SOME PHARMACOLOGICAL STUDIES OF CERTAIN ANTIBIOTICS ON SOME BACTERIAL PATHOGENS OF OREOCHROMAIS NILOTICUS

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ABSTRACT

Sensitivity of some bacteria (Aeromonas hydrophila, Pseudomonas fluorescence. P.anguilliseptica, P.aeroginosa and E.coli) to some antimicrobials was studied in vitro. These bacteria were highly sensitive to ciprofloxacin, danofloxcin and cephazon, while they were resistant to ampicillin and orbenin. Fish were experimentally infected with the tested bacteria. After the development of clinical signs of experimental infection, fish were treated successively by using ciprofloxacin intraperitoneally at dose of 20 mg/kg body weight for three successive days.

Pseudomonas fluorescence infected fish group was chosen to study the pharmacokinetics of ciprofloxacin after first dose and tissue residues after multiple doses (3days).The kinetics of ciprofloxacin showed distribution half t 0. 5 (a b) 0.41 ± 0.02 and 0.61 ± 0.03 and elimination half life to t 0. 5 el was 6.9 ± 0.41 and 5.7 ± 0.37 hrs in normal and infected fish respectively. The clearance of ciprofloxacin from all tissues was 120 hrs following treatment. High tissue residues of drug were recorded in kidney, liver and muscles respectively and were higher in infected fish than healthy one.

INTRODUCTION

Bacterial diseases, particularly those caused by gram negative organisms are the major causes of mortality in both wild and cultured fish **(Roberts ,1987)**. Fish diseases caused by aeromonas and pseudomonas are considerd to be the major bacterial problems facing the aquaculture development causing mortalities reduce production **(Ghittino,1976)**. Several bacterial species in genus Pseudomonas have been associated with disease in fish. P. fluorescence P.chlororaphis, P.putida and P.anguilliseptica were recognized as the causative agents of bacterial heamorrhagic septicaemia in different species of fish **(Sch perclaus et al., 1992 & Austin and Austin ,1999)**

In Egypt the most prevalent bacteria affecting tilapia are P. fluorescence , P. aeroginosa and motile A. hydrophila **(Azza,1996)**. Also A. hydrophila was isolated from naturally infected Oreochromis niloticus M,ugil cephalus, Cyprinus carpio and Mormyrus Kannume **(Eissa et al., 1990 , Ahmed et al., 1991 and Badran & Eissa 1991)**.

Antibiotic therapy for bacterial fish pathogens have evolved in fish farming. There is a few literature on the efficacy, pharmacokinecties and tissue residues of ciprofloxcacin in healthy or diseased fish. The withdrawal time of veterinary drugs given to fish and studies should be carried to avoid unacceptable drug residues in food used for human consumption. Therefore, it is essential to determine drug concentration in muscles, the edible fish tissue, in liver, the site of detoxification and kidneys , the organ for drug excretion.

The present work was carried out to study the sensitivity of some bacterial pathogens to some antiblotic in vitro and in vivo. Also to study the kinetic parameters of Ciprofloxacin, with referring to its residues.

MATERIAL AND METHODS

1- Fish :-

A total number of 180 apparently healthy Oreochromis niloticus with an average body weight 90 ± 5 gm were collected alive from El Wafa farm at Giza and transported alive to fish disease Dept., Animal Health Research Institute, Dokki, Giza in large plastic bags supplied with dechlorinated tap water with aeration . Fish were kept in glass aquaria supplied with dechlorinated tap water for two weeks for aeclimatization. During this period, fish were fed about 3% of their body weight twice daily. Random samples were taken from fish for bacteriological examination to exclude their natural infection.

2- Bacterial strains :-

A well identified virulent Isolates Pseudomonas fluoresces LD 50 2.5x104 c.f.u. , Aeromonas hydrophila LD 50 5x105 c.f.u., Pseudomonas aeroginosa, Pseudomonas angillsepticume and E.coli were kindly supplied from bacteriological lab, Fish Diseases Department, Animal Health Research Institute, Dokki, Giza, Egypt. All isolates were propagated in trypticase soya agar and trypticase soya broth to be used in experimental infection.

