



Pharmacokinetics and Tissue residues of Ceftiofur in normal and *Aeromonas Hydrophilia* Infected Catfish (*Clarias lazera*)

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ABSTRACT

The pharmacokinetics of ceftiofur were studied in 78 catfish divided into 3 groups following IV and IM (single and repeated) administrations. Following a single IV injection of 5 mg/kg body weight of ceftiofur in normal catfish (*Clarias lazera*), serum concentration-time curve was best described by a two compartments open model with elimination half life ($t_{0.5\beta}$), volume of distribution (V_{dss}) and total body clearance (CL_{tot}) of 5.700 h, 229.71 ml/kg and 0.642 ml/kg/min, respectively. Following a single IM administration of 5 mg ceftiofur /kg body weight in normal catfish (*Clarias lazera*), the peak serum concentration (C_{max}) was 21.77 μ g/ml, achieved at a maximum time (T_{max}) of 2.15 h. The mean systemic bioavailability was 67.22%. The serum concentrations of ceftiofur following repeated IM administration of 5 mg/kg body weight once daily for five consecutive days in healthy and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) showed a lower significant values recorded in experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) than in normal ones. Ceftiofur showed accumulative behavior in serum of fish. Results of this study indicated that ceftiofur was useful for treatment of *Aeromonas hydrophilia* infections in fish. Ceftiofur was assayed in serum, liver, kidney, dorsal muscle, abdominal muscle and skin after 24, 48, 72, 96 and 120 h from the last daily dose of 5mg ceftiofur/kg body weight for five days. . Ceftiofur could not be detected by spectrophotometer assay in all tested tissues in normal fish except in liver (four days), kidney (four days), and dorsal muscle (four days) post last administrations. Ceftiofur was completely cleared from serum and tissues at five days after the stoppage of drug dosage but in experimentally infected fish Ceftiofur could not be detected in all tested tissues except in liver (three days) and kidney (three days) post last administrations. Ceftiofur was completely cleared from all tissues at (four days) after the stoppage of drug dosage.

Key words: Pharmacokinetics Tissue residues Ceftiofur *Aeromonas Hydrophilia*

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1.Introduction

Ceftiofur sodium (CEFTIOPHARCO) ® is a

chemotherapeutic agent is used in veterinary practice (Hornish et al.,2002) not only for large

and small animals but also for poultry and fishes against Gram-positive and Gram-negative bacteria (Abd-Ellateif *et al.*, 1998 and Fayaz *et al.*, 2010) Ceftiofur sodium is one of the third generation cephalosporins. It is a broad spectrum antibiotic active against both Gram-positive and Gram-negative bacteria, including β -lactamase producing strains. It is bactericidal; destroying bacteria by preventing the synthesis of the cell wall (Yancey *et al.*, 1987 and Li XL *et al.*, 2011) The pharmacokinetics of ceftiofur has been investigated in many animal species including calves, chicken, pigs, foals, ducks, goats, elephants (Liu MC *et al.*, 2010, Doré-Elizabeth *et al.*, 2011 and Adkesson MJ *et al.*, 2012) respectively. Therefore, the aim of present work was undertaken to study the pharmacokinetic parameters of ceftiofur after IV and IM administration in normal and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*). Also, the bioavailability of ceftiofur was calculated after IM administration in normal fish. Residues for ceftiofur in fish's tissues were studied in normal and *Aeromonas hydrophilia* infected catfish (*Clarias lazera*).

2. Material and Methods

Drug:

Ceftiofur was used in this study under the trade name (Ceftiopharco®, sterile powder). Each vial contains ceftiofur sodium equivalent to 1 gm ceftiofur. Each ml of reconstituted solution contains ceftiofur sodium equivalent to 50 mg ceftiofur, which was manufactured by Pharco B International, Alexandria, Egypt.

Experimental fish:

Catfish (*Clarias lazera*) were used in this investigation. The weights of fish were 300 ± 0.5 . Catfish (*Clarias lazera*) were obtained from local farms in Benha city, El Qualubia government, Egypt. It were feed on

pelleted feed (25% proteins, 8% fat) from El-Abassia farm, El- Sharkia governorate, Egypt twice daily.

