ was 2.59 hours and fosfomycin was cleared by all clearance processes (Cl_{tot}) with rate equal to 0.0027 ml/kg/min.

The mean systemic bioavailability of fosfomycin following a single oral administration in normal chickens was 46.79 %, this value referred a better absorption of absorption from its oral administration.

The serum concentrations of fosfomycin in normal and experimentally *Escherichia coli* infected chickens following repeated oral administration of 80 mg/kg b.wt. once daily for five consecutive days, peaked 2 hours after each oral dose with a lower significant values recorded in experimentally *Escherichia coli* infected chickens than in normal chickens. This observation might be attributed to the higher penetrating power of the drug to diseased tissues. The absorption half-lives [$t_{0.5(ab)}$] following a single oral administration of fosfomycin was significantly higher in experimentally *Escherichia coli* infected chickens than normal chickens. The maximum serum concentration (c_{max}) was significantly lower in experimentally *Escherichia coli* infected chickens than in normal chickens. These concentrations were reached at maximum time (t_{max}) which were significantly higher in experimentally *Escherichia coli* infected chickens than in normal chickens. The elimination half-lives [$t_{0.5(\beta)}$] of fosfomycin were significantly higher in experimentally *Escherichia coli* infected chickens than in normal chickens. Fosfomycin was cleared by all clearance processes [Cl_{tot}] in the body at a higher significant rates in experimentally *Escherichia coli* infected chickens than in normal chickens.

INTRODUCTION

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969. There are three forms of fosfomycin: fosfomycin tromethamine (a soluble salt) and fosfomycin calcium for oral use, and fosfomycin disodium for intravenous use. Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase. It has a

broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. It is highly active against Gram-positive pathogens such as *Staphylococcus aureus* and Enterococcus, and against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Its unique mechanism of action may provide a synergistic effect to other classes of antibacterials including beta-lactams, aminoglycosides, and fluoroquinolones **(Argyris et al., 2011).**

Little literatures were found concerning the pharmacokinetics of fosfomycin in chicken. Thus the aim of present work was undertaken to study the pharmacokinetic parameters of fosfomycin after intravenous and oral administration in normal and experimentally bacterial infected chickens with *E.coli*. Also the bioavailability of fosfomycin will be calculated in normal chickens. The disposition kinetics as well as the tissue residues after repeated administration of fosfomycin once daily for five consecutive days in normal and experimentally infected chickens will be studied.

MATERIALS AND METHODS

Fosfomycin

Fosfomycin (phosfomycin) C3H7O4P, a phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid) [(2R,3S)-3-methyloxiran-2-yl]phosphonic acid obtained from Adwia company (fig.1) .

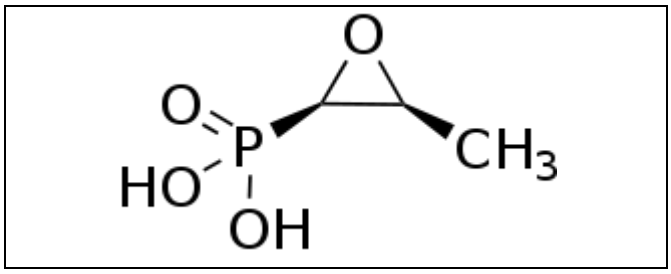

Figure. (1): Chemical structure of fosfomycin (Hendlin et al., 1969).

It is crystals, soluble in water, melting point is ~94 and molecular weight is almost the lowest of all the antimicrobials**,** 138.06.

Chickens: Fourty clinically normal Habard chickens of 8-10 weeks age weighing about 2000-2500 grams were used in this study. Each chickens were chosen randomly from poultry farm, Menufya Governorate, Egypt. Chickens were fed on balanced ration free from

antibacterials for two weeks to ensure complete excretion of antibacterial from their bodies. Water and feed free from antibacterial additives were *ad-libitum*.

Grouping of chickens: Chickens were grouped into 3 groups:

Group (1): It included 4 normal chickens. Each bird was injected intravenously into the left wing vein with 80 mg of fosfomycin per kilogram body weight.

These chickens were left for 15 days after the intravenous injection to ensure complete excretion of fosfomycin from their bodies. Then, each chicken was orally administered 80 mg fosfomycin per kilogram body weight. The aim of this group was to calculate the bioavailability of fosfomycin in normal chickens.

