



Disposition Kinetics and Tissue Residues of Cefotaxime in Healthy and Experimentally *Staphylococcus Aureus* Infected Broiler Chickens

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ABSTRACT

The pharmacokinetic parameters of cefotaxime were studied following I.V. and I.M. (single & repeated) injection in normal and experimentally *Staphylococcus aureus* infected broiler chickens. Following a single intravenous injection of 25 mg cefotaxime/kg b.wt in normal chickens, cefotaxime could be detected therapeutically for 12 hours post intravenous injection with mean value 2.34 µg/ml. The serum concentration – time curve of cefotaxime following intravenous injection showed that the drug obeyed two compartments open model with elimination half- life ($t_{0.5(\beta)}$) = 3.11 h, volume of distribution ($V_{dss} = 496.90$ ml/kg) and total body clearance of the drug ($CL_{tot} = 137.63$ ml/hr/kg). Following a single intramuscular injection of 25 mg/kg body weight cefotaxime in normal chickens, the peak plasma concentration (C_{max}) was 19.54 µg/ml was achieved at a maximum time (T_{max}) of 2.42 h. The intramuscular bioavailability of cefotaxime in normal chickens was 81.92 %. Intramuscular injection cefotaxime twice daily for five consecutive days in normal and *Staphylococcus aureus* infected chickens revealed a lower significant serum cefotaxime concentration after the first, third, fifth, seventh, ninth doses in *Staphylococcus aureus* infected chickens compared with normal chickens. Cefotaxime showed accumulative behavior in blood of chickens. After repeated intramuscular injection of 25 mg cefotaxime/kg b.wt every 12 h, cefotaxime was assayed in liver, kidney, lung, heart, breast muscle, thigh muscle and skin after 24, 48, 72, 96, 120 and 144 h post last dose. Drug concentrations in liver, kidney and lung were (23.17 ± 0.614) (15.51 ± 0.31), (16.69 ± 0.405) (10.94 ± 0.04) and (14.04 ± 0.52) (7.92 ± 0.395) µg/g in normal and *Staphylococcus aureus* infected chickens respectively 24 hours after the stoppage of drug medication. Cefotaxime was completely cleared from tissues at 144 and 120 hours after the stoppage of drug dosage in normal and *Staphylococcus aureus* infected chickens. Results of this study indicated that cefotaxime was useful for treatment of *Staphylococcus aureus* infections in chickens.

Key words: Pharmacokinetics, cefotaxime, tissue residues, broiler chickens.

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1.INTRODUCTION:

The pharmacokinetics of cefotaxime

has been investigated in sheep (Guerrini *et*

al., 1983), dogs (Guerrini *et al.*, 1986), cats (McElory *et al.*, 1986), goats (Atef *et al.*, 1990; Dutta *et al.*, 2004; Elsayed *et al.*, 2015b), cattle (Sharma *et al.*, 1995), horses (Orsini *et al.*, 2004), buffaloes (Sharma *et al.*, 2003; Sharma and Srivastava, 2006) and muscovy ducks (Aboubakr, 2016).

Therefore, the present work aimed study the pharmacokinetic parameters of cefotaxime after intravenous and intramuscular injections normal and experimentally *Staphylococcus aureus* infected chickens. Also, the bioavailability of cefotaxime was calculated after intramuscular injection in normal chickens. Residues for cefotaxime in chickens's tissues were studied in normal and *Staphylococcus aureus* infected chickens.

2. MATERIALS AND METHODS

2.1. Drug:

Cefotaxime was used in this study under trade name (Cefotax[®], sterile vial), each vial contains cefotaxime sodium 1048 mg equivalent to ceftaxime 1000 mg. Each ml of reconstituted solution contains cefotaxime sodium equivalent to 1000 mg cefotaxime, which was manufactured by Egyptian International Pharmaceutical Industries company (E.I.P.I.Co) 10th of Ramadan City – industrial area B1, EGYPT.

