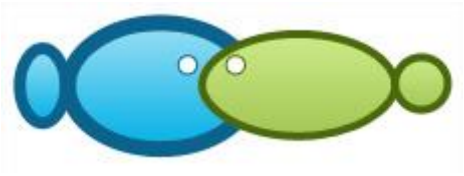

Pharmacokinetics and withdrawal time of amoxicillin in striped catfish (*Pagasianodon hypophthalmus*) after oral administration

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Abstract. Amoxicillin (AMX) has been commonly used to treat bacterial disease in striped catfish (*Pangasianodon hypophthalmus*) aquaculture in Vietnam. The aims of this study were to determine the pharmacokinetics parameters of AMX in striped catfish plasma, kidney and liver, as well as its withdrawal time in striped catfish muscle. AMX levels were determined using high-performance liquid chromatography mass spectrometry. Pharmacokinetics parameters were investigated through oral administration by the gavage method at a single dose of 50 mg AMX kg^{-1} body weight, blood and tissue sampling were done at 0.5, 1, 2, 4, 6, 12, 24, 72 and 96 hours post-administration of AMX. The absorption of AMX followed oral administration was fast, the time to get maximum concentration in plasma (C_{max} = 127.5 ng mL^{-1}) was 1 hour. The maximum concentration of AMX in kidneys was 3 times as high as that in plasma and T_{max} in this organ was the longest at 8 hours compared with 1 hour in plasma and liver. The C_{max} of the investigated organs were in the order of kidney > liver > plasma. The relationship of pharmacokinetics/pharmacodynamics (PK/PD) was estimated based on the curves of AMX concentration of plasma, liver and kidney over the minimum inhibitory concentration (MIC) of AMX, i.e., 135 ng mL^{-1} against *Edwardsiella ictaluri*, it was indicated that the time during which the kidney AMX concentration was above the MIC (T>MIC) was about 10 hours, but it was low in liver at about 1 hour. The withdrawal time of AMX was determined after feeding medicated feed once a day for five consecutive days at the dose of 50 mg AMX kg^{-1} body weight. Fish muscle was collected on day 1 and day 5 during medication and 6, 12, 24 and 72 hours after administration. Based on the maximum residue limit (MRL) of 50 µg kg^{-1} set by the Commission of the European Communities (EU), the withdrawal time of AMX in composite muscle and skin samples of striped catfish was 11 hours (at 30°C) after the last day of medication.
Key Words: *Edwardsiella ictaluri*, gavage method, MRL, PK/PD.

Introduction. Striped catfish (*Pagasianodon hypophthalmus*), mainly cultured in the Mekong Delta, Vietnam, is one of developed sectors in Vietnam with total export production that gradually increased and reached 1.61 million tons and contributed to more than 50% of global striped catfish production in 2023 (VASEP 2022). Along with the increase of striped catfish production and culture area, due to the occurring of diseases antibiotic use become popular in striped catfish farming. The two common diseases are bacillary necrosis of pangasius (BNP) caused by *Edwardsiella ictaluri* and motile *Aeromonas* septicaemia (MAS) caused by *Aeromonas hydrophila* (Crumlish et al 2002; Dung et al 2008b; Rico et al 2013). A survey of Ström et al (2019) showed that antibiotics were used in 69% striped catfish farms in the upper area of Mekong River in Vietnam. Plenty of drugs and chemicals are used in aquaculture for many purposes of operation, such as, pond preparation, water quality treatment, fish health enhancement, and fish disease management (Nguyen & Tran 2021). In striped catfish culture, antibiotics use belong to many groups included beta-lactam, quinolone, tetracycline, phenicol, co-trimoxazole and polymyxin.