Experimental design:

The fish were divided into 3 groups:-

Group (1): Group (1): It consist of 18 catfish (*Clarias Lazera*) divided into 6 glass aquaria. Each fish was injected IVly in the caudal vein with 5 mg ceftiofur /kg b.wt. These fish were left for 15 days after the IV injection to ensure complete excretion of ceftiofur from their bodies. Then the fish were injected IMly 5 mg of ceftiofur /kg b.wt in dorsal muscle to calculate bioavailability of ceftiofur in normal catfish (*Clarias Lazera*).

Group (2): It consist of 30 catfish (*Clarias lazera*) divided into 10 glass aquaria. Each fish was injected IMly into dorsal muscle with 5 mg ceftiofur /kg b.wt, once daily. Serum samples were taken and then IM dose was administered every 24 h for five consecutive days. Tissue samples were taken for assaying of drug residues after the last sampling.

Group (3): It included 30 catfish (*Clarias lazera*) divided into 10 glass aquaria. Twenty four h pure culture of chosen isolates of *Aeromonas Hydrophilia* was suspended in sterile saline using McFarland opacity tube number 3, bacterial suspension contain approximately 9×10^8 cell/ml. according to (Abd El Aziz *et al.*, 1994). Each fish was inoculated with 0.2 ml of bacterial suspension (each contain 9×10^8 cell/ml). The clinical symptoms as hemorrhage all over the skin especially at the base of the fins, erosion of the fins appeared after 48 h of injection with *Aeromonas Hydrophilia* suspension. Each fish was injected IMly with 5 mg ceftiofur /kg b. wt. every 24 h for five consecutive days. After that serum and tissue samples were taken for assaying of residues till disappearance of the drug from tissues.

Collection of samples:

Blood samples:

Blood samples were collected from caudal vein following IV or IM administration in normal and experimentally infected cat fish. Blood samples are collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h of administration in single study, and after 0.167, 0.25, 0.50, 1, 2, 4, 8, 12 and 24 h in the first day, second, third, fourth and fifth dose in the same study in repeated IM administration in normal and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*). Serum samples were separated by centrifugation and stored until assay of ceftiofur.

Tissue samples:

Three fish were slaughtered, serum, Liver, kidney, muscle with skin (dorsal and abdominal muscles) were taken from fish after repeated IM injection in normal and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) for assaying of residues of ceftiofur at 24,48,72,96,120,186 h after the last sampling.

Analytical procedures:

Ceftiofur was assayed in serum by modified spectrophotometric method according to (Annapurna V *et al.*,2009). The standard solution of ceftiofur was prepared by dissolving 25 mg ceftiofur in 25 ml distilled water to obtain a concentration of 1000 µg/ml. Standard concentrations were obtained by further dilution in distilled water and fish serum to obtain concentrations of 0.313, 0.625, 1.25, 2.5, 5, 10, 25 and 50µg/ml for preparation of standard curve of ceftiofur. The pharmacokinetic parameters were calculated by Winnonlin program, version 1.1 and other parameters according to (Baggot,1978a,b). All statistical analysis was carried out according to (Berly *et al.*,1990).

Assay of tissue samples:

Three milliliters of distilled water were added to one gram of the obtained tissue sample and homogenized in a porcelain mortar by the aid of sterile sand. The homogenate was left in the refrigerator overnight then centrifuged. One milliliter of the supernatant was taken and subjected to the same procedures for assay in serum sample.

3. Results

Following a single IV injection of 5 mg /kg b.wt. in normal fish, ceftiofur could be detected therapeutically for 24 h post IV injection. The serum concentration – time curve of ceftiofur following IV injection showed that the drug obeyed two compartments open model. The disposition kinetics of ceftiofur following a single IV and IM administration were recorded in tables (1) and showed in figure (1). IM administration of 5mg/kg b.wt every 24 h for five consecutive days in normal and *Aeromonas hydrophilia* infected catfish (*Clarias lazera*). revealed a lower significant serum ceftiofur concentration at all time sampling in *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) than in normal fish. The pharmacokinetic parameters of ceftiofur after repeated IM administration in normal fish were compared to those in *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) in table (2).

Tissue residues for ceftiofur in, liver, kidney, dorsal muscle and abdominal muscle with skin after repeated IM administration in normal fish were compared to those in *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) were recorded in table (3).

