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RESEARCH PAPER

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Pharmacokinetics and Tissue Residues of Minocycline in Carp (*Cyprinus carpio*) after Oral Administration

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Abstract

The pharmacokinetics and residues elimination of Minocycline(MINO) were studied in healthy carp (*Cyprinus carpio* , 400±30 g) kept at water temperatures of 10 and 25°C. The concentrations of MINO in plasma and tissues were determined using high-performance liquid chromatography (HPLC) using an ultraviolet detector. The plasma concentrations of MINO concentration-time data were fitted using a single-compartment model at 10 and 25°C. The absorption half-life ($t_{1/2ka}$) of MINO was 2.65 h at 10°C and 1.65 hat 25°C, whereas the elimination half-life ($t_{1/2ke}$) was 11.16 h at 10 °C and 16.343.78 h at 25°C; the maximum plasma concentration (C_{max}) and the time-point of maximum plasma concentration (T_p) were calculated as 2.34 µg mL^{-1} and 7.21 h at 10°C, 2.97 µg mL^{-1} and 3.50 h at 25°C. The distribution volume (V_d/F) of MINO was estimated to be 4.09 L kg^{-1} at 10 °C and 2.66 L kg^{-1} at 25 °C; the total body clearance (CL_b) of MINO were computed as 0.25 and 0.49 L/ (h·kg) at 10 and 25°C, respectively; the areas under the concentration-time curve (AUC) was 59.07 µg mL^{-1}h at 10°C and 30.72 µg mL^{-1}h at 25°C. The concentrations of MINO were detected in muscle, skin, liver and kidney. The MINO could still be detected at 5 d time-point after administration at both temperatures in all tissues. The results revealed that the depletion of MINO in carp was slower with a long half-life time, especially at lower water temperature. If fish were administered MINO orally with a single dose (10 mg/kg·bw) for several days, the withdrawal periods of MINO could be not less than 19 d at winter water temperature (10℃) and 8 d at summer water temperature (25℃).

Introduction

Fish farming is now an important industry in china. However, fish disease is becoming a serious problem. The abuse of fishery drugs leads to disposition of residues in the edible parts of treated fish. However, Chinese climate shows significant seasonal variations (Cao *et al*., 2015; Hu *et al*., 2016). Therefore, carrying out the aquatic animal pharmacokinetic studies and residue elimination rules is of great significance for clinical medication consultation, determining withdrawal times for drugs and reducing bacterial drug resistance.

Minocycline (MINO) is one of the strongest antimicrobial activities in tetracycline broad-spectrum antibiotics. Increased penetration of MINO into bacterial cells results in activity against penicillinase-resistant strains of staphylococcus aureus and a variety of other gram-positive and gram-negative organisms (Alfouzan *et al*., 2017). The increased concentration of the drug within the cell, which results in an overall increase in pharmacologic activity, is the primary

advantage of MINO. It often used in the treatment of systemic infection of companion animals in the United States (Ito &Uemura, 2016). At present, MINO has been studied less in veterinary medicine than the other tetracyclines.

Teracyclines have been used in human and veterinary medicine since 1950s and were the first broad-spectrum antibacterial agents to be discovered. In humans, MINO is rapidly and completely absorbed from the gastrointestinal tract, which results in high bioavailability by this route and produces less disturbance of the normal bacterial flora of the gastrointestinal tract. As with other tetracycline, food, milk, and iron decrease the absorption of MINO, but no to as great an extent (Leyden, 1985). Tetracycline antibiotics have been used in aquaculture for treatment of various infectious diseases because of their good antimicrobial activity and relative lack of side effects. Tetracyclines are abroad-spectrum antimicrobial agent used against the most important infectious bacteria in fish (Turk &Oguz, 2016).

Carp (*Cyprinus carpio*) is one of the most important fresh water fish in the world, which is easy to suffer the infectious disease. Chemotherapy is widely used to control bacterial infection. Now HCL-MINO is also gradually used to control fish diseases (Yang *et al*., 2018). So HCL-MINO would have a good prospect of application and market.