As farmers regularly use antibiotics, antimicrobial resistance can develop not only by the bacteria found in cultured fish but also in the surrounding environment. Amoxicillin (AMX) belongs to beta-lactam group. Structure of this antimicrobial class contain a 3-

carbon and 1-nitrogen ring that is highly reactive. They interfere with proteins essential for synthesis of bacterial cell wall, and in the process either kills or inhibits their growth. More succinctly, certain bacterial enzymes termed penicillin-binding protein (PBP) are responsible for cross linking peptide units during synthesis of peptidoglycan. Members of beta-lactam antibiotics can bind themselves to these PBP enzymes, and in the process, they interfere with the synthesis of peptidoglycan resulting to lysis and cell death (Heesemann 1993). The most prominent representatives of the beta-lactam class include penicillins, cephalosporins, monobactams and carbapenems.

Material and Method

Time and location. The experimental setting, residue quantification and data processing were conducted from February 2020 to February 2022. The Pharmacokinetics experiment was firstly performed in the wet lab of College of Aquaculture and Fisheries, Can Tho University. The elimination experiment in practical ponds was then performed in Thoi An, O Mon District, Can Tho City, Vietnam.

Chemicals and equipment. AMX standards and penicillin V (internal standard) were purchased from Dr. Ehrenstorfer (Augsburg, Germany) with a purity above 98%. Amoxi 500 (Vemedim Co Ltd, Vietnam) containing 50% AMX (w/v) was used to prepare medicated feed. Acetonitrile, methanol, and distilled water were purchased from Merck (Darmstadt, Germany). C18 Bondesil powder with a particle size of 40 µm was obtained from Agilent (Santa Clara, CA, USA). A Waters ACQUITY Ultra high-performance LC system (Waters, Milford, MA, USA) with Acquity UPLC CSH C18, 2.1 mm x 50 mm, 1.7 µm column (Waters, Milford, MA, USA) was used in AMX quantification.

Fish. Healthy striped catfish (*Pagasianodon hypophthalmus*) (approximately 100 g fish^{-1}) were purchased from a hatchery in Dong Thap Province, Vietnam. The fish was acclimated in a static aerated 1 m^3 tank (100 fish tank^{-1}) for two weeks before the start of the experiment process. Tap water was used in both acclimation and experiment, the temperature was 30.2±0.5°C. The fish was fed with commercial feed according to fish demand and the remaining feed was removed from tank after feeding. The absence of AMX residues in fish was confirmed with 5 fish by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analysis before the experiment. The fish were starved one day prior to the start of the experiment. Amoxi 500 (Vemedim Co Ltd, Vietnam) containing 50% AMX (w/v) was used in this experiment. The actual concentration of AMX in the product was confirmed by LC-MS/MS. AMX was dissolved in water and mixed with minced feed to obtain the suspension before feeding 3 mL (corresponding to 3% of body weight) via oral gavage to each fish.

Pharmacokinetics experiment. A single oral dose administration of medicated feed was provided by the gavage method to obtain the dose of 50 mg kg^{-1} fish. The applied dose is the common therapeutic dose proposed by producers of commercial products. After drug application via oral gavage, the fish were separately observed for 15 minutes in a clean water tank. The fish were then moved to an aerated 200 L tank at a density of 8 fish per tank, 9 tanks in total corresponding to 9 sampling times. The average water temperature was 30.2±0.5°C. Blood and tissue sampling were done at 0.5, 1, 2, 4, 6, 12, 24, 72 and 96 hours post-administration of AMX. Before sampling, eight fish were rapidly anaesthetized in 4°C ice water. Blood samples of individual fish were centrifuged at 6000 rpm for five minutes to collect plasma. All samples were kept in a -20°C freezer until analysis. The concentrations of AMX in the prepared medicated feed were determined in duplicate by LC-MS/MS analysis. The temperature, pH and dissolved oxygen concentration of the water were monitored using a pH meter (SevenGo, Mettler Toledo, USA) and oxygen meter (SevenGo pro, Mettler Toledo, USA).