3-The in-vitro antibiotic sensitivity test :

The test was carried out against various chemotherapeutie agents by diffusion technique which was applied according , **Finegold and Mortin, (1982)** using Mueller Hinton broth and ager . The results were interpreted according to **Oxoid manual, (1982)** Manufacture Company. The used antibiotic disc were obtained from Oxoid Comp. They include

Oxtetracycline OT (30 ug) , Danofloxacin DFX (5 ug), Ampicillin AMP(10 ug) , Oxolinic acid OA (2 ug), Tetracycline TE (30 ug) Orbenin OS (5 ug), Nitrofurantine F (300 ug) , Nalidixic acid NA (30 ug), Amoxeyllin AML (10 ug), Gentamicine CN (10 ug), Cefazone CFP (75 ug) and Ciprofloxacin CIP(5ug).

4-Drug :

Ciprofloxacin was obtained as 100 ml injectable solution bottle in a concentration of 200 mg/ 100ml (El America pharmaceutical Industries Co.).

5- Experimental design :-

Experiment (1):

A total of 150 apparently healthy Oreochromis niloticus were divided into 6 groups (25 fish / each.). Fisb in groups from 1 to 5 were experimentally infeeted (I/P) with 0.2ml of 24 hr old broth culture which contain 2x10 4 c.f.u. of P. fluorescence (LD 50 2.5x104 c.f.u.) in case of group 1, contain 3.2x 107 c.f.u. of P. aeroginosa in case of group 2 according to Eman 2004, contain 2.8 x10 6 c.f.u. of P. angillsepticum in case of group 3 according to Eman 2004 , contain 0.2x 104 c.f.u. of A. hydrophila (LD 50 5x105 c.f.u.) in case of group 4 and contain 0.5x 106 E.coli in case of group5 according to El-Hady 2000). Last group was injected I/P with 0.2 ml sterile normal saline / fish, and kept as negative (non-infected) control during experimental time. All fish were observed for any clinical signs and mortality rates were recorded. After development of the clinical signs or appearance of mortality (24 hours post inoculation), Fish in groups from 1 to 5 were divided into two sub-gronps, sub groups number 1,3,5,7 & 9 were treated with ciprofloxacin 20 mg/kg.b.wt. according to **(Sturat 1983)**, by intra peritoneal route once daily for three successive days.While fish in the other sub-groups (2,4,6,8,&10) were kept non-treated as a positive control. Clinieal signs were observed and mortality rates were recorded. Tissue samples from liver, kidney and muscle were collected 10 successive days post drug stoppage and used for determination of tissue residues for ciprofloxacin concentration. Tissue samples were diluted 1 : 6 with phosphate buffer, thoroughly homogenized and centrifuged the su-

pernatant fluid were collected and frozen until used **(Grove and Randall, 1955).**

Experiment (2):

A total of 60 apparently normal Oreochromis niloticus were divided into 2 equal groups. Fish in group 1 were experimentally infected (I/P) with 0.2 ml of 24 hr old broth culture of Pseudomonas fluorescence which contain 2x104 e.f.u. by count . Twenty four hours post inoculation fish were injected intra peritoneal with a single dose of ciprofloxacin 20 mg. kg. b. wt. The 2nd group was intra peritoneal injected with ciprofloxacin at the same dose.

Blood samples were collected according to the method described by **(Lucky 1977)** from fish in the 1st group (infected and treated) and the 2nd group (non-infected and treated) at the 15, 30 minutes, 1, 2, 4, 6, 8, 12 and 24 hours post drug administration.

Assay of samples : Serum and tissue samples were assayed by microbiological method using Bacillus subtilis as standard organism (obtained from Animal Health Research Institute, Dokki, Egypt) according to **Arret et al. (1971).** The pharmacokinetic data was calculated according to the method described by **(Baggot 1978).**

RESULTS

1-The in-vitro sensitivity of tested bacteria to the used antibiotics:

Five bacterial isolates were screened for susceptibility to some antibiotics (Table 1) .All tested isolates showed susceptibility to Oxtetracycline, Danofloxacin, Oxolinic acid, Nitrofurantine , Nalidixic acid, Amoxcyllin, Gentamicine, Cefazone and Ciprofloxacin while they resistant to ampicillin, orbenin and tetracycline. Also all tested isolates were resistant to oxolinic acid except A.hydrophila. & P.angillsepticum. While all tested isolates were sensitive to Danofloxacine ,Cefazone, Ciprofloxacin & Gentamycin. All tested pseudomonas species were resistant to Oxytetracyclin. P. fluorescence, A. hydrophila & E.coli were sensitive to Nitrofuantine. Only P. fluorescence was sensitive to Amoxcycline. All isolates were resistant to Nalidixic acid except A. hydrophila .

