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Pharmacokinetics of Furazolidone in Orange-spotted Grouper, *Epinephelus coioides*

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ABSTRACT

The pharmacokinetics of furazolidone (FZ) was examined in the orange-spotted grouper (*Epinephelus coioides*) after intravascular, oral and bath administration. FZ contents in blood and tissues were determined by high performance liquid chromatography. The recoveries of the analytical method applied were 102, 102, 94 and 94% for serum, muscle, liver and kidney, respectively. A two-compartment pharmacokinetic model was found in serum through the mean concentrations of FZ, exhibiting a rapid, biphasic decline after an intravascular dose of 0.1 mg/kg at 23°C. The absorption and elimination half-lives of FZ in serum were 0.2 and 3.3 h, respectively. A one-compartment model could be observed from the serum concentration of FZ after an oral dose at 50 mg/kg; the elimination half-lives were found 1.4 and 0.8 h at 23 and 30°C, respectively. During a 24-hour bath period, variable temperatures gave significant effects on rate of absorption and elimination of FZ, while different doses showed different peak concentrations and integrated areas under the concentration-time curve. The bioavailabilities of FZ in the oral and bath applications were 0.4 and 26.4%, respectively. FZ was found mainly distributed in the serum and muscle, rather than in the liver or kidney.

***Key words**: Furazolidone, Pharmacokinetics, Grouper.*

INTRODUCTION

Furazolidone (FZ), a nitrofuran drug, is a highly effective synthetic antimicrobial compound widely used as a prophylactic or therapeutic agent in domesticated terrestrial and aquatic animals. FZ is effective in treating bacterial infections, especially vibriosis, through oral or bath applications in aquatic animals (Guo *et al*., 2003a). Because of its mutagenic and carcinogenic activities (Bryan 1978), the vast utilization of FZ in aquaculture has become a public health concern. The use of nitrofuran antimicrobials in food-production has been prohibited within the European Union (EU) and United States (US) since no safe levels for human health can be set.

Marine aquaculture, which accounts for about 49% in quantity of the total aquaculture production in year 2006, is an important industry in Taiwan. Among the fish species being cultured, grouper has a high market value, and shares 15% of the total yield of marine aquaculture (Fisheries Administration 2006). Aquaculture industry of grouper, like those of many other cultured species, has been facing heavy losses from various disease problems caused by virus, bacteria and parasites, especially from vibriosis (Wong and Leong 1990, Lee 1995). Antibiotics commonly used to avoid the adverse effect of pathogens in aquaculture are FZ, chloramphenicol, streptomycin,

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erythromycin, kanamycin, oxytetracyclin, neomycin, and oxolinic acid (Benbroock, 2002).

Drug pharmacokinetics is essential in understanding the absorption, distribution and elimination of antibacterial drugs in fish. It also provides information on the possible marker residues and target tissues. In this study, the pharmacokinetics of FZ was determined in the orange-spotted grouper, *Epinephelus coioides*, which were subjected to intravascular, oral and bath treatment of the drug. Our main focuses were the absorption, distribution, elimination, and bioavailability of FZ. The temperature and dose effects on these parameters were also determined.

MATERIALS AND METHODS

Chemicals

FZ and tricaine methanesulphonate (MS-222) were obtained from Sigma (St Louis, MO, USA). Unless otherwise indicated, chemicals used were analytical or HPLC grade.

Fish

Orange-spotted grouper, mean body weight 654 ± 67 g, were obtained from a fish farm in southern Taiwan. The fish were acclimated for two weeks in cages in 40 m × 15 m × 1.5 m pond with running water of 30 ppt salinity and pH 7.9. The experiments were performed at water temperatures of 23 ± 2°C and 30 ± 2°C. The fish were fed on sand borer (*Sillago sihama*) two times a day. The fish were starved for 1 day before FZ application.

Dosing and sampling

The study was conducted at the Tung-kang Marine Laboratory of the Taiwan Fisheries Research Institute. Intravascular dosing solutions were prepared by dissolving FZ in saline to yield a final concentration of 40 µg/ml. Dosing solutions were injected as a single bolus into the caudal vein at a dose of 0.1 mg/kg of body weight at water temperature of 23°C. Three fish were sampled at different time intervals after administration.

Oral doses of FZ were administered in feed mixture at a dose of 50 mg/kg body weight in separate experiments at water temperatures of 23 and 30°C. Before drug administration, the fish were anaesthetized in well-aerated water containing 200 mg/l MS-222 for 2-3 min and then weighed. FZ was mixed with a commercial soft eel feed, which was force-fed orally to the fish. Four fish were sampled for analysis before drug administration and at different intervals after administration.