Amoxicillin tissue depletion experiment. Striped catfish (~100 g fish^{-1}) were stocked in three ponds with fish biomasses of 8, 14 and 19 tons. The average pond water

temperature was 30.3±1.1°C. The AMX was mixed into commercial pelleted feed following farmers' normal practice (i.e., the AMX was mixed with water and sprayed over the feed and kept for 15 minutes before feeding the fish) at the dose of 50 mg AMX kg^{-1} fish and feed was provided once a day for five consecutive days. Samples of muscle with skin were collected at the rate similar to the tank experiment. On day 1 and day 5 of medication, after one hour of feeding medicated feed, 20 fish were taken from each pond for AMX quantification. After the final dose of medication, sampling was performed at 6, 12, 24 and 72 hours. Fish muscle with skin samples were stored in a freezer at -20°C until analysis. AMX concentrations in striped catfish muscle with skin were analyzed by LC-MS/MS.

Amoxicilline quantification. AMX in striped catfish plasma was extracted and analyzed. Briefly, plasma (0.5 mL) was fortified with penicillin V solution as internal standard (IS), then mixed with acetonitrile (3 mL) and centrifuged at 9,503 *g* for 10 min. The supernatant was collected, dried under N_2 gas, suspended in mobile phase and filtered through a 0.22 µm nylon membrane, and injected onto the LC-MS/MS system.

Kidney, liver and muscle samples were separately homogenized by Ultra Turrax homogenizer (T-25, IKA), extraction method was applied and modified from the description of the United States Department of Agriculture (USDA 2010). Briefly, 3.00 ± 0.1 g of milled sample was placed into a 50 mL centrifuge tube with 60 µL of 1 µg/mL IS, vortexed, and incubated for 15 min at room temperature. After that, 1 mL of phosphate buffer 0.1 M, pH 8.0 was added into the tube which was vortexed for 1 min, then, acetonitrile (20 mL) was added, vortexed for 30 sec and sonification for 15 min in an Elma ultrasonic bath (Elma Hans Schmidbauer, Singen, Germany). Samples were then centrifuged (22R, Andreas Hettich, Tuttlinggen, Germany) at 3,501 *g* for 5 min to collect supernatant, acetonitrile was added to 24 mL final volume, then 8 mL was moved to a 15 mL glass test tube containing 40 mg Bondesil C18, vortexed for 20 min, followed by centrifugation at 3,501 *g* for 4 min. The supernatant was collected into a 10 mL glass test tube. The extract was then evaporated at 40±1°C in a water bath under nitrogen flow. The residues were reconstituted in 1 mL of mobile phase (acetonitrile and methanol (1:1): 0.1% formic acid in water), then filtered through a 0.22 µm nylon membrane filter (Advantec MFS, CA, USA) before injection into LC-MS/MS.

Triple quadrupole mass spectrometry (Xevo™ TQ-S, Waters, Milford, MA, USA) combined with electrospray ionization (ESI) probe operated in the positive ion mode (Waters) and was used for detection and quantification of AMX. The mass spectrometry parameters were optimized, including a capillary voltage, an ion source temperature, a cone gas flow, a desolvation gas flow and desolvation temperature. Argon was used as the collision gas. The following two specific fragmentations transitions (precursor>product ion, *m/z*) were used for quantitation and confirmation (collision energy indicated in brackets): AMX 366.05 > 114,02 and 208,09184.94 (24 eV) and 366.05>208.09 (12 eV); penicillin V (IS) 351.04 > 229.09 (18 eV) and 351.04.1>257.04 (14 eV).

The limits of detection (LOD) and limits of quantification (LOQ) of the analytical methods for AMX were 2.5 and 5 µg kg^{-1} in all matrices, respectively. The working ranges of standard curves built on blank samples for AMX was 5-80 µg kg^{-1}. Extraction recovery ranged between 92% and 99%. Linearity, specificity, precision (repeatability and within-laboratory reproducibility), apparent recovery, decision limit (CC_α) and detection capability (CC_β) were evaluated and validated according to Commission Decision 2002/657/EC (EC 2021), and parameters fell within the acceptance criteria. The validation data are presented by Luy (2017).

