COMPARATIVE PHARMACOKINETICS AND BIOAVAILABILITY OF OXOLINIC ACID IN BLACK TIGER SHRIMP

Koolvara Sangrungruang¹, Amornthep Chotchuang¹ and Ryuji Ueno²

¹Kung Krabaen Bay Fisheries Development Study Centre, P.O. Box 17, Thamai, Chantaburi 22120, Thailand,
²Faculty of Bioresources, Mie University, Kamihama 1515, Tsu, Mie-5148507, Japan.

Abstract

Oxolinic acid, which is a synthetic agent with a pyridopyrimidine ring, is an effective drug against gram-negative pathogenic bacteria in cultured fish and shrimp in Thailand. The pharmacokinetics of oxolinic acid after intramuscular and oral administration in black tiger shrimp was examined by using a rapid HPLC method. The kinetics of oxolinic acid can be described by a two-compartment model after intramuscular administration. The distribution half-life (T1/2) of 0.37 h) of oxolinic acid was shorter than the elimination half-life (T1/2) of 8.4 h). The kinetics data of orally administered oxolinic acid were fitted to a one-compartment model. Oxolinic acid was assimilated quickly (T1/2 of 0.78 h) and cleared slowly (T1/2 of 12.7 h) after oral dosing. The bioavailability was calculated to be 86.5%. The time required for drug absorption (TDA), defined as the time for absorption to reach 90% of the maximum level, was about 96 h. In a free feeding study, the shrimp preferred oxolinic acid mixed with fresh minced fish over commercial pellet. The intake of oxolinic acid was 12.4% after a single free feeding.

Keywords: pharmacokinetics, oxolinic acid, black tiger shrimp, shrimp, Penaeus monodon
INTRODUCTION

Oxolinic acid (OA), which is a 4-quinolone antimicrobial compounds having a pyridopyrimidine ring. This first-generation 4-quinolone displays a broad-spectrum of activity, particularly against gram-negative pathogenic bacteria in part by interfering with DNA-gyrase (Tsoumas et al., 1989). It is an effective drug against yersiniosis and vibriosis (Rodgers and Austin, 1983; Gogny et al., 1990). OA is officially licensed and widely used in France and many other countries in cultured fish e.g. rainbow trout, Atlantic salmon, channel catfish, Atlantic halibut etc. (Hustvedt et al., 1991; Schlotfeldt, 1992; Aoki et al, 1983; Aoki et al., 1985; Takashima et al., 1985; Ledo et al., 1987; Björklund and Bylund, 1991; Ishida, 1992; Rodgstad et al., 1993; Kleinow et al., 1994; Samuelsen and Ervik, 1999; Samuelsen et al., 2000). In Thailand. OA has been introduced for the treatment of vibriosis in shrimp farm about 2 decades ago.

Black tiger shrimp, Penaeus monodon, is a very important exporting item of Thailand and commands a high price in the world market. With the advances of aquaculture technology, the production of black tiger shrimp has been increasing year by year. However, severe outbreaks of shrimp diseases such as vibriosis and luminous bacterial infection have occurred. Several drugs have been used to cure these diseases. Consequently, residue of OA in black tiger shrimp has been assign to monitor in grow-out ponds since the 3rd month of rearing until harvesting (Ruangpan, 1995). The mis-use of drugs, sometimes resulting from over-dosing or under-dosing, is economically wasteful and can have adverse environmental impacts. It also can lead to outbreaks of drug-resistant bacteria. However, there are very few pharmacokinetic reports of drugs in shrimp. Therefore, the behavior of a drug in shrimp after dosing needs to be examined in order to obtain suitable dosing regimens.

In a previous paper, Sangrungruang et al. (2004a) reported comparative pharmacokinetics of oxytetracycline (OTC) in black tiger shrimp. In the present paper, we describe the pharmacokinetics and bioavailability of OA in black tiger shrimp, to compare of medicated feed and intake of OA by a single free feeding method.

MATERIALS AND METHODS

Shrimp

Black tiger shrimp, Penaeus monodon, were obtained from a shrimp farm in Chantaburi Province, Thailand. The average body weight was 25 g. They were maintained in 4-ton concrete ponds containing 2.5 tons of brackish water with 50% daily water exchange. The shrimp were found to be free of OA by HPLC analysis and were acclimatized in the ponds for 5 days. They were given 1% of commercial shrimp pellet feed (Star feed 5005, Pokkaphan Aquatech Co.,Ltd., Thailand) per kg bodyweight per day and were starved for 16 h prior to the dosing. During the experimental period, water temperature was 30°C and pH was 8.2.

