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A survey of six fluoroquinolones in live aquatic product from the regions surrounding the Dongting Lake in Hunan, China

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Abstract

Ultra-performance liquid chromatography (UPLC) was used to detect six fluoroquinolones (FQs) in live aquatic product sampled from the region surrounding the Dongting Lake in Hunan, China. Results showed that 8.3% of samples were contaminated with norfloxacin in the range of 4.5 to 10.3 µg/kg, and 7.3% of samples carried residual ofloxacin in the range of 6.7 to 76.0 µg/kg. One crucian carp sample was pefloxacin-positive, and one blunt snout bream sample was lomefloxacin-positive, and the level in these two samples were 18.3 and 25.1 µg/kg, respectively. Further, 3.1% of samples contained residues of enrofloxacin and (or) ciprofloxacin higher than their maximum residue limits. This survey demonstrated that banned drugs were occasionally used, and that enrofloxacin was occasionally used in excess in aquaculture in the surveyed area.

Introduction

Food safety is a major concern of consumers around the world. Aquatic product are important sources of animal proteins in the human diet, and drug residues are one of the most concerning hazards in aquatic product. China is the largest global producer and trader of aquatic product; however, aquatic product from China have been banned several times due to drug residue issues in past years (Liu *et al.,* 2012; 2015). Dongting Lake, located in the middle south of China, and is surrounded by Hunan and Hubei provinces, is the second largest freshwater lake, and an important aquatic-producing region in China. The produce from this region constitute a large portion of the total aquatic production from China, especially fish such as grass carp (*Ctenopharyngodon idellus*), blunt snout bream (*Megalobrama amblycephala*), crucian carp (*Carassius auratus*), and yellow catfish (*Pseudobagrus fulvidraco*). The issues of drug residues in aquatic product from the regions surrounding Dongting Lake have aroused widespread interest among the researchers. In our previous study (He and Cui, 2016), residues of malachite green and chloramphenicol in live aquatic product from regions surrounding the Dongting Lake were observed. Recently, the contamination level and health risk of 12 antibiotics in eight species of fish and shrimp from the Dongting Lake was assessed by Liu *et al.* (2018b).

Fluoroquinolones (FQs), synthetic antibacterial agents that add fluorine or (and) piperazino moiety to a quinolone backbone, are very effective in combating various pathogens, and have been widely used in agriculture and aquaculture. However, with the adverse effects of these agents towards human health have been clearly demonstrated (Rubinstein, 2001), their application has become limited, and the residues of FQs in foods of animal origins have raised attention worldwide. Several sensitive multi-FQ residue detection methods, such as chromatographic methods and immunoassays, as well as effective sample preparation methods, such as QuEChERS (quick, easy, cheap, effective, rugged, and safe) protocols, have been developed and applied to different food matrices (Zhang and Cheng, 2016). Additionally, studies on the monitoring of FQ residues in foodstuffs, such as bovine milk (Meng *et al.,* 2015), chicken eggs (Cho *et al.,* 2010), and chicken meat and beef (Er *et al.,* 2013) have been widely reported from different regions around the world. However, studies addressing the profiles of FQ residues in aquatic product are still lacking.

Many countries or regions, such as the European Union, Australia, New Zealand, and the USA

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have established corresponding laws to limit the use of FQs in aquaculture and agriculture (Quesada *et al.,* 2013). According to Bulletin No. 2292 of the Ministry of Agriculture of the People's Republic of China (MAPRC, 2015), the use of norfloxacin, ofloxacin, pefloxacin, and lomefloxacin in aquaculture was banned beginning in 2016. Therefore, the presence of any of them at any level is illegal, which means a zero-tolerance policy is in effect for these drugs in fish. According to the standard NY 5071-2002 (Standard of China, 2002) ciprofloxacin is forbidden in pollution-free aquatic product production. Enrofloxacin is permissible in aquaculture, but a maximum residue limit (MRL) has been established by the Chinese government. As ciprofloxacin is the major metabolite of enrofloxacin, the MRL for enrofloxacin has been set as the sum of enrofloxacin and ciprofloxacin, and the limit is 100 μg/kg.