2- Efficacy of ciprofloxacin in treatment of bacterial infection in Oreochromis niloticus:

Pseudomonas infected fish showed signs of heamorrage in body surface with lose of scales 24 hrs post inoculation . In non treated sub groups (1,3 and 5), fish showed areas of hemorrhage on body surface and at base of fins, opercula and genital opening, intestinal prolapse, exophthal-

mia and superficial ulcer Fig. (1). PM examination of sub groups 1, 3 and 5 fish showed congestion of internal organs, patches of necrosis in liver, congestion of blood vessels of mesentery with accumulation of asitic fluid in the body cavity. The mortality rates in infected non treated subgroups were 60%, 50% & 50% in P. fluorescence , P.aeroginosa and P. angillseptieum respectively. While fish in sub groups (2,4& 6) which treated with Ciprofloxacin at dose of 20 mg/kg body weight once daily for three successive days showed remarkable decrease in manifested clinical signs and decline of mortality which reach 10,10 & 0% respectively after end of treatment . Some treated fish suffered from tail erosion with lose of some scales.

In case of sub group 7 which infected with Acromonas hydrophila, fish showed areas of hemorrhage on body surface and fins .In addition to abdominal distension, erosion of skin with superficial ulcers with an average of 16 % mortality rate 24 hours post inoculation among infected group Fig (2). The manifested clinical signs progressed greatly and rapidly among members of non-treated fish sub group 7. Complete necrosis of fins and tail, abdominal distension with skin erosion, lesions were progressed to sever hemorrhagic signs with reddish yellow dropsical exudates, congested internal organs . The mortality rate reached 80% among non-treated subgroup. Fish treated with Ciprofloxacin at dose of 20 mg/kg body weight intraperitoneally for three successive to fish led to remarkable decrease in manifested clinical signs and mortality to reach 20%.

In case of sub group 9 which inoculated with E. coli the inoculated fish showed slight haemorrhage ,darkening in skin Fig. (3) PM examination of infected fish showed general septicemia . The mortality rates among infected treated sub group reached 10% compared to 30% in non-treated subgroup. Table (2) showed the mortality rates among infected treated and non-treated fish.

3- Pharmacokinetics and tissue residues in normal and experimentally infected O. niloticus:

Concerning the pharmacokinetic data the results showed that Ciprofloxacin persisted in sera of treated fish in concentrations higher than the minimal inhibitory concentration (0.0025-0.3 ug/ml) (table 3). Ciprofloxcin was rapidly absorbed with half life time 0.41±0.02 and 0.61 ± 0.03 hrs in normal and infected fish respectively. The elimination half life (t0.5 el) of ciprofloxacin was 6.9±0.41 and 5.7±0.37 in normal and diseased fish. Ciprofloxacin showed very rapid withdrawal time and could not be detected in fish tissues 120 hrs post injection .