2.2. Experimental birds:

Forty-six clinically normal Hubbard chickens of four weeks of age weighting about 1500 to 2000 gm, each chosen randomly from poultry farm, Qalubia government, EGYPT, were used in investigation. Chickens were feed balanced ration free from antibacterial for two weeks to ensure complete excretion of any drugs from their bodies. Water and feed free from antibacterial additives were provided *ad-libitum*.

2.3. Experimental design

Chickens were divided into 3 groups:

Group (1):

It includes six normal chickens were administered intravenously into the wing vein with single dose of 25 mg cefotaxime / kg. b.wt. (Aboubaker, 2016). These chickens were left for 15 days after the intravenous injection to ensure complete elimination of cefotaxime from their bodies and then administered intramuscularly with 25mg cefotaxime per kilogram body weight, to determine the bioavailability of cefotaxime in normal chickens.

Group (2):

It includes twenty normal chickens were administered intramuscularly 25 mg cefotaxime per kilogram body-weight twice daily for five consecutive days, to determine pharmacokinetics and at the end of fifth day of administration, three chickens were slaughtered after 24, 48, 72, 96, 120 and 144 h post last administration to determine tissue residues of cefotaxime.

Group (3):

It includes twenty experimentally *Staphylococcus aureus* infected chickens were injected intramuscularly 25 mg cefotaxime / kg. b.wt. twice daily for five consecutive days after the appearance of the symptoms, 48 hours after experimental infection with *Staphylococcus aureus* to determine pharmacokinetics and tissue residue of cefotaxime. Each chicken was intramuscularly challenged with 1 ml of concentration of 2.5×10^9 c.f.u/ml of *Staphylococcus aureus* suspension (*Staphylococcus aureus* ATCC 29213 strain of poultry origin was obtained from Poultry Department, Animal Health Research Institute- Dokki, Giza, EGYPT) according to Gu *et al.*, (2013). After the

appearance of symptoms of bacteremia as chickens suffering from severe watery diarrhea, lack of appetite, ruffled feathers, drooping wings, skin reddening, swollen joint and lameness, each chickens was injected with 25 mg cefotaxime/kg b.wt every 12 h for five consecutive days. After that tissue samples were taken for assaying of residues till disappearance of the drug from tissue.

2.4. Collection of samples:

2.4.1. Blood samples

About one milliliter of blood was taken from the right-wing vein, following injection of the drug. Blood samples were collected at 5, 10, 25, 30 minutes, 1, 2, 4, 6, 8, 12 and 24 h after single intravenous and intramuscular injection of cefotaxime. Blood samples following repeated intramuscular injection of cefotaxime in normal and experimentally infected chickens for 5 consecutive days were collected at 15, 30 minutes, 1, 2, 4, 6, 8, 12 h and before third, fifth, seventh and ninth doses.

All blood samples were collected in sterilized centrifuged tubes and allowed to clot. Serum was separated by centrifugation for 15 minutes at 3000 r.p.m. Sera were kept frozen until assayed.

2.4.2. Tissue samples

At the end of fifth day of repeated I.M. injection of cefotaxime, three chickens were slaughtered from group (2) and group (3). From each slaughtered chicken, samples of brain, heart, lung, liver, kidney, breast muscle, thigh muscle, fat and skin were taken for assaying of residues of cefotaxime at 24, 48, 72, 96, 120 and 144 h after last dosing.

2.5. Analytical procedure:

Cefotaxime in both collected blood and tissue samples were assayed using microbiological method of antibiotic

according to Arret *et al.*, (1971), using *E. coli* ATCC 6633 as test organism for cefotaxime. The test organism was obtained from Department of Microbiology, Animal Health Research Institute, Dokki, Giza, EGYPT.

Three plates were used for each sample. One well in each plate was filled with reference concentration (6.25 µg/ml of cefotaxime in distilled water or normal chickens' serum). The plates were incubated at 37°C for 24 h, then the diameter of inhibitory zones was measured. The average diameter of inhibition zone of the samples was corrected by using the diameter of the reference concentration as mentioned previously in the preparation of the standard curve. From the standard curve, the concentration corresponding to the correct values of the zone diameter were obtained.