Chemicals

Oxolinic acid (OA) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). All reagents were of analytical or HPLC grade (Merck, Germany).

Pharmacokinetic study

Drug administrations

For intramuscular administration, OA was dissolved in 0.03 M NaOH containing 0.9% NaCl and injected into the pericardial sinus of shrimp at a dose of 10 mg/kg of body weight according to the method of Sangrungruang et al., 2004a. For oral administration, the OA solution was mixed with a ground shrimp feed paste and orally administered by syringe according to the method of Sangrungruang et al. (2004b). In this method, the medicated feed paste was drawn in a 1 ml syringe fitted with a feeding needle, then an aliquot (100 µl) of the paste was administered from the mouth into the stomach. The dosage was 10 mg/kg body weight. The shrimp were transferred into the experimental ponds. Ten shrimp were sampled at 0.5 h - 10 days after administrations. The hemolymph was sampled from the ventral thoracic sinus and kept at -20°C until analysis.

Assay procedure

For hemolymph analysis was carried out by the method of Ueno et al. (1999) with a slight modification, 1 ml of hemolymph was put into a 10 ml centrifuge tube and 1 ml of acetonitrile: tetrahydrofuran (95:5) was added. The sample was homogenized and centrifuged at 4,000 rpm for 10 min. The supernatant was filtered through a syringe filter unit (0.2 µm).
A Waters HPLC system (Milford, MA, USA) with a pump model 515 was used. Effluent was monitored with a Waters UV-486, UV detector. A Waters model 717plus autosamplers was used for sample injection. The analytical column was a Hisep shielded hydrophobic phase column, 15 cm x 4.6 mm I.D., 5 \( \mu \)m particle size (Supelco, Bellefonte, PA, USA), protected with a guard column, 2 cm x 4.6 mm I.D., packed with the same material. Peak areas were quantified using software provided by Waters (Millennium 32 ver.3.05.01). The mobile phase consisted of 0.05 M citric acid : 0.2 M disodium hydrogen phosphate buffer, pH 2.5, in 10 mM tetra-n-butyl ammonium bromide : acetonitrile (85 :15). The injection volume was 20 \( \mu \)l. The flow rate was 1.0 ml/min, and the UV detector was set at 265 nm and 0.01 a.u.f.s. All analyses were performed at ambient temperature. Standard solutions were 1 mg/ml oxolinic acid in 0.1 M borate buffer, pH 10.0. The solutions were kept at -20\(^{\circ}\)C. Each solution was diluted to the required concentration before use.

Pharmacokinetic analysis

The most common method of pharmacokinetic evaluation is to assume that the drug concentration-time data can be described by one of several compartment models and to fit the data to an equation consistent with the assumed model using a non-linear least-squares regression. In our study, a pharmacokinetic analysis was applied assuming a one- or two-compartment model using the non-linear least-squares program MULTI (Yamaoka et al. 1981).

Wagner and Nelson (1964) reported that the drug absorption rate could be calculated from serum level versus time data using the following equation when the behavior of the drug is expressed by a one-compartment model:

\[
\text{Fraction absorbed} = \frac{A_t}{A_{\infty}} = \frac{C_t + K_e \int_0^t C \, dt}{K_e \int_0^\infty C \, dt}
\]

where \( A_t \) is the cumulative amount of the drug absorbed up to time \( t \), \( A_{\infty} \) is the amount of drug ultimately absorbed, \( C_t \) is the concentration at time \( t \), and \( K_e \) is the first-order elimination rate constant (the value for the drug following intravascular administration).

This equation relates the cumulative amount of drug absorbed after a certain time to the amount of drug ultimately absorbed, rather than to the dose administered.

Statistical Moment Analysis

The area under the concentration-time curve (AUC) was calculated by using the trapezoid rule including the terminal portion. The mean residence time (MRT) of the drug was obtained by a non-compartment analysis based on the statistical moment theory (Yamaoka and Tanigawara, 1983).

The bioavailability was calculated from the following equation:

\[
F(\%) = \left[ \frac{\text{AUC (p.o.)} \times \text{dose (i.s.)}}{\text{AUC (i.s.)} \times \text{dose (p.o.)}} \right] \times 100
\]

where p.o. represents the oral administration, and i.s. represents the intrasinus administration.