Pharmacokinetic analysis and withdrawal time estimation. Plasma and tissue concentration data were analyzed using sparse sampling non-compartmental analysis. The following pharmacokinetic parameters were calculated: maximum concentration (C_{max}), time to maximum concentration (T_{max}) and area under the tissue concentration−time curve from time 0 to 8 hours ($AUC_{0-8\ h}$) which was computed using

the linear up-log down trapezoidal method. All data were processed using Phoenix 8.1 (Certara, Princeton, NJ, USA).

Withdrawal time for AMX treatment was estimated based on the guidelines of the European Medicines Agency (EMA 2022). The concentrations of AMX in muscle with skin were calculated at several interval time points post-treatment and subjected to a linear regression analysis versus time (degree-days) using the statistical program WT1.4. Withdrawal period was determined at the time when the upper one-sided 95% tolerance limit for the residue was below the MRL with 95% confidence.

Results

Pharmacokinetic analysis. The results showed that the amoxicillin (AMX) concentration in plasma reached a maximum concentration at 127.5 ng mL^{-1} in a very short time (T_{max}=1 hour). The area under the $AUC_{0\text{-}8h}$ curve was 375 ng.h mL^{-1}. Other parameters such as absorption constant kα, half-time absorption in fish blood $t_{1/2\alpha}$, volume of distribution Vd, body clearance of Cl, half-elimination constant k_β and time for AMX to be eliminated 50% $t_{1/2\beta}$ cannot be determined according to pharmacokinetic analysis software because the elimination of AMX in striped catfish (*Pagasianodon hypophthalmus*) occurs too quickly. The maximum concentration of AMX in kidney was 3 times as high as that in plasma and the T_{max} was the longest at 8 hours compared with 1 hour in plasma and liver. The C_{max} of three investigated organs were in the order of kidney > liver > plasma (Table 1). After oral administration at the dose of 50 mg AMX kg^{-1} body weight, the T>MIC of AMX in kidney was about 10 hours, but it was low in liver at about 1 hour and for plasma, the AMX concentration was lower than MIC (Figure 1).

Table 1

Values for the main pharmacokinetic parameters of AMX in catfish plasma, liver and kidney tissues after oral administration of 50 mg AMX/kg body weight. Values of C_{max} and $AUC_{0-8\ h}$ are presented as mean ± standard error (SE)

Organs	*Pharmacokinetics parameters*	*Value*
Plasma	C_{max} (ng mL^{-1})	127.5±45.2
	T_{max} (h)	1
	$AUC_{0-8\ h}$ (ng.h mL^{-1})	375.8±58.4
Liver	C_{max} (µg kg^{-1})	183.8±138.2
	T_{max} (h)	1
	$AUC_{0-8\ h}$ (µg.h kg^{-1})	783.3±215.9
Kidney	C_{max} (ng mL^{-1})	372.5±71.2
	T_{max} (h)	8
	$AUC_{0-8\ h}$ (µg.h kg^{-1})	1665.3±243.6

Note: Maximal plasma tissue concentration (C_{max}), time to maximal tissue concentration (T_{max}) and area under the plasma tissue concentration−time curve from time 0 to 8 hours ($AUC_{0-8\ h}$).