Group (2): It included 5 normal chickens. Each bird was orally administerd 80 mg fosfomycin per kilogram body weight, once daily for five consecutive days. At the end of the fifth day of administration, three chickens were slaughtered after 24, 48, 72, 96 and 120 hours.

Group (3): It included 5 experimentally *Escherichia coli* infected chickens. Each bird was infected with *Escherichia col* and administered 80 mg fosfomycin per kilogram body weight, once daily for five consecutive days after the appearance of the symptoms 48 hours.

Experimental infection: *E.coli* strain O_{78} serotype of poultry origin was obtained from poultry department Animal Health Research Institute. Dokki, Giza, Egypt. The preparation of the infecting dose was performed according to ***Shen et al.* (2002)**, where it was 0.1 ml from a concentration of 1X 106 C.F.U/1ml. The infected chickens were injected subcutaneously in the tissue of infraorbital sinues. The clinical symptoms of bacteraemia as diarrhea, lack of appetite and ruffled feathersly appeared after 48 hours of injection with *Escherichia coli* suspension.

Collection of samples

Blood samples: Blood samples were taken from either right or left wing vein of chickens. Blood samples were collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8 and 12 hours of administration. Blood samples following the second, third, fourth and fifth oral doses were collected at 0.167, 0.25, 0.50, 1, 2, 4, 8 and 12 hours post injection of fosfomycin and after oral administration. The collected blood samples from chicken were allowed to clot and the

serum was separated by centrifugation at 3000 r. p.m. for 15 minutes. All serum samples were stored at – 20°C until assay.

Analytical Procedure

Assay of fosfomycin: Fosfomycin was assayed in serum by microbiological method according to **(Bergan et al., 1993).**

Pharmacokinetic analysis: The pharmacokinetic parameters were calculated by **winnonlin** program, version 2.1 and other parameters according to ***Baggot*** **(1978 a& b)**.

Statistical Analysis: The data were calculated as mean ± standard error. All statistical analysis was carried out according to (***Berly and Lindgren*** **1990).**

RESULTS

Pharmacokinetics of fosfomycin in chickens

Single intravenous injection of fosfomycin in normal chickens

Following a single intravenous injection of 80 mg fosfomycin/kg b.wt. in normal chickens, fosfomycin could be detected therapeutically till 12 hours post intravenous injection with mean values of 4.38±0.197 µg/ml **(Table 1 and Figure 2).** The serum concentration time curve of fosfomycin following intravenous injection showed that the drug obayed a first order two compartments open model.

The pharmacokinetic parameters of fosfomycin following a single intravenous injection **(Table 2)** revealed that, fosfomycin concentration in the serum at zero time immediately after a single intravenous injection **(C°)** equaled to 96.78±0.649 µg/ml. The serum drug concentration at zero time intercepts of biphasic intravenous disposition curve (A) equaled to 80.78±0.575 µg/ml. The distribution phase (α) equaled to 0.567±0.001h^{-1} with a distribution half life [$t_{0.5(\alpha)}$] equaled to 1.23±0.021 h. Fosfomycin was transferred from central to peripheral compartment (K_{12}) at 0.169±0.002 h^{-1} while its passage from the peripheral to the central compartment (K_{21}) equal to 0.178±0.002 h^{-1}. The apparent volume of distribution of fosfomycin to steady – state [V_{dss}] method was 1.63±0.013 ml/kg. The coefficient B which based on the terminal exponential phase was16.00±0.08 µg/ml. The distribution phase (**β**) equaled to 0.098±0.001 h^{-1}.

Fosfomycin was eliminated after intravenous injection with half – life [$t_{0.5(\beta)}$] value of 7.06±0.09 h and cleared by all clearance processes[Cl_{tot}] in the body at a rate of 0.26±0.001 ml/kg/min.

Single oral administration of fosfomycin in normal chickens.

Following a single oral administration of 80 mg fosfomycin/ kg b.wt., the drug reached its maximum serum concentrations 28.50±1.50 µg/ml after two hours post administration. Fosfomycin could be detected in serum in a therapeutic level for 12 hours (**Table 1**) and (**Figure 2**).

The pharmacokinetic parameters following a single oral administration of fosfomycin were recorded in **table (2).** The obtained results revealed that the apparent first order absorption rate constant (K_{ab}) was 2.25± 0.031h^{-1}, while absorption half life ($t_{0.5(ab)}$) was 0.31±0.004h. Fosfomycin was reached its maximum concentrations (C_{max} =25.95±0.763 µg/ml) at maximum time equal to t_{max} (2.05±0.055 h^{-1}).