Although strict laws concerning FQs use in aquaculture have been established, illegal use of banned antibiotics or excessive use of approved drugs may occur due to the lack of awareness among aquaculture farmers. In the present work, the residual amounts of six FQs in four aquatic product from the regions surrounding the Dongting Lake in Hunan, China were surveyed to provide critical information to consumers and governments.

Materials and methods

Instruments and chemicals

Instruments

An Acquity H-Class Ultra Performance Liquid Chromatography (UPLC)® system coupled with fluorescence detector from Waters Inc. (USA) was used for FQ analysis. Separation was performed using an Acquity UPLC® BEH C_{18} column (50 mm × 2.1 mm × 1.7 μm) from Waters Inc. (USA). A home kitchen blender (Media Inc. Guandong, China), freezing centrifuge (Themo Fisher Scientific Inc., USA), homogeniser (IKA Inc. Germany), solid phase extraction (SPE) apparatus (Supelco Inc. USA), and pressure blowing concentrator (Organomation Inc. USA) were other key instruments used in the present work.

Chemicals

Organic reagents such as acetonitrile, methyl alcohol, and formic acid were of chromatographic grade, and purchased from Merck Inc. (Germany). Standard FQs (norfloxacin, ofloxacin, ciprofloxacin, pefloxacin, lomefloxacin, and enrofloxacin) were purchased from A ChemTek Inc. (USA). Cleanert® PEP-2 SPE columns (200 mg/6 mL) were purchased from Bonna-Agela Technologies Ltd. (Tianjin, China). All other chemicals, such as phosphoric acid, monopotassium phosphate, citric acid, and ammonium acetate were of analytical grade, and purchased from local company. The water used was ultra-pure grade water prepared using a Labinstru VDUPF-20 ultrapure water system (Beijing, China).

Samples

The survey was conducted in 2017 to analyse six FQs residues in grass carp (*Ctenopharyngodon idellus*), blunt snout bream (*Megalobrama amblycephala*), crucian carp (*Carassius auratus*), and yellow catfish (*Pseudobagrus fulvidraco*). In the middle of each of three months (January, May, and September), eight samples of each fish species were randomly collected from aquafarms or supermarkets, and three fish were included for each sample. A total of 96 samples (8 samples × 4 species × 3 months) were collected in this survey. Afterward, the samples were transported to our laboratory, and a sample of muscle from each fish was cut into small pieces (approximately 0.5 × 0.5 × 0.5 cm). The chopped samples (200 g) were then stored at -20°C prior to residue extraction and analysis in the same month.

FQ extraction and analysis

The procedure used to determine FQ concentration was based on a standard prescribed by the China Entry-Exit Inspection and Quarantine Bureau (Standard of China, 2011), and the methods developed by Zhao *et al.* (2007) and Christodoulou *et al.* (2008) with slight modifications.

Extraction

A thawed sample (5.00 g) was placed in a 50 mL centrifuge tube, and 10 mL phosphate buffer solution (pH = 7) was added. The sample was then homogenised and extracted with ultrasonic-assist for 10 min. The samples were then centrifuged at 8000 *g* at 4°C for 10 min, and the supernatant was then collected. The precipitates were extracted two more times, and the supernatants were pooled for further purification.

Purification

Cleanert® PEP-2 SPE columns were activated using 6 mL of methanol and 6 mL pure water, and the pooled extract was then transferred to the column at a flow rate of 2 to 3 mL/min. Next, 3 mL of a 5% methanol aqueous solution was used to wash the column. Afterwards, 6 mL of methanol was applied to elute the analytes from the column, and the eluents were collected and evaporated to dryness under a flow

of nitrogen at 50°C. The residues after nitrogen blowing were then dissolved in 1 mL of a 0.2% formic acid solution, and then filtered through a 0.22 μm filter (Chrom Tech Inc., Apple Valley, MN, USA) prior to UPLC analysis.