Because the use of tetracycline in animal production industries has been increasing over the last decade, what's more, the problems that the abuse of drugs leads to residues in the edible parts of treated fish has become serious (Joseph, Marti, Didelot, Read, & Dean, 2016). In order to guide the use of HCL-MINO for the treatment of fish disease in the farming of carp, information was needed on the pharmacokinetics in carp. The data is only on the pharmacokinetics of HCL-MINO in crucian carp (Yang *et al*., 2018). Nevertheless, no date on carp, especially at different water temperatures. Studies on pharmacokinetics of HCL-MINO were performed in horse, goat and other species. The parameters of pharmacokinetics and residues are alterable in different species, temperature and salinity (Fangke *et al*., 2006; Yanlei *et al*., 2009; Li *et al*., 2012a), so it is not reasonable that these pharmacokinetic data is used directly in carp.

Under these conditions, this study was undertaken to research pharmacokinetics and tissue residues of MINO in carp at 10 and 25°C. The objectives of this study were twofold: (1) to analyze the pharmacokinetics of MINO at two water temperatures, to serve as reference for the dosage regimen; (2) to determine the elimination half-lives of MINO in the tissue of the carp at two water temperatures, to calculate the withdrawal times of the drug in different seasons.

Materials and Methods

Chemicals

All chemical agents used for the analysis were of the high-performance liquid chromatography (HPLC) grade. MINO with a chemical purity of 98.0% (No. 130514-200401) was purchased from Yangguang, Shanghai, China. All other organic solvents were of analytical grade.

Animals

Four hundred disease-free carp (mean body weight, 400±30g) were placed in a tank with a capacity of 20m^3 and were supplied with circulating water. The water quality was tested daily. The pH was approximately (7±0.2) and the oxygen level was approximately (10±0.5) mg L^{-1} due to the inflation pump. The water temperature was adjusted to 10±1°C and 25±1°C by means of a heat bar in two separate seasons. The fish were allowed to acclimate for one week by feeding a drug-free commercial diet. On the day before drug administration, the fish were not fed.

Drug Administration and Sampling

During the study of pharmacokinetics by oral gavages, fish were given a single dose of 10 mg kg^{-1} body weight of an aqueous solution containing MINO. In the residues study, fish were given a multi-dose of 10 mg kg^{-1} body weight for 3 consecutive days by oral gavages. Four hundred carp were divided into two groups of 200 individuals each according to the temperature: one group at 10°C and the other at 25°C. In each group, fish were further divided into two subgroups for the pharmacokinetics and residues studies, respectively. After oral administration in the study of pharmacokinetics, five fish were sampled at each time-point (Table 1), using evacuated syringes containing heparin to prevent clotting. The plasma was stored at -20°C after sampling, until assayed.

For the purpose of the residues study of MINO, tissues such as liver, muscle, kidney and skin were sampled at 4, 8, 12, 24, 48, 60, 72, 96, 120, 144, 168 and 240 hours after the last administration. The tissues of five fish were collected at each sampling. Control samples were collected alternately from the control tanks. All samples were marked and immediately frozen (-20 °C).

Sample Analysis

The HPLC system used was Agilent 1100 series equipment, with a variable wavelength detector (Agilent 1100, G1314-90003). MINO detection was performed at 280 nm. An automatic injection of 20 µL was performed on Agilent TC-C_8 stainless steel column

Table 1. MINO concentrations in plasma at 10 and 25°C following oral administration (n=5)

Time（h）	Mean drug concentration（μg mL^{-1}）±S.D.	
	10°C	25°C
0.25	0.31±0.08	0.41±0.12
0.5	0.43±0.11	0.77±0.18
1	0.87±0.19	1.52±0.21
2	1.24±0.24	2.47±0.39
4	1.86±0.31	3.26±0.43
6	2.34±0.36	2.74±0.38
8	2.97±0.45	2.02±0.35
10	2.41±0.48	1.47±0.29
12	1.94±0.37	0.83±0.18
24	0.85±0.26	0.32±0.11
36	0.56±0.14	0.11±0.07
48	0.24±0.09	0.05±0.02
60	0.17±0.07	ND
72	0.06±0.02	ND

S.D. =standard deviation ND=No Detection

(150×4.6 mm, 5 μm). Thermostatted Column Compartment (Agilent 1100, G1316-90003) was used to maintain the column temperature at 45 °C. The mobile phase consisted of 0.02 mol L^{-1} ammonium acetate solution, dimethyformamide, terahydrofuran (600:398:2, v/v/v), and the flow rate was 1.0mL min^{-1}.