Fosfomycin was eliminated at a rate (K_{el}) equal to 0.271±0.02 h, The elimination half life $t_{0.5(\beta)}$ was 2.59±0.159 h. Fosfomycin was cleared by all clearance processes [Cl_{tot}] in the body was 0.0027±0.0002 ml/kg/min.

Bioavailability of fosfomycin after a single oral administration in normal chickens.

A comparison of serum fosfomycin concentrations following a single intravenous and oral administration in the same normal chickens were tabulated in **table (1)** and plotted on arithmetic coordinates **(Figure 2).**

The area under the serum fosfomycin concentration curve following a single oral administration $(AUC)_{oral}$ of each normal chicken was compared with the area under the serum fosfomycin concentration curve following a single intravenous injection $(AUC)_{i.v}$ in the same normal chicken. The calculated systemic bioavailability was 46.79±1.38% **(Table 3).**

The *in Vitro portein binding* of fosfomycin in normal chicken's serum

A Comparison between diameters of inhibition zones in distelled water and those in serum were tabulated in **table (4)**. Fosfomycin showed low level of binding to plasma proteins (10.79 ± 1.45) to broiler chicken serum.

Comparision of blood concentrations of fosfomycin between normal and *Escherichia coli* infected chickens during repeated oral administration of 80 mg/kg b.wt. once daily for five consecutive days (n=5).

Data in **table (5) and figure(3)** following repeated oral administration of 80 mg fosfomycin / kg b.wt once daily for five consecutive days in normal and *Escherichia coli* infected chickens revealed a significant lower serum fosfomycin concentrations at all times sampling in *Escherichia coli* infected chickens than in normal chickens.

Comparision of pharmacokinetics parameters of fosfomycin between normal and *Escherichia coli* infected chicken during repeated oral administration of 80 mg/kg b.wt. once daily for five consecutive days (n=5). The pharmacokinetic parameters of fosfomycin after repeated oral administration in normal and *Escherichia coli* infected chickens **(Table 6)** showed a significant lower in elimination half-life $t_{0.5(\beta)}$ and non significant increase in absorption half-life $t_{0.5(ab)}$ in *Escherichia coli* infected chickens than in normal chickens. The apparent first order absorption rate constant (K_{ab}) was significantly lower in *Escherichia coli* infected chickens than in normal chickens following administration of all doses. Fosfomycin was cleared by all clearance processes (CL_{tot}) in the body at a high significant rates in *Escherichia coli* infected chickens than in normal chickens than in normal chickens.

Table. (1): Serum concentrations of fosfomycin (µg/ml) following a single intravenous injection and oral administration of 80 mg/kg b.wt. in normalmal **chickens (n=4).**

Time after administration (h)	Intravenous ($\bar{X}$± S.E.) (µg/ml)	Oral ($\bar{X}$± S.E.) (µg/ml)
0.167	88.25±1.65	2.13±0.075
0.25	86.25±0.629	3.40±0.041
0.50	74.78±2.71	6.85±0.185
1.00	59.00±3.54	25.25±0.629
2.00	41.25±3.84	28.50±1.50
4.00	17.00±1.68	17.38±9.38
6.00	12.36±0.24	9.00±0.265
8.00	9.05±0.236	5. 60±0.91
12.00	4. 38±0.197	2.75±0.337

Table (2): Pharmacokinetic parameters of fosfomycin following a single intravenous injection and oral administration of 80 mg/kg b.wt. in normal chickens (n=4).

Parameter	Unit	Intravenous ($\bar{X}$± S.E.) (µg/ml)	Oral ($\bar{X}$± S.E.) (µg/ml)
C^{o}	µg/ml	96.78±0.649	-
A	µg/ml	80.78±0.575	91.58±1.179
A	h^{-1}	0.567±0.01	-
$t_{0.5(\alpha)}$	h^{-1}	1.23±0.021	-
K_{ab}	h^{-1}	-	2.25±0.031
$t_{0.5(ab)}$	h^{-1}	-	0.31±0.004
K_{12}	h^{-1}	0.169±0.002	-
K_{21}	h^{-1}	0.178±0.002	-
T_{max}	h^{-1}	-	2.05±0.055
C_{max}	µg/ml	-	25.59±0.763
B	µg/ml	16.00±0.08	48.83±0.713
B	h^{-1}	0.098±0.001	-
$t_{0.5(\beta)}$	h^{-1}	7.06±0.09	2.59±0.159
V_{dss}	ml/kg	1.63±0.013	-
Cl_{tot}	ml/kg/h	0.26±0.001	0.0027±0.0002
MRT	h^{-1}	6.16±0.042	-