Analysis

A mixture of citric acid-ammonium acetate buffer solution and acetonitrile (93:7, v/v) was used as a mobile phase for FQ analysis. The concentrations of citric acid and ammonium acetate in the buffer solution were 0.05 and 0.1 M, respectively. The flow rate of the mobile phase was 0.42 mL/min, and the column temperature was 50°C. To determine the identity of substances, 0.2 μL of the samples were injected into the UPLC system, and the excitation and emission wavelengths of the fluorescence detector were 278 and 465 nm, respectively.

Quantification

A series of mixed standard sample solutions with concentrations ranging from 10 to 640 ng/mL was prepared and analysed as previously described. Standard curves of each FQ were then developed to calculate the amount of corresponding FQs in each aquatic product sample.

Quality control

In each tested batch of products, a blank sample and a 10 μg/kg spiked sample were analysed as per the procedures previously mentioned together with the actual samples. If the analytical result of the blank sample was undetectable, and the recovery of the spiked sample was higher than 60%, the test results of the actual samples were reported. To eliminate the effect of migration on retention time, a standard sample was analysed after every five samples. Each sample was independently measured three times, and the mean values were reported as the detection results for each sample.

Results and discussion

Performance of the proposed FQ detection method

The six FQs were efficiently separated using the described chromatographic operating conditions, and their retention times ranged from 3 to 10 min, with only 12 min was required for the analysis of each sample. The standard curves of each FQ are listed in Table 1, with the correlation indices (R^2) of each curve being equal to or higher than 0.999, which indicated a strong linear relationship between the respective FQs concentrations and their corresponding chromatographic response within the selected range.

Matrix-matched standard samples of the six FQs were serially 10-fold diluted, and then analysed using UPLC to estimate the sensitivity of this detection method, where concentrations corresponding to S/N = 3 and 10 were defined as the limit of detection (LOD) and limit of quantification (LOQ), respectively. The LODs and LOQs of each FQ are also listed in Table 1. The accuracy of the detection method was estimated by supplemented blank samples in the recovery experiments. The results indicated that the recoveries of each FQ ranged from 63.38 to 90.83%. The intra- and inter-batch reproducibility of this detection method was also evaluated by injecting three replicates of the spiked sample on the same day, and on three different days, respectively. The relative standard deviations (RSD) in intra-day and inter-day experiment ranged from 4.05 to 6.86% and 5.97 to 9.85%, respectively. The performance of the FQ analysis method is summarized in Table 1, the recoveries and RSDs meet the criterions in method GB/T 27404-2008 (Standard of China, 2008) and it indicates the effectiveness and reproducibility of this FQ detection method.

Survey of six FQs in live aquatic product from the regions surrounding the Dongting Lake

The survey results of six FQs in live aquatic product from the regions surrounding the Dongting

Table 1. Performance of the method used for six fluoroquinolones detection in a survey of live aquaculture products.

Fluoroquinolones	Liner range (μg/kg)	LOD[a] (μg/kg)	LOQ[b] (μg/kg)	Recovery[c] (%) Mean ± SD (n = 3)	RSD[d] (%) (n = 3)	
					Intra-day	Inter-day
Norfloxacin	8.0 - 92.0	1.3	5.2	76.79 ± 4.29	4.05	5.97
Ofloxacin	8.0 - 92.0	1.8	7.3	78.55 ± 5.50	5.03	7.01
Ciprofloxacin	8.0 - 92.0	1.2	4.6	63.38 ± 2.02	6.86	9.85
Pefloxacin	2.0 - 32.0	0.5	2.0	66.26 ± 4.40	5.35	6.64
Lomefloxacin	8.0 - 92.0	1.3	5.2	63.69 ± 2.65	6.32	9.68
Enrofloxacin	4.0 - 64.0	0.8	3.0	83.52 ± 8.85	4.93	7.00

[a]Limit of detection, concentrations corresponding to S/N = 3; [b]Limit of quantification, concentrations corresponding to S/N = 10; [c]The spiked level of each fluoroquinolones was 10 μg/kg; [d]Relative standard deviations.