After samples were thawed at room temperature, extraction of MINO in plasma and tissues was carried. A sample of 1 mL plasma was placed in a 15 mL plastic centrifuge tube. 1 mL PBS and 5 mL of ethylacetate used as extractant were added, the mixture was vortexed for 2 min and then centrifuged for 10min at 4000 rpm. The supernatant was removed to a fresh tube and dried at 65 °C under nitrogen. Extraction of MINO in muscle and skin samples was carried out according to the method of plasma analysis with some modification. The homogenate (1.0 g) was transferred to a 15 mL plastic centrifuge tube. The samples were extracted twice using ethylacetate (3 mL) in order to achieve high recovery. Based on the method of muscle and skin, 1.0 g (liver) and 0.5 g (kidney) of homogenate was transferred to a 15 mL plastic centrifuge tube. After adding 5 mL of ethylacetate, the samples were vortexed and treated with hypersound for 5 min. The mixture was then centrifuged for 10min at 4000 rpm and the organic layer was transferred into a clean centrifuge tube. The remaining tissue pellet was extracted for another time using 3 mL of ethylacetate. The extracts were combined and dried at 65 °C under nitrogen. The residue was reconstituted in 200 μL of the mobile phase and then degreased by N-hexane before analysis.

Method Validation

The method was validated for plasma, muscle, skin, liver and kidney tissues. The standard calibration curves were prepared within the concentrations of 0.05, 0.25, 0.5, 1, 2, 5, 10 μg mL^{-1} in plasma and 0.05, 0.1, 0.5, 1, 5, 10, and 20 μg g^{-1} in tissues. Linearity, recovery, intra- and inter-assay precision and accuracy were determined by the standard curve. Recovery was calculated by comparing the peak area of the drugs from processed samples with that from the drugs standard in the mobile phase. Accuracy was determined by comparing the measured concentration to its true value. The variability in the peak area ratios at each concentration was determined as an indicator of the precision. The limit of detection (LOD) of the drugs was defined as the drugs concentration resulting in a peak height three times the signal noise.

Pharmacokinetic and Residue Analysis

Pharmacokinetic analysis was performed by the computer program 3p97 (version 1.0, edited by Chinese Pharmacological Society). Following a single dose of an oral administration, the pharmacokinetic parameters of MINO at 10 and 25°C were both calculated according to the one-compartment open models with first-order rate processes, using the following equation (Jiyue&Xiaocong, 2005):

$$C=M(e^{-ket}-e^{-Ka\,t})$$

Where C is the plasma concentration at any time (t); M is zero time intercepts of the elimination phase; k_e is the elimination rate constant; K_a is the absorption rate constant.

The area under the curve (AUC) was determined according to the following equations:

$$AUC\ (\mu g\ ml^{-1}h) = M\ (1/K_e - 1/K_a)$$

The volume of distribution was calculated from the equation:

$$V_d\ /F = X_0\ /\ (AUCK_e)$$

Total body clearance (CL_b) was calculated using the following equations:

$$CL_b\ (1h^{-1}\ kg^{-1}) = V_dK_e$$

The elimination half-life ($t_{1/2Ke}$) and was determined by the following equation:

$$t_{1/2Ke} = 0.693/K_e$$

In the residues study, the elimination characteristic of the drug from each tissue was estimated according to first-order rate processes using the equation: $C=C_0e^{-kt}$, where C is the tissue concentrations of MINO at time t; C_0 is an extrapolate concentrations of MINO in target tissues after oral administration; *k is* the elimination rate constant. The data were analyzed by the least squares method.