For bath treatment, the fish were exposed in FZ solution at a concentration of 10 or 20 ppm in 500-liter FRP tank at water temperatures of 23 and 30°C. After 24 hours, the fish were transferred to fresh seawater. Three fish were sampled at different intervals during bathing and post-dosing periods. Blood of each fish sample was drawn from the caudal vein. The liver, kidney and muscle tissues were also collected separately. The blood was allowed to clot, and centrifuged at 3000 rpm at 4°C for 20 min. The serum, liver, kidney and muscle were stored at -80°C until analyzed.

Extraction and analysis

FZ concentrations in serum, muscle, liver and kidney were determined by a reversed-phase high performance liquid chromatography (HPLC) with UV detector. Muscle (5 g), liver (5 g) and kidney (2 g) samples were homogenized for 2 min in 30 ml of cold ethyl acetate using Bio-mixer (Nihonseiki Kaisha, Japan). After centrifugation at 3000 rpm for 5 min, the supernatant was filtered through an anhydrous sodium sulfate layer. The filtrate was then evaporated to dryness at 37°C under vacuum. To remove fat from muscle, liver and kidney extracts, the residue of each sample was re-dissolved in the 30 ml of acetonitrile and extracted with 40 ml of n-hexane. The acetonitrile layer was then separated from n-hexane by a separatory

funnel and was evaporated to dryness at 37°C under vacuum. The residues of acetonitrile extract of muscle, liver and kidney tissues were again re-dissolved in 0.8 ml acetonitrile-water mixture (25:75), and then filtered through a 0.2 μm membrane prior to HPLC analysis. The serum samples, 1.25 ml each, were agitated in 30 ml of cold acetonitrile for FZ extraction. The acetonitrile extracts were then filtered, defatted and analyzed according to the above method applied for tissue samples.

The HPLC system consists of a Waters 600 controller, a Waters 717 Plus autosampler and a Waters 996 photodiode array (PDA) detector with the Millennium software (Waters Corp., USA) for data processing and output. A reversed-phase 4 μm Nova-Pak C18 column, 3.9 mm × 30 cm, was used with a 4 μm Nova-Pak C_{18} guard column (Waters Corp., USA) attached ahead. The mobile phase was an acetonitrile-water solution (25:75) at flow rate of 0.8 ml/min. The wavelength of PDA detector was set at the range from 200 to 400 nm. The sample volume for injection was 20 μl.

Pharmacokinetics

The computer program PCNONLIN (Scientific Consulting, Inc., North Carolina, USA) was used to derive pharmacokinetic values describing serum concentration of FZ after dosing. The one- and two-compartment pharmacokinetic models best described mean serum concentrations of FZ after oral and intravascular dosing, respectively. The area under the concentration-time curve (AUC), from the moment of drug administration to the moment where the last sample was taken, was calculated from the actual serum data, using the trapezoidal rule. An estimate of the bioavailability was made by comparing the AUC of the oral dose (or bathing concentration) with the AUC of the intravascular administration, both divided by the drug dose.

RESULTS

Chromatography

With the on-line PDA detector of HPLC, the maximum absorption at 259 and 367 nm of FZ in mobile phase were used for the qualitative and quantitative identification. FZ was determined at a retention time around 6.7 min in HPLC and a linear range of responses from 0.025 to 10 μg/ml with a good correlation (r^2 = 0.99999) between sample concentrations and peak areas. By spiking the tissue samples with authentic FZ through the established extraction method and analysis, mean recoveries of FZ were found to be 101.6 ± 3.8% for serum, 101.6 ± 4.2% for muscle, 94.2 ± 2.4% for liver and 93.9 ± 2.4% for kidney samples (Table 1). Detection limits of FZ in the established analysis of this research were also determined as 16 ng/ml, 4 ng/g, 4 ng/g and 10 ng/g in samples of serum, muscle, liver and kidney, respectively.

Table 1. Recovery of furazolidone from the spiked tissues[a] of the orange-spotted grouper using the extraction and analysis method described in the text.

Tissues	Recovery (%)[b]	C.V. (%)[c]
Serum	101.6 ± 3.8	3.7
Muscle	101.6 ± 4.2	4.2
Liver	94.2 ± 2.4	2.5
Kidney	93.9 ± 2.4	2.6

[a] Six different concentrations of FZ were added to each sample tissue; [b] The mean ± standard deviation of five replicates; [c] The coefficient of variation.