Lake in Hunan, China are summarised in Table 2. Four detection results in the overall survey were higher than the LOD but lower than the corresponding LOQ. As ciprofloxacin is the main metabolite of enrofloxacin, and the MRL value of enrofloxacin established by Chinese government is the sum of ciprofloxacin and enrofloxacin content, the detection result of ciprofloxacin and enrofloxacin contents in aquatic product are summed up in Table 2.

The results indicated that 8.3% of samples (*n* = 8/96) were contaminated with norfloxacin in a content ranging from 4.5 to 10.3 µg/kg. Among these norfloxacin-positive samples, five samples were blunt snout bream, two samples were crucian carp, and one sample was grass carp. Around 7.3% of samples (*n* = 7/96), including one grass carp, two blunt snout bream, two crucian carp, and two yellow catfish carried residues of ofloxacin in the range of 6.7 to 76.0 µg/kg. One crucian carp sample was pefloxacin-positive and one blunt snout bream sample was lomefloxacin-positive, and the residual levels of these two samples were 18.3 and 25.1 µg/kg, respectively. Samples with detectable amounts of ciprofloxacin also had detectable amounts of enrofloxacin. Thus, it could be estimated that the ciprofloxacin was not from direct application, but rather from the metabolism of enrofloxacin. Around 35.4% of samples (*n* = 34/96) had detectable amounts of enrofloxacin and (or) ciprofloxacin, but only three samples, including one grass carp and two crucian carp samples, carried a total of these two drugs higher than the corresponding MRL guidelines from the Chinese government (100 µg/kg). Table 2 further indicates that most of these unacceptable samples were sampled in May, and most or all of these positive samples were sampled from supermarkets. In addition, there were nine samples contaminated with more than one FQ (Table 3), and five (55.6%) of these multi-residue contaminated samples were sampled in May and seven (77.8%) of them were sampled from supermarkets.

This survey demonstrated that these four banned drugs were still occasionally used, and that enrofloxacin was occasionally used in excess in aquaculture in the surveyed area. The contaminated samples mainly sampled in May might have been due to the atmospheric temperature in the survey area being increased during this time period (according to National Meteorological Information Centre of China). This time of the year is more suitable for the growth and propagation of fish pathogenic bacteria than in January or September, when temperatures are too low or too high for optimal bacterial growth, respectively (Ortega *et al.,* 1995). Hence, drugs are more likely widely used in May. The fact that the contaminated samples were mainly sampled from supermarkets illustrates that illegal banned drug application and excessive enrofloxacin utilisation might exist in the circulation process of live aquatic

Table 2. The results of survey of six fluroquinolones in live aquatic product from the regions surrounding the Dongting Lake.