Assay of tissue samples, two grams of tissue were homogenized by automatic homogenizer with 2 ml of distilled water. Mixtures were centrifuged at 3000 r.p.m. for 10 minutes and the supernatant fluid of each sample was taken and directly assayed microbiologically for cefotaxime concentration.

2.6. Pharmacokinetic analysis

The pharmacokinetics parameters were calculated by Winnonlin program, version 4.1 and other parameters according to Ritchel (1973) and Baggot (1978 a&b).

2.7. Statistical analysis

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

3. RESULTS:

Following a single I.V. injection of 25 mg cefotaxime/kg b.wt. in normal chickens,

cefotaxime could be detected therapeutically for 12 hours post intravenous injection. The plasma concentration-time curve of cefotaxime following intravenous injection showed that the drug obeyed two compartments open model. The disposition kinetics of cefotaxime following a single intravenous and intramuscular injection were recorded in table (1) and showed in figure (1).

Intramuscular injection of 25 mg/kg.b.wt every 12 hours for five consecutive days in normal and *Staphylococcus aureus* infected chickens revealed a lower significant plasma cefotaxime concentration at all-time sampling

in *Staphylococcus aureus* infected chickens than in normal chickens. The pharmacokinetic parameters of cefotaxime after repeated oral administration in normal chickens were compared to those in *Staphylococcus aureus* infected chickens (Table 2).

Tissue samples from liver, kidney, lung, heart, breast muscle, thigh muscle, skin and fats were taken for assaying of residues of cefotaxime at 24, 48, 72, 96,120 and 144 hours after the last intramuscular dose of 25 mg/kg.b.wt from normal chickens were compared to those in *Staphylococcus aureus* infected chicken (Table3).

Table 1: Pharmacokinetic parameters of cefotaxime following a single intravenous and intramuscular injection of 25mg/kg b.wt. in normal chickens (n=6).

	Unit	Intravenous	Intramuscular
C^0	$\mu\text{g/ml}$	119.83 ± 2.46	-
A	$\mu\text{g/ml}$	85.34 ± 2.34	-
A	h^{-1}	2.97 ± 0.313	-
$t_{0.5(\alpha)}$	h	0.246 ± 0.025	-
K_{12}	h^{-1}	1.51 ± 0.207	-
K_{21}	h^{-1}	1.02 ± 0.088	-
V_{dss}	ml/kg	496.90 ± 15.47	-
B	$\mu\text{g/ml}$	34.41 ± 0.640	-
β	h^{-1}	0.224 ± 0.009	-
$t_{0.5(\text{el})}$	h	3.11 ± 0.113	3.7 ± 0.221
AUC	hr/ $\mu\text{g/mL}$	181.92 ± 3.19	149.02 ± 3.78
AUMC	hr/h/ $\mu\text{g/ml}$	656.37 ± 18.04	932.52 ± 57.01
MRT	h	3.61 ± 0.084	6.24 ± 0.244
CL_{tot}	L/hr/kg	137.63 ± 2.34	-
K_{ab}	h^{-1}	-	0.561 ± 0.051
$t_{0.5(\text{ab})}$	h	-	1.27 ± 0.114
T_{max}	h	-	2.42 ± 0.039
C_{max}	$\mu\text{g/ml}$	-	19.54 ± 0.366
K_{el}	h^{-1}	-	0.19 ± 0.01
MAT	h	-	2.63 ± 0.16

A, B and C Zero-time serum drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase ($\mu\text{g/ml}$); 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 plasma drug concentration versus time curve from $t = 0$ to $t = \alpha$ after administration of a single dose; C_{max} , Maximum serum concentration of drug in blood after extra vascular administration ($\mu\text{g/ml}$); 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}); $t_{0.5(\alpha)}$, 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_{dss} , The apparent volume of distribution which was calculated by Steady - state method(ml/kg).

