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EFFECTS OF FLORFENICOL ON HEPATIC AND RENAL FUNCTIONS IN NILE CATFISH *(CLARIAS LAZERA)*

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A B S T R A C T

Effects of florfenicol on hepatic and renal functions were studied in four groups of Nile catfish *(Clarias Lazera)*. The study investigated that a significant decrease in globulin at first day post drug administration in 2nd group (infected only) in comparison with 1st group (not infected and not treated) then it return to normal at 7th day and 14th day. A significant increase in albumin: globulin ratio in second group in comparison with first group at 1st day then decreased significantly at 7th day and 14th day. Concerning liver enzymes, a significant increase in aspartate aminotransferase (AST) and alanine transaminase (ALT) at 7th day and 14th day - post drug administration in second group in comparison with first group. In the third group (treated only), the same parameters where increased significantly at 7th day and returned to the normal values at 14th day post administration. Concerning kidney function found a significant increase in uric acid at 7th days and 14th days post drug administration in the second group in comparison with the first group and fourth group (infected and treated). In 3rd group a significant decrease in uric acid at the 1st day post drug administration then significant increase at 7th day and 14th day It was concluded that florfenicol has no dangerous effects on liver and kidney functions, a factor, which indicating that florfenicol safe to be used therapeutically in Nile catfish.

Keywords: hepatic, renal, florfenicol, Nile catfish (*Clarias Lazera*)

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1. INTRODUCTION

Florfenicol is a broad-spectrum primarily bacteriostatic antibiotic with a range of activity similar to that of chloramphenicol, including many Gram-negative and Gram-positive organisms; however, florfenicol does not carry the risk of inducing human aplastic anemia that is associated with chloramphenicol **[1]** .Florfenicol has been demonstrated to be active *in- vitro* and *in-vivo* against *Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, and Haemophilus somnus. In-vitro* studies have demonstrated florfenicol activity against *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Salmonella typhi*, and *Shigella dysenteriae* but with at least a 2 to 10 fold higher minimum inhibitory concentration than that for the *Mannheimia, Pasteurella* and *Haemophilus* species listed above [2] .Florfenicol has also activity against some chloramphenicol resistant strains of bacteria, possibly because it is less affected by the major enzyme produced in plasmid-mediated bacterial resistance against chloramphenicol and thiamphenicol [3]**.** The objectives of the study were to determine the effect of florfenicol on hepatic and renal functions in the nile catfish following repeated oral administrations.

2. MATERIAL AND METHODS

2.1. Drug:

Florfenicol was obtained from Pharma swede Pharmaceutical Company under trade name Floricol®. It is dispensed as oral

solution (10%), each one milliliter contains 100 mg florfenicol base.

2.2. Bacterial isolate for infection:

Twenty four hours 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[4,5] .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 hours of injection with *Aeromonas Hydrophilia* suspension**.**

2.3. Experimental design:

The fish were divided into 4 groups:-
Group (1): Six normal nile catfish (not infected – not treated). Group (2): Six nile catfish were infected experimentally with *Aeromonas hydrophila* and kept without treatment (infected – not treated).
Group (3): Six normal nile catfish were administered florfenicol orally at dose 10 mg /Kg. B.wt. twice with 60 hours intervals (not infected – treated). Group (4): Six experimentally *Aeromonas hydrophila* infected nile catfish were administrated florfenicol orally at dose 10 mg /kg B.wt. twice with 60 hours interval (infected - treated)**.**

2.4. Blood samples:

Two milliliters of Blood were taken from the dorsal vein following repeated oral administrations of florfenicol in normal and infected nile catfish at 1, 7 and 14 days after the last oral dose. All blood samples were collected in sterilized centrifuged tubes and allowed to clot. Serum was separated by centrifugation for 10 minutes at 3000 r.p.m. Sera were kept frozen until assayed for liver and kidney functions.