DISCUSSION

In table (1), all tested isolates showed susceptibility to used the antibiotics except ampicillin, orbenin and tetracycline. They were resistant to oxilinic acid except A.hydrophila. & P.angillsepticum. All tested pseudomonas species were resistant to oxytetracyclin. These results agree with that reported by **Austin & Austin (1999), El Hady (2000), Ahmed & Shoreit (2001) and Eman (2004)**. Regarding to bacterial inoculation, the motality rates in infected non treated subgroups were 60% ,50% & 50% in P. fluorescence & P.aeroginosa and P. angillsepticum respectively Table (2).The observed results agree with that reported by **Murega et al. (1977)** who recorded that P.angillisepticum eliminated 14% of the total weight of farm stock in Scotland clevers , **Ahmed and Shoriet (2001)** who reported that P. fluorescence, P. aeroginosa and P. putida cause 60%, 40% and 50% mortality among O.niloticus fish respectively. Similar results were reported by **Azza et al. (2002)**. The observed clinical signs due to experimentally infection with pseudomonas species summarized as signs of septiccamia and this agree with **Noga (1995) ,Aoki(1999) and Azza et al .(2002)** who recorded clinical signs due to pseudomonas spp. infection. Sub groups 2,4 & 6 which treated with ciprofloxacin at dose of 20mg/kg body weight once daily for three successive days led to remarkable decrease in manifested clinical signs and decline of mortality which reach 10,10 & 0 % in P. fluorescence, P.aeroginosa and P. angillsepticum respectively. Tbese results showed that ciprofloxacin has great ability to eliminate pseudomonas infection in fish. In sub group 7 which infected with Aeromonas hydrophila, fish showed areas of hemorrhage on body surface and fins, abdominal distension with skin erosion. The mortality rate reached 80% among non-treated subgroup. Similar results were recorded by **(Ingles 1993, Stoskpf 1993, Noga 1995 and Aoki 1999)**. Fish treated with ciprofloxacin showed remarkable decrease in manifested clinical signs and drop of mortality to 20% ,this prove sensitivity of A. hydrophila to Ciprofloxacin. In sub group 9 which inoculated with E. coli there is a little informations about the pathogenicity of E. coli among fish, infeeted fish showed slight haemorrhage and darkening in skin. The mortality rates was 30% among non-treated fish. The same results were reported by **El-Hady (2000)**.

The presistance of Ciprofloxacin in sera of treated fish in concentration higher than the minmal inhibitory concentration (0.0025-0.3 ug/ml) was agree with **Barnes et al., (1990), Martinsen et al. (1991)**, and **Martinsen et al . (1992)**. The same results were reported also by **Sumano et al.(2001)**, in poultry and **Ovando et al. (1999)** in chickens. The absorption half life time of Ciprofloxcin (0.41±0.02 and 0.61 ± 0.03 hrs) in normal and infected fish was longer than those repoted by **Bowser et al. (1992)** in rainbow trout following injection of enrofloxacin (6-7 min). The elimination half life (t0.5 el) of ciprofloxacin was 6.9±0.41 and 5.7±0.37 in normal and diseased fish may be due to high penetration power of the drug within the diseased tissues

Pennington et al. 1975 The high distribution rate and volume of distribution were supported by high tissue concentration (liver, kidney and muscles). These results were also recorded for sarafloxacin in Atlantic salmon by **Martinsen et al., 1993 and Martinsen et al. 1994.** These results were associated with relative shorter elimination half—life and shorter withdrawal time than other antibacterial where it was 6 days for sarafloxacin in Atlantic salmon **Martainsen et al. 1994**. These results are promising for ciprofloxacin toword its effective usage in treatment of fish bacterial infection.

Table (1) : Sensitivity of tested bacteria to the used antibiotics.

			E.coli	P.angill.	P.fluro.	P.aerg.	A. hy.	S R
Oxytetracycline	OT	30	10mm	15mm	15mm	15mm	10mm	≤9 >14
Danofloxocin	DFX	5	25mm	30mm	3mm	19mm	35mm	≤21 >15
Ampicillin	AMP	10	0	0	0	0		≤4 >11
Oxolinic acid	OA	2	0	13mm	0	0	31mm	<12 >8
Tetracycline	TE	30	0	15mm	14mm	11mm	10mm	<19 >14
Orbenin	OS	5	0	0	0	0	0	<14 >14
Nitrofurantine	F	300	32mm	13mm	25mm	12mm	38mm	≤7 >17
Nalidixic acid	NA	30	10mm	15mm	11mm	11mm	40mm	≤9 >13
Amoxcyclin	AML	10	10mm	0	18mm	0	10mm	≤8 >14
Gentamicin	CN	10	20mm	15mm	15mm	14mm	20mm	≤5 >12
Cefazone	CFP	75	40mm	25mm	30mm	20mm	40mm	<20 >14
Ciprofloxacin	CIP	5	34mm	36mm	34mm	32mm	50mm	≤21 >15