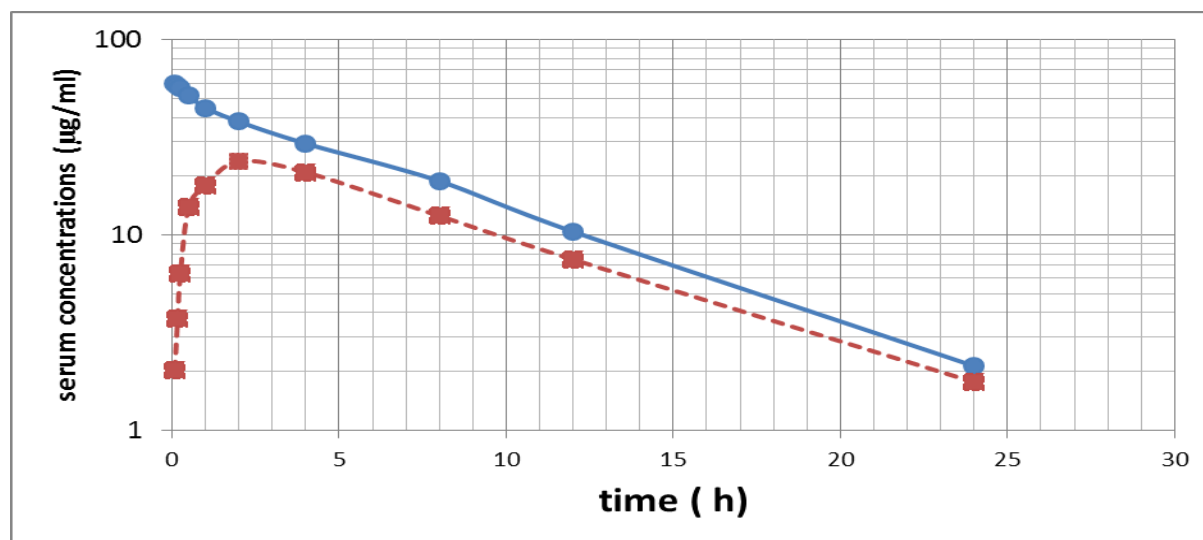


Figure (1): Arithmetic plot of serum of ceftiofur concentrations in normal catfish (*Clarias lazera*) following a single intramuscular injection of 5 mg/kg b.wt. in catfish previously given the same dose by a single intravenous injection (n=6).

Table (1): Pharmacokinetic parameters of ceftiofur following a single IV and IM injection of 5 mg/kg b.wt. in normal fish (n=6).

Parameter ¹	Unit	IV $\bar{x} \pm S.E.$	IM $\bar{x} \pm S.E.$
B.wt	Kg	1.900±0.053	2.064±0.059
C ^o	µg/ml	58.11±0.684	-
A	µg/ml	16.489±0.338	27.00±0.357
A	h ⁻¹	1.815±0.0364	-
t _{0.5(a)}	H	0.382±0.008	-
K _{ab}	h ⁻¹	-	1.191±0.012
t _{0.5(ab)}	H	-	0.581±0.006
AUC	µg/ml/h	349.52±4.713	334.60±2.031
V ^{1c}	ml/kg	172.10±2.00	-
V _{d(B)}	ml/kg	229.70±3.02	-
V _{dss}	ml/kg	224.20±2.22	-
K _{el}	h ⁻¹	-	0.119±0.001
K ₁₂	h ⁻¹	0.435±0.012	-
K ₂₁	h ⁻¹	1.376±0.021	-
B	µg/ml	41.398±0.478	29.226±0.203
B	h ⁻¹	0.121±0.002	-
t _{0.5(β)}	h	5.700±0.077	-
K ₁₃	h ⁻¹	0.165±0.002	-
C _{max}	µg/ml	-	21.77±0.172
T _{max}	h	-	2.153±0.020
Cl _{tot}	ml/kg/min	0.642±0.008	0.121±0.001

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A & B : Zero time plasma 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 serum drug concentration versus time curve from $t = 0$ to $t = \alpha$ after administration of a single dose.

C° : Drug concentration in the serum at zero time immediately after a single intravenous injection ($\mu\text{g} / \text{ml}$).

C_{max} : Maximum serum concentration of drug in blood after extra vascular administration ($\mu\text{g} / \text{ml}$).

C_{max} : Maximal serum concentration at steady - state during a multiple dose regimen ($\mu\text{g/ml}$).

C_{min} : Minimal serum concentration at steady - state during a multiple dose regimen ($\mu\text{g/ml}$).

