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Drug residue profiles of Cefquinome in the mullet (*Mugil cephalus*) in saltwater at 24 °C.

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ABSTRACT

The present study was performed to estimate the residue concentration of cefquinome in mullets using High-performance thin-layer chromatography (HPTLC). A total of 40 apparently healthy mullets (*Mugil cephalus*) weighing 750±50g were transported alive to 8 glass aquaria. Cefquinone sulfate (Cobactan® 2.5%) was given as a single intramuscular dose of 10 mg/kg body weight. At each sampling point (6, 24, 48-, 72-, 96- and 120 hrs post-medication), serum, muscle, liver, and kidney samples were collected to investigate cefquinome residual concentrations using the HPTLC technique. The maximum concentrations were recorded in the following order: liver > kidney > serum > muscle. Cefquinome concentration in muscles decreased gradually to become under the detection limit (35ng/mL) at 4 days (96 hrs) post-medication. At this time, cefquinome concentrations were still detectable in both the liver and kidney and up to the end of the 5th-day post-medication. Furthermore, the cefquinome withdrawal times were calculated to be 61.7, 105.6, and 90.5 hrs in Mugil's muscles, liver, and kidney respectively. Hence, cefquinome withdrawal time was estimated to be 3 days in mullet's muscles after a single intramuscular dose of 10 mg/kg body weight under 24 C water temperature. If cefquinome will be used therapeutically in broader mullet, 2-3 intramuscular doses of 10 mg/Kg b.wt. with 2.5-day intervals should ensure a sufficient MIC for most of the bacterial pathogens.

INTRODUCTION

Unrestrained use of antibiotics in the aquaculture industry for the production of farm-raised fish and shrimp may lead to concerns with food safety and human health that are typically disregarded in the majority of developing countries of the world. The primary causes of the high residue level are the misuse of antibiotics in aquaculture without veterinary prescription and the absence of food safety controls. As a result, it was necessary to establish veterinary supervision of fish drug use, monitor residue, and educate producers and consumers about food safety (Olatoye *et al.,* 2013).

The emergence of antibiotic-resistant bacteria strains has made it necessary to consistently approve new antibiotics for use in treating fish infections, particularly those caused by Gram-negative bacteria. The fourth generation of cephalosporins, particularly cefquinome, was one of the finest options available. It has a broad therapeutic spectrum and may treat a variety of Gram-negative bacteria, including those that cause significant illnesses in fish such as Aeromonas and Pseudomonas species (Limbert *et al.*, 1991; Maes *et al.*, 2007).

To guarantee that the treated animals are free of potentially dangerous residues, the FDA has also defined safe maximum residual limits (MRLs) for these medications and other veterinary compounds that may reach the human food chain. Cefquinome has received approval in several nations to treat

bacterial infections in a variety of animal species, including cattle, pigs, and pets (Aarestrup *et al.*, 2010; Zonca *et al.*, 2011). The Pharmacokinetic (PK) profile of Cefquinome has been investigated in piglets (Li *et al.*, 2008), sheep (Tohamy, 2011), chickens (Yuan *et al.*, 2011), ducks (Yuan *et al.*, 2011), bovine (Shan *et al.*, 2014). Cefquinome has favorable pharmacokinetic properties, including high bioavailability, and low protein binding, and is mostly excreted unchanged through the kidneys. These properties suggest that it could be useful for treating bacterial infections in fish (Shan *et al.*, 2015).
The current study was carried out to detect cefquinome residual concentrations in the serum and tissues of Mullet, and to estimate the cefquinome withdrawal time in Mullet fish. This may assist in the design of subsequent studies examining the possibility of using cefquinome in fish.

MATERIALS AND METHODS

1. Drug and chemicals:

Cefquinome sulfate injectable suspension (Cobactan® 2.5%) was purchased from Intervet International GmbH-Germany Company. Ammonium acetate (E. Merck, Germany), cefquinome sulfate standard drug (Sigma-Aldrich), acetonitrile (Lobachemie, India). All other used chemicals were HPLC grade with purity of at least 99.9%.