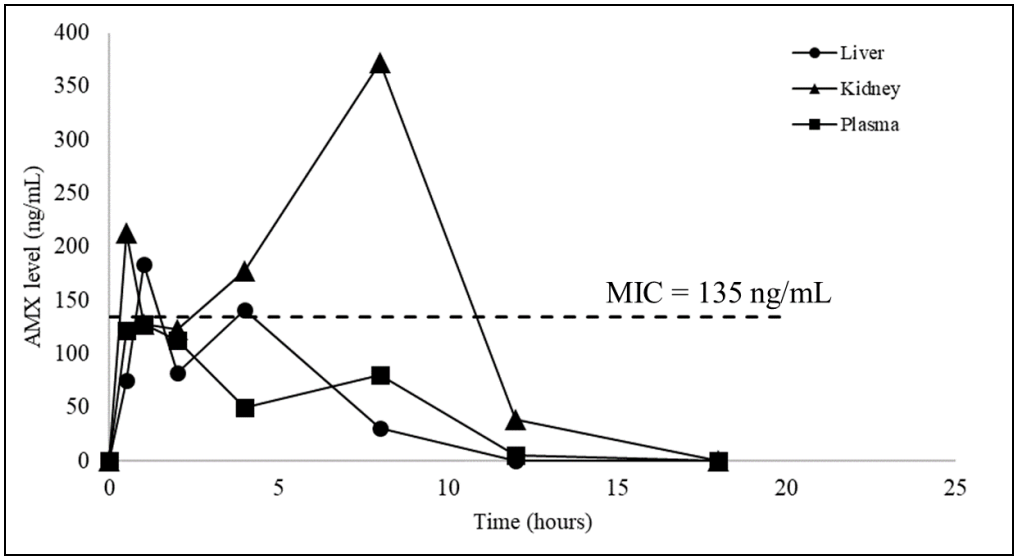

Figure 1. AMX levels in liver, kidney and plasma after oral administration at the dose of 50 mg kg^{-1} fish and the minimum inhibitory concentration of AMX toward *Edwardsiella ictaluri* (MIC reference value from Dung et al 2008a).

Withdrawal time estimation. Results of striped catfish treated in ponds suggest that the withdrawal time of AMX in composite muscle and skin samples was 11 hours (at 30°C) after medication according to the MRL set by the EU (50 µg kg^{-1}) (Figure 2).

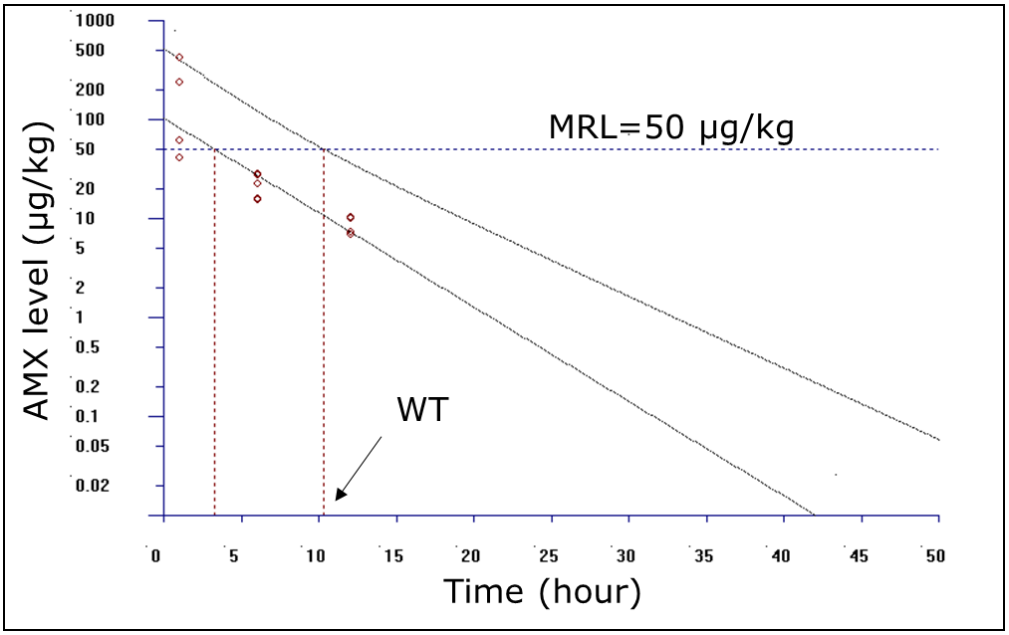

Figure 2. Plot of the withdrawal time (WT) calculation of AMX in composite striped catfish muscle and skin at the time when the one-sided 95% upper tolerance limit is below the MRL for AMX set by the EU (50 µg kg^{-1}) after multiple oral administration of 50 mg kg^{-1} body weight per day for five consecutive days in pond conditions (sampling points of three ponds).