Pharmacokinetics

The orange-spotted grouper were held in 23°C seawater after intravascular administration of FZ for pharmacokinetic analysis. FZ concentrations in the serum and muscle are shown in Fig. 1. The changes of mean serum concentrations of FZ that exhibited a rapid, biphasic decline after intravascular administration were best described as a two-compartment pharmacokinetic model. Pharmacokinetic parameters calculated from this model are given in Table 2. The distribution and elimination half-lives of FZ in orange-spotted

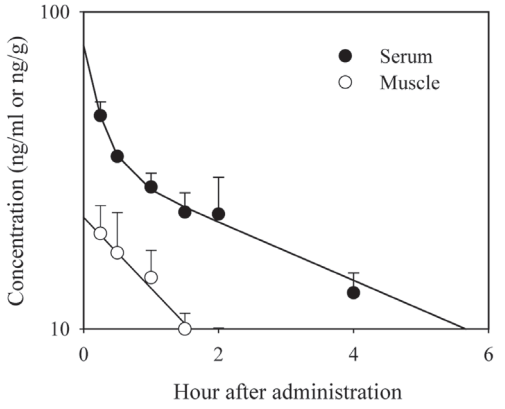

Fig. 1. Semi-logarithmic plot of furazolidone concentrations (mean ± s.d., n = 3) in the orange-spotted groupers held at 23°C seawater after intravascular administration.

Table 2. Pharmacokinetic values for furazolidone after intravascular administration to the orange-spotted grouper at 23°C.

Parameters*	Values	Parameters*	Values
Dose, mg/kg	0.1	C_0, ng/ml	78.2
A, ng/ml	45.0	k_{10}, h^{-1}	0.5
B, ng/ml	33.2	k_{12}, h^{-1}	2.1
α, h^{-1}	4.3	k_{21}, h^{-1}	1.9
β, h^{-1}	0.2	MRT, h	4.4
$t_{1/2(\alpha)}$, h	0.2	V_{ss}, l/kg	2.7
$t_{1/2(\beta)}$, h	3.3	Cl, ml/kg·h	598.1

*C_0 is serum drug concentration at time 0; A, B are the coefficients and α, β are the rate constants of the biexponential equation; $t_{1/2(\alpha)}$, $t_{1/2(\beta)}$ are the half-lives for distribution and elimination phase, respectively; k_{10} is the first-order rate constant for disappearance of drug from the central compartment; k_{12}, k_{21} are the first-order rate constant for drug distribution between the central and peripheral compartment; MRT is the mean residence time; V_{ss} is the apparent volume of distribution at steady situation; Cl is the total body clearance.

grouper were 0.2 and 3.3 h, respectively. FZ concentrations in the serum were found below the detection limit 3.5 h after administration.

Temperature Effect

Two temperatures, 23 and 30°C were selected for experiments of oral and bath administration of FZ to the orange-spotted grouper in order to observe its effect on the absorption and elimination of the drug. Temperature effects on the pharmacokinetics of FZ by oral administration are shown in Fig. 2 and Table 3. A one-compartment pharmacokinetic model was best to describe the changes of serum concentration of FZ after oral administration. The peak concentrations for serum and

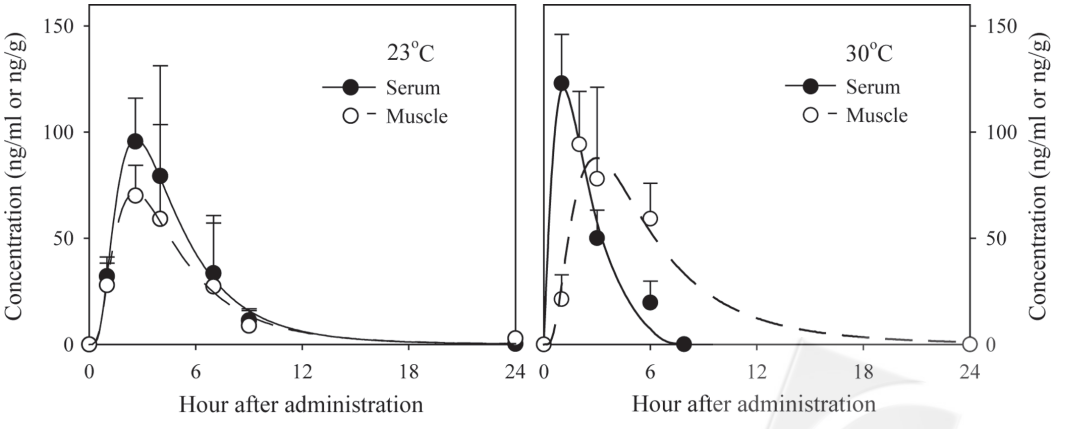

Fig. 2. Furazolidone concentrations (mean ± s.d., n=4) in the orange-spotted groupers held at 23 and 30°C seawater after oral administration at a dose of 50 mg/kg b.w. Circles indicate the observed values. The lines are the best-fitted curves based on PCNONLIN software.