2.5. Analytical procedures:

1. Alanine aminotransferse (ALT) and Aspartate aminotransferse (AST).

It was assayed by colorimetric method [6, 7], and was performed by kit manufactured by Diamond diagnostics, Egypt, according to previous method

2. Alkaline phosphatases (ALP)

It was assayed by colorimetric method [8], and was performed by kit manufactured by Vitro Scient, Egypt.

3. Total protein

Total protein was assayed by colorimetric method [9, 10], and was performed by kit manufactured by Diamond diagnostics, Egypt.

4. Albumin

It was assayed by Bromocresol green colorimetric method [11], and was performed by kit manufactured by Diamond diagnostics Egypt

5. Urea

It was assayed by urease –modified Berthelot reaction [12], and was performed by kit manufactured by spectrum diagnostic company, Egypt.

6. Creatinine

It was assayed by Jaffe **.**Colometric –Kinetic method [13] and was performed by kit manufactured by Diamond diagnostics, Egypt,

2. RESULTS

Effect of florfenicol on serum protein profile in nile catfish.

The effect of repeated oral administrations of florfenicol (10 mg /kg.b.wt.) on protein profile in nile catfish was evaluated in table (1). A significant decrease in globulin at first day post drug administration in 3rdgroup in comparison with 1stgroup then it returns to normal at 7th day and 14th day. A significant increase in albumin: globulin ratio in 2nd group in comparison with 1st group at 1st day then decreased significantly at 7th and 14th day.

Effect of florfenicol on some liver enzymatic activities in nile catfish.

The effect of repeated oral administrations of florfenicol (10 mg/kg.bwt.) on some enzymes related to liver function in nile catfish was evaluated in table (2). It has shown a significant increase in (AST) and (ALT)

Table (1): Effect of repeated oral administrations of 10 mg florfenicol /kg.b.wt given twice with 60 hours intervals on serum protein profile in Nile catfish (*Clarias Lazera*) (n=6)

groups	Days after the last administrations											
	1				7				14			
	Total protein	albumin	globulin	A/G ratio	Total protein	albumin	globulin	A/G ratio	Total protein	albumin	globulin	A/G ratio
G1	40.30 ±3.60	20.30 ±2.20	20.00 ±1.65	1.02 ±0.06	42.10 ±2.60	19.90 ±1.95	22.20 ±1.70	0.90 ±0.004	41.30 ±2.20	22.60 ±3.30	18.70 ±1.50	1.21 ±0.07
G2	33.20 ±2.40	19.20 ±1.60	14.00 ±0.90*	1.37 ±0.04**	35.50 ±2.50	13.20 ±0.30*	22.30 ±1.05	0.59 ±0.002***	31.50 ±3.20	11.40 ±2.10*	17.10 ±1.45	0.84 ±0.04**
G3	37.50 ±3.20	19.85 ±1.35	17.65 ±1.40	1.12 ±0.08	43.00 ±2.40	21.40 ±1.60	21.60 ±1.45	0.99 ±0.01$^{\Delta}$	43.30 ±2.10	19.40 ±1.10	23.90 ±1.60	0.81 ±0.06$^{\Delta}$
G4	38.10 ±3.10	21.60 ±1.40	16.50 ±1.30	1.30 ±0.08	40.15 ±2.65	22.40 ±0.09^{ooo}	17.75 ±1.40	1.26 ±1.40 $^{ooo\ \square}$	40.60 ±2.70	20.15 ±1.30^{o}	20.45 ±1.60	0.98 ±0.07

G1= not infected and not treated.
G2 = infected only.
G3= treated only.
G4= infected and treated.

- Total protein ⟶ g/ dl
- Albumin ⟶ g/ dl
- Globulin ⟶ g/ dl

* T-test between G1& G2	* P< 0.05	** P<0.01	*** P<0.001
Δ T-test between G1& G3	$^{\Delta}$ P< 0.05	$^{\Delta\Delta}$ P<0.01	$^{\Delta\Delta\Delta}$ P<0.001
^{o} T-test between G4& G2	^{o} P< 0.05	^{oo} P<0.01	^{ooo} P<0.001
□ T-test between G4& G3	$^{\square}$ P< 0.05	$^{\square\square}$ P<0.01	$^{\square\square\square}$ P<0.001

at 7th day and 14th day post drug administration in 2nd group in comparison with 1st group. In the 3rd group, the same parameters where increased significantly at 7th day and returned to the normal values at 14th day post administration. In the same direction, it has shown a significant increase in (ALP) activates at 7th and 14th days in 2nd group in comparison with 1st group

Effect of florfenicol on kidney function in nile catfish.