Analysing the survey result from different perspectives		Frequency and level of FQs (µg/kg)					
		Norfloxacin	Ofloxacin	Pefloxacin	Lomefloxacin	Sum of Enrofloxacin and Ciprofloxacin	
						Detectable	Above MRL[c]
Comparing between fish species	grass carp	1/24[a] 10.3[b]	1/24 25.8	0/24 /	0/24 /	5/24 3.3 - 522.6	1/24 522.6
	blunt snout bream	5/24 5.0 - 9.0	2/24 10.0 - 22.4	0/24 /	1/24 25.1	10/24 3.1 - 86.3	0/24 /
	crucian carp	2/24 4.5 - 4.7	2/24 12.5 - 76.0	1/24 18.3	0/24 /	13/24 3.2 - 489.3	2/24 195.2 - 489.3
	yellow catfish	0/24 /	2/24 6.7 - 30.3	0/24 /	0/24 /	6/24 3.7 - 66.8	0/24 /
Comparing between sampling times	January	2/32 4.7 - 6.0	3/32 6.7 - 22.4	0/32 /	1/32 25.1	6/32 3.7 - 92.1	0/32 /
	May	4/32 4.5 - 10.3	4/32 10.0 - 76.0	0/32 /	0/32 /	19/32 3.2 - 522.6	2/32 489.3 - 522.6
	September	2/32 6.2 - 7.2	0/32 /	1/32 18.3	0/32 /	9/32 3.1 - 195.2	1/32 195.2
Comparing between sampling sites	Supermarket	5/48 4.5 - 10.3	5/48 6.7 - 76.0	1/48 18.3	1/48 25.1	21/48 3.2 - 522.6	3/48 195.2 - 522.6
	Aquafarm	3/48 4.7 - 6.2	2/48 10.0 - 12.5	0/48 /	0/48 /	13/48 3.1 - 92.1	0/48 /
Total		8/96 4.5 - 10.3	7/96 6.7 - 76.0	1/96 18.3	1/96 25.1	34/96 3.1 - 522.6	3/96 195.2 - 522.6

[a]The frequency of detectable fluroquinolones is expressed as number of detectable samples/number of tested samples; [b]Level of detectable fluroquinolones is expressed as the concentration (range) of the fluroquinolones in detectable samples; [c]The MRL of sum of enrofloxacin and ciprofloxacin set by Chinese government is 100 µg/kg.

Table 3. Live aquatic product samples contaminated with multiple fluroquinolone residues.

Sample ID[a]	Concentration of fluroquinolones (μg/kg)					
	Norfloxacin	Ofloxacin	Pefloxacin	Lomefloxacin	Ciprofloxacin	Enrofloxacin
Jan-A-2	6.0 ± 0.8[b]	22.4 ± 4.6	ND[c]	25.1 ± 3.1	ND	10.4 ± 1.0
Jan-C-4	ND	6.7 ± 0.7	ND	ND	ND	3.7 ± 0.2
Jan-E-3	ND	12.5 ± 1.3	ND	ND	9.2 ± 1.2	82.8 ± 9.2
May-C-1	ND	25.8 ± 5.2	ND	ND	29.3 ± 2.6	493.2 ± 20.3
May-C-4	ND	30.3 ± 8.7	ND	ND	26.6 ± 1.7	40.2 ± 2.6
May-D-2	9.0 ± 1.1	ND	ND	ND	ND	8.5 ± 0.2
May-D-3	ND	76.0 ± 10.0	ND	ND	119.0 ± 10.3	370.3 ± 15.6
May-F-2	5.0 ± 0.6	10.0 ± 1.0	ND	ND	ND	5.2 ± 0.3
Sep-D-3	ND	ND	18.3 ± 2.9	ND	13.9 ± 0.9	181.3 ± 8.6

[a]In samples ID, "Jan", "May", and "Sep" indicates the sampling time; "A" to "H" indicates the sample sites, in which "A" to "D" were supermarkets and "E" to "H" were aquafarms; "1" to "4" mean grass carp (*Ctenopharyngodon idellus*), blunt snout bream (*Megalobrama amblycephala*), crucian carp (*Carassius auratus*), and yellow catfish (*Pseudobagrus fulvidraco*), respectively; [b]Mean ± SD, n = 3; [c]ND: Nondetectable.

product, such as that used during the transportation process (Berka, 1986). Apart from illegal drugs usage, contaminated aquaculture environments might also cause drug residues in live aquatic product. According to Zhang *et al.* (2017), ciprofloxacin and norfloxacin were detected with high frequencies at concentrations ranged from 9.5 to 18.8 ng/L in the Dongjiang River and Beijiang River, in South China. The residues of antibiotics, such as sulphonamides, tetracyclines, trimethoprim, and quinolone in Dongting Lake have recently been studied by Yang *et al.* (2016) and Liu *et al.* (2018c), and these antibiotics were also detected with certain frequencies at part per trillion to part per billion level. However, the situation of the six FQs analysed in the present work from Dongting Lake has not been reported yet. Hence, further study is needed to reveal the accurate source of the FQ residues in aquatic product that were investigated in the present work.