Cl_{tot} : The total clearance of a drug , which represents the sum of all clearance processes in the body ($\text{ml/kg} / \text{min}$).

K_{ab} : Apparent first order absorption rate constant (h^{-1}).

K_{el} : First - order elimination rate constant for disappearance of drug from central compartment (h^{-1}).

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}).

$t_{0.5(\text{ab})}$: The absorption half- life (h).

$t_{0.5(\alpha)}$: Distribution half - life (h).

$t_{0.5(\beta)}$: Elimination half - life (h).

t_{max} : The time at which the maximum concentration of drug was reached after extra vascular administration (h) .

$V1_c$: The apparent volume of central compartment (ml/kg).

$Vd_{(B)}$: The apparent volume of distribution which calculated by extrapolation method (ml/kg).

$Vd(\text{area})$: 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).

Table (2): Pharmacokinetic parameters of ceftiofur in normal (N) and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*). (I) during repeated IM injections of 5 mg /kg b.wt. once daily for five consecutive days (n=3).

Parameter	Unit	1 st day		2 nd day		3 rd day		4 th day		5 th 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.)
C ⁰	µg/ml	59.34±1.8 4	61.94±1.55	63.32±1.84 ***	56.84±1.31 ***	55.90±1.90 ***	57.85±1.45 ***	60.44±2.12 ***	67.13±1.54 ***	65.61±1.97 ***	68.50±1.71 ***
A	µg/ml	28.92±0.9 25	30.07±0.63 2	31.09±0.99 5***	25.87±0.59 5	24.65±0.73 9***	25.32±0.58 2***	23.32±0.81 6	33.08±0.76 1	25.78±0.87 6***	32.35±0.84 1***
K _{ab}	h ⁻¹	1.23±0.03 9	1.34±0.031	1.73±0.014 ***	1.60±0.037 *	2.04±0.063 ***	1.64±0.038 ***	2.60±0.083	2.21±0.052	2.86±0.094 ***	3.20±0.074 **
t _{0.5(ab)}	h	0.563±0.0 20	0.517±0.01 4	0.401±0.01 2*	0.433±0.01 0***	0.340±0.01 0	0.423±0.01 1**	0.267±0.01 0***	0.314±0.00 7*	0.243±0.00 7***	0.217±0.00 5***
t _{max}	h	2.24±0.08 1	2.64±0.061	2.54±0.084 ***	2.95±0.068 ***	2.49±0.085 ***	3.10±0.074 ***	2.42±0.077 ***	3.26±0.078 ***	2.12±0.074 ***	3.14±0.072 ***
C _{max}	ug/ml	22.67±0.8 16	21.56±0.53 9	25.74±0.95 2***	25.07±0.60 2***	27.86±0.80 8***	29.37±0.67 6***	31.26±1.09 ***	35.04±0.84 1***	35.98±1.22 ***	39.07±0.93 8***
B	µg/ml	30.42±0.8 16	31.87±0.73 3	32.23±0.95 2***	30.97±0.71 2***	31.25±1.00 ***	32.53±0.78 1***	37.12±1.11	34.05±0.81 7***	39.83±1.27 *	63.15±0.83 1**
K _{el}	h ⁻¹	0.129±0.0 04	0.379±0.00 8	0.106±0.00 7**	0.339±0.00 8***	0.059±0.00 2***	0.323±0.00 7***	0.051±0.00 2***	0.316±0.00 7***	0.044±0.00 1***	0.319±0.00 8***
t _{0.5(kel)}	h	5.37±0.19 3	1.83±0.046	6.54±0.189 *	2.04±0.049 *	11.75±0.36 4	2.15±0.051 ***	13.39±0.45 5***	2.19±0.053 ***	15.60±0.53 0	2.17±0.054 ***
Cl _{tot}	ml/kg/ min	0.0004±0. 00001	0.0005±0.0 001	0.0003±0.0 0001***	0.0005±0.0 0001**	0.0002±0.0 0004***	0.0005±0.0 0001***	0.00001±0. 00002***	0.0004±0.0 0001***	0.00009±0. 00003***	0.0004±0.0 0001***

(*): Represent the significance in comparison with data of normal group. *P<0.05 ** P<0.01 *** P<0.001

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Table (3): Serum ($\mu\text{g/ml}$) and tissue ($\mu\text{g/g}$) concentrations of ceftiofur ($\mu\text{g/ml}$) in normal (N) and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) (I) during repeated IM injections of 5 mg /kg b.wt. once daily for five consecutive days ((n=3).).