2. Animal

A total of 40 apparently healthy Mugil (*Mugil cephalus*) weighing 750±50 g was reared in 8 well-aerated glass tanks (0.3 m3 each). Tanks were supplied with sand-filtrated marine water obtained from the Mediterranean Sea. The pH was ≈7, and the dissolved oxygen ranged from 6–8 mg/L. The water temperature was maintained at 24 ± 0.5 °C. The fish were acclimated for 7 days prior to the experiment and fed a commercial fish pellet diet till visual satiety.

3. Experimental design

3.1. Fish grouping

Fish were divided into two groups; non-treated (5 fish) and treated (35 fish) groups. Fish of the treated group were injected with a single i.m. cefquinome dose (10 mg/kg.b.w.) at the dorsal muscle (epaxial) using a disposable syringe (Shan *et al*., 2015), while non-treated fish were used cefquinome standard curve after being spiked with known concentrations.

3.2. Sampling

Blood (collected from the caudal vein using non-heparinized syringes to obtain serum) and tissue samples (muscle, liver, and kidney) were collected at different sampling points (6, 24, 48, 72, 96, and 120 hrs post-injection), then stored at -20°C until cefquinome concentrations assessment.

4. Analytical method

Cefquinome concentrations were determined in fish's serum and tissue samples by high-performance thin layer chromatography (HPTLC, CAMAG®, Swiss) system according to a previously separation and detection method HPTLC reported by Shantier *et al.*, 2013. A mobile phase of ammonium acetate pH (6.2): acetonitrile (85:15 v/v) was used. A UV light detector was used to record drug concentrations at 220 nm wavelength. A 20×10 cm HPTLC silica gel 60F254 plate (Merck) was used.

5. Standard preparation

Stock solution containing 500µg cefquinome base/ml (prepared in Milli-Q® ultrapure water) was used to spik blank serum, muscle, liver, and kidney. Working standard solutions containing 50-1000 ng/mL cefquinome were prepared by diluting the stock solutions with blank serum or tissue to the appropriate concentrations.

5.1. Sample application

All samples and standards were applied to the plates by means of CAMAG Linomat 5 with the dosing syringe with a volume of 10-20 µL for samples and 2-5 µL for standards.

5.2. Chromatogram Development

HPTLC plates were developed to a distance of 70 mm in the CAMAG Automatic Developing Chamber ADC 2. The development occurs in two stages using 10 and 25 ml of the mobile phase for preconditioning and development, respectively.

5.3. Detection

The plates were scanned using a CAMAG TLC Scanner 4 with a slit dimension of 60X0.30 mm and multi-wavelength of 220 to 310 nm UV light.

6. Statistical analysis

The arithmetic mean and standard deviation were calculated for all parameters except for half-life values where harmonic mean values and standard deviation were calculated according to Lam *et al*., (1985). For the cefquinome residual study, data were analyzed using one way-ANOVA (Placha *et al*., 2014) followed by Duncan's Multiple Range test Duncan (1955). Differences were considered at significant at $p<0.05$.

RESULTS

1. Standard curves in serum and tissues:

Cefquinome Rf (retention factor) was found to be located between 0.32 and 0.36, and the best absorption wavelength was obtained at 230 nm. Recovery percentages were assessed to be 93.4% in serum, 86.6% in muscle, and 68.1% in liver & kidney samples. All curves showed a linear relationship between 50 to 1000 ng cefquinome/mL with R2 over 0.996. The detection limit was found to be 35 ng cefquinome/ml.

2. Cefquinome Sulfate residues in serum, muscle, liver, and kidney:

Six hours after cefquinome i.m. injection, the highest concentration was observed in the liver compared with serum, muscle, and kidney. Starting from the 2nd till the 5th-day post-injection, the liver, and kidney showed significantly higher concentrations than serum and muscle, out of that, the liver cefquinome concentrations were even significantly higher than those recorded in the kidney.

Cefquinome became under the detection limit (35 ng/mL) in most of the muscle samples on the 4th day and in the most of serum samples on the 5th-day post of administration, while persisted detectable in liver and kidney tissues up to the 5th day post administration as shown in table 1.