The elimination half-life ($t_{1/2ke}$) was calculated from the equation:

$$t_{1/2ke} = 0.693/k$$

The withdrawal period can be established when the tolerance limit of the concentration of all tissue samples is located below the established maximum residue limit (MRL) (Sternesjo, 2003).

Results

Method Validation

The values of correlation coefficient (r), recovery, accuracy, precision of inter-day and intra-day and LOD of the analytical method for MINO in all tissues and plasma are listed in Table 2.

Pharmacokinetics at Two Water Temperatures

MINOwas recovered in plasma between 0.25 and 72 h after MINO oral administration. Pharmacokinetic parameters of MINO in carp obtained after oral administration with MINO of 10mg kg^{-1} at two water temperatures are shown in Table 3. The maximum plasma concentration (C_{max}) of MINO with 2.34 μg mL^{-1} and 2.97μg mL^{-1} was obtained at 7.21 h and 3.50 h at 10 and 25 °C, respectively. The absorption half-lives ($t_{1/2ka}$) of MINO were calculated to be 2.65 h at 10°C and 1.65 hat 25 °C, whereas the elimination half-lives ($t_{1/2ke}$) were 11.65 h at 10 °C and 3.78 h at 25 °C. The distribution volume (V_d/F) of MINO was estimated to be 4.09 L kg^{-1} at 10 °C and 2.66 L kg^{-1} at 25 °C. The total clearance (CL_b) of MINO was computed as 0.25 and 0.49 L/ (h·kg) at 10 and 25 °C respectively. The area under the concentration-time curve (AUC) of MINO

Table 2. The method validation in plasma, muscle, liver, skin and kidney

Tissue	Recovery (%)	Precision (%)		LOD(μg g^{-1})
		Intra-day	Inter-day	
Plasma	90.54±3.91	＜3.63	＜5.54	0.02
Muscle	81.59±6.73	＜4.84	＜8.65	0.025
Skin	81.58±6.77	＜4.54	＜9.83	0.025
Liver	79.89±6.57	＜4.73	＜7.56	0.02
Kidney	81.85±7.93	＜7.32	＜7.98	0.02

LOD: defined as concentration of drug resulting in a peak height 3 times the signal noise.

Table 3. Pharmacokinetic parameters of MINO following oral administration at 10 and 25℃ (n=5)

		Value	
Parameters	Units	10°C	25°C
A	μg/mL	4.81	9.98
Ke	1/h	0.06	0.18
Ka	1/h	0.26	0.42
$t_{1/2ka}$	h	2.65	1.65
$T_{1/2ke}$	h	11.16	3.78
T_{max}	h	7.21	3.50
C_{max}	μg/mL	2.34	2.97
AUC	μg·h/mL	59.07	30.77
V_d/F	L/kg	4.09	2.66
CL_b	L(h·kg)	0.25	0.49

A: Zero time intercepts of the absorption; Ka: absortion rate constant; Ke: elimination rate constant; $t_{1/2ka}$: absorption half-life of the drug; t1/2Ke: elimination half-life of the drug; V_d/F: extensive apparent volume of the central compartment; AUC: area under curve; CL_b: total body clearance of the drug; T_{max}: the time point of maximum plasma concentration. C_{max}: the maximum plasma concentration.

Table4. The concentrations of MINO in different carp tissues at different temperature (n=5)