Discussion

Pharmacokinetics of AMX in striped catfish. In striped catfish (*Pagasianodon hypophthalmus*), the absorption of AMX followed by oral administration is fast, i.e. the time to get maximum concentration in plasma (C_{max} = 127.5 ng mL^{-1}) was 1 hour, if compared with other species, i.e., in olive flounder (*Paralichthys olivaceus*) after AMX sodium muscle injection at the dose of 12.5 and 125 mg/kg, the drug showed that the time to reach peak concentration T_{max} was 2.6 hours and 2.2 hours, the highest plasma concentration (C_{max}) was 2.05 µg/mL and 106.76 µg mL^{-1}; elimination half-times are

15.52 hours and 10.42 hours and the area under the curve ($AUC_{0-\infty}$) was 273.69 μg.h mL^{-1} and 2,755.37 μg.h mL^{-1}, respectively (Park et al 2016). In the experiment performed on olive flounder (*Paralichthys olivaceus*) of Lim et al (2017), after muscle injection at the dose of 40 mg kg^{-1}, AMX was absorbed and got the C_{max} of 62.64 μg mL^{-1} with time to peak plasma concentration of 1.59 hours and AUC of 933.23 μg.h mL^{-1}. At a dose of 80 mg kg^{-1} fish, the C_{max} was 87.61 μg mL^{-1}, T_{max}=3.02 hours and AUC=1592.55 μg.h mL^{-1}. The research on Japanese eel (*Anguilla japonica*) after oral dosage of 40 and 80 mg kg^{-1} fish, the pharmacokinetic values were determined C_{max}=3.04-3.4 μg mL^{-1}, T_{max}=2.1-3.6 h, $AUC_{0-\infty}$=464-667 μg.h mL^{-1}; $t_{1/2\alpha}$ and $t_{1/2\beta}$ 0.4-0.6 hours and 88-125 hours respectively, corresponds to a feeding dose of 40 mg kg^{-1} and 80 mg kg^{-1}, respectively (Jeon et al 2010). Beside the concentration of antibiotic in organs, the bioavailability also influents the effectiveness of an antibiotic toward pathogens. Previous studies showed that the bioavailability is varied depending on species and route of medication. In Japanese eel, after calculating with intravenous application, bioavailability was reported as 1.6% (40 mg kg^{-1}) and 1.1% (80 mg kg^{-1}) (Jeon et al 2010). In addition, tested on sea bream (*Sparus aurata*) with a similar dose, AMX concentration measured in plasma was 0.66-0.94 μg mL^{-1} after 72 hours and bioavailability was very low at 0.33% (della Rocca et al 2004). The result of pharmacokinetics in olive flounder (*Paralichthys olivaceus*) also showed low bioavailability at doses of 40 mg kg^{-1} and 80 mg kg^{-1} of 9% and 3.6%, respectively. However, in the muscle injection experiment, the bioavailability was very high with the dose of 30 mg kg^{-1} being 86% and 60 mg kg^{-1} being 53% (Seo et al 2015). Those evident indicated that the pharmacokinetic parameters of AMX applied in fish are not only different from the routes of application but also the fish species. According to Yanong et al (2005), differences in pharmacokinetics depend on different fish species because of physiological and anatomical diversity. These differences between species can lead to different pharmacokinetics for a given drug. Moreover, the pharmacokinetics of AMX in fish is also influenced by temperature (Kim et al 2015). This study found that the distribution of AMX in striped catfish is different from organs and the level of AMX in kidney is higher than in liver and plasma. These results agree with those found in olive flounders (Kim et al 2015).