Table 3. Pharmacokinetic values for furazolidone after oral dosing at 50 mg/kg to the orange-spotted grouper at 23 and 30°C.

Parameters*	23°C		30°C	
	Serum	Muscle	Serum	Muscle
T_{max}, h	2.6	2.6	1.1	2.0
C_{max}, ng/ml or ng/g	95.6	70.0	120.9	93.3
$t_{1/2a}$, h	1.4		0.7	
$t_{1/2e}$, h	1.4		0.8	
T_{lag}, h	0.7		0	
AUC, ng · h/ml or ng · h/g	544.0	431.5	614.0	492.0
T_{eli}, h	8.2	11.0	4.4	9.0

*T_{max} is time after administration at which the maximum drug concentration was observed; C_{max} is the maximum drug concentration; $t_{1/2a}$ and $t_{1/2e}$ are half-lives for first-order absorption and elimination, respectively; T_{lag} is lag time; AUC is the area under the concentration-time curve; T_{eli} is the elimination time.

muscle samples (95.6 ng/ml and 70 ng/g, respectively) were reached at 2.6 h after dosing at 23°C. Both absorption and elimination half-life of the drug at this treatment was 1.4 h. At 30°C, the peak concentration of FZ was obtained 1.1 h after oral dosing for serum (120.9 ng/ml), and 2 h after oral dosing for muscle sample (93.3 ng/g). Absorption and elimination half-lives were 0.7 and 0.8 h, respectively. The lag time of the drug absorption was found 0.7 h in fish held at 23°C and 0 h in fish held at 30°C. A less elimination time was found at 30°C when compared with the treatment at 23°C. The total amount of FZ in tissues during the treatment, represented by the area under the concentration-time curve, showed a higher value in both serum and muscle at 30°C than those at 23°C.

The absorption and elimination of FZ after bath administration at a concentration of 10 ppm at 23 and 30°C are shown in Fig. 3 and Table 4. At 23°C, peak serum concentration of FZ was 306.7 ng/ml at 0.25 h during the 24-hour bath administration, and the elimination half-life was 0.41 h in the fresh seawater after dosing. The maximum FZ concentration in muscle, 138 ng/g, was reached 1 h after the start of dosing treatment. FZ concentration in the serum and muscle were below the detection limit 1.7 and 1.4 h, respectively, after transferring the treated fish to fresh seawater. At 30°C, peak serum concentration of FZ was 315 ng/ml at 0.25 h during the 24-hour bath administration, and the elimination half-life was 0.25 h in fresh seawater after treatment. The maximum concentration in muscle, 127 ng/g, was observed 0.25 h after the start of dosing. FZ concentration in the serum and muscle were not detectable after transferring the fish to fresh seawater for 0.8 and 0.6

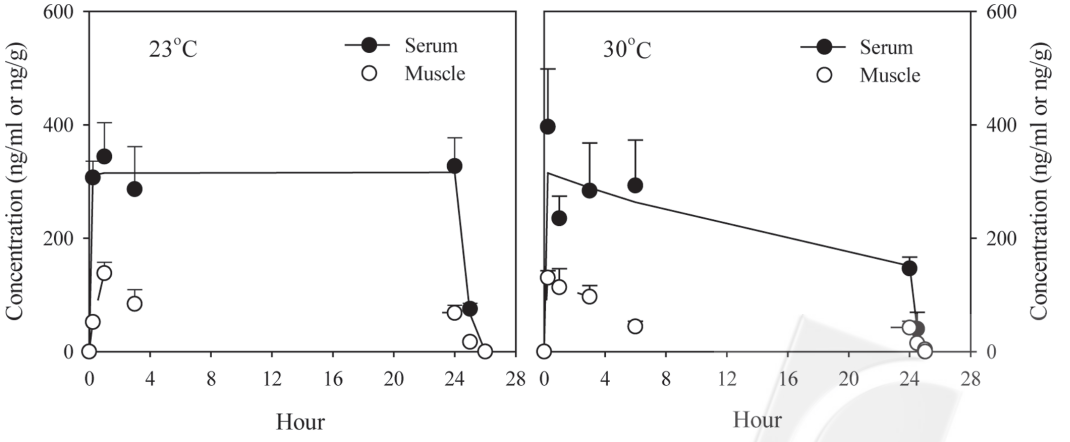

Fig. 3. Furazolidone concentrations (mean ± s.d., n=3) in the orange-spotted groupers during the 24-hour bath administration and depuration in fresh seawater, of 10 ppm of furazolidone at 23 and 30°C.