Table 1: Serum, muscle, liver, and kidney cefquinome concentrations for 5 days post single intramuscular dose of 10 mg cefquinome /kg body weight

Sampling points (h)	Concentration (µg/ml or g) ppm			
	Serum	Muscle	Liver	Kidney
6	1.19 ± 0.20 ^{b}	1.14 ± 0.08 ^{b}	3.25 ± 0.12 ^{a}	1.09 ± 0.05 ^{b}
24	1.70 ± 0.22 ^{c}	1.43 ± 0.05 ^{c}	10.34 ± 0.64 ^{a}	7.31 ± 0.40 ^{b}
48	0.63 ± 0.09 ^{c}	0.19 ± 0.02 ^{c}	6.19 ± 0.37 ^{a}	1.76 ± 0.10 ^{b}
72	0.13 ± 0.03 ^{c}	0.01 ± 0.01 ^{c}	1.43 ± 0.14 ^{a}	0.85 ± 0.11 ^{b}
96	0.024 ± 0.01 ^{c}	0.00 ± 0.00 ^{c}	1.09 ± 0.10 ^{a}	0.44 ± 0.08 ^{b}
120	0.01 ± 0.01 ^{b}	0.00 ± 0.00 ^{b}	0.47 ± 0.11^{a}	0.07 ± 0.04 ^{b}

Means in the same row carrying different superscript letter are significantly different at $p<0.05$.

3. Withdrawal time calculations:

Based on the administered dose and water temperature, the cefquinome withdrawal times were calculated to be 61.7, 105.6 and 90.5 hrs in mugil's muscles, liver and kidney, respectively (Figure 1). Although, all these values were accurately calculated, only the withdrawal time in muscle is reliable as there is no standard daily consumption of fish's liver or kidney. Hence, the cefquinome MRL can't be considered as a good guide for withdrawal time calculation in their organs.

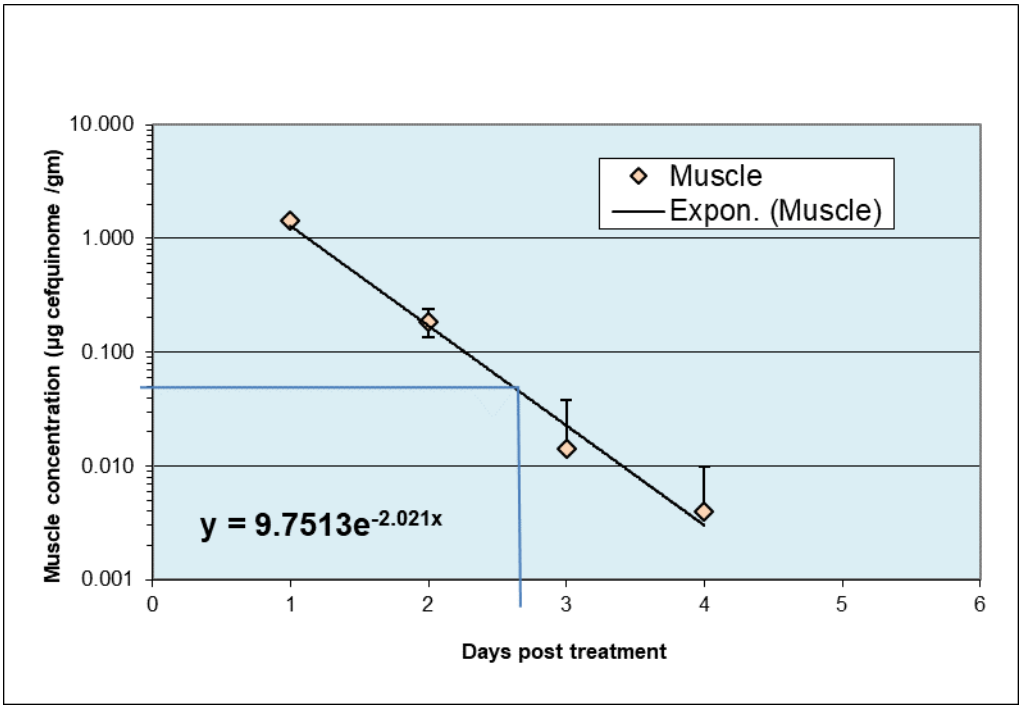

Fig. (1): Cefquinome withdrawal time calculation in muscle estimated by linear regression analysis of the logarithmic-transformed muscle concentrations.

