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Toxopathological Studies on Some Antimicrobial Drugs in Nile Tilapia (*Oreochromis Niloticus*) and Catfish (*Clarias Gariepinus*)

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Abstract

Tissue distribution, residue depletion and side effect of Ciprofloxacine (CIP), Oxytetracycline (OTC) and Sulphadimethoxine (SDM) were evaluated in Nile tilapia (*Oreochromis niloticus*) and catfish (Clarias gariepinus). The activities of Aspartate Amino Transferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (AP), creatinine, blood urea, were estimated. Histopathological examinations were done. Fish of groups 1 were fed a basal diet and those of 2-4 fed a medicated diet containing 1g CIP/Kg, 7.5g OTC /kg and 25mg SDM/kg ration, respectively daily for five successive days. Serum, liver, kidneys and muscles samples were collected at 0, 1st, 3rd, 7th, 14th, and 21st days of treatment. CIP, OTC and SDM concentrations were estimated by ELISA. The peak concentrations of the three drugs in serum were seen at 0 day (5th day of medication); they were (1.91±0.38ug/ml) and (1.78±0.36ug/ml) for CIP, (2.15±0.41ug/ml) and (2.02±0.31ug/ml) for OTC, (3.12±0.32ug/ml) and (2.98±0.46ug/ml) for SDM in Nile tilapia and catfish; respectively. The highest kidney concentrations of CIP were (2.1±0.65ug/g) at 1st day in Nile tilapia and (1.80±0.64ug/g) at 0 day in catfish. SDM was also concentrated in kidney at 0 day post-treatment (44.2±5.1ug/g) and (31.2±4.6ug/g) in Nile tilapia and catfish; respectively. The highest residues of OTC were estimated in liver at 0 day of treatment (6.1±1.21ug/g) and (7.4±1.35ug/g) in Nile tilapia and catfish; respectively. The lowest drug residues were in muscles throughout the entire experiment. CIP didn't detect in muscles at 14th and 21st days post-treatment. Biochemical parameters revealed significant increase in treated groups. The histopathological examination revealed variable pathological alterations in the examined organs depending on the type of antimicrobials. It could conclude the use of antimicrobials in aquaculture should be regulated, although CIP is considered as the safest one, however its use should be limited.

Introduction

Fish consider one of the healthiest food as it is low in fat and rich in protein and omega 3 Fayet-Moore [1] & Yipel [2]. The fish farming industry is rapidly expanding in Egypt, as well as in other countries, it has been associated with recurrent bacterial infectious diseases. Farmed Nile tilapia represents more than 58.45, while catfish production is about 3.08% of the total aquaculture harvest in Egypt Gafrd [3]. Antimicrobial medications are used extensively in aquacultures for prophylactic or therapeutic purposes during microbial infections which may result in environmental pollution, development of resistant bacteria and my induce toxicity to human and animals Aly [4] & Khalil [5]. The availability of adequate data on the pharmacokinetics of antimicrobial agents in farmed fish is very important in order to minimize the environmental impacts of the drugs used in aquaculture. Since the excess amount of drugs can do harm to people, the European Union (EU) and the U.S. Food and Drug Administration (FDA) prescribed a Maximum Residue Limits (MRLs) for these drugs. The EU MRLs of CPX and SDM in fish were established at 100µg/kg Rezk [6] and 6-8µg/kg for quinolens in the edible tissues of fish Victoria [7].

Quinolones are effective antibacterial drugs widely used in human and veterinary medicine because of their potential therapeutic efficacy Plakas [8], Guo [9], Victoria [7] & Koc [10]. Ciprofloxacin is one of the most potent quinolones used to treat infections with gram negative bacteria as Escherichia coli, Pseudomonas aeruginosa, Salmonella spp., Shigella spp. and Haemophilus spp., and is also effective against some gram-positive bacteria such as Staphylococcus aureus Davis [11] & Van Bambeke [12]. Oxytetracycline (OTC) is an antibacterial agent of tetracycline family that is extensively used for treatment of certain bacterial diseases in aquaculture all over the world Ambili [13]. The withdrawal time for edible tissue is differing according to the water temperature and the type of aquatic system Jeffry [14]. Because of the wide spread and long-time use of OTC, many residue studies have been recorded Rigos [15-16] & Julie [17].