P.aerg. = P.aeroginosa S = sensitive R resistance

P.angill = P.angilliseptica A. hy = A. hydrophila

Table (2) : Mortality rates among infected and treated *O. niloticus* with ciprofloxacin and infected non treated *O. niloticus* with some bacterial pathogens.

pathogen	24 hrs.p.i.		g	Sub/g.	No.of.fish		Mortality rate			
							24hr	96hr	2w.	%
P. fluroscence	4/25	16%	1	1	Inf.non.T	10	3/10	5/10	6/10	60
		mortality		2	Inf. T.	10	1/10			10
P. aeroginosa	3/25	12%	2	3	Inf.non.T	10	2/10	3/10	5/10	50
		mortality		4	Inf. T.	10	1/10			10
P.angilliseptieum	5/25	20%	3	5	Inf.non.T	10	2/10	3/10	5/10	50
		mortality		6	Inf. T.	10	1/10			10
A.hydrophila	4/25	16	4	7	Inf.non.T	10	3/10	5/10	8/10	80
		mortality		8	Inf. T.	10	1/10		1/10	20
E.coli	0/25	0%	5	9	Inf.non.T	10		1/10	3/10	30
		mortality		10	Inf. T.	10			1/10	10
Sterial sailn	0/25	mortality	6	11	--------	10				0

p.i.= post inoculation Inf.T. = infected treated

Inf. Non.T. = infected non treated g.= group Sub/g. =subgroup

Table (3) : Ciproflloxacine concentrations (ug / ml) in sera of O. niloticus following intra peritoneal injection of 20mg/kg.body weight.

Sampling time	Non infected	infected
0.25h	0.87 ± 0.03	0.61 ± 0.02
0.5h	1.61 ± 0.07	1.54 ± 0.06
1h	2.14 ± 0.03	1.9 ± 0.02
2h	2.45 ± 0.08	2.12 ± 0.03
4h	2.01 ± 0.04	1.83 ± 0.05
6h	1.7 ± 0.02	1.4 ± 0.03
8h	1.31 ± 0.06	1.12 ± 0.06
12h	0.90 ± 0.02	0.72 ± 0.02
24h	N.D.	N.D.

Table (4) : Pharmacokinetic parameters for ciprofloxcine following intra peritconeal injection in a single dose of 20 mg/kg.b.wt. in normal and infected O. niloticus with ***Pseudomonas fluorescens***

Parameters	Unit	Non infected	Experimentally infected
A	µg / ml	3.01± 0.04	3.7 ± o.o5
α	h^{-1}	1.69 ± 0.02	1.13 ± 0.06
$t_{0.5\,(ab)}$	h	0.41 ± 0.02	0.61 ± 0.03
B	µg / ml	3.01 ± 0.04	2.7± 0.06
β	h-1	3.01 ± 0.04	0.12 ± 0.01
$t_{0.5\,(B)}$	h	6.9 ± 0.41	5.7 ± 0.37
$C_{max\ calc}$	µg / ml	2.77 ± 3.01	2.09 ± 0.01
$T_{max\ calc}$	h	1.77 ± 0.02	2.2 ± 0.01
Interval between doses	h	41.05 ± 3.62	33.55± 2.63

Table (5) : Tissue concentration (µg / gm) of eiprofloxacin in normal and infeeted O. niloticus with Pseudomonas fluroscene after intraperitoneal injection of 20 mg./kg/b./ wt.

Time after administration of the last dose (days)	Liver		Kidney		Muscle	
	Normal	Infected	Normal	Infected	Normal	Infected
1	1.1±0.03	1.3±0.04	1.41±0.04	1.71±0.02	0.9±0.01	1.31±0.02
2	0.91±0.04	1.1±0.2	1.01±0.03	0.31±0.02	0.63±0.02	0.91±0.03
3	0.76±0.01	0.82±0.31	0.83±0.06	0.93±0.02	0.41±0.02	0.69±0.03
4	0.51±0.01	0.61±0.41	0.61±0.04	0.73±0.02	0.41±0.02	0.53±0.02
5	0.31±0.02	0.41±0.02	0.45±0.02	0.51±0.03	0.21±0.02	0.31±0.03
6	-------	------	-----	----	----	----

Fig (1) : A.O.niloticus fish experimentally infected with P. aeroginosa showing erosion of fin and tail with scale lose B. O. niloticus fish experimentally infected with P. anguilliseptica showing erosion of fin and tail with scale lose.