Free feeding study

Comparison of medicated feed

The shrimp were separated into 2 groups. Each group was reared in a concrete pond containing 2.5 tons of brackish water. They were starved for 16 h prior to medication. Then each group was fed with either medicated commercial pellet or medicated minced fish. The stock solution of OA was prepared by dissolving OA in a small amount of 1.0 M NaOH and diluted to the desired concentration with 0.9% NaCl. The medicated pellet was prepared by mixing the commercial pellet with the OA stock solution (corresponding to a dose of 30 mg OA/kg shrimp/day), then coated with starch as a binder (approximately 5% of pellets) and air-dried. The medicated minced fish (Yellowstripe trevally, Selaroides leptolepis) was prepared by well mixing minced fish with the OA stock solution (corresponding to a dose of 30 mg OA/kg shrimp/day) and adding starch as a binder (approximately 5% of minced fish). Both of the medicated feeds were freshly prepared before giving to the shrimp. The rate of feeding was about 1% of body weight per day. Each medicated feed was given to the shrimp every 8 h for 7 days. The uneaten feed in the ponds was removed before next feeding. After the last medication, the shrimp were then given to a non – medicated pellet. About 50% of the water was exchanged daily throughout the experiment. Ten shrimp were collected the hemolymph at each sampling time for 15 days.

Intake of OA after a single free feeding
The shrimp were fed with developing medicated shrimp pellets. The commercial shrimp pellet was mixed with the OA solution, then coated with starch and fresh minced fish (approximately 5% of pellets) at a dose of 40 mg OA/kg body weight. The shrimp were fed just one time until satiety. Then the uneaten feed was removed from the experimental pond. The shrimp were collected hemolymph at each sampling time and HPLC analysis as described above. The data of AUC value was calculated the intake of OA by shrimp.

RESULTS
Pharmacokinetic analysis
Intrasinus and oral administration

Fig. 1 shows the hemolymph level of OA versus time after intrasinus and oral administrations in black tiger shrimp at a dose of 10 mg/kg body weight.

When OA was administered by intrasinus, the drug concentration in the hemolymph reached $C_{\text{max}}$ (15.3 $\mu$g/ml) just after dosing, and then decreased gradually to 0.21 $\mu$g/ml at 6 days. The concentration-time profiles showed a sharp distribution phase ($\alpha$ phase) within 3 h and a mild elimination phase ($\beta$ phase) from 6 h to 4 days after dosing. The concentration-time profile could adequately be described by a two-compartment model:

$$C_t = 6.44 \times \exp(-0.08t) + 23.3 \cdot \exp(-1.89t)$$

The pharmacokinetic parameters of OA following intrasinus administration in black tiger shrimp at a dose of 10 mg/kg body weight are shown in Table 1.

Table 1 Comparative pharmacokinetic parameters for oxolinic acid following intrasinus or intravascular administration in black tiger shrimp, kuruma prawn and rainbow trout

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Black tiger shrimp</th>
<th>Kuruma prawn</th>
<th>Rainbow trout</th>
<th>Rainbow trout</th>
<th>Rainbow trout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>25</td>
<td>18-25</td>
<td>514</td>
<td>798</td>
<td>126</td>
</tr>
<tr>
<td>Water temp. (°C)</td>
<td>30</td>
<td>25</td>
<td>16</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>$\alpha$ (h$^{-1}$)</td>
<td>1.89</td>
<td>1.54</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\beta$ (h$^{-1}$)</td>
<td>0.08</td>
<td>0.028</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$K_{\alpha}$ (h$^{-1}$)</td>
<td>0.33</td>
<td>-</td>
<td>0.057</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$K_{\beta}$ (h$^{-1}$)</td>
<td>1.17</td>
<td>-</td>
<td>1.821</td>
<td>-</td>
<td>0.55</td>
</tr>
<tr>
<td>$T_{1/2\alpha}$ (h)</td>
<td>0.37</td>
<td>0.59</td>
<td>0.307</td>
<td>0.68</td>
<td>0.78</td>
</tr>
<tr>
<td>$T_{1/2\beta}$ (h)</td>
<td>8.4</td>
<td>33.2</td>
<td>69.7</td>
<td>69.3</td>
<td>69.3</td>
</tr>
<tr>
<td>AUC (μg·h/ml)</td>
<td>133</td>
<td>348</td>
<td>453</td>
<td>-</td>
<td>968</td>
</tr>
<tr>
<td>AUC/Dose (μg·h/ml)</td>
<td>13.3</td>
<td>-</td>
<td>45.3</td>
<td>-</td>
<td>48.4</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>47.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>79.2</td>
</tr>
<tr>
<td>$Cl_p$ (ml/kg/h)</td>
<td>75</td>
<td>28.8</td>
<td>20.2</td>
<td>16.9</td>
<td>20.7</td>
</tr>
<tr>
<td>$V_o$ (ml/kg)</td>
<td>1,170</td>
<td>1,300</td>
<td>1,900</td>
<td>1,820</td>
<td>1,880</td>
</tr>
<tr>
<td>$V_i$ (ml/kg)</td>
<td>340</td>
<td>-</td>
<td>399</td>
<td>-</td>
<td>690</td>
</tr>
</tbody>
</table>