Table 2: Pharmacokinetic parameters of cefotxime in healthy (H) and experimentally *Staphylococcus aureus* infected chickens (I) during repeated intramuscular injection of 25 mg/kg b.wt. twice daily for 5 consecutive days (n=4).

Parameter	Unit	1 st dose		3 rd dose		5 th dose		7 th dose		9 th dose	
		H	I	H	I	H	I	H	I	H	I
K_{ab}	h^{-1}	0.590 ± 0.036	0.431 ± 0.03*	0.886 ± 0.046	0.77 ± 0.035	1.01 ± 0.065	0.963 ± 0.065	0.93 ± 0.007	0.988 ± 0.043	1.18 ± 0.036	1.68 ± 0.049***
$t_{0.5(ab)}$	H	1.19 ± 0.075	1.63 ± 0.101*	0.789 ± 0.039	0.905 ± 0.038*	0.694 ± 0.044	0.729 ± 0.044	0.746 ± 0.006	0.706 ± 0.031	0.587 ± 0.018	0.414 ± 0.012***
T_{max}	H	2.36 ± 0.021	2.45 ± 0.022*	2.23 ± 0.043	2.30 ± 0.039	2.48 ± 0.062	2.50 ± 0.084	2.46 ± 0.007	2.33 ± 0.039*	2.27 ± 0.033	1.85 ± 0.025***
C_{max}	$\mu g/ml$	19.05 ± 0.107	17.23 ± 0.312**	20.96 ± 0.273	18.63 ± 0.108***	30.3 ± 0.290	27.34 ± 0.687**	45.53 ± 0.035	38.85 ± 0.543***	51.03 ± 0.32	42.38 ± 0.183***
K_{el}	h^{-1}	0.20 ± 0.005	0.217 ± 0.016	0.142 ± 0.004	0.161 ± 0.002**	0.10 ± 0.005	0.104 ± 0.003	0.09 ± 0.008	0.104 ± 0.006	0.071 ± 0.006	0.060 ± 0.010
$t_{0.5(\beta)}$	H	3.48 ± 0.093	3.25 ± 0.243	4.9 ± 0.139	4.32 ± 0.062**	7.00 ± 0.379	6.69 ± 0.213	7.88 ± 0.748	6.72 ± 0.407**	9.96 ± 0.748	12.30 ± 1.54***
AUC	$hr/\mu g/mL$	139.26 ± 0.508	123.01 ± 2.45***	186.21 ± 3.71	153.7 ± 2.97***	380.16 ± 10.7	328.81 ± 8.87**	574.47 ± 21.94	445.88 ± 7.45**	766.65 ± 27.61	728.32 ± 48.65
AUMC	$hr/hr/\mu g/ml$	819.37 ± 12.14	693.16 ± 42.72*	1428.0 ± 43.56	1070.7 ± 34.18***	4162.4 ± 306.4	3452.36 ± 149.88	6873.67 ± 733.58	4651.23 ± 257.17**	11248.45 ± 1036.21	13197.7 ± 2059.15
MRT	H	5.88 ± 0.067	5.62 ± 0.243	7.72 ± 0.111	6.96 ± 0.09**	10.91 ± 0.502	10.49 ± 0.249	11.87 ± 0.816	10.41 ± 0.412	14.58 ± 0.854	17.75 ± 1.85