Sulfonamides are the oldest antimicrobial agents and still play an important role in aquaculture treatments. Sulfamethazine (SMZ) is the most used antimicrobial drug in Veterinary field. Sulfonamides residues have been repeatedly detected in the aquatic environment Kolpin [18] & Batt [19]. Moreover sulphamethoxazole residues have been reported in shrimp by Wang [20]. Sulfamethoxazole is an effective bacteriostatic against gram positive as well as gram negative bacteria; it affects bacteria by inhibiting folic acid synthesis Baran [21]. Antimicrobial drug residues may be transferred through food-chain to human and induce antibiotic resistance. To our knowledge, however, very few data are available about residues of ciprofloxacin, oxytetracycline and SDM in farmed Nile tilapia (*O. niloticus*) and catfish (*C. gariepinus*) reared under field conditions. However, this study aimed to investigate serum concentration peaks of ciprofloxacin, oxytetracycline and SDM post-treatment and their residues in liver, kidney and muscles together with serum biochemical estimation and histopathological examinations.

Materials and methods:

Animals and diet

Three hundred and sixty fish from each of Nile tilapia (*O. niloticus*), and catfish (*C.gariepinus*) (weight, about 50 and 75g for tilapia and catfish, respectively) were supplied from Central Lab for Aquaculture Research (CLAR), Egypt and used in this experiment that was performed in triplicates, following the Universal Directive on the protection of animals used for scientific purposes. Four different basal diets (control, CIP, oxytetracycline and sulfadimethoxine) were prepared in the form of pellets to use in the study. Basal diets were prepared by grinding the corn to granules using 0.5mm mesh (Thomes-Willey Laboratory Mill Model 4). Ingredients were mixed mechanically by horizontal mixture (Hobarts model D300T) at a low speed for 30 minutes. Oil (vegetable & cod liver) was added gradually to assure the homogeneity of the ingredients, the mixing speed increased for 5 minutes during the addition of water (600ml water) until the mixture began to clump. Pellets were then prepared using a pellet machine (CPM California pellet mill Co.) with 0.5cm diameter, and pellets were left to dry in air for 24 hrs (Table 1).

Table 1: Composition of the basal diet used throughout the experiment.

Ingredients	Diet %
Fish meal	7.85
Soybean meal	52.9
Ground corn	29.1
Wheat flower	5
Vegetable oil	2
Cod liver oil	2
Di-calcium phosphate	1
Mineral mix	0.07
Vitamin mix	0.05
Total	100

Fish with a history of no previous medication, were divided into 4 groups (each of three replicates, 30 fish each) and held in floating cages placed in fish farm ponds and group 1 fed a basal diet while groups 2-4 fed a medicated diet containing 1g CIP, 7.5g OTC and 25mg SDM/kg ration; respectively on a daily bases for five successive days. The temperature was recorded every 12h and adjusted to (26-30°C). The treatment was carried out once daily at 9 a.m. for 5 successive days at a rate of 1 .0% biomass using automatic feeders. Salinity, pH and total hardness were adjusted to, 3±1.1%, 8.21±0.21 and 38.9±1.9mg/L; respectively.

Sampling of the fish

The first sampling day was the 5th day of medication (0 day post treatment), and on the 1st, 3rd, 7th, 14th, and 21st days after the end of treatment with the antimicrobials. At each time of sampling, 15 fish from each group (5fish/replicate) were netted. Fish were anesthetized by immersion in water containing 0.1ppm MS-222 and blood samples were collected. Serum samples and muscle, liver and kidney specimens were collected from all groups. Muscle samples were taken from the dorso-lateral body area just posterior to the operculum. Each specimen was placed in a polyethylene bag and stored at -80°C until they were analyzed. CIP, OTC and SDM concentrations were estimated by ELISA.

Biochemical Studies

The activities of Asparate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (AP), creatinine and urea, were estimated using commercial diagnostic Kits (Human Diagnostics, Germany). Methods were carried out according to the company directions.

Histopathological examinations

Tissues specimens from the muscles, liver and kidneys were collected at 5th day post-treatment and processed routinely according to Drury and Wallington (1980). Sections were

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stained with hematoxylin and eosin (H&E) and examined by light microscope.

Statistical analysis:

Statistical analysis was performed using the one way analysis of variance (ANOVA) followed by Duncan's multiple range test to determine the differences among the six fish groups (mean at significance level of $P<0.05$). All analyses were run on the computer using SAS program Chris Hemedinger [2].