Time(h)	Mean MINO concentration (μg mL^{-1})±S.D. in tissue							
	10℃				25℃			
	Muscle	Skin	Liver	Kidney	Muscle	Skin	Liver	Kidney
4	1.64±0.43	1.86±0.47	2.43±0.67	1.76±0.39	4.93±1.31	4.23±1.06	11.31±2.34	6.56±1.24
8	4.17±0.89	1.63±0.41	3.92±0.78	3.14±0.65	3.97±1.13	3.75±0.95	8.24±2.03	4.63±0.98
12	3.62±0.83	3.96±0.79	6.89±1.24	4.98±0.98	3.01±0.84	3.53±0.91	6.72±1.67	4.02±0.85
24	2.96±0.59	3.54±0.76	3.87±0.65	4.07±0.77	1.97±0.54	3.26±0.79	3.35±0.92	3.67±0.82
48	2.19±0.53	3.35±0.67	2.93±0.64	3.36±0.74	1.32±0.31	2.85±0.68	2.54±0.63	2.84±0.67
72	1.52±0.44	2.97±0.68	2.04±0.51	2.15±0.54	0.49±0.14	2.42±0.72	1.73±0.45	1.65±0.41
96	1.21±0.36	2.54±0.53	1.21±0.28	1.32±0.46	0.19±0.06	1.93±0.57	0.83±0.24	0.95±0.32
120	0.83±0.24	2.08±0.47	0.87±0.24	0.95±0.31	0.09±0.03	1.37±0.42	0.48±0.15	0.49±0.14
144	0.47±0.08	1.77±0.43	0.63±0.19	0.71±0.22	ND	0.88±0.28	0.21±0.06	0.25±0.08
168	0.26±0.07	1.36±0.39	0.32±0.08	0.56±0.19	ND	0.43±0.12	0.08±0.03	0.12±0.08
240	ND	ND	ND	ND	ND	ND	ND	ND

S.D. =standard deviation ND=No Detection

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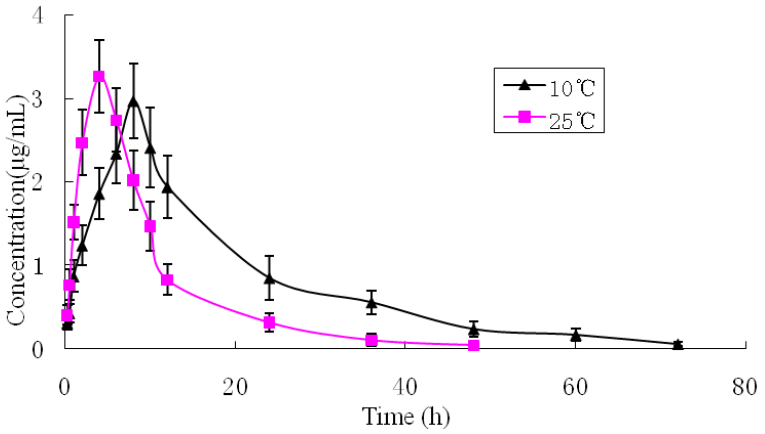

Figure 1.MINO levels in plasma of carp at 10°C and 25°C following a single oral administration (10mg kg^{-1}).

was 59.07 μg mL^{-1}h at 10 °C and 30.77 μg mL^{-1}h at 25 °C, respectively. Plasma concentration of MINO vs. time curve detected in the carp at the two water temperatures is given in Figure 1.

Residues of MINO in Carp at Two Temperatures

MINO concentration in liver, kidney, skin and muscle are listed in Table 4. It was obvious that the $t_{1/2ke}$ at 10°C was longer than that at 25 °C. MINO in all tissues at the lower temperature was higher than that at the higher temperature. At the two water temperatures, MINO was detected in all tissues. In two water temperature groups, the concentration of MINO was found to be higher in skin than that in other tissues after 50h post-administration. However, it decreased rapidly in all tissues after the 12 h post-administration at 10 °C. MINO concentration-time curves at the two water temperatures in all tissues are given in Figure 2.

The MRLs for the tetracycline drugs in the food animals (muscle: 100 μg kg^{-1};skin+fat: 300 μg kg^{-1}; liver: 300 μg kg^{-1}; kidney: 600 μg kg^{-1}) (EEC No. 2377/90) were referred to calculate the withdrawal time (WDT) of MINO in muscle, skin, liver and kidney of carp. Based on the elimination half-life ($t_{1/2Ke}$) and the MRL of MINO, the WDT were calculated using the following equation: $MRL=C_0e^{-k\,(WDT)}$.