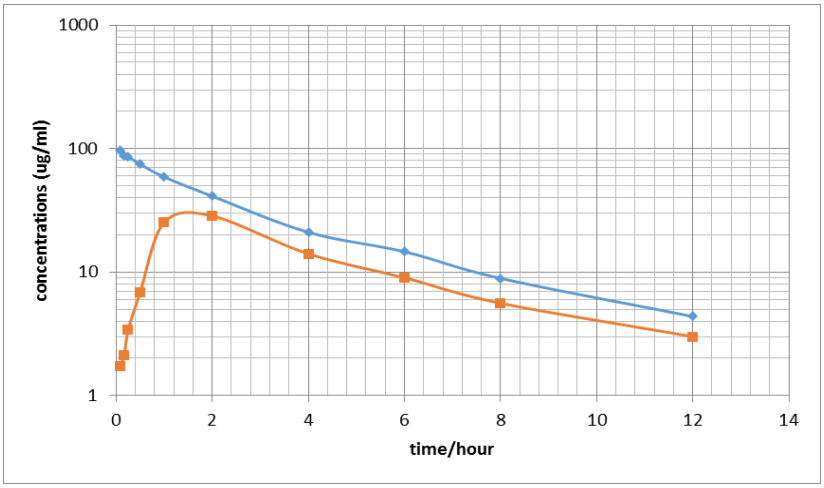

Figure. (2): Semilogarithmic graph depicting the time course of fosfomycin in serum of normal chickens following a single intravenous injection and oral administration of 80 mg/kg b.wt. in normal chickens (n=4).

Table. (3): Bioavaibility of fosfomycin in normal broiler chicken following a single oral dose of 80 mg /kilogram body weight in normal broiler chicken previously given the same dose by a single intravenous injection (n=4).

Chicken's number	AUC (oral) (µg/ml/h)	AUC (Intravenous) (µg/ml/h)	Bioavailability Percent (%)
(1)	140.66	303.02	46.42
(2)	146.23	312.12	46.85
(3)	143.22	307.98	46.50
(4)	144.52	305.02	47.38
($\bar{X}$±S.E.)	143.66± 1.74	307.04± 1.98	46.79±1.38

Table (4): The *in –vitro* protein binding of fosfomycin in normal broiler chicken's serum.

Concentration (µg/ml)	Average corrected values of inhibition zones (mm)		Average protein binding %
	Physiological saline	Normal chicken's serum	
1.56	16.10	13.51	16.09
3.125	17.10	15.38	10.06
6.225	19.10	17.43	8.74
12.5	21.10	19.36	8.25
25	24.40	21.36	12.46
50	26.64	24.73	7.16
100	31.36	27.36	12.75
(Mean ±S.E.)	22.26 ±0.235	19.88 ±1.89	10.79 ± 1.45

Table. (5): Serum concentrations of fosfomycin (µg/ml) in normal (N)and experimentally *Escherichia coli* infected chickens (I) during repeated oral administration of 80 mg /kg b.wt. once daily for five consecutive days (n=5).