Results

Drug residues

Mean concentrations of the drugs (mean ± SE) vs. time in the serum, liver, kidney and musculature were recorded in (Table 1-3). The peak concentrations of the three drugs in serum were at 0 day. The lowest drug residues were seen in the muscles throughout the entire experiment.

Table 2: Mean concentrations (±S.E) of CIP in *O. niloticus and C. gariepinus* after oral administration of medicated feed (1g CIP/kg ration).

Time post treatment	Serum		Liver		Kidney		Muscle	
	Tilapia µg/ml	Catfish µg/ml	Tilapia (µg /g)	Catfish (µg /g)	Tilapia (µg /g)	Catfish (µg /g)	Tilapia (µg /g)	Catfish (µg /g)
0 day	1.91±0.38	1.78±0.36	1.82±0.59	1.92±0.42	1.98±0.58	1.80±0.64	1.15±0.31	1.28±0.31
1st day	1.81±0.25	1.74±0.31	1..90. ±0.51	1.84±0.34	2.10±0.65	1.74±0.62	0.71±0.11	0.82±0.14
3rd day	0.74±0.18	0.68±0.15	0.89±0.23	0.71±0.21	1.41±0.58	1.24±0.38	0.09±0.03	0.07±0.03
7th day	Nd	Nd	0.17±0.09	0.14±0.08	0.31±0.09	0.24±0.06	0.03±0.01	0.02±0.01
14th day	Nd	Nd	0.08±0.03	0.05±0.02	0.22±0.08	0.16±0.05	Nd	Nd
21st day	Nd	Nd	Nd	Nd	0.12±0.04	0.10±0.03	Nd	Nd

Table 3: Mean concentrations (±S.E) of OTC in *O. niloticus and C. gariepinus* after oral administration of medicated feed (75mg OTC/kg ration).

Time post treatment	Serum		Liver		Kidney		Muscle	
	Tilapia (µg / ml)	Catfish (µg / ml)	Tilapia (µg /g)	Catfish (µg /g)	Tilapia (µg /g)	Catfish (µg /g)	Tilapia (µg /g)	Catfish (µg /g)
0 day	2.15±0.41	2.02±0.31	6.10±1.21	7.40±1.35	3.10±0.45	2.80±1.35	0.94±0.14	0.99±0.16
1st day	0.89±0.21	0.78±0.19	5.01±0.71	6.24±0.72	2.30±0.41	2.12±0.35	0.82±0.10	0.89±0.09
3rd day	0.22±0.05	0.26±0.06	3.48±0.21	4.52±0.41	1.40±0.21	1.21±0.26	0.71±0.06	0.82±0.08
7th day	Nd	0.03 a	1.62±0.15	2.18±0.18	0.52±0.10	0.44±0.11	0.58±0.04	0.64±0.05
14th day	Nd	Nd	0.92±0.08	1.51±0.10	0.12±0.05	0.09±0.04	0.36±0.05	0.38±0.06
21st day	Nd	Nd	0.51±0.07	0.98±0.09	0.08±0.04	0.05±0.02	0.10±0.03	0.14±0.02

Ciprofloxacine: Results obtained after oral dose of 1 g CIP/kg ration for 5 successive days were shown in (Table 2). The highest recorded concentrations of CIP in sera of Nile tilapia and Catfish were (1.91±0.38ug/ml) and (1.78±0.36ug/ml), respectively at 0 day. CIP concentrations were identified all over the experiment in kidneys with the highest concentrations (2.1±0.65ug/g) at 1st day in Nile tilapia and (1.80±0.64ug/g) at 0 day in kidneys in catfish. CIP neither detected in muscles of Nile tilapia nor of Catfish at 14th and 21st days post-treatment while, were not detect in livers of both kinds of fish at 21st days post-treatment.

Oxytetracycline: (Table 3) shows the serum, liver, kidney and muscle concentrations of OTC versus time in Tilapia and Catfish after oral administration of 75mg OTC/kg ration for 5 successive days. Peaks of OTC in serum were (2.15±0.41ug/ml) and (2.02±0.31ug/ml) at 0 day in Nile tilapia and Catfish; respectively while, it was not detect in sera of both fish species after 14th and 21st days but detected only in one Catfish (0.03µg / ml) at 7th day post treatment. The highest tissue residues of OTC were (6.1±1.21ug/g) and (7.4±1.35ug/g) in liver of Nile tilapia and Catfish; respectively at 0 day of the treatment. In Nile tilapia and Catfish the OCT concentrations in kidneys were 0.08±0.04 and 0.05±0.02 (µg /g); respectively at 21st day post treatment. The lowest drug residues were in muscles throughout the entire experiment. OCT concentrations were detected in muscles of Nile tilapia and Catfish at (0.10±0.03ug/g) and (0.14±0.02ug/g); respectively after 21 days post treatment.