The results reveal that the WDT was 7, 7, 19 and 9 days at 10 °C, and 5, 5, 8 and 5 days at 25 °C separately. Comparing with the other tissues, the concentrations of MINO were higher in skin and Kidney after 50h post-administration. But skin is the edible products of most fish; the elimination of MINO in skin was the slowest, which behaved as a reservoir in carp. The WDT of MINO in carp should not be less than 19 days at 10 °C and 8 days at 25 °C when administered orally with a single dosage of 10 mg kg^{-1} body weight.

Discussion

After oral administration, MINO was rapidly absorbed, especially at 25°C. Temperature played an important role in the absorption rate of MINO. The K_a of MINO in carp is more rapidly than that in horse, goat and crucian carp after oral administration (Alfouzan*et al*., 2017; Giguère, Burton, Berghaus, &Haspel, 2017; Yang *et al*., 2018). Nagata (2010) studied the pharmacokinetics of MINO in horse after injected administration (Nagata *et al*., 2010). The results showed that the absorption of MINO in carp is faster, whereas the elimination rate of this drug was lower than that in mammals. The study was performed on healthy fish in a laboratory. The conditions differ from a field situation where a population of sick fish can only be treated by medicated feed. However, the data generated in the present study may be used as a guideline in the field situation to formulated an effective dose regimen and legitimate WDT (Sternesjo, 2003). The analysis of distinction at two water temperature can also serve as a reference to therapeutic needs in different seasons (Fangke *et al*., 2006; Yanlei *et al*., 2009; Li *et al*., 2012a).

A minor difference was observed in the C_{max} between the two water temperature groups. At 10 °C, the C_{max} of MINO was 2.34 μg mL^{-1}, which is slightly lower than that at 25 °C (2.97μg mL^{-1}). At two water temperatures conditions, the drug was all in the form of prototype. Metabolism may not play a major role in the elimination of MINO in animals (Maaland, Guardabassi, &Papich, 2014; Alfouzan *et al*., 2017). With the temperature increasing, the fish of all kinds of activity include the hepatic microsomal enzyme has been raising; basal metabolism is exuberant and it showed that the oxygen consumption rate has been increased. The results of this study indicated that the drug metabolism of fish is influenced significantly by temperature , which was consistent with Li's study (Li *et al*., 2012b). This conclusion had provided the actual guide for clinical treatment in different seasons (Fangke *et al*., 2006; Yanlei *et al*., 2009; Li *et al*., 2012a).

The V_d/F of MINO was 4.09 and 2.66 L kg^{-1} at 10 and 25°C, which indicated a good penetration and a