DISCUSSION

To the best of our knowledge, the present study is the first study of cefquinome residues and withdrawal time in mullet fish (*Mugil Cephalus*). The main objective of this study was to measure the drug residues in the blood, muscles, and some organs of the fish, and determination of the withdrawal period of the cefquinome from the body of the fish (until it becomes fit for human consumption) in salt water & warm weathered countries (about 24 °C in the present study).

After a single i.m. injection of 10 mg cefquinome /kg body weight, there was no local or systemic adverse effects have been observed in mullet. This observation agrees with those of **San Martin *et al.*, 1998; Shan *et al.*, 2015** and **2018** who have been reported the absence of adverse effects after oral and parenteral (intraperitoneally & intramuscularly) administrations of cefquinome at doses of 5–20 mg/kg doses in coho salmon, tilapia, and crucian carp.

With the exception of the liver, cefquinome concentrations in serum, muscle & dropped rapidly to became less than 1 µg/ml or g respectively after 2 days of drug administration. While, it tokes 3 and 4 days in the liver, respectively, to became less than 1 µg/g. The maximum concentration of cefquinome in mullet toke place in the following order: liver > kidney > serum > muscle. A similar organotropic pattern was recorded in coho salmon by **San-Martin *et al.*, (1998)**. The serum and tissue concentrations of cefquinome in coho salmon were 2-4 times higher than those measured in mullet fish in our study; not only higher, but also persisted for more

than 14 days in the liver and kidney. This difference between results recorded by **San-Martin *et al.,* (1998)** in coho salmon and in our study was expected and can be attributed to the higher dose (20 mg/kg) and the lower water temperature (10 °C) in the coho salmon experiment.

In the present study, the serum samples had detectable concentrations of cefquinome up to 4 days (96 hrs), and four fish out of 5 were under the limit of detection at 5 days (120 hrs) after the single intramuscular dose of 10 mg cefquinome /kg body weight. This blood concentration profile is in agreement with other researchers' data such as **Aly *et al.,* (2020)** who recorded that the cefquinome blood level decreased gradually and became under the limit of detection (0.01µg/ml) after 120 hours post-medication with a single intramuscular dose of 10 mg/ kg in Nile tilapia fish at 30°C fresh water.

Furthermore, the presented results showed that there was a relatively lower cefquinome concentration in the muscles of the mullet fish that decreased gradually to reach under our detection limit (35 ng/mL) at 4 days (96 hrs) post-medication compared with cefquinome concentration in serum. That result was parallel to that obtained by **Aly *et al.,* (2020)** who recorded that the cefquinome concentrations became 0.02 µg/g muscles at 96 hrs post intramuscular injection of 10 mg cefquinome/kg in tilapia at 30°C. In contrast, muscles concentrations in our study were out half of those obtained by **San-Martin *et al.,* (1998)** who concluded that cefquinome became under the limit of detection (0.015 µg/ml) after 7 days of intramuscular injection of 20 mg cefquinome/kg in salmon fish. Obviously, this difference can be assigned to the species, dose, and water temperature differences, as San-Martin and his co-authors calculated the cefquinome residues in salmon fish at 10 °C while we calculated the cefquinome residues in mugil at 24 °C.

Our result showed that there was a high cefquinome concentration in a healthy mullet's liver which decreased gradually but was still detectable even after 120 hrs post-medication. At that time, cefquinome concentrations were under the detection limit in serum and muscles, and barely in the kidney. That result was parallel to that obtained by **Aly *et al.,* (2020)** who recorded that the cefquinome concentrations persisted detectable in the liver up to 120 hrs post intramuscular injection of cefquinome in tilapia fish. Also, this result agrees with that of **San-Martin *et al.,* (1998)** who recorded that the cefquinome concentrations persisted detectable in the liver up to 14 days post intramuscular injection of cefquinome (20 mg/kg) in salmon fish.