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Sulphadimethoxine: (Table 4) showed the mean concentrations of SDM in Nile tilapia and Catfish sera and tissues versus time profile after oral administration of 25mg SDM/kg ration for 5 successive days. The highest serum concentrations of SDM were (3.12±0.32ug/ml) and (2.98±0.46ug/ml) at 0 day in Nile tilapia and Catfish; respectively while it was detected in only one Tilapia fish (0.04µg /ml) at 7th day of treatment and not thereafter was detected. SDM was detected in kidneys of both Tilapia and catfish all over the experiment. SDM highest concentrations in kidney were at 0 day post-treatment (44.2±5.1ug/g) and (31.2±4.6ug/g) in Nile tilapia and Catfish; respectively. At 21st day of treatment; SDM was not detected in muscles and liver of Catfish but detected only in one Tilapia fish (0.11ug/g and 0.03ug/g in liver and muscles; respectively).

Table 4: Mean concentrations (±S.E) of SDM in *O. niloticus and C. gariepinus* after oral administration of medicated feed (25mg SDM/kg ration).

Time post treatment	Serum		Liver		Kidney		Muscle	
	Tilapia (µg /ml)	Catfish (µg /ml)	Tilapia (µg /g)	Catfish (µg /g)	Tilapia (µg /g)	Catfish (µg /g)	Tilapia (µg /g)	Catfish (µg /g)
0 day	3.12±0.32	2.98±0.46	8.95±1.16	6.14±1.01	44.2±5.10	31.2±4.60	2.15±0.32	2.02±0.25
1st day	2.45±0.22	2.07±0.32	6.24±0.94	4.12±0.65	28.2±4.40	21.2±3.10	2.04±0.26	1.92±0.24
3rd day	0.84±0.06	0.42±0.05	3.45±0.46	2.18±0.35	21.4±4.20	16.6±2.60	1.02±0.14	0.91±0.13
7th day	0.04a	Nd	2.14±0.28	1.12±0.19	12.3±2.20	8.8±1.60	0.25±0.06	0.32±0.08
14th day	Nd	Nd	1.08±0.11	0.45 a	5.40±0.62	3.1±0.41	0.08±0.01	0.06±0.01
21st day	Nd	Nd	0.11 a	Nd	2.10±0.04	1.1±0.03	0.03 a	Nd

Biochemical results

(Figure 1,2) represented the biochemical results at 5th day of oral administration of CIP, OTC and SDM in both Nile tilapia and Catfish. ALT was significantly increased in both fish species after 5 days of oral administration of the three drugs compared with control. In Tilapia fish AST was significantly increased after administration of the three tested drugs while, in Catfish AST was significantly increased after administration of OTC and SDM in comparison with control. Creatinine was significantly increased in Nile tilapia with all three drugs but in Catfish it was significantly increased with OTC and SDM whereas not increased with CIP. Urea was significantly increased in Tilapia fish after administration of all drugs except OTC while, in Catfish urea was significantly increased in both OTC and SDM but not significantly changed in case of CIP compared with control.

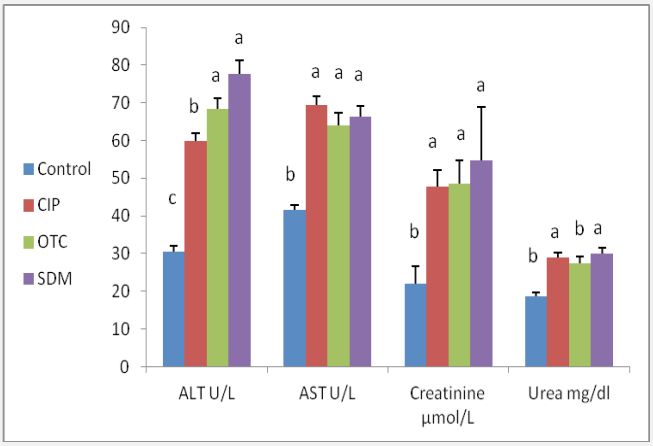

Figure 1: Serum biochemical parameters (mean ± SE) in *Oreochromis niloticus* after 5 days of oral administration of medicated feed (1g CIP, 75mg OTC and 25mg SDM /kg ration). Different alphabetic letters indicate significant difference at (P<0.05)