Repeated oral administrations of florfenicol (10 mg /kg.bwt.) on kidney function in nile catfish was evaluated in table (3). A significant increase in uric acid at 1st, 7th and 14th days post drug administration in the 2nd group in comparison with the 1st group. In 3rd group, it has shown a significant decrease in uric acid at the 1st day post drug administration then returned to the normal values at 7th and 14th day post administration, also it has shown that significant increase in uric acid levels at 1st, 7th and 14th days in 4th group in comparison with 2nd group.

4. DISCUSSION

The effect of repeated administrations of florfenicol (10 mg /kg. b.wt.)

Table (2): Effect of repeated oral administrations of 10 mg florfenicol /kg.b.wt. given twice with 60 hours intervals on some enzymes related to liver function in Nile catfish *(Clarias Lazera)* (n=6)

groups	Days after the last administrations								
	1			7			14		
	AST	ALT	ALP	AST	ALT	ALP	AST	ALT	ALP
G1	18.60 ±1.40	11.50 ±0.50	65.10 ±2.40	19.00 ±0.66	12.10 ±0.65	63.15 ±2.40	20.10 ±1.10	11.35 ±0.75	64.80 ±2.60
G2	21.40 ±0.45	12.90 ±0.35	71.30 ±2.30	23.50 ±0.60**	15.10 ±0.06**	69.50 ±2.20	26.30 ±1.50*	15.15 ±0.60*	74.70 ±2.40*
G3	19.40 ±0.90	13.20 ±0.40$^{\Delta}$	66.50 ±0.25	22.10 ±0.55$^{\Delta}$	16.55 ±0.75$^{\Delta}$	66.50 ±2.10	20.30 ±1.70	13.10 ±0.40	65.00 ±1.35
G4	21.10 ±1.15	14.50 ±0.90	67.20 ±2.10	20.10 ±1.60	13.60 ±1.10	62.15 ±2.20	21.40 ±1.15	10.60 ±0.35$^{o\square\square}$	66.60 ±2.40

G1= not infected and not treated.
G2= infected only
G3= treated only.
G4= infected and treated

-Aspartate aminotransferase (AST) ⟶ U/L
Alanin aminotransferase (ALT) ⟶ U/L
Alkaline phosphatase (ALP) ⟶ U/L

* T-test between G1& G2 * P< 0.05 ** P< 0.01 *** P< 0.001
Δ T-test between G1& G3 $^{\Delta}$ P< 0.05 $^{\Delta\Delta}$ P< 0.01 $^{\Delta\Delta\Delta}$ P< 0.001
º T-test between G4& G2 ^{o} P< 0.05 ^{oo} P< 0.01 ^{ooo} P< 0.001
□ T-test between G4& G3 $^{\square}$ P< 0.05 $^{\square\square}$ P< 0.01 $^{\square\square\square}$ P< 0.001

on protein profile in nile catfish was evaluated in the present study. The decreased serum total protein levels in the present data might be explained by the renal damaged provoked by the drug [14]. The hypoproteinaemia could occur with renal diseases [15]. The decreased albumin was attributed to its small size and osmotic sensitivity to fluid movements as in cases of renal disease as glomeruonephritis, nephrosis and nephritic syndrome [16]. Furthermore, the liver is the sole site of albumin synthesis and hypoalbuminaemia is an important feature of liver diseases [17].