Table 4. Pharmacokinetic values for furazolidone in the orange-spotted grouper after 24-hour bath administration of 10 ppm at 23 and 30°C.

Parameters*	23°C		30°C	
	Serum	Muscle	Serum	Muscle
T_{max}, h	0.25	1	0.25	0.25
C_{max}, ng/ml or ng/g	306.7	138	315	127
$t_{1/2e}$, h	0.41		0.25	
AUC, ng · h/ml or ng · h/g	7352	2180	6386	1225
T_{eli}, h	1.7	1.4	0.8	0.6

*T_{max} is time after administration at which the maximum drug concentration was observed; C_{max} is the maximum drug concentration; $t_{1/2e}$ is the half-life for first-order elimination; AUC is the area under the concentration-time curve; T_{eli} is the elimination time.

h, respectively. FZ concentrations showed significant degradation during bathing period at 30°C compared with 23°C.

Dose Effect

Two concentrations of 10 and 20 ppm of FZ were administered by bath method to the orange-spotted groupers, and the dose effects on the absorption and elimination of FZ are shown in Fig. 4 and Table 5. Peak concentrations in both serum and muscle were reached at 0.25 and 1 h, respectively, but were higher at 20 ppm than 10 ppm concentration (Table 5). The elimination half-lives after treatment were not significantly different between 20 and 10 ppm treatment. The elimination time in serum and muscle were 2 and 2.9 h, respectively, after 20 ppm treatment, which were also longer than those after 10 ppm treatment.

Tissue Distribution and Bioavailability

FZ treatment to the orange-spotted groupers by intravascular, oral and bath administration revealed that the drug residues were mainly distributed in serum and muscle tissue, but not in liver and kidney. Average concentrations of FZ in muscle were much lower than in serum (Figures 1, 2, 3 and 4; Tables 3, 4 and 5).

The areas under the serum concentration-time curve or the drug bioavailabilities in orange-spotted groupers after intravascular, oral and bath administration of FZ at 23°C are listed in Table 6. The oral and bath bioavailabilities were 0.4 and 26.4%, respectively. According to absorption rate, peak concentration and bioavailability of FZ, the bath treatment revealed better results than oral administration (Tables 3, 4, 5 and 6).

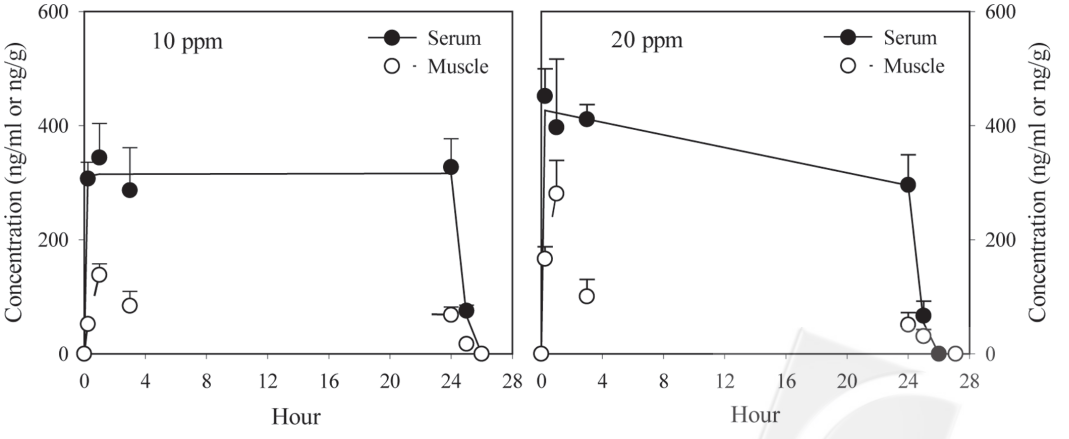

Fig. 4. Furazolidone concentrations (mean ± s.d., n=3) in the orange-spotted groupers during the 24-hour bath administration and depuration in fresh seawater, of 10 and 20 ppm furazolidone at 23°C.

Table 5. Pharmacokinetic values of furazolidone during and after 24-hour bath administration at 10 and 20 ppm to the orange-spotted grouper at 23°C.