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

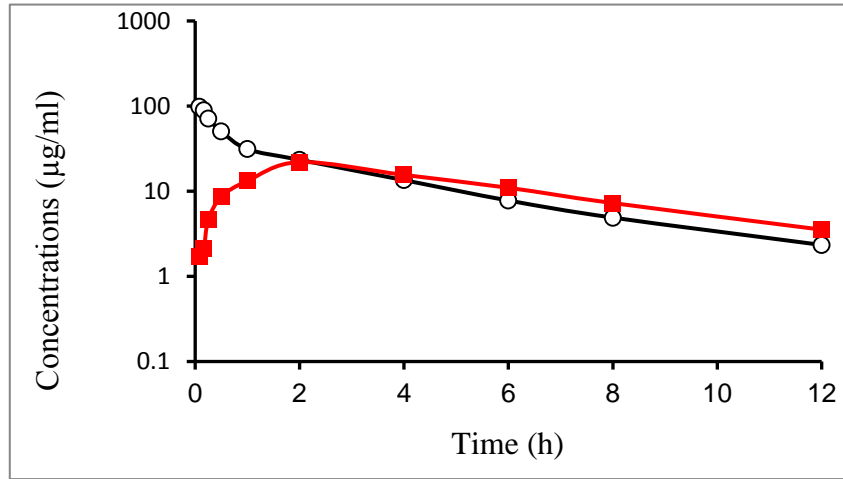
Table 3: Tissue concentrations of cefotaxime ($\mu\text{g/ml}$) in healthy (H) and experimentally *Staphylococcus aureus* infected chickens (I) during repeated intramuscular injection of 25 mg/kg b.wt. twice daily for 5 consecutive days (n=3).

Tissue	After 24 h		After 48 h		After 72 h		After 96 h		After 120 h		After 144 h		
	H	I	H	I	H	I	H	I	H	I	H	I	
Liver	23.17 \pm 0.614	15.51 \pm 0.31***	17.52 \pm 0.311	11.56 \pm 0.34***	10.5 \pm 0.324	7.72 \pm 0.16***	5.66 \pm 0.592	2.01 \pm 0.312 **	2.05 \pm 0.087	-	-	-	-
Kidney	16.69 \pm 0.405	10.94 \pm 0.04***	7.43 \pm 0.233	5.34 \pm 0.347**	4.64 \pm 0.319	1.3 \pm 0.29***	1.14 \pm 0.063	-	-	-	-	-	-
Lung	14.04 \pm 0.52	7.92 \pm 0.395***	5.57 \pm 0.367	2.71 \pm 0.147***	2.36 \pm 0.427	-	-	-	-	-	-	-	-
Heart	-	-	-	-	-	-	-	-	-	-	-	-	-
Brain	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin & Fat	-	-	-	-	-	-	-	-	-	-	-	-	-
Breast muscle	-	-	-	-	-	-	-	-	-	-	-	-	-
Thigh muscle	-	-	-	-	-	-	-	-	-	-	-	-	-

*P<0.05,

**P<0.01,

***P<0.001



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Figure (1): Arithmetic plot of serum of cefotaxime concentration in healthy chickens following a single intramuscular injection of 25 mg/ kg.b.wt. (■—■) in chickens previously given the same dose by intravenous injection (—) (n=6).

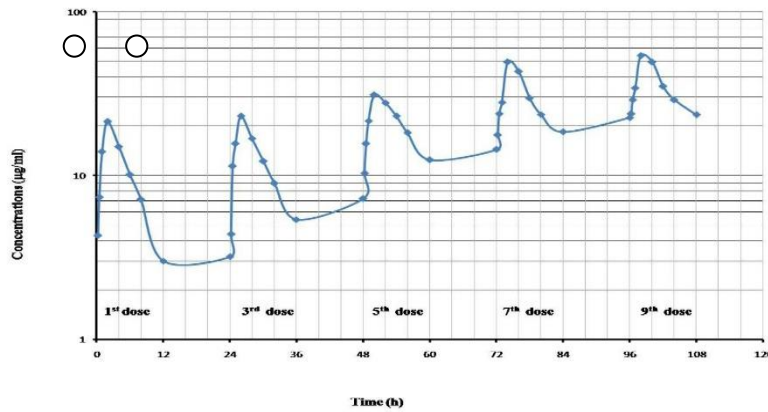


Figure (2): Semi logarithmic graph depicting the time course of cefotaxime following repeated intramuscular injection of 25mg/kg b.wt. twice daily for 5 consecutive days in serum of healthy chickens (n=4).