Histopathological results

The oral administration of 1g CIP/kg ration for 5 successive days in Nile tilapia and Catfish at 5th days post-treatment, revealed minimal histopatholoigical alterations in comparison with the other treated groups. The musculature exhibited hyaline degeneration in few muscle bundles (Figure 3), the liver displayed nuclear pyknosis of some hepatocytes with mild parenchymal

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edema (Figure 4) while the kidneys showed proliferation of melanomachrophage cells and mild tubular nephrosis in the renal epithelium (Figure 5). The oral administration of 75mg OTC/kg ration, for 5 successive days in Tilapia and Catfish at 5th day post-treatment, revealed edema and focal hyaline degeneration in the musculature (Figure 6). Focal proliferation of melanomoacrophage cells was observed in the liver and kidney parenchyma. Wide spread vacuolar degeneration in the hepatocytes (Figure 7) and tubular nephroses in the renal tubular epithelium (Figure 8) were evident.

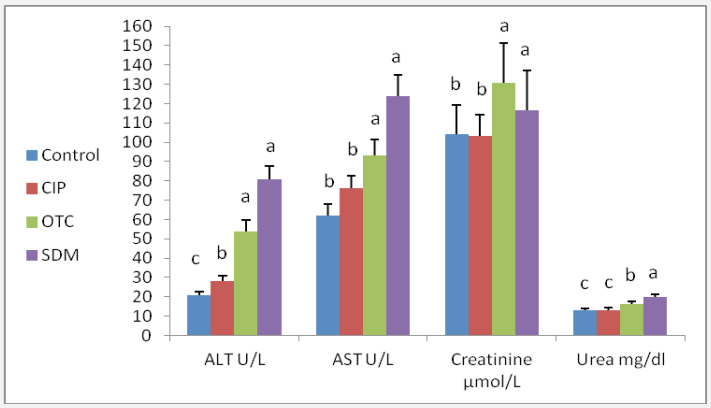

Figure 2: Serum biochemical parameters (mean ± SE) in *Clarias gariepinus* after 5 days of oral administration of medicated feed (1g CIP, 75mg OTC and 25mg SDM/kg ration). Different alphabetic letters indicate significant difference at (P<0.05)

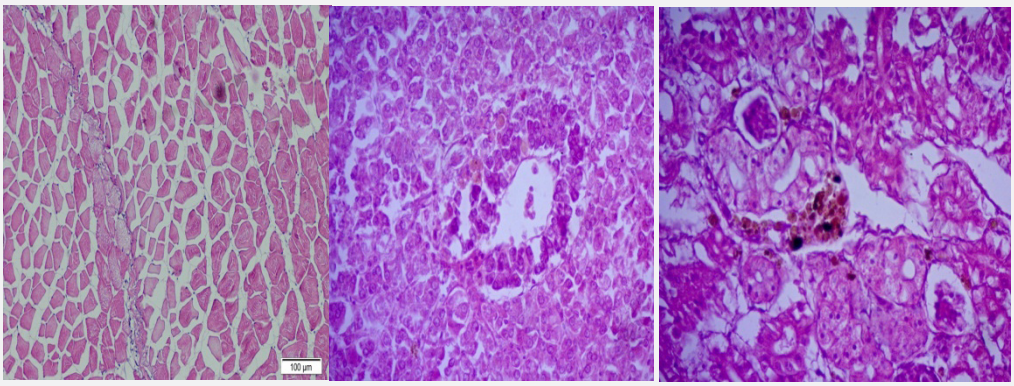

Figure 3-5: Nile tilapia, administered 1g CIP/kg ration for 5 successive days at 5th day pos-treatment, showing hyaline degeneration in few muscle bundles.
Figure 3: Nuclear pyknosis of some hepatocytes with mild parenchymal edema.
Figure 4: Proliferation of melanomachrophage cells with mild tubular nephrosis in the renal epithelium. Figure 5: H&E stain, X 250.