The effect of repeated administrations of florfenicol on some enzymes related to liver function in nile catfish was reported. Significant increase in AST & ALT at 7th day and 14th day post drug administration in 2nd group. In comparison with 1st group in the 3rd group, the same parameters where increased significantly at 7th day and returned to the normal values at 14th day post administration [18] .Animal had the highest clearance value and it therefore seemed improbable that impaired liver function affected the pharmacokinetics of florfenicol [19]. The capacity of the liver for metabolism of drugs might exceed the normal requirement consequently extensive liver dysfunction might be required to affect metabolism of some

Table (3): Effect of repeated oral administrations of 10 mg florfenicol /kg.b.wt. daily given twice with 60 hours intervals on kidney functions in Nile catfish *(Clarias Lazera)* (n=6)

groups	Days after the last administrations								
	1			7			14		
	Urea	Uric acid	Creatinine	Urea	Uric acid	Creatinine	Urea	Uric acid	Creatinine
G1	3.20 ±0.08	0.75 ±0.003	52.30 ±2.10	2.95 ±0.06	0.74 ±0.002	51.60 ±2.35	3.05 ±0.03	0.77 ±0.003	52.65 ±1.65
G2	4.10 ±0.06***	0.78 ±0.006**	56.70 ±1.20	4.40 ±0.07***	0.81 ±0.004***	57.10 ±2.10	3.95 ±0.06***	0.84 ±0.006***	58.80 ±2.10
G3	3.50 ±0.06$^{\Delta}$	0.72 ±0.006$^{\Delta}$	51.20 ±2.60	3.15 ±0.09	0.76 ±0.08	53.10 ±2.90	2.95 ±0.08	0.76 ±0.007	53.60 ±2.45
G4	3.70 ±0.07^{o}	0.77 ±0.006$^{\square\square}$	55.10 ±2.20	3.35 ±0.05 ^{o}	0.76 ±0.006 ^{oo}	52.15 ±2.45	3.25 ±0.04$^{ooo\square}$	0.81 ±0.005 ^{ooo}	54.20 ±2.25

G1= not infected and not treated

G2= infected only.

G3= treated only.

G4= infected and treated.

Urea ⟶ mg/dl .

Uric acid ⟶ mg/ dl

Creatinin ⟶ mg/ dl

* T-test between G1& G2	* P< 0.05	** P< 0.01	*** P< 0.001
Δ T-test between G1& G3	$^{\Delta}$ P< 0.05	$^{\Delta\Delta}$ P< 0.01	$^{\Delta\Delta\Delta}$ P< 0.001
^{o} T-test between G4& G2	^{o} P< 0.05	^{oo} P< 0.01	^{ooo} P< 0.001
□ T-test between G4& G3	$^{\square}$ P< 0.05	$^{\square\square}$ P< 0.01	$^{\square\square\square}$ P< 0.001

xenobiotics [20]**.** It was well documented that the increase of AST activity was concomitantly recorded with liver damage and a myocardial infarction leading to alteration in cellular permeability due to change in normal cell membrane. This allowed the escape of this enzyme into serum in abnormal high levels [21, 22, and 23]**.** Elevations in ALT, AST, and ALP were most commonly reported in liver damage [24, 25, and 26]**.** All such elevations were usually mild and reversible when the drug was discontinued, although discontinuation is rarely necessary [27]**.** The effect of repeated oral administrations of florfenicol on kidney function in Nile catfish was evaluated. A significant increase in urea and uric acid at 1st days and 14th days post drug administration in the 2nd group in comparison with the 1st group. Significant decrease in urea and uric acid at the 1st,7th and 14th day post drug administration in 4th group in comparison to 2nd group. The represented data showed that no significant changes in