Abbreviations: $\alpha$, $\beta$; Values related to the slopes of distribution and terminal phases, respectively, of the biexponential drug disposition curve, $K_{\alpha}$; Elimination rate constant, $K_{\beta}$; $K_{\alpha\beta}$; Distribution rate constant from between the central and peripheral compartment, $T_{1/2\alpha}$, $T_{1/2\beta}$; Distribution half-life and elimination half-life of drug, AUC; The area under serum concentration-time curve, $Cl_p$; Total body clearance, MRT; The mean residence time, $V_o$; Apparent steady state distribution, $V_i$; Apparent volume of central compartment
When OA was administered orally, $C_{\text{max}}$ (3.89 μg/ml) was obtained at 3 h after dosing. OA was still measurable at 6 days after dosing (0.10 μg/ml). The concentration-time profile could adequately be described by a one-compartment model with first-order absorption:

$$C_t = 4.97(\exp(-0.05t) - \exp(-0.89t)).$$

The pharmacokinetic parameters of OA following oral administration in black tiger shrimp at a dose of 10 mg/kg body weight are shown in Table 2.

**Table 2** Comparative pharmacokinetic parameters for oxolinic acid following oral administration in black tiger shrimp and kuruma prawn

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Black tiger shrimp</th>
<th>Kuruma prawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Water temp. (°C)</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>$K_{a}$ (h$^{-1}$)</td>
<td>0.89</td>
<td>-</td>
</tr>
<tr>
<td>$K_{e}$ (h$^{-1}$)</td>
<td>0.05</td>
<td>-</td>
</tr>
<tr>
<td>$T_{1/2a}$ (h)</td>
<td>0.78</td>
<td>-</td>
</tr>
<tr>
<td>$T_{1/2e}$ (h)</td>
<td>12.7</td>
<td>34.3</td>
</tr>
<tr>
<td>AUC (μg·h/ml)</td>
<td>115</td>
<td>573</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>36.5</td>
<td>40.3</td>
</tr>
<tr>
<td>Vd (ml/kg)</td>
<td>186,000</td>
<td>-</td>
</tr>
</tbody>
</table>

Sources: $^{1}$ Present study, $^{2}$ Uno (2004)

Abbreviations: $K_{a}$, $K_{e}$: Absorption and elimination rate constant, $T_{1/2a}$, $T_{1/2e}$: Absorption and elimination half-life of the drug, AUC: Area under the serum drug concentration-time curve from zero to infinity, MRT: The mean residence time, Vd: Apparent volume of distribution.

**Free feeding study**

**Selection of medicated feed**

The hemolymph levels of OA in shrimp after free feeding at 30 mg/kg body weight were shown in Table 3. Hemolymph levels of OA in shrimp fed medicated pellet varied widely, and those in shrimp fed medicated fresh minced fish were quite constant during medication. The average hemolymph levels in shrimp fed medicated pellet and medicated minced fish were 0.74 and 0.84 μg/ml, respectively. After the last medication, OA disappeared from the hemolymph within 2 days in the shrimp fed the pellets and within 5 days in the shrimp fed fresh minced fish.

**Single free feeding**

The $C_{\text{max}}$ of OA in the hemolymph (5.01 μg/ml) was reached between 3-5 h after a single free feeding, and OA was still measurable at 3 days after (0.1 μg/ml). By using the AUC value of the data, the intake of OA by black tiger shrimp after single free feeding was calculated to be 12.4%. Fig. 3 showed hemolymph level versus time plots of OA after a single free feeding.
Fig. 1. Hemolymph level vs time plots of oxolinic acid in black tiger shrimp after intrasinus (A) and oral (B) administrations. Symbols indicate the mean and standard deviations of ten shrimp. The hemolymph level scale is logarithmic.

Fig. 2. Percent absorbed-time curve of oxolinic acid in black tiger shrimp by the Wagner-Nelson method.
Fig. 3. Hemolymph level vs time plots of oxolinic acid in black tiger shrimp after a single free feeding. Symbols indicate the mean and standard deviations of ten shrimp. The hemolymph level scale is logarithmic.