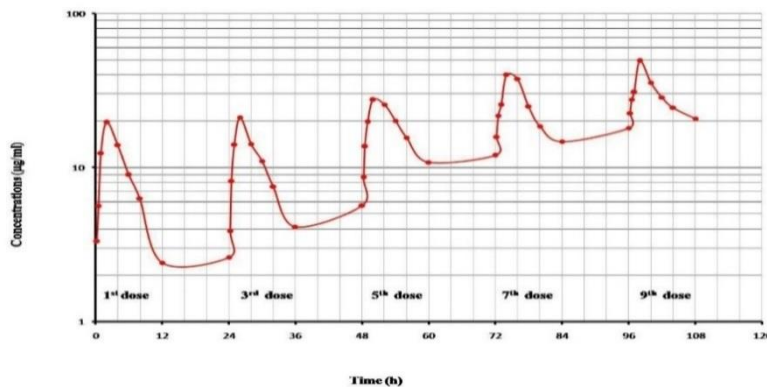


Figure (3): Semi logarithmic graph depicting the time course of cefotaxime following repeated intramuscular injection of 25 mg/kg b.wt. twice daily for 5 consecutive days in serum of experimentally *Staphylococcus aureus* infected chickens (n=4).

4.DISCUSSION:

In the present investigation, I.V. injection of 25 mg of cefotaxime /kg b. wt. in normal chickens showed that the disposition best fitted two compartments open model. The obtained result was consistent with those reported for cefotaxime in goats (El-Sayed *et al.*, 2015b), in muscovy ducks (Aboubaker, 2016) and in broiler chickens (Hesham and El-bakery, 2017).

The V_{dss} is a clearance – independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions. The V_{dss} for cefotaxime was 496.90 ± 15.47 ml/kg suggesting higher penetration through biological membranes and tissue distribution after intravenous administration in broiler chickens. The obtained value was shorter than the data reported after intravenous administration of cefotaxime in buffalo calves (1.48 L/kg) and in Muscovy ducks (0.51 L/kg) (Sharma *et al.*, 2005; Aboubakr, 2016), respectively. On the other hand, volume of distribution was higher than these recorded for cefotaxime in broiler chickens (0.45 L/kg; Hesham and El-bakery, 2017).

In comparison with other cephalosporins, this V_{dss} value agreed with the data reported after intravenous injection of cefpime in calves (0.43 L/kg; Urvesh *et al.*, 2006), cefquinome in ducks (0.41 L/kg; Yaun *et al.*, 2011), cefquinome in chickens (0.49 L/kg; Xie *et al.*, 2013), cefepime in goats (0.44 L/kg; El-Heweity, 2014) and cefoperazone in goats (0.44L/kg; Taha *et al.*, 2015).

On the other hand, this V_{dss} value was higher than those recorded for ceftriaxone in dogs (0.217 L/kg; Rebuelto *et al.*, 2002); cefepime in calves and ewes (0.21 and 0.32

L/kg; Ismail, 2005a; Ismail, 2005c, respectively; ceftiofur in calves (0.134 L/kg; El-Gendy *et al.*, 2007); ceftiofur in camel (0.13 L/kg; Goudah, 2007); ceftiofur in cow (0.178 L/kg; Tohamy, 2008); ceftriaxone in buffalo (0.36 L/kg; Gohil *et al.*, 2009); cefpirome in cow calves (0.33 L/kg; Patel *et al.*, 2013); ceftiofur in chickens (198.60 ml/kg; El-Sayed *et al.*, 2015a); cefquinome in chickens (389.23 ml/kg; El-Sayed *et al.*, 2015c); ceftriaxone in goats (0.355 L/Kg; El-Sayed *et al.*, 2016a) and cephradine in chickens (328.94 ml/kg; El-Sayed *et al.*, 2016b).