The oral administration of 25mg SDM/kg ration, for 5 successive days in both Nile tilapia and Catfish at 5th days post-treatment, revealed edema and hyaline degeneration as well as focal Zenker's necrosis in the musculature with focal of mononuclear leukocytic infiltration (Figure 9). The liver exhibited wide spread vacuolar degeneration as well as coagulative necrosis in the hepatocytes with some mononuclear cells infiltration and melanomacrophages (Figure 10). The kidney showed tubular nephrosis mainly vacuolar degeneration with few cells exhibited coagulative necrosis, hyaline casts and few mononuclear cells infiltrations were evident (Figure 11).

Discussion:

Using of antimicrobial drugs in aquaculture production is one of the main sources of environmental pollution Pruden [23]; Rico & Van den Brink [24]. During the past years there was increase in the occurrence of antibiotic resistant bacteria and this is of critical implications on public health Gouvêa [25] & Rezk [6]. Quesada [26] & Guidi [27] mentioned that tetracycline, oxytetracycline (tetracyclines), enrofloxacin (quinolones), and sulfadimethoxine (sulfonamide) are most commonly used antibiotics in aquaculture worldwide and the presence of their residues in food could resulted in health hazards and toxic effects. Therefore, understanding the

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depletion of drugs from different tissues of fish is of extreme importance and the drug residues must be assessed in order to determine the time needed before the antimicrobials disappear from the tissues and to judge when the treated fish can be safely consumed. There are limited data about the occurrence of drug-residues in intensive culture of freshwater fishes in Egypt, hence the goal of this study was to estimate tissue distribution and residue depletion after oral administration of CIP, OTC and SDM in Nile tilapia (*O. niloticus*) and catfish (*C. gariepinus*).

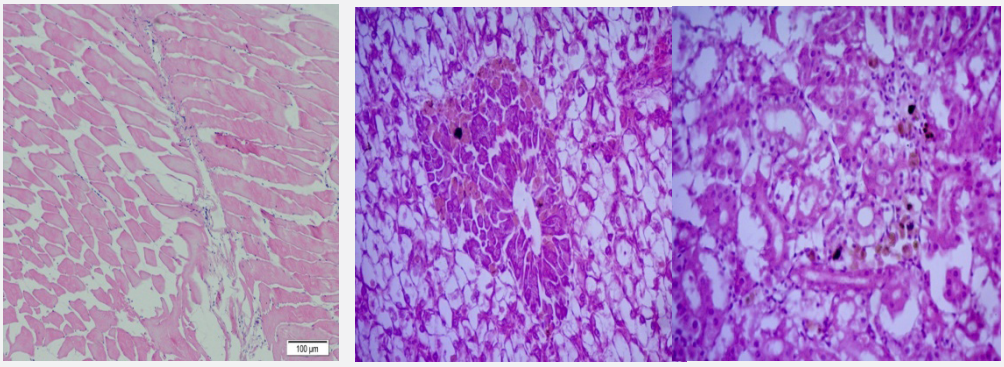

Figure 6-8: Nile tilapia administered 75mg OTC/kg ration for 5 successive days at 5th day post-treatment, showing edema and focal hyaline degeneration in the musculature.
Figure 6: Focal proliferation of melanomoacrophage cells in the liver and kidney parenchyma and wide spread vacuolar degeneration in the hepatocytes.
Figure 7: As well as tubular nephrosis in the renal tubular epithelium.
Figure 8: H&E stain, X 250.