Time	After first day		After second day		After third day		After forth day		After fifth day	
	N	I	N	I	N	I	N	I	N	I
Tissue	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)	($\bar{X} \pm \text{S.E.}$)
Serum	13.65 \pm 0.372	10.830 \pm .662	1.083 \pm 0.0124	-	-	-	-	-	-	-
Liver	33.68 \pm 0.110	12.633 \pm 1.26	16.173 \pm 0.191	4.546 \pm 0.329	-	0.289 \pm 0.072	0.865 \pm 0.070	-	-	-
Kidney	35.74 \pm 0.248	17.688 \pm 0.996	22.09 \pm 0.435	7.363 \pm 0.449	7.796 \pm 0.124	0.649 \pm 0.0135	1.37 \pm 0.190	-	-	-
Dorsal muscle	26.86 \pm 0.330	8.230 \pm 0.375	15.886 \pm 0.191	865 \pm 0.124	10.106 \pm 0.073	-	0.732 \pm 0.067	-	-	-
abdominal muscle	19.64 \pm 0.190	4.043 \pm 0.591	7.146 \pm 0.329	-	6.356 \pm 0.286	-	-	-	-	-

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

** P<0.01

*** P<0.001

4. Discussion

In the present investigation, IV injection of 5 mg ceftiofur / kg b.wt. in normal catfish (*Clarias lazera*), showed that the drug disposition best fitted a two-compartments open model, compartment of plasma and rapid equilibrating tissues, and a deeper slower compartment. The obtained result was consistent with those reported for ceftiofur in ducks (Liu *et al.*, 2010) in neonatal foals (Hall, 2011) and for cefquinome in chicken (Xie, 2013).

The $V_{d_{ss}}$ is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions (Toutain *et al.*, 2004) The $V_{d_{ss}}$ for ceftiofur was 224.20 ml/kg, suggesting limited penetration through biological membranes and tissue distribution after IV administration in catfish (*Clarias lazera*). The obtained result agreed with the data reported after IV administration of ceftiofur in calves (0.200 L/kg) by (Whittem *et al.*, 1995). On the other hand, volume of distribution was smaller than those recorded in calves (0.284 L/kg) (Brown *et al.*, 1996), in goats (0.25 L/kg) (Courtin *et al.*, 1997) in foals (0.83 L/kg) (Meyer *et al.*, 2009) and in ducks (0.48 L/kg) (Xu *et al.*, 2012). These differences might be due to the specific interspecies variations.

Ceftiofur was transferred from central to peripheral compartment at a slower rate ($K_{12} = 0.435 \text{ h}^{-1}$) than its passage from peripheral compartment to central compartment ($K_{21} = 1.376 \text{ h}^{-1}$). These values were nearly similar to that reported for ceftiofur in cows ($K_{12} = 0.473 \text{ h}^{-1}$) and ($K_{21} = 0.950 \text{ h}^{-1}$) by (Tohamy, 2008).

The elimination half-life ($t_{0.5(\beta)}$) of ceftiofur following a single IV injection was equal to 5.700 h. This observation agreed with the data reported after IV administration of ceftiofur in cows and calves ($t_{0.5(\beta)} = 5.09, 5.05 \text{ h}$) by (El-Gendy 2007 and Tohamy, 2008), respectively.

On contrast, this obtained value was longer than those recorded in other species as chickens (4.23 h) (Amer *et al.*, 1998) camels (3.18) (Goudah, 2007) and ducks (2.28, 3.64 h) (Liu *et al.*, 2010 and Xu *et al.*, 2012) On the other hand, it was shorter than those showed in cattle (7.12 h) (Whittem *et al.*, 1995) and in foals (7.8 h) (Meyer *et al.*, 2009).

The rate of total body clearance (CL_{tot}) of ceftiofur following IV injection was $0.642 \pm 0.008 \text{ ml/kg/min}$.