On the other hand, volume of distribution (V_{dss}) was shorter than that recorded in cefepime in rabbits (1.168 L/kg; Abd El-Aty *et al.*, 2007); ceftriaxone in domestic cats (0.57 L/kg; Albarellos *et al.*, 2007); cefepime in sheep (0.42 L/kg; Patel *et al.*, 2010); cefoperazone in sheep (0.51 L/kg; Soni *et al.*, 2012) and cefquinome in goats (0.51 L/kg; Dumka *et al.*, 2013).

Cefotaxime was transferred from central to peripheral compartment at a slower rate ($K_{12} = 1.51$ h⁻¹) than its passage from peripheral compartment to central compartment ($K_{21} = 1.02$ h⁻¹). These values were nearly similar to that reported for ceftiofur in buffalo calves ($K_{12} = 1.557$ h⁻¹) and ($K_{21} = 2.003$ h⁻¹) by El-Gendy *et al.*, (2007) and cefquinome in chickens ($K_{12} = 0.713$ h⁻¹) and ($K_{21} = 1.06$ h⁻¹) by El-Sayed *et al.*, 2015c).

The elimination half-life [$t_{0.5(\beta)}$] of cefotaxime following single intravenous injection of 25 mg/kg b.wt was equal to 3.11 h. This observation agreed with the data reported after intravenous administration of cephalixin in calves (3.17 h; Garg *et al.*, 1996); ceftazidime in rabbits (2.22 h; Abd El-Aty *et al.*, 2001), cefepime in calves (3.7 h;

Urvesh *et al.*, 2006), cefepime in rabbits (2.935 h; Abd El-Aty *et al.*, 2007), cefoperazone in sheep (3.8 h; Soni *et al.*, 2012), ceftazidime in dromedary camels (2.85 h; Goudah *et al.*, 2013) and cefepirome in cow calves (2.41 h; Patel *et al.*, 2013) and cephradine in chickens (2.79 h; El-Sayed *et al.*, 2016b).

On contrast, the obtained value was longer than those recorded in cefuroxime in goats (1.48 h; Abo El-Sooud *et al.*, 2000), cefepime in ewes (1.76 h; Ismail, 2005c), ceftriaxone in cats (1.73 h; Albarellos *et al.*, 2007), ceftiofur in buffalos (1.607 h; El-Gendy *et al.*, 2007), cefquinome in piglets (1.85 h; Li *et al.*, 2008), ceftriaxone in buffalo (1.27 h; Gohil *et al.*, 2009), ceftriaxone in cows (1.02 h; Kumar *et al.*, 2010), cefquinome in ducks and chickens (1.57, 1.29 h; Yuan *et al.*, 2011 and Xie *et al.*, 2013, respectively), ceftriaxone in goats (1.82±0.13 h)(Prashant *et al.*,2014); cefquinome in chickens (0.712±0.05 h)(El-Sayed *et al.*,2015c) and cefoperazone in goats (1.97±0.14 h)(Taha *et al.*,2015).

On the other hand , it was shorter than those showed in cephradine in goats (4.00 h ; El-Sayed *et al.*, 1994); ceftriaxone in calves (4.39±0.63h ; Johal *et al.*,1999) ; ceftiofur in fresian calves (5.047 h ;El-Gendy *et al.*, 2007) ; cefquinome in goats (5.76 h ; Dumkaet *al.*, 2013); cefepimein goats (3.34±0.12 h ; El-Hewaity ,2014); ceftiofur in chickens (5.47 h ; El-Sayed *et al.*, 2015a) and ceftriaxone in goats (5.19 h ; El-Sayed *et al.*, 2016a).

The rate of total body clearance [CL_{tot}] of cefotaxime following intravenous injection was 0.138 ± 2.34 L/kg/hr.The clearance values of cefotaxime in muscovy ducks and broiler chickens were (0.22 ± 0.008 and 0.08 ± 0.01 L/Kg/hr) (Aboubaker, 2016 ; Hesham and El-bakery,2017, respectively).