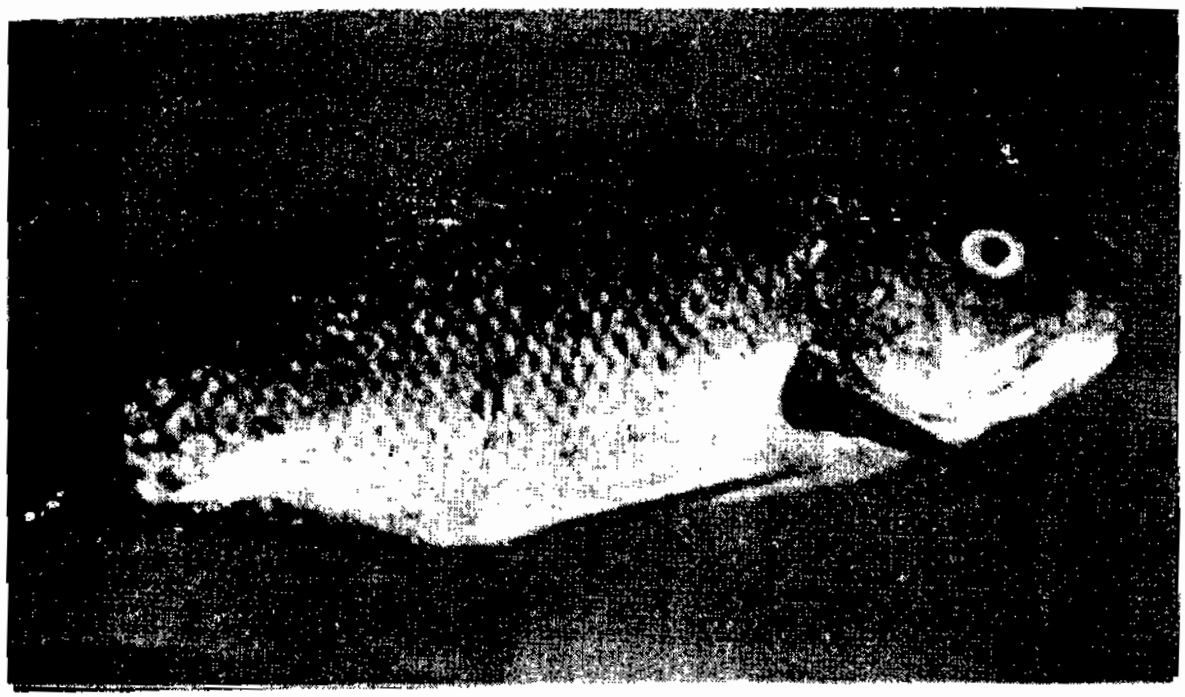

Fig (2) : A.O.niloticus fish experimentally infected with A.hydrophila showing erosion of fin and tail with heamorrage of all body surface.