Following a single IM administration of 5 mg ceftiofur / kg b.wt, the drug reached its maximum serum concentrations after 2 h of administration (22.01 $\mu\text{g/ml}$). Ceftiofur could be detected in serum in a therapeutic level (1.85 $\mu\text{g/ml}$) at 24 h. The mean peak serum concentrations of ceftiofur (C_{max}) was (21.771 $\mu\text{g/ml}$) achieved at maximum time ($t_{max} = 2.15 \text{ h}$). These values were similar to those recorded for ceftiofur in chickens (27.83 $\mu\text{g/ml}$ at 2.39 h)

(Amer *et al.*, 1998). On contrast, the obtained results were different from those reported in camels (10.34 $\mu\text{g/ml}$ at 1.22 h) (Goudah, 2007), in cows (7.83 $\mu\text{g/ml}$ at 1.55 h) (Tohamy, 2008), in ball python (7.09 $\mu\text{g/ml}$ at 2.17 h) (Adkesson *et al.*, 2011)

in guinea fowl (5.26 $\mu\text{g/ml}$ at 19.3 h) (Wojick *et al.*, 2011), in ducks (6.44 $\mu\text{g/ml}$ at 0.49 h) (Xu *et al.*, in chickens (3.04 $\mu\text{g/ml}$) (Xie *et al.*, 2013) and in pigs (28.3 $\mu\text{g/ml}$ at 2 h) (Brown *et al.*, 1999) These variations might be attributed to anatomical differences between species, healthy status and the dose administered in each case (El-Sayed *et al.*, 1989).

The bioavailability of ceftiofur in normal fish was (67.22%). This value referred to a good absorption of ceftiofur from its site of IM administration. This value was close to those recorded for ceftiofur in camels (68.70%) (Goudah, 2007) and in ducks (79.25%) (Xu *et*

al.,2012). On contrast, this value was lower than that reported for ceftiofur in horses (100%)(Collard *et al.*,2011) and for cefquinome in ducks (93.28%)(Yuan *et al.*,2011)and in chickens (95.81%)(Xie *et al.*,2013).

The obtained blood levels of ceftiofur in experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) were significantly decreased than those in normal fish following repeated IM administrations. These lower blood concentrations in infected fish might be attributed to the higher penetrating power of ceftiofur to the diseased tissues(Baggot, 1980). The relative higher serum concentrations of ceftiofur after the last dose compared to the first doses indicated the accumulation of ceftiofur in blood during multiple dosing at 24 h intervals for five consecutive days. These observations agreed with data reported by(El-Banna *et al.*,1998), who found that progressive daily increase in the mean serum concentrations following the IM injection of ciprofloxacin in lactating goats in a daily dose of 5 mg/kg b. wt. for five consecutive days and (Credille *et al.*,2012), who recorded a progressive daily increase in mean concentration in blood following IM injection of ceftiofur in weanling foals at a daily dose of 6.6 mg/kg b.wt. for four consecutive days. The obtained result was inconsistent with that reported by(Brown *et al.*,1990) who found a little drug accumulation after multiple dosing of norfloxacin in dogs.

Repeated IM administration of 5 mg ceftiofur /kg b.wt every 24 h for five consecutive days in normal and experimentally *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) were revealed that the drug could only be detected in blood, muscle and skin till 72 h post last dose and till 96 h post last administration in liver, kidney and dorsal

muscle. The high clearance of ceftiofur indicated the reduced possibility of finding residues of ceftiofur in fish after treatment and shorter withdrawal time for this antimicrobial (five days). Results showed that kidney and liver contained the highest drug concentrations (35.74, 33.68 µg/g respectively), while the lowest drug concentrations was found in abdominal muscle with skin (19.64 µg/g), 24 h after the stoppage of drug medication. This result slightly agreed with that recorded for ceftiofur in swines that reported by (Li *et al.*,2013), who found that the highest concentration in kidney (2.589 µg/g) at 12 h, while the concentration of ceftiofur in all of tissues at three days was lower than the Maximum Residue Limit (MRL).

5. Conclusion

The IM bioavailability of ceftiofur is excellent, so it is recommended to be used against enteric and systemic *Aeromonas hydrophilia* infected catfish (*Clarias lazera*) infection. Repeated IM administrations of 5 mg/kg b.wt. ceftiofur once daily for five consecutive days would provide an effective concentration against *Aeromonas hydrophilia* in infected catfish (*Clarias lazera*) . Treated fish must not be slaughtered before 5 days from last dose of repeated administration of ceftiofur to withdraw the drug residues from all tissues of treated fish.

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