Parameters*	10 ppm		20 ppm	
	Serum	Muscle	Serum	Muscle
T_{max}, h	0.25	1	0.25	1
C_{max}, ng/ml or ng/g	306.7	138	451.7	281
$t_{1/2e}$, h	0.41		0.47	
AUC, ng · h/ml or ng · h/g	7352	1959	8602	2240
T_{eli}, h	1.7	1.4	2.0	2.9

*T_{max} is time after administration at which the maximum drug concentration was observed; C_{max} is the maximum drug concentration; $t_{1/2e}$ is the half-life for first-order elimination; AUC is the area under the concentration-time curve; T_{eli} is the elimination time.

Table 6. Area under the serum concentration-time curve and bioavailability of furazolidone after intravascular, oral and bath administration to orange-spotted groupers at 23°C.

Parameters*	I.V.	Oral	Bathing
Dose	0.1 mg/kg	50 mg/kg	10 ppm
AUC, ng · h/ml	279	544	7352
F, %		0.4	26.4

*AUC is the area under the concentration-time curve; F is bioavailability.

DISCUSSION

FZ was absorbed, distributed and eliminated from the serum of orange-spotted groupers very rapidly after intravascular, oral or bath administration (Figures 1, 2, 3 and 4; Tables 2, 3, 4 and 5). Similar results have also been reported in eel, carp, catfish and adult swine (Sugimoto *et al*. 1979, Plakas *et al*. 1994, McCracken *et al*. 1995, Xu *et al*. 2006). Rapid absorption, distribution and elimination are general characteristics of the disposition of FZ in farm animals. We report similar pharmacokinetic characteristics of FZ in orange-spotted grouper, a marine fish gaining its popularity in aquaculture.

The increase in water temperature had a significant effect on the enhancement of both absorption and elimination rates of FZ in fish tissues (Tables 3 and 4). These temperature-dependent differences in pharmacokinetics apparently resulted from the effect of temperature on blood circulation and drug biotransformation in animals (Evans 1998). In this study, both absorption and elimination half-lives in the 30°C were 43-50% lower than those in the 23°C after oral administration (Table 3). In bath treatment, the absorptions of drug were faster in both test temperatures but the elimination half-life was 39% lower in 30°C than in 23°C (Table 4). The water temperature-dependency of drug kinetics was also reported in oxytetracycline and oxolinic acid (Björklund and Bylund 1990, Namdari *et al*. 1996). Furthermore, Ellis *et al*. (1978) have suggested that a 1°C change in water temperature generally results in a 10% change in the metabolic and elimination rate of drug in fish. Water temperature, therefore, plays a significant role in the drug disposition in aquatic animals. Also, serum concentrations of FZ at 30°C could not be maintained as stable as those in fish treated at 23°C during the 24-hour bath period. Although muscle concentrations of FZ remained almost constant during the rest of bath period after the initial peak in both temperature treatments, lower concentration was observed at higher temperature 6 h after the start of drug treatment (Fig. 3). These phenomenon may be explained by the faster decline (biotransformation or degradation) rate of FZ in tissue when treated at higher temperature.

Dose effect as shown by the increasing peak concentrations in serum and muscle (Table 5) could be speculated from the different absorption efficiency of drug through the different diffusion rates from concentration gradients (Evans 1998). Due to the characteristic rapid absorption and distribution of FZ, and the relatively hypertonic drug solution in bath administration, the serum concentration of FZ revealed an extremely rapid absorption at the beginning of bath treatment, especially at higher concentration (as 20 ppm in this

experiment). Concurrently, the muscle concentration of drug also rapidly reached to the peak. Meanwhile, a continuous high concentration during bathing may be harmful to the fish. However, through the control of different speed in the concurrent drug absorption, distribution, and elimination, the fish will sustain the drug concentration in a steady state under the functions of homeostasis and the pharmacokinetic interaction in it on a constant dosage regimen.

The estimated oral bioavailability was found 0.4% in the orange-spotted grouper (Table 6), far below the values found in the channel catfish. Plakas *et al*. (1994) reported that the bioavailabilities in the channel catfish were 58 or 28%, respectively, for the fish administered orally of FZ in solution or in feed mixture. These differences in bioavailability may be due to the different fish species, culture environments and/or medicated feed formulation. The bioavailability of nitrofurantoin, a nitrofuran drug, is also very low in channel catfish compared to that in humans (Stehly and Plakas 1993).