creatinine concentrations all over the tested groups among the 1st, 7th and 14th days post drug administration. These elevations are consistent with those reported in pet birds [26], in domestic animals [16], in healthy chick [27] and in experimental animals. The increased uric acid levels in infected animals could be attributed to the degenerative changes in the kidney tubules preventing their excretion, thereby increasing their serum concentrations [16]. In another study [24], it was shown that elevation of uric acid and creatinine levels and then regained to their normal values because of treatment with norfloxacin (5 mg/kg. b.wt.) for five successive days. The mechanism of hepatotoxicity and nephrotoxicity induced by several antibacterials was discussed [24,]. Serum creatinine was slightly elevated with renal failure due to nephrotoxic drugs but it was less reliable than uric acid. Moreover, the oral ciprofloxacin therapy might lead to acute renal failure [27], secondary to tubulointerstitial nephritis characterized by increased creatinine, to blood urea nitrogen ratio and the nephrotoxicity caused by quinolones had been linked the development of crystal urea in experimental animals. The acute renal failure in all cases was completely reversed after discontinuation of ciprofloxacin. The administration of danofloxacin to healthy chicks [23] resulted in an elevated serum AST, ALP, Uric acid and creatinine levels and these changes were reversible and needs about one week to return to their normal levels.

According to a review of safety data related to long-term (> 30 days) therapy with ciprofloxacin, urogenital adverse effects occurred in four (1.2%) of 339 patients, but the review did not specify their nature. The analysis did state that neither interstitial nephritis nor crystalurea was reported; it appeared that the risks of such toxicities were not increased with long-term ciprofloxacin therapy. Nearly all cases of acute renal failure after ciprofloxacin administration occurred in patients older than 50 years, and the onset of renal dysfunction was typically within 3-7 days of the start of therapy [25, 27]. The disorder usually resolved promptly with discontinuation of the drug, and renal function returned to normal within several weeks, with no long-term consequences [21, 22, and 27]

The obtained results concluded that florfenicol has no dangerous effects on liver and kidney functions, a factor which indicating that florfenicol safe to be used therapeutically in Nile catfish.

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مجلة بنها للعلوم الطبية البيطرية
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دراسة تأثير الفلورفنيكول على وظائف الكبد والكلى في اسماك القراميط السليمة والمصابة تجريبيا

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الملخص العربي

في هذا العمل تم دراسة تأثير عقار الفلورفنيكول على وظائف الكبد والكلى في أربع مجموعات من اسماك القراميط . الدراسة اوضحت انخفاض معنوي في الجلوبيولين في أول يوم بعد انتهاء إعطاء الدواء في المجموعة الثانية بالمقارنة مع المجموعة الأولى ثم عادت إلى طبيعتها في اليوم السابع واليوم الرابع عشر. وأيضا زيادة معنوية في نسبة الألبومين الى الجلوبيولين في المجموعة الثانية بالمقارنة مع مجموعة الأولى في اليوم الأول ثم انخفضت معنويا في اليوم السابع واليوم الرابع عشر. وفيما يتعلق بإنزيمات الكبد، وجدت زيادة معنوية في إنزيم اسبارتيت امينو ترانسفيريز وانزيم الانين امينو ترانسفيريز في اليوم السابع والرابع عشر بعد انتهاء إعطاء الدواء في المجموعة الثانية بالمقارنة مع المجموعة الأولى. في المجموعة الثالثة وجد أن نفس الإنزيمات زادت بشكل معنوي في اليوم السابع، وعادة إلى القيم العادية في اليوم الرابع عشر بعد انتهاء إعطاء الدواء .وفيما يتعلق بوظائف الكلى وجدت زيادة معنوية في حمض اليوريك في اليوم السابع واليوم الرابع عشر بعد انتهاء إعطاء الدواء في المجموعة الثانية بالمقارنة مع مجموعة الأولى والمجموعة الرابعة، وجد أيضا في المجموعة الثالثة انخفاض معنوي في حامض اليوريك في اليوم الأول بعد انتهاء إعطاء الدواء ثم زيادة معنوية في اليوم السابع واليوم الرابع عشر. ويستخلص من هذه الدراسة ان إعطاء دواء الفلورفنيكول بجرعة 10مجم/كجم مرتين متتاليتين (60 ساعة فاصل) ليس له تأثير معنوي خطير على وظائف الكبد والكلى لأسماك القراميط المعالجة.

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