Days	1st day		2nd day		3rd day		4th day		5th day	
Time (h)	N ($\bar{x}$± S.E.)	I ($\bar{x}$± S.E.)	N ($\bar{x}$± S.E.)	I ($\bar{x}$± S.E.)	N ($\bar{x}$± S.E.)	I ($\bar{x}$± S.E.)	N ($\bar{x}$± S.E.)	I ($\bar{x}$± S.E.)	N ($\bar{x}$± S.E.)	I ($\bar{x}$± S.E.)
0.167	2.23± 0.037	1.50± 0.045***	8.52± 0.108	4.74± 0.071***	11.2± 0.0000	8.7± 0.045***	12.00± 0.179	12.41± 0.000***	13.50± 0.109	17.60± 0.045***
0.5	7.26± 0.040	5.50± 0.045***	13.20± 0.063	10.90± 0.032*	18.76± 0.103	13.2± 0.045***	21.94± 0.175	18.50± 0.045***	26.00± 0.219	24.40± 0.000***
1	13.86± 0.117	10.66± 0.060**	18.48± 0.111	17.70± 0.045***	25.04± 0.068	20.00± 0.045***	30.00± 0.127	22.70± 0.045***	37.00± 0.094	27.50± 0.045***
2	33.36± 0.051	28.40± 0.045	39.68± 0.206	33.50± 0.045***	43.38± 0.037	38.9± 0.045***	49.40± 0.145	42.20± 0.45***	55.90± 0.089	50.40± 0.045***
4	25.16± 0.040	20.74± 0.087***	31.30± 0.045	26.0± 0.045***	37.20± 0.032	31.62± 0.049***	43.20± 0.063	38.50± 0.045***	49.84± 1.66	44.50± 0.045***
6	15.00±071	11.30±0.45	20.62 ±0.041	15.10± 0.45	25.66± 0.098	20.40± 0.032	29.70± 0.114	24.00± 045	35.00± 0.219	30.80± 0.045
8	7.74± 0.098	4.99± 0.047***	12.50± 0.089	9.78± 0.058***	18.30± 0.032	13.60± 0.058***	23.62± 0.128	19.70± 0.071***	29.00± 0.114	24.20± 0.044***
12	3.36± 0.068	2.20± 0.063***	8.4± 0.346	5.00± 0.045***	14.00± 0.063	9.5± 0.048***	18.50± 0.114	15.70± 0.048***	21.60± 0.071	20.20± 0.045***

(*): Represent the significance in comparison with data of normal group.

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

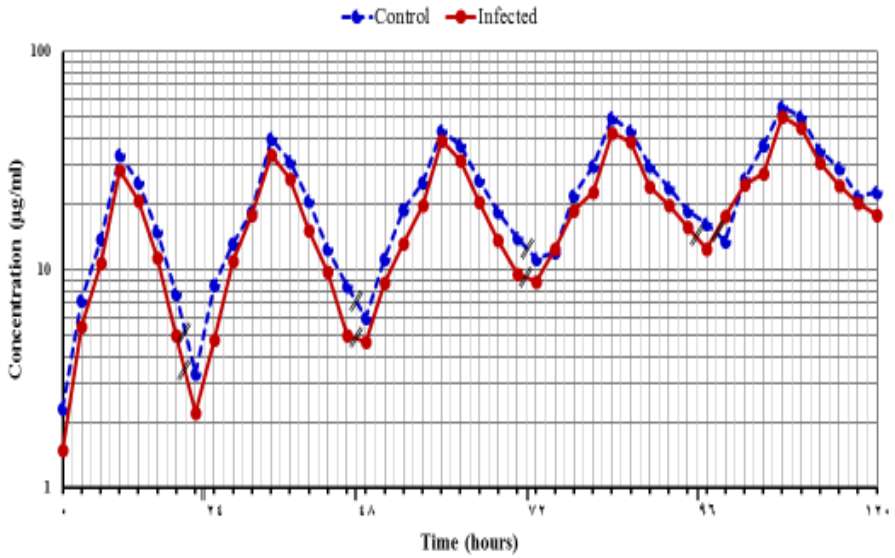

Figure (3): Semilogarithmic graph depicting the time course of fosfomycin in serum of normal chickens following a repeated oral administration of 80 mg/kg b.wt. in normal and *Escherichia coli* infected chickens (n=4).

Table. (6): Pharmacokinetic parameters of fosfomycin in normal (N) and experimentally *Escherichia coli* infected chickens (I) during repeated oral administration of 80 mg /kg b.wt. once daily for five consecutive days (n=5).