Most researchers who studied antibiotic residues in fish, including **Uno (1996)**, **Wang *et al.,* (2015)**, **San-Martin *et al.,* (1998)**, **and Shiry *et al.,* (2019),** noted that

drug and antibiotic residues typically persist longer in the liver and kidney than in the serum and muscles.

Cefquinome's MIC varies from 0.2 to 2 mg/ml for pathogenic organisms isolated from different animal species, such as Enterobacteriaceae. This concentration is 8 mg/ml or less for Pseudomonas aeruginosa. Staphylococcus aureus 90% were inhibited by 2 mg/ml. MIC values for Haemophilus injuenzae and Streptococcus species range between 0.03-0.06 mg/ml and 0.06 to 1 mg/ml, respectively, making them the most sensitive organisms **(CHIN *et al.*, 1992; MURPHY *et al.*, 1994)**.

Our results suggest that a single dose of 10 mg/kg of cefquinome administered intramuscularly at 24 °C could achieve quite safe concentrations in serum and muscle comparable to those of pathogenic organisms with low MIC values. The same situation does not occur with organisms such as *P. aeruginosa* and some *Enterobacteriaceae*.

The defining of an acceptable MRL, for human consumption, is the central element in the establishment of regulation for drug withdrawal periods in Mugil cephalus **(WHO, 1995)**, which assumes that a person consumes 300 g of muscle and skin from fish each day in their natural proportions **(COMMISSION and THE EUROPEAN COMMUNITIES, 1991)**. Because there is no information in the literature regarding the MRL of cefquinome in this species, the withdrawal time definition in the current study was based on the detection limit of the method (0.015 g/ml) and the time when 99.9% of the drug had been eliminated during the elimination phase **(San Martin *et al.*, 1998).**

In the present investigation, the cefquinome withdrawal times were calculated to be 61.7, 105.6, and 90.5 hours in Mugil's muscles, liver, and kidney respectively. These values are shorter than the result reported in coho salmon by **San Martin *et al.*, (1998)** who estimated the withdrawal times 104.2, 668, and 860.7 hours in muscles, liver, and kidney respectively. This variation between the 2 studies in the estimated withdrawal times could be explained mainly by the variations in the doses and water temperatures besides the difference in fish species used in each investigation.

The calculation of the withdrawal time depends mainly on 2 parameters; the human daily intake (which is 300 g of fish muscle and skin, fixed value for all fishes) and the slope of the regression line of the logarithmic-transformed tissue concentrations. The latter varies depending on some factors; the most important in fish and most poikilothermic species is the water temperatures. In a series of research papers for **Björklun *et al.*, (1990 and 1992)**, the researchers investigated the effect of water temperature on eliminations and withdrawal periods for 2 antibacterial agents in rainbow trout. They reported that the oxytetracycline

withdrawal period in trout muscles was significantly prolonged from 37 days at 16 °C to 92 days at 5 °C water temperature (2.5 times increment). Even more, the oxolinic acid withdrawal period in trout's muscle tissue was extended from 28 days under 16 °C to 140 days at 5 °C water temperature (5 times increment). Temperature-related effects of several antimicrobials' excretion have been extensively studied and endorsed, both *in vivo* & *in vitro* in aquaculture by many researchers such as **Björklund and Bylund (1990)**; **Bowser *et al.*, (1992)**; **Martinsen *et al.*, (1992)**; **Sohlberg *et al.*, (1994)** and **Khalil *et al*., (2016)**.

CONCLUSION

The fish flesh can be consumed safely 4 days post (10mg/kg, IM) cefquinome treatment. Besides, to avoid antimicrobial resistance, the fish liver should not be consumed or used in fishmeal before five days after treatment.

Future studies can be directed toward studying the effect of cooking, processing, and preservation on the residues detected in the tested tissues and their impacts on public health hazards.

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