Following a single intramuscular administration of 25 mg/kg b.wt. the drug reached its maximum concentration (22.14 ± 0.418 µg/ml) at 2 hours and could be detected in serum in therapeutic level (3.54 ± 0.210 µg/ml) for 12 hours. On the bases of cefotaxime concentration for avian pathogenic microorganisms, it was suggested that intramuscular administration of 25 mg/kg b.wt. with 12 hours intervals should be adequate for control of avian bacterial diseases. These concentrations exceeded the minimum inhibitory concentrations 4 µg/ml for *staphylococcus* species (Craig, 1995).

Maximal serum concentration (C_{max}) (19.54 ± 0.366 µg/ml) achieved at (t_{max}) (2.42 ± 0.039 hours). These values were higher than to those recorded for cefotaxime in Muscovy ducks (C_{max}) (14.72 ± 0.29 µg/ml) and (t_{max}) (2.30 ± 0.02 hours) (Aboubaker, 2016) and lower than to those recorded for cefotaxime in chickens (C_{max}) (25.02 ± 0.01 µg/ml) and (t_{max}) (1.08 ± 0.01 h) (Hesham and El-bakery, 2017).

The bioavailability of cefotaxime in normal chickens, which estimated the rate and extent of the dose entered the systemic circulation after oral administration was 81.92 ± 2.81 %. This percent indicated a good absorption of cefotaxime after intramuscular administration. This value was nearly similar to those recorded for ceftriaxone in goats and calves (85% and 85.72 %) (Ismail, 2005b; Albarellos *et al.*, 2007) and cefotaxime in Muscovy ducks and chickens (79.61 ± 1.82 % and 85.11 ± 1.00 %) (Aboubaker, 2016; Hesham and El-bakery, 2017).

In this study, results indicated that cefotaxime could be detected in a therapeutic level for 12 hours in serum following repeated intramuscular administrations. These concentrations exceeded the minimum

inhibitory concentrations (4 µg/ml) for *staphylococcus species* (Craig, 1995).

The study showed that the blood concentrations of cefotaxime in *Staphylococcus aureus* infected chickens were significantly lower than those in normal chickens following repeated intramuscular administrations. This phenomenon agreed with the data recorded by (Soliman, 2000), who found that enrofloxacin concentrations in plasma of infected birds were lower than those of healthy ones. El- Sayed *et al.* (1994) proved that, the serum concentrations of cephradine following intramuscular administration on 10 mg/kg. b.wt. twice daily for five consecutive days, peaked 2 hours after each intramuscular dose with lower significant values recorded in *Escherichia coli* infected goats than in normal goats.

Following repeated intramuscular injection of 25 mg cefotaxime/kg b.wt twice daily in normal and *Staphylococcus aureus* infected chickens for five consecutive days, the drug could not be detected by microbiological assay in all tested tissues except in liver (120 h), kidneys (96 h) and lung (72 h) of chickens post last administrations. Drug concentrations in liver, kidney and lung were (23.17 ± 0.614), (16.69 ± 0.405) and (14.04 ± 0.52) µg/g respectively 24 hours after the stoppage of drug medication in normal chickens. Drug could not be detected in all tested tissues except in liver (96 h), kidney (72 h) and lung (48 h). Drug concentrations in liver, kidney and lung were (15.51 ± 0.31), (10.94 ± 0.04) and (7.92 ± 0.395) µg/g respectively 24 hours after the stoppage of drug medication in *Staphylococcus aureus* infected chickens. In particular the high clearance of cefotaxime indicates the reduced possibility of finding residues of antimicrobial in broiler chickens a few days after treatment and necessity of

shorter withdrawal time for this antimicrobial i.e. five days.

5. CONCLUSION:

The intramuscular bioavailability of cefotaxime is excellent, so it is recommended to be used against *Staphylococcus aureus* infection. Repeated intramuscular injection of cefotaxime (25 mg/kg b.wt.) twice daily for five consecutive days would provide an effective concentration against *Staphylococcus aureus* in broiler chickens. Treated chickens must not be slaughtered before six days from last dose of repeated injection of cefotaxime to withdraw the drug residues from all tissues of treated chickens.

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