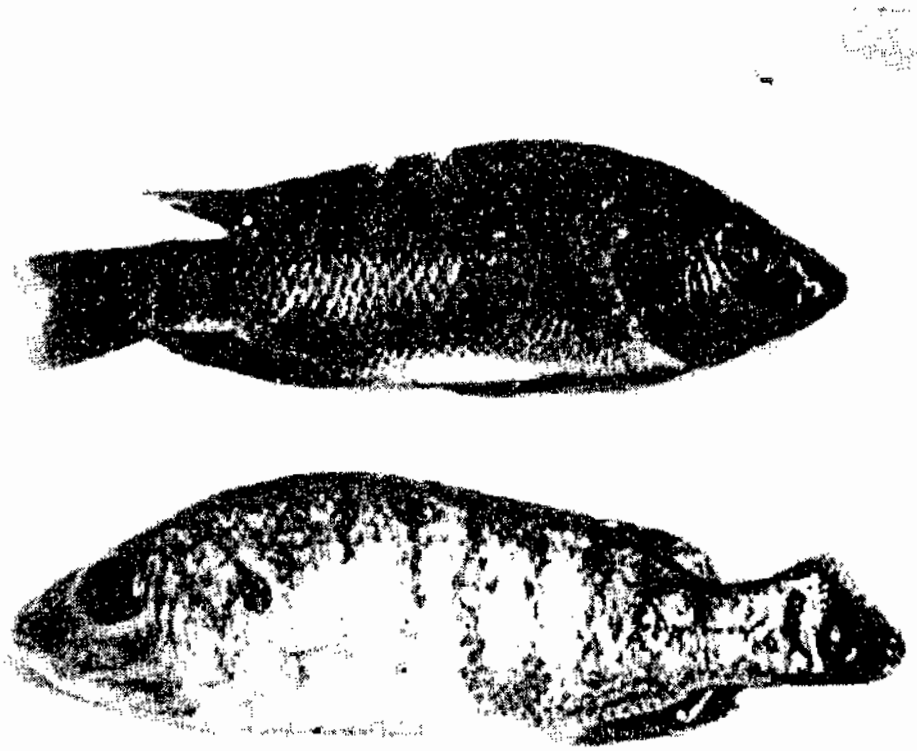

Fig. (3) : A.O.niloticus fish experimentally infected with E. coli showing erosion of tail with dark skin .

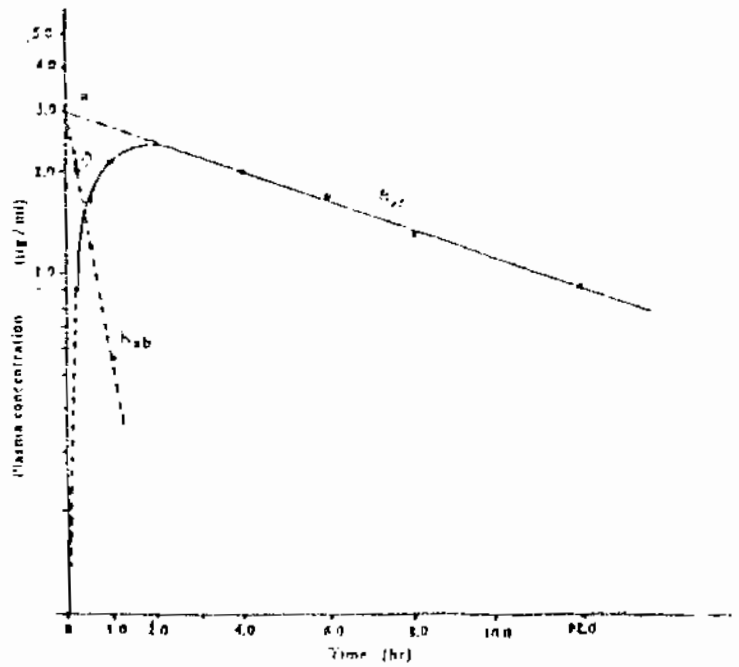

Fig. (4) : Semilogarithmic graph depecting the time concentration course of ciprofloxacin in normal fish.