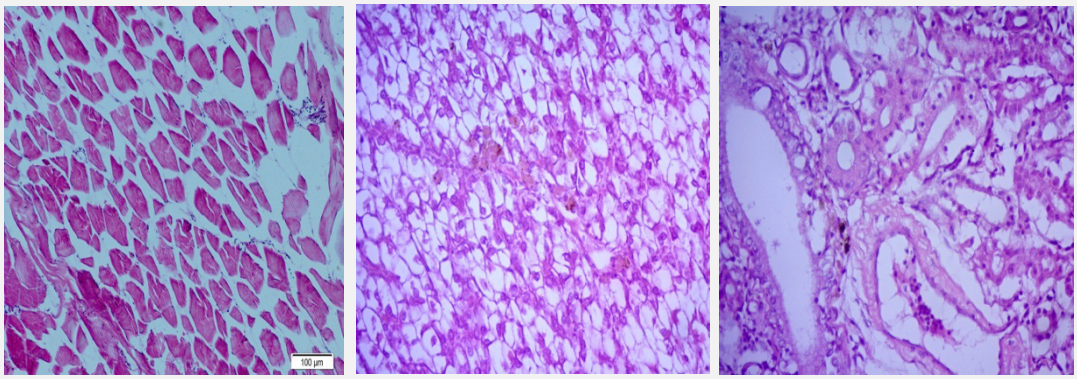

Figure 9-11: Catfish, administered 25mg SDM/kg ration for 5 successive day at 5th day post-treatment, showing mononuclear & melanomacrophage cells with hyaline degeneration & Zenker's necrosis in the musculature.
Figure 9: Wide spread vacuolar degeneration & coagulative necrosis in the hepatocytes.
Figure 10: Tubular nephrosis (vacuolar degeneration & coagulative necrosis) in kidney.
Figure 11: H&E stain, X 250.

The elimination and residues of antimicrobials depend upon dose, duration, fish species, and aquaculture conditions He [28]. Nile tilapia and catfish are kinds of tropical fish and the appropriate temperature for survival is ranging between 24–32°C. The water temperature in this study was 26-30°C and the research was conducted on healthy fish in conditions those are quite close to actual aquaculture. In this study the withdrawal time of CIP from serum in both *O. niloticus* and *C. gariepinus* was almost 7days. Guo [9] concluded that CIP in eels eliminated from plasma for about 298h, after oral gavage of a single dose (10μg / kg). Wu [30] reported that, elimination half life of enrofloxacine and its metabolite ciprofloxacin were 15.61, 16.83, and 17.19h in muscle, liver, and plasma of Tilapia; respectively. Ciprofloxacin concentration was 0.3 and 0.1μg/g in liver and muscle of Chinese mitten-handed crab after single intramuscular injection of 5.0mg enrofloxacin/kg body weight Guanghong [31]. The maximum enrofloxacin concentrations in the muscle, liver and plasma of *O. niloticus* were 3.61μg/g, 5.96μg/g and 1.25μg/ml; respectively after oral dose of enrofloxacine (50mg/kg) for 7 days and the predicted withdrawal time was 22 days Weihai [32]. Withdrawal

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time of CIP from muscle and liver under our experimental conditions was 14 days in both *O. niloticus* and *C. gariepinus*. Enrofloxacin metabolized into ciprofloxacin therefore, extended withdrawal time for enrofloxacin is recommended. Renal CIP concentrations in both *O. niloticus* and *C. gariepinus* were 0.12µg/g and 0.10µg/g; respectively at 21 days post-treatment. The main target organ for CIP metabolism is kidney Ole [33]. Our results showed that, serum OTC concentrations at 0 day post-treatment (5th day of medication) in Nile tilapia and catfish were 2.15 and 2.02µg/mL; respectively. Food and Drug Administration (FDA) regulations specify OTC treatment in finfish culture at 55 to 83mg/kg fish per day for 10 days with a 21-day withdrawal prior introducing for food. After 21 days, OTC concentrations must be below the tolerance of 2ppm (µg/g). The mean peak concentrations of OTC at 0 day post-treatment in fish muscle of *O. niloticus and C. gariepinus* were 0.94 and 0.99µg/g; respectively. Comparable to other studies carried out in farmed fish; Bjorklund & Bylund [34] found peak OTC concentrations of 0.6-1.5ug/g in farmed rainbow trout and salmon. Our study showed that, OCT concentration in muscle was 0.10µg/g and 0.14µg/g in *O. niloticus* and *C. gariepinus* at 21 day post-treatment. Rigos [16] recorded plasma and muscle concentrations of OCT were 0.9±0.2µg/ml and 3.0 ±1.1 µg/g in seabream 150 hours post single intravascular injection (40mg/kg) while, at 24h post-oral dosing (75mg/kg) muscle and liver concentrations of OCT were 0.008 and 6.2±1.8 (µg/g); respectively. Julie [17] observed that OCT concentrations in muscles of adult rainbow trout were below 2ug/g by 21 days after withdrawal of OTC medicated feed for 10 days. Bjorklund & Bylund [34] reported OCT concentration in muscle of rainbow trout (*Salmo gairdneri)* to be below 1ug/g by 14 days after drug withdrawal. Josè [35] concluded OTC concentrations in sea bream muscle were lower than in all the other tissues and declined under 0.1ug/g 20 days after treatment ceased. Meanwhile, Rigos [17] concluded poor intestinal absorption of OCT and that oral administration was unsuccessful in sharp snout sea bream. Reda [36] found that, the OTC residues in *O. niloticus* muscles were 0.05ug/g after a withdrawal period of 15 days when supplemented in diet at 100mg/kg diet for 12 weeks, this level was lower than the MRLs of OTC (0.1ug/g) that established by commission regulations, EU [37]. The differences between these species are likely the result of physiological differences between species and/or differences in experimental design. Hepatic accumulation of OCT in our work was observed in both *O. niloticus* & *C.s gariepinus* (0.51 and 0.98µg/g) 21 day post-treatment, respectively. Hepatic metabolism is the major route for OCT metabolism in different fish species. Rigos [17] and Bjorklund & Bylund [34] recorded OTC hepatic accumulation. Ole [38] recorded the highest average concentrations of SDM in plasma and muscles of Atlantic salmon (14.30µg/ml and 17.72µg/g, respectively) after oral administration in feed for 5 consecutive days as well as the withdrawal time was 288, 300 and 350 hrs in muscle, liver and kidney; respectively. The elimination half-life of SDM from blood of rainbow trout was 24.5 hours after a single oral administration (200mg/kg), at a water temperature of 15°C Kauzauki [39]. Our work showed that, the highest average concentration of SDM in liver, kidney and muscle were 8.95, 44.2 and 2.15µg/g; respectively in Nile tilapia at 0 day post-treatment. The corresponding values in catfish were 6.14, 31.2 and 2.02µg/g; respectively. SDM was not detectible at the 21th day post-treatment in muscle of *C. gariepinus* and detected only in one *O. niloticus.*