In all of the FZ applications in this experiment, no drug residue had been found in liver and kidney, nor in muscle 11 h after treatment. These observations were consistent with the results obtained in studies with other animals. For instance, FZ was undetectable in the muscle of carp and eel, one day after 1-hour bath treatment (Sugimoto *et al*. 1979), so was in muscle of channel catfish 8 h after dosing (Plakas *et al*. 1994). It was also reported that FZ was undetectable in tissues of piglet and swine 2 h after oral dosing (Vroomen *et al*. 1986). There have been several reports describing the rapid and extensive metabolic activity of FZ in various animals in vivo or in vitro, such as milk xanthine oxidase and rat liver (Tatsumi *et al*. 1981, Tatsumi *et al*. 1984), Escherichia coli and rat liver (Abraham *et al*. 1984), chicken and swine (Winterlin *et al*. 1984), piglet and swine liver (Vroomen *et al*. 1986; 1987, Hoogenboom *et al*. 1992, Gottschall and Wang 1995), trout (Law *et al*. 1992, Law and Meng 1996), channel catfish (Plakas *et al*. 1994), and eel (Nakabeppu and Tatsumi 1984). The enzymatic formation of hepatic protein-bound radioactive metabolite after the cessation of ^{14}C-labelled FZ treatment and its dose- and temperature-dependent responses further support the hypothesis of reactive FZ metabolite formation in trout (Law and Meng 1996). It can be concluded that the parent FZ has a shorter elimination time but its metabolites remain in an animal body for a longer time.

In conclusion, FZ is rapidly degraded in grouper and becomes undetectable in edible tissues after oral and bath administration. However, FZ's extensive activities and longer residual characteristics in its metabolites (Guo *et al*., 2003b) make the studies of the disposition of FZ metabolites in aquatic animal need further attention for the consumer's health concern. The data of temperature-dependent absorption and elimination, dose-dependent peak concentrations in drug application at different seasons and the effectiveness of FZ against various pathogens give strong support to the application of FZ in marine fishes. The results of higher bioavailability and rapid uptake of FZ after bath treatment revealed that bath administration of FZ is the simplest route for therapeutic treatment of bacterial infections in aquatic animals.

REFERENCES

Abraham, R. T., J. E. Knapp, M. M. Minnigh, L. K. Wong, M. A. Zemotis and J. D. Alvin (1984). Reductive metabolism of furazolidone by *Escherichia coli* and rat liver *in vitro*. *Drug Metab. and Dispos*., **12**: 732-741.

Benbroock, C. M. (2002). Antibiotic drug use in U.S. aquaculture: information available on the World Wide Web. http://www.latp.org.2002.

Björklund, H., and G. Bylund (1990). Temperature-related absorption and excretion of oxytetracycline in rainbow trout (*Salmo gairdneri* R.). *Aquaculture*, **84**: 363-372.

Bryan, G. (editor) (1978). *Nitrofurans: Chemistry, Metabolism, Mutagenesis, and Carcinogenesis* (New York: Raven).

Ellis, A. E., R. J. Roberts and P. Tytler (1978). The anatomy and physiology of teleosts. *Fish Pathology*, edited by R. J. Roberts (London: Baillière Tindall), pp. 13-54.

Evans, D. H. (editor) (1998). *The Physiology of Fishes* (2nd ed.) (New York: CRC).

Fisheries Administration, Council of Agriculture (2007). *Fisheries Statistical Yearbook, Taiwan Area 2006* (Taiwan: Fisheries Administration).

Gottschall, D. W. and R. Wang (1995). Depletion and bioavailability of ^{14}C furazolidone residues in swine tissues. *J. Agric. Food Chem.*, **43**: 2520-2525.

Guo, J. J., M. C. Tung, H. N. Chou and I C. Liao (2003a). *In vitro* and *in vivo* antibacterial activities of furazolidone. *J. Fish. Soc. Taiwan*, **30(2)**: 121-129.

Guo, J. J., H. N. Chou and I C. Liao (2003b). Disposition of 3-(4-cyano-2-oxobutylidene amino)-2-oxazolidone, a cyano-metabolite of furazolidone, in furazolidone-treated grouper. *Food Addit. and Contam*., **20(3)**: 229-236.

Hoogenboom, L. A. P., M. C. J. Berghmans, T. H. G. Polman, R. Parker and I. C. Shaw (1992). Depletion of protein-bound furazolidone metabolites containing the 3-amino-2-oxazolidinone side-chain from liver, kidney and muscle from pigs. *Food Addit. and Contam*., **9**: 623-630.

Law, F. C. P., S. Abedini, Y. T. He and K. J. Greenlees (1992). Metabolic disposition of ^{14}C-furazolidone (^{14}C-FZ) in trout following oral administration of medicated feed. *Pharmacologist*, **34**: 181.

Law, F. C. P., and J. Meng (1996). Binding of ^{14}C-furazolidone metabolites to the muscular and hepatic protein of trout. *Food Addit. and Contam*., **13**: 199-209.