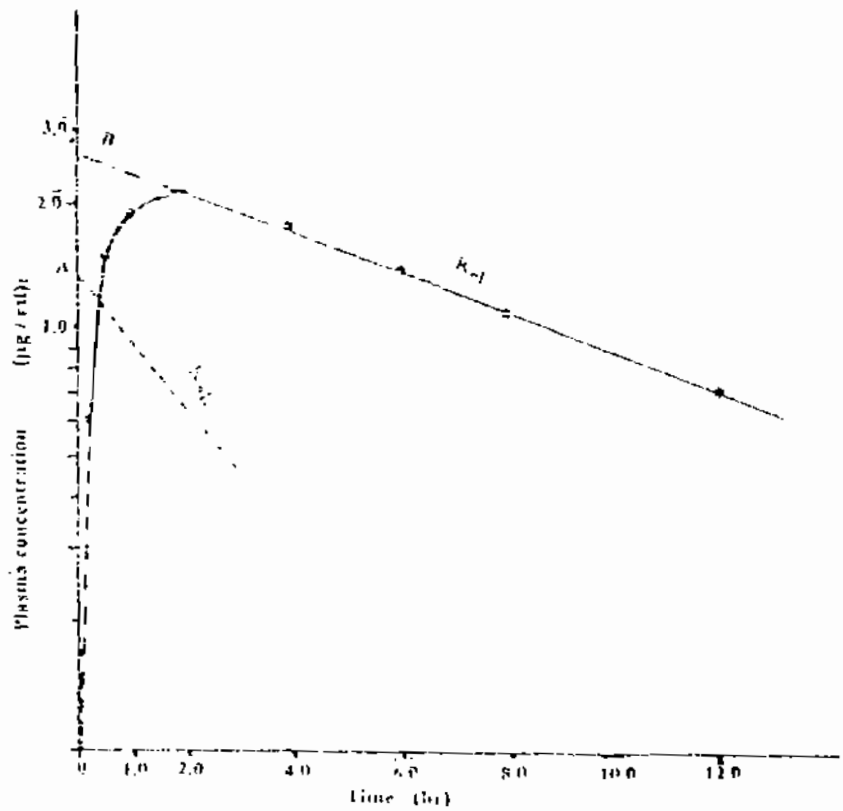

Fig. (5) : Semilogarithmic graph depecting the time concentration course of ciprofloxacin in infected fish .

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الملخص العربى

بعض الدراسات الفارماكولوچية لمضادات حيوية معينة على بعض البكتريا المرضية لأسماك البلطى النيلى

المشتركون فى البحث

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تم دراسة حساسية بعض البكتريا المرضية (الأيرومونس هيدروفيلا - السيدومونس فلورسنس - السيدومونس إنجيليسبتيكم - السيدومونس إيروجينوزا - اللإشيريشيا كولاى) لعدد من المضادات الحيوية حيث ثبت أن هذه البكتريا شديدة الحساسية إلى السبروفلوكساسين والدانوفلوكساسين والسيفازون وإنها مقاومة إلى الأمبسلين والأوبرونين.

تم حقن خمس مجموعات من الأسماك كل مجموعة بعترة بكتيرية من العترات المختبرة وبعد ٢٤ ساعة من الحقن قسمت كل مجموعة إلى مجموعتين حيث تم علاج إحدى المجموعتين بالسبروفلكساسين ٢٠مج لكل كم من وزن السمكة لمدة ثلاثة أيام وقد إنخفضت نسبة النفوق فى هذه المجموعات إلى ١٠٪ فى حالة العدوى بكلا من السيدومونس فلورسنس - السيدومونس إنجيليسبتيكم - السيدومونس إيروجينوزا - اللإشيريا يشيا كولاى) وإلى ٢٠٪ فى حالة العدوى بالأيرومونس هيدروفيلا.

وبدراسة المسار الحركى لعقار السبروفلوكساسين فى أسماك البلطى المصابة بميكروب السيدومونس فلورسنس ومقارنته بمجموع الأسماك الظابطة الغير مصابة لوحظ زيادة سرعة إمتصاص العقار فى الأسماك المصابة عنة فى الأسماك الغير مصابة حيث ارتفع تركيز العقار المستخدم لألى معدل له (٢ر٠٩ ميكروجرام / ملليلترسيرم) خلال ٢ر٢ ساعة فى الأسماك المصابة مقارنة ب (٢ر٧٧ ميكروجرام / ملليلتر سيرم) خلال ١ر٧٧ ساعة فى الأسماك الغير مصابة وقد بلغت فترة نصف العمر لزمن الامتصاص ٦١ر٠ ساعة فى الأسماك المصابة مقارنة ب٤١ر٠ ساعة فى الأسماك الغير مصابة.

وقد أثبتت هذه الدراسة من خلال العمليات الحسابية لمعدلات الإفراز والامتصاص حدوث إنخفاض فى الفترة الزمنية بين الجرعات العلاجية فى الأسماك المصابة عنة فى الأسماك الغير مصابة كما أوضحت الدراسة أن إعطاء العقار موجوداً بأنسجة الجسم لمدة لاتقل عن ثلاثة أيام لذا نوصى عند إستخدام هذا العقار فى علاج الأسماك بعدم إستخدامها فى الاستهلاك الأدمى إلا بعد مرور هذه الفترة.