In addition, after single oral administration, multiple peaking profiles were observed for AMX in all tested tissues concentration-time curves (Figure 1). Similar results have also been reported in turbot (*Scophthalmus maximus*), Atlantic salmon (*Salmo salar*), red pacu (*Piaractus mesopotamicus*), yellowbelly pufferfish (*Takifugu flavidus*), Koi carp (*Cyprinus carpio*), and gibel carp (*Carassius auratus gibelio*), reviewed by Yang et al (2022). This phenomenon is explained by a process called enterohepatic recycling which was speculated to explain multi peaking in gibel carp after oral antibiotic application (Fang et al 2012).

Amoxicillin effectiveness against bacteria in fish. AMX, exhibit their greatest efficacy in a "time-dependent" manner rather than a "concentration-dependent" one and, T>MIC has been reported as the appropriate PK/PD (pharmacokinetics/ pharmacodynamic) index (Akhavan et al 2023). According to AliAbadi and Lees (2000), a dose of treatment should maintain concentrations in excess of MIC at the site of infection for bacteriostatic drugs and bactericidal drugs acting primarily by time-dependent mechanisms for 40% to 50% of the dose interval during the medication period. According Dung et al (2008a), the MIC of AMX toward *Edwardsiella ictaluri* varied from 0.12 to 0.25 μg mL^{-1} upon the collected strains (Figure 1) which showed that after oral administration at 50 mg kg^{-1} body weight the activity of amoxicillin against this bacterium may not be effective, especially in plasma and liver, and the increase of the dose is needed to improve the effectiveness of oral therapeutic in striped catfish in the case of *Edwardsiella ictaluri* treatment. The effectiveness of AMX on bacteria is different depending on pathogens. For example, the minimum inhibitory concentration (MIC) for *Streptococcus iniae* is 0.008-0.06 μg mL^{-1}, for *Streptococcus parauberis* is 0.03-1 μg mL^{-1}, for *Edwardsiella tarda* a higher concentration is required, 0.06-16 μg mL^{-1} (Lim et al 2017; Park et al 2016). Moreover, Park et al (2016) also found the similar result i.e. the MIC of

AMX toward *Streptococcus iniae* and *Streptococcus parauberis* were from 0.0078 μg mL^{-1} to 0.25 μg mL^{-1} and from 0.031 μg mL^{-1} to 0.50 μg mL^{-1}, respecively.

Elimination of AMX from striped catfish muscle. In striped catfish, after 5 days AMX-medication at 50 mg kg^{-1} body weight, the AMX muscle level got highest at 115.5 μg kg^{-1} and then sharply decreased after medication stopped. Based on the MRL of 50 μg kg^{-1} set by the European Union (EU 2009), the withdrawal time of AMX in striped catfish muscle was only 11 hours (at 30.3±1.1°C). The withdrawal times is different from species to species, in olive flounder (*Paralichthys olivaceus*), the retention time in muscle is 12 days based on the established maximum residue level of 0.05 μg g^{-1} for AMX in fish tissue at 23°C (Park et al 2016), and in yellowtail (*Seriola* spp.), the number is 5 days after oral administration (Okocha et al 2018). In this experiment on striped catfish, AMX shows a short withdrawal time, besides being used on a different species, it may be due to the higher temperature in current experiment, 30°C compared with 23°C.

Conclusions. Amoxicillin (AMX) showed quick absorption in striped catfish (*Pagasianodon hypophthalmus*) after oral administration with two peaks phenomenon due to the enterohepatic recycling. After 5-day consecutive medication in practice culture pond, AMX was eliminated quickly with one day of withdrawal time based on 50 μg kg^{-1} MRL. Although AMX can protect fish against several bacterial pathogens, but an increased dose may be needed in the case of *Edwardsiella ictaluri* infection.

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Conflict of interest. The authors declare that there is no conflict of interest.

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