Table 4 gives a comparison of the survey results between the present work and other published works on the residues of FQs in aquatic product.

Table 4. Comparison of the survey result of the present work with similar studies on fluroquinolone residues in aquatic product.

Reference	Sample information	Detection frequency and concentration range of fluroquinolones (μg/kg)					
		Norfloxacin	Ofloxacin	Pefloxacin	Lomefloxacin	Ciprofloxacin	Enrofloxacin
Tittlemier *et al*. (2007)	Thirty samples collected and prepared as part of the Canadian Total Diet Study	0% /	0% /	NC[a]	NC	0% /	10% 0.3 - 0.73
He *et al*. (2012)	Nine kinds of fish species (45 samples in total) collected from marine aquaculture regions of the Pearl River Delta, China[b]	100% 1.95 - 13.51	NC	NC	NC	20% 1.03 - 2.16	40% 0.65 - 1.71
He *et al*. (2016)	Sixty kinds of cultured fish samples (94 samples in total) from the Pearl River Delta, South China[c]	100% 2.0 - 100.5	NC	NC	NC	54.3% 2.2 - 33.3	63.8% 1.7 - 51.9
Yipel *et al*. (2016)	Three different farmed fish species (96 samples in total) from five cities in Turkey	18.7% 15.0 - 19.8	NC	NC	NC	NC	6.7% 43.0 - 354.0
Wang *et al*. (2017)	Seventy-one aquatic products sampled in Shanghai, China	0% /	11.3% < 15.7[d]	NC	NC	7.0% < 6.9	42.3% < 148.4
Liu *et al*. (2018a)	Fourteen cultured fish species (68 samples in total) from Dalian, a coastal city in the northern China	0% /	8.8% < 2.0	NC	0% /	21% < 31.0	62% < 120.0
Current study	Four kinds of fish species (96 samples in total) from regions surrounding the Dongting Lake in Hunan, China	8.3% 4.5 - 10.3	7.3% 6.7 - 76.0	1.0% 18.3	1.0% 25.1	5.2% 9.2 - 119.0	35.4% 3.1 - 493.2

[a]Not considered in the present work; [b]The residues of fluroquinolones in both muscle and liver were detected, but only data on residues in muscle are listed here; [c]Both freshwater and marine fishes were included, and higher levels of FQ residues were found in freshwater fish rather than in marine fish; [d]Only the maximum concentration was reported.

Overall, it can be concluded that the findings reported in the present work are comparable to those works. The difference in the FQs residue profile in aquatic product from different regions might be due to the difference in drug utilisation and the specific environmental situation of those regions. For example, the detection rate of norfloxacin in fish samples from the Pearl River Delta, China (100%) is significantly higher than the current study, but this might be due to both studies were carried out before 2016, when norfloxacin was still allowed to be used in aquaculture.

Conclusion

In the present work, the residue levels of six FQs in live aquatic products sampled from the region surrounding Dongting Lake in Hunan, China were detected by a verified UPLC method. In total, 8.3% of samples were contaminated with norfloxacin in the range of 4.5 to 10.3 µg/kg, and 7.3% of samples carried residual ofloxacin in the range of 6.7 to 76.0 µg/kg. One crucian carp sample was pefloxacin-positive, and one blunt snout bream sample was lomefloxacin-positive; and the level in these two samples were 18.3 and 25.1 µg/kg, respectively. Further, 3.1% of samples carried sum residues of enrofloxacin and (or) ciprofloxacin higher than the corresponding maximum residue limits. According to these results, banned drugs were occasionally used, and enrofloxacin was used in excess in the surveyed area. Hence, strict strategies must be implemented by the local government to control the usage of these substances and ensure consumers' safety.

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