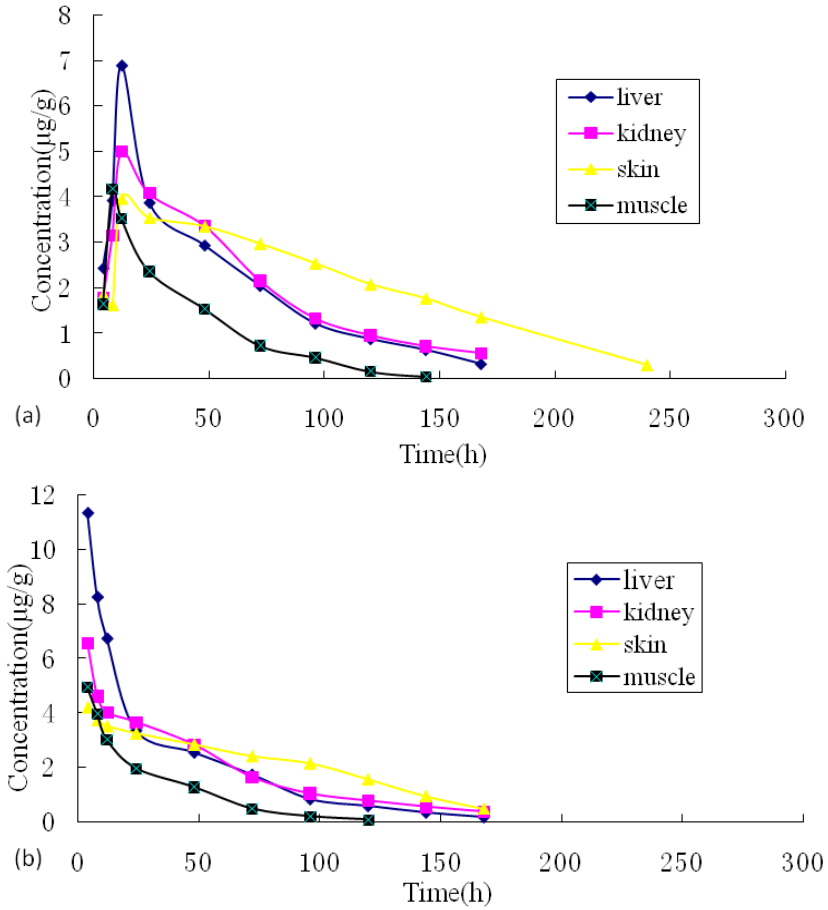

Figure 2. MINO in all tissues of carp after the last dosing at 10°C (a) and at 25°C (b).

widespread distribution in tissues. It was assessed that MINO was well distributed throughout the body. This was in accordance with the values found in other species, such as crucian carp, cats, foals and horse (Tynan, Papich, Kerl, & Cohn, 2016; Giguère, Burton, Berghaus, &Haspel, 2017; Yang *et al*., 2018). Since the bacteria were generally located in the skin and muscle, the distribution characteristic was considered as an advantage of MINO. So MINO in preventing and treating Fish disease would have broad prospect.

The $t_{1/2ke}$ of MINO in carp had significant deviation at two temperatures. The $t_{1/2ke}$ at 10 °C was longer (11.16 h) than that at 25 °C (3.78 h). The fast elimination of the drug at high water temperature may partly due to the high production of bile and urine (Haug& Hals, 2000). The speed of absorption and elimination in the intestine was increased at high water temperature. It was reported that a temperature increment of 1 °C corresponds to a 10% increase in the metabolic and excretory effect of fish (Ellis, Roberts, &Tytler, 1978). The CL_b of MINO was also influenced by water temperature, which was 0.25 and 0.49 L/ (h·kg) at 10 and 25 °C, respectively. It was considered that plasma protein binding may be an important influence on the elimination of MINO (Schulte, 2015; Nation, Theuretzbacher, & Tsuji, 2018). The low clearance could maintain a long therapeutic period of the drug in fish. There was a significant deviation for AUC between the lower and higher water temperature groups. The AUC at 10 °C was about 2 times higher than that at 25 °C. These results was in accordance with the research of difloxacin, marbofloxacin and albendazole sulfoxide in crucian carp (Fangke *et al*., 2006; Yanlei *et al*., 2009; Li *et al*., 2012a) and oxalinic acid in rainbow trout (Coyne *et al*., 2005)

Some studies have been performed with MINO in crucian carp. Tissue distribution studies in crucian carp given a 5mg/kg intravenous dose of MINO showed that the drug penetrated most tissue very well, much like other tetracycline (Yang *et al*., 2018). MINO residues were detected in the tissue of the carp. It was indicated that the $t_{1/2ke}$ of MINO in tissues at 10°C was slower than that at 25 °C ($P<0.01$). This may be caused by slow gastric evacuation in cold water (Amundsen &Klemetsen, 1998). MINO was detected in muscle, skin, liver and kidney. The drug in all tissues eliminated slowly at both water temperatures, which could still be detected at 168 h time-point after oral administration. Comparing with other tissues, the concentration of MINO was highest in skin at this time-point. What's more, skin is the edible products of most fish. The elimination MINO in skin was slowest, which behaved

as a reservoir in carp. The study of the eliminative profiles of MINO in carp showed that elimination of MINO was slow and it was largely affected by the water temperature.

Conclusion

Based on the results of the present study, it can be concluded that temperature over the range of 10 to 25 °C was a significant factor to influence the absorption and distribution of MINO. Likewise, the elimination of the drug in carp was largely influenced by water temperature. To guarantee tissue samples are safe for consumption, it is suggested that the WDT should not be less than 19 and 8 days at 10 and 25 °C seperately when administered orally with a single dosage of 10 mg kg^{-1} body weight.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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