Parameter	Unit	1st day		2nd day		3rd day		4th day		5th day	
		N (X± S.E.)	I (X± S.E.)	N (X± S.E.)	I (X± S.E.)	N (X± S.E.)	I (X± S.E.)	N (X± S.E.)	I (X± S.E.)	N (X± S.E.)	I (X± S.E.)
A	µg/ml	95.72± 1.44	57.85± 0.463*	99.42± 1.49	50.04± 0.70	45.00± 0.630	67.98± 0.925*	52.00± 0.832	59.00± 1.00**	109.12± 1.75	61.38± 0.982***
K_{ab}	h^{-1}	2.22± 0.038	0.64± 0.005	1.95± 0.029	0.47± 0.010**	2.00± 0.003	1.46± 0.022**	0.125± 0.0017	0.66± 0.011	2.40± 0.036	0.78± 0.013***
$t_{0.5(ab)}$	H	0.312± 0.005	1.081± 0.009	0.355± 0.005	0.930± 0.013	3.47± 0.049	0.475± 0.008*	5.54± 0.083	1.05± 0.016	0.289± 0.004	0.888± 0.015***
B	µg/ml	51.98± 0.884	48.51± 0.340	47.81± 0.765	49.85± 0.698	52.73± 0.738	52.32± 0.837***	61.25± 0.919	49.89± 0.848**	67.98± 1.02	60.18± 0.405***
K_{el}	h^{-1}	0.263± 0.004	0.235± 0.002***	0.250± 0.004	0.185± 0.003***	0.0133± 0.002	0.135± 0.002***	0.125± 0.188	0.100± 0.002*	0.158± 0.002	0.150± 0.002*
$t_{0.5(\beta)}$	H	2.92± 0.047	2.95± 0.018***	2.77± 0.039	3.75± 0.053***	4.82± 0.072	5.13± 0.082***	5.54± 0.078	7.11± 0.114**	4.40± 0.062	4.62± 0.079***
C_{max}	µg/ml	25.10± 0.037	27.82± 0.223***	36.03± 0.504	31.82± 0.477***	39.26± 0.628	37.57± 0.526***	44.48± 0.623	38.68± 0.619*	54.52± 0.763	52.32± 0.785***
t_{max}	H	2.03± 0.037	2.38± 0.017*	2.48± 0.040	2.53± 0.040	1.43± 0.020	2.35± 0.038*	2.75± 0.041	2.76± 0.047***	1.43± 0.020	1.89± 0.028***
Cl_{tot}	ml/kg/min	0.0030± 0.00003	0.0035± 0.00003***	0.0035± 0.00005	0.003± 0.004***	0.0021± 0.00003	0.0025± 0.0024***	0.0018± 0.00002	0.0012± 0.00002***	0.0027± 0.00004	0.0021± 0.00003***

(*): Represent the significance in comparison with data of normal group.

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

DISCCUSION

Fosfomycin is a bactericidal, low-molecular weight, broad-spectrum antibiotic, with putative activity against several bacteria, including multidrug-resistant Gram-negative bacteria,by irreversibly inhibiting an early stage in cell wall synthesis. Evidence suggests that putative activity against several bacteria, including multidrug-resistant Gram-negative bacteria ,by irreversibly inhibiting an early stage in cell wall synthesis. Evidence suggests that fosfomycin has a synergistic effect when used in combination with other antimicrobial agents that act via a different mechanism of action, thereby allowing for reduced dosages and lower toxicity. Fosfomycin does not bind to plasma proteins and was cleared via the kidneys. Due to its extensive tissue penetration, fosfomycin may be indicated for infections of the CNS, soft tissues, bone, lungs, and abscesses,(**Anneke- Corinne et al. 2017).**

This study aimed to investigate the pharmacokinetics of fosfomycin in normal and experimentally infected broiler chickens following single intravenous injection, single oral and repeated oral adminstrations. The bioavailability of fosfomycin in normal chickens following oral administration was calculated.

Pharmacokinetics studies of fosfomycin in chickens

Single intravenous injection of fosfomycin in normal chickens

The kinetic parameters of fosfomycin following a single intravenous injection of 80 mg/kg b.wt. in normal chickens indicated that serum concentration of fosfomycin obeyed a first order two compartments open model; a compartment of serum and rapid equilibrating tissues, and a deeper slower compartment. The obtained result was consistent with those reported for fosfomycin in human **(Gobernado *et al*., 1977) ,(Goto *et al*., 1981) and (Tosnita *et al*., 2013),.** Also this phenomena is in agreement with healty volunteers fosmidomycin in animals **(Murakawa *et al*., 1982),** in rabbits **(Lastra et al.,1987**) in chickens **(Aramayona *et al*., 1997) and (Gutierrez *et al*., 2010),** in cattle(**Sumano *et al*., 2007**) and in dogs **(Gutierrez *et al*., 2008).**