Lee, K. K. (1995). Pathogenesis studies on *Vibrio alginolyticus* in the grouper, *Epinephelus malabaricus*, Bloch et Schneider. *Microb. Pathog*., **19**: 39-48.

McCracken, R. J., W. J. Blanchflower, C. Rowan, M. A. McCoy and D. G. Kennedy (1995). Determination of furazolidone in porcine tissue using thermospray liquid chromatography-mass spectrometry and a study of the pharmacokinetics and stability of its residues. *Analyst*, **120**: 2347-2351.

Nakabeppu, H. and K. Tatsumi (1984). Metabolism of furazolidone in eels. *Chem. and Pharmaceu. Bull*., **32**: 4193-4195.

Plakas, S. M., K. R. El Said and G. R. Stehly (1994). Furazolidone disposition after intravascular and oral dosing in the channel catfish. *Xenobiotica*, **24**: 1095-1105.

Stehly, G. R. and S. M. Plakas (1993). Pharmacokinetics, tissue distribution, and metabolism of nitrofurantoin in the channel catfish (*Ictalurus punctatus*). *Aquaculture*, **113**: 1-10.

Sugimoto, N., S. Kashiwagi and T. Matsuda (1979). Research on the change in concentration of furazolidone (N-(5-nitro-2-furyliden)-3-amino-2-oxazolidone) in fish muscle using a fluorescent spectrophotometric determination. *Bull. Jan. Soc. Sci. Fish*., **45**: 353-362.

Tatsumi, K., H. Nakabeppu, Y. Takahashi and S. Kitamura (1984). Metabolism *in vitro* of furazolidone: evidence for formation on an open-chain carboxylic acid and α-ketoglutaric acid from thee nitrofuran in rats. *Arch. Biochem. and Biophys*., **234**: 112-116.

Tatsumi, K., H. Yamada, H. Yoshimura and Y. Kawazoe (1981). Metabolism of furazolidone by milk xanthine oxidase and rat liver 9000g supernatant: formation of a unique nitrofuran metabolite and an aminofuran derivative. *Arch. Biochem. and Biophys*., **208**: 167-174.

Vroomen, L. H. M., M. C. J. Berghmans, P. Van Leeuwen, T. D. B. Van Struija, P. H. A. De Vries and H. A. Kuiper (1986). Kinetics of ^{14}C-furazolidone in piglets upon oral administration during 10 days and its interaction with tissue macro-molecules. *Food Addit. and Contam*., **3**: 331-346.

Vroomen, L. H. M., J. P. Groten, K. V. Muiswinkel, A. Van Velduizen and P. J. Van Bladeren (1987). Identification of reactive intermediate of furazolidone formed by swine liver microsomes. *Chem-Biol. Interact*., **64**: 167- 179.

Winterlin, W., C. H. Mourer, G. Hall, M. F. Kratzer, G. L. Werver, L. F. Tribble and M. S. Kim (1984). Furazolidone residues in chicken and swine tissues after feeding trials. *J. Environ. Science and Health*, **B19**: 209-224.

Wong, S. Y. and T. S. Leong (1990). A comparative study of *Vibrio* infections in healthy and diseased marine finfishes cultured in floating cages near Penang, Malaysia. *Asian Fish. Sci*., **3**: 353-359.

Xu, W., X. Zhu, X. Wang, L. Deng and G. Zhang (2006). Residues of enrofloxacin, furazolidone and their metabolites in Nile tilapia (*Oreochromis niloticus*). *Aquaculture*, **254**: 1-8.

富來頓在點帶石斑之動力學研究

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本研究旨在解析富來頓對點帶石斑進行靜脈注射、口投及藥浴方式投藥之動力學。富來頓含量以高效能液相層析儀檢測，在血液、肌肉、肝臟及腎臟的回收率分別為102、102、94及94%。富來頓以劑量0.1 mg/kg魚體重在23°C對點帶石斑進行靜脈注射，血中的藥物動向以二室式動力學模式解析最為合適，呈雙相快速衰減，其吸收與排除半衰期分別為0.2及3.3 h。若在水溫23和30°C，以劑量50 mg/kg魚體重對點帶石斑進行單次口投，則排除半衰期各為1.4及0.8 h。若在不同溫度進行24 h藥浴，則對藥物的吸收與排除速率具影響；若以不同劑量進行藥浴，對高峰濃度及曲線下面積具影響。此外，富來頓經口與藥浴方式投藥的生物可用率各為0.4及26.4%；主要分布在魚體的血液與肌肉，而非肝臟與腎臟。

關鍵詞：富來頓，藥物動力學，石斑。

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