The significant increases in the activities of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) act as biomarkers of organ and tissue damage caused by stress, toxicity and drug mediated hepatic damage Kori-Siakpere [40] & Lavanya [41] and this disrupted the cell membranes resulting in extracellular leakage of enzymes. Sanderson [42] declared that biochemical and physiological function of aquatic organisms affected by high drug concentrations in the environment. Fish react to environmental pollutants by changing their metabolic functions in the gills, liver, and kidneys which are the most sensitive tissues Pacheco & Santos [43]. Ambili [13] recorded alterations in AST and ALT activities in gills, liver, and muscle of *Labeo rohita* administered different concentrations (20, 40, 60, 80, 100, and 120mg/L) of OTC for 25 days. Rodrigues reported that OTC exposure caused physiological and biochemical disturbances in rainbow trout. Pyriyadharshiri & Vanithakumari [44] that ciprofloxacin could evokes a mild or high effects on serum liver biomarkers when administered for a short or long duration. Osonwa [45] was administered ciprofloxacin orally to albino mice at doses of 7.14mg/kg, 14.2mg/kg and 21.4mg/kg for fourteen days and recorded an elevation in ALT level at dose 7.14mg/kg ciprofloxacin as well as histological lesions includes mild areas of hepatocellular degeneration and inflammatory cell infiltrates. The observed elevations of AST and ALT activities in the present study indicate the pathological alterations in the liver tissue or to relieve medication-induced stress by raising the rate of metabolism. Serum creatinine, urea and uric acid act as an index of glomerular filtration rate Hernandez & coulson [45] & Reda [36]. The biochemical results were confirmed by the histopathological findings of liver and kidney where variable degenerative changes and focal necrosis were evident based on the type of the antimicrobials administered. The histopathological changes in the muscles, liver and kidneys of experimented fishes were similar to the previous studies where necrosis of renal tissue and tubular epithelial degeneration with hepatocellular vacuolation and fatty degeneration were evident Soler [46], Sovobodova and Gaikowski [47].

Conclusion

The antimicrobial drugs based on dose and type may negatively impact the liver and kidney functions with significant changes in enzymatic parameters and histopathological picture [48-55]. Also, the three tested medications had residues in the liver, kidney

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and muscles of Nile tilapia and catfish, the lowest drug residues were in muscles. CIP is considered as the safest one with the least residues. For the control of fish bacterial diseases, preventive measures should be applied and during urgent need, the selection of correct antimicrobial agent is very important through frequent antimicrobial sensitivity testing. An antimicrobial with minimal residue limit should be selected to protect animal and human health from potential hazards caused by contaminated fish. However, further studies are needed to estimate the toxicity of therapies in the aquatic creatures and environment.

Ethical approval

All the animals were maintained in accordance with the National and International Institutional Guidelines for the Care and Use of Animals for Scientific purposes.

Competing interest

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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