Following a single intravenous injection of 80 mg fosfomycin /kg b.wt. in normal chickens , the drug showed high serum level (88.25 ±1.65 ug/ml) at 10 minutes post injection , then its concentration decreased gradually till reached its minimum level at 12 hours post injection (4.38±0.197 ug/ml). Also the kinetic parameters of fosfomycin following a single intravenous injection of 80 mg/kg b.wt. in normal chickens indicated that the drug concentration in serum at zero time **C°** was 96.7±0.649 µg/ml, this was lower than that in horses **(Zozaya et**

al.,2008), also lower than in volunteers **C**°was 201.43 +/- 1.56 µg/ml **(Goto et al., 1981)**, and in human **C**°was 259.3 +/- 32.5 µg/ml **(Pfeifer et al., 1985)**,. The half-life in the post-distributive phase in chickens was 2 hours, approximately, which agreed with that observed in mammals **(Bouchet et al.,1988)**, and **(Kirby et al.,1977)** the serum half life was 1.5-2 hours, fosfomycin in volunteers was 2.23± 0.62 hour **(Goto et al., 1981**), in dogs was 1.14 hour**(Murakawa et al., 1982)**.The half-life of fosfomycin distribution($t_{0.5(\alpha)}$) was 4.05±1.77 hour, much lower than that established in human **(** Lastra et al., 1984).

The Vdss is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions **(Aramayona *et al.*, 1997)**. The V_{dss} for fosfomycin was 1.63±0.013 ml/kg. The obtained value was higher than the data reported for fosfomycin in volunteers **(Goto *et al.*, 1981)** V(dss) 0.34 liter/kg, also in cattle **(Sumano et al.,2007)**, (483 ± 11 mL/kg).

Elimination half –life $t_{0.5(\beta)}$ (h) was 7.06±0.09 hours this higher than fosfomycin in human **(Borsa et al.,1988)**, in dogs **(Gutierrez et al.,2008)** 2.09±0.06 hours, and in cattle**(Sumano et al.,2007)**, 1.33 ± 0.3hours.

The total body clearance (cltot) was 0.26±0.001l kg/h and this agreed with **(Aramayona et al, 1997).** The area under the curve AUC was 307.04±1.98, this agreed with fosfomycin in horses **(Zozaya et al.,2008)** and with **(Soraci et al.,2011)** in post weaning piglets.

Single oral administration of fosfomycin in normal chickens

Following a single oral administration of 80 mg/kg b.wt. the drug reached its maximum concentration (28.50±1.50 u,g/ml) at 2 hours and could be detected in serum in therapeutic level 55.90±0.089 u,g/ml. On the bases of fosfomycin concentration for avian pathogenic microorganisms, it was suggested that oral administration of 80 mg/kg b.wt. once daily should be adequate for control of avian bacterial diseases. These concentrations exceeded the minimum inhibitory concentrations was 8 (mg/l) for *Escherichia coli species* **(Anneke Corinne *et al.*, 2017)** and 1mirog/ml to 16 microg/ml of fosfomycin in sensitive bacteria**.(Gutierrez et al.,2008),**and was 0.25-0.50 microg/ml of fosfomycin in weaning piglets**(Perez et al.,2013).**

Chickens after single oral administration with a short absorption half-life (t0.5(ab) =0.31± 0.004 hours) . This value lower than that reported for fosmidomycin in animals and human 1.14 hours(**Murakawa *et al.*, 1982).**

Maximal serum concentration (C_{max}) (25.59 ± 0.763 jig/ml) achieved at (tmax) 2.05 ±0.055 hours. These value were higher to those recorded for fosfomycin in cattle (C_{max})(10.18 ± O.lljig/ml) and (t_{max}) (1.02 ± 0.07 h) (**Sumano *et al.*, 2007)**.

These variations in C_{max} and t_{max} are common and might be attributed to anatomical differences between species , healthy status and those administered in each case interspecies variation, assay methods used, age, breed and health status of the animal and formulation of the drug used **(Anneke *et* a/., 2017).**

The elimination half-life (t 0.5(p) expresses the overall rate of elimination of the drug and allows the predication of drug accumulation . The t 0.5(p) after oral administration was 2.59±0.0159 hours. These value is nearly similar to that reported for fosfomycin in healthy volunteers (2.04 ± 0.06 hours) **(Cadorniga *et al.*, 1977),** and (4.81 ± 1.90 hours.) **(Borsa *et* a.,1988)** , but higher than fosfomycin in rabbits (1.9 hour) **(Lastra *et al.*, 1987**).

Bioavailability of fosfomycin after a single oral administration in normal chickens.

The bioavailability of fosfomycin in normal chickens, which estimated the rate and extent of the dose entered the systemic circulation after oral administration was 46.79%. This percent indicated a good absorption of fosfomycin after oral administration . This value was similar to those recorded for fosfomycin in post weaning piglets (45.48%) **(Perez *et* al., 2012).**

The *in vitro protein binding* of fosfomycin in normal chicken's serum.

Protein binding has long been considered one of the most important physicochemical characteristics of drugs, playing a potential role in distribution, excretion, and therapeutic effectiveness as a low protein binding general enables a rapid and extensive distribution into the intracellular and extracellulai space **(Lutsar *et al.*, 2000) and (Perez et al., 2014).**

In this study, the *in vitro* plasma protein binding experiment showed that fosfomycin displayed a low level of binding to plasms proteins (10.79%) to broiler chicken plasma. The results of *in vitro* protein binding of antibiotics vary considerably depending upon the methodi in experimental conditions (**Zeitlinger *et* al., 2004).**protein binding of fosfomycin was negligible (less than 1.0%);**(Gutierrez et al.,2010).**

Comparasion of blood concentrations of fosfomycin between normal and *Escherichia coli* infected chickens during repeated oral administration of 80 mg/kg b.wt. once daily for five consecutive days (n=5).

In this study , results indicated that fosfomycin could be detected in therapeutic level for 24 hours in serum following repeated oral administrations .These concentrations exceeded the minimum inhibitory concentrations (8 microg/ml) for *Escherichia coli species* **(Soraci *et al.*, 2011)**.

The study showed that the blood concentrations of fosfomycin *Escherichia coli* infected chickens were significantly lower than those in normal chickens following repeated oral administrations. These lower blood concentrations in infected chickens might attributed to higher penetrating power of drug to the diseased tissues **(Baggot.,1980).** This phenomenon agreeud with data recorded by **(Gutierrez et al., 2010)**, who found that fosfomycin concentrations in plasma of infected birds were lower than those of healthy ones , the serum concentrations of fosfomycin following oral administration of 80 mg/kg. b.wt. once daily for five consecutive days, peaked 2 hours after each oral dose with lower significant values recorded in *Escherichia coli* infected poultry than in normal poultry (**Aramayona *et al.*, 1997)** reported that the blood concentration of fosfomycin in *Escherichia coli* infected chickens were significantly lower than those in normal chickens following repeated oral administrations. (**Ilya - Nikolaevich *et al.*, 2018)** established that the blood concentrations of fosfomycin in *Escherichia coli* infected chicken were significantly lower than those in normal chickens following repeated oral administration.

Also**(Anneke and Natalia., 2017)** concluded that higher plasma concentrations in febrile condition due to faster absorption of drug from its site of administration. Similar observation had been recorded for fosfomycin in human **(Lastra *et al.*, 1983)** and fosfomycin in volunteers **(Bergan *et al*, 1993).**

Ortiz et al., (2017) reported that highly significant differences in blood plasma concentrations of fosfomycin were observed between febrile and healthy volunteers at all sampling times . This could explain the greater area under the plasma level- time curve of the drug febrile compared with healthy volunteers. It is concluded that, although experimental infection had an effect on the disposition kinetics of fosfomycin in healthy and febrile

volunteers, this was not sufficiently pronounced to require alteration of the dosage during disease.

The serum concentration of fosfomycin after the last dose were relatively higher than the serum concentrations of the first doses of fosfomycin, the indicated the accumulation of fosfomycin in blood during multiple dosing for five consecutive days. These observations agreed with dat reported by **Lastra et al., (1983),** who recorded a progressive daily increase in mean concentration in blood following oral administration of fosfomycin in human at a daily dose of 30 mg/ kg b.wt. for five consecutive days.

The maximal serum concentrations (C_{max}) were ranged 56.14 microg/ml achieved at (T_{max}) ranged 2.50 hours during multiple dosage regimen in normal chickens and in experimentally *Escherichia coli* infected chickens indicated that when fosfomycin administrated orally in a dose 80 mg/kg b.wt.once daily for five sucseesful days provided an effective therapeutic and safe concentrations exceeded the IV for most microorganisms sensitive to fosfomycin (MIC90= 8 jig/ml) (**Ocampo *et* al.,2010).**

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