<table>
<thead>
<tr>
<th>Table 3 Hemolymph levels of oxolinic acid in black tiger shrimp after free feeding at a dose of 30 mg/kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolymph level (µg/ml±standard deviation)</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>During medication</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>After medication</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

**DISCUSSION**

We applied a low concentration (10 mg/kg body weight) of OA to the experiment of intrasinus and forced oral administration in order to avoid serious hindgut diarrhea in black tiger shrimp as resulting after the report of Sangrungruang et al. (2004b).

The pharmacokinetics of OA after intrasinus administration in black tiger shrimp could be described by a two-compartment model. The same model was found for kuruma prawn after intrasinus administration (Uno, 2004). In rainbow trout, the pharmacokinetics of OA after intravascular administration could also be described by a two-compartment model (Björklund and Bylund, 1991; Kleinow et al., 1994; Ueno and Tatsuno, 2003). Two-compartment models have been used to explain the pharmacokinetics of sulfadimethoxine in lobsters (Barron et al., 1988; James and Barron, 1988) and the OTC in black tiger shrimp (Sangrungruang et al., 2004a). Table 1 showed comparative pharmacokinetic parameters for OA following intrasinus or intravascular administration in black tiger shrimp, kuruma prawn...
and rainbow trout. In black tiger shrimp after intramuscular administration, the half-life for hemolymph distribution (T1/2α) was 0.37 h, and the half-life for elimination (T1/2β) was 8.4 h.

Comparison of pharmacokinetics between black tiger shrimp and kuruma prawn indicate that different kinetic was found in distribution and elimination half-life of OA. In kuruma prawn, that is, T1/2α and T1/2β were 0.59 and 33.2 h, respectively. This may due to the effect of water temperature; where black tiger shrimp was experimented under 30°C, but kuruma prawn was done at 25°C. Rainbow trout, after given a dose of OA, exhibited T1/2α and T1/2β values of 0.68 and 69.3 h (Kleinow et al., 1994), 0.31 and 69.7 h (Björklund and Bylund, 1991) and 0.78 and 69.3 h (Ueno and Tatsuno, 2003), respectively. That is, the rate of absorption of OA in black tiger shrimp is approximately similar to that of trout, but the rate of elimination of OA in black tiger shrimp is about eight times faster than in trout.

An apparent steady-state distribution (Vss) was found for OA in black tiger shrimp. The volume of the peripheral compartment (Vp) was obtained from Vα - Vss. The Vα OA in shrimp was 830 ml/kg. The Vp in rainbow trout were calculated to be 1,501 (Björklund and Bylund, 1991) and 1,190 ml/kg (Ueno and Tatsuno, 2003). The large Vp suggests a wide distribution and concentration of OA into tissues outside the hemolymph.

The total body clearance (Cl) in black tiger shrimp (75 ml/kg/h) was 2.6 times faster than in kuruma prawn (28.8 ml/kg/h). The Clα of OA in black tiger shrimp was much higher than the values reported for rainbow trout (20.2 ml/kg/h), Björklund and Bylund (1991); 16.9 ml/kg/h, Kleinow et al. (1994); 20.7 ml/kg/h, Ueno and Tatsuno (2003). The clearance time for OA from the body tissues in black tiger shrimp and kuruma prawn obtained from Cλ/Clα were 0.064 and 0.022 h (Uno, 2004), respectively. In rainbow trout, the clearance time for OA, calculated from the data of Björklund and Bylund (1991), Kleinow et al. (1994) and Ueno and Tatsuno (2003) was 0.011, 0.009 and 0.011 h, respectively. Therefore, the terminal elimination rate in black tiger shrimp and kuruma prawn are quite slow when compared to that in trout.

The OA pharmacokinetics by oral administration in kuruma prawn could not fit with any compartment models (Uno, 2004) while in black tiger shrimp the pharmacokinetic data could fit with one-compartment model with first order absorption by using simple developed method for forced oral administration of Sangrungruang et al. (2004b). The bioavailability in kuruma prawn was 32.9% (Uno, 2004). In this study, the bioavailability of OA was calculated to be 86.5%, by using the AUC values. This difference was explained by the fact that high doses of OA (50 and 100 mg/kg body weight) caused serious hindgut diarrea of black tiger shrimp (Sangrungruang et al., 2004b). Uno (2004) used higher dose of OA (50 mg/kg body weight) in kuruma prawn but not our experiment (10 mg/kg body weight) as described above. In fish, Björklund and Bylund (1991) reported the bioavailability of OA to be 13.6% in rainbow trout at a dose of 75 mg/kg body weight. However, Kleinow et al. (1994) reported a very high bioavailability (90.8%) in trout at a dose of 5 mg/kg and this study, in black tiger shrimp was calculated to be 86.5% at a dose of 10 mg/kg body weight. This difference may be due to the fact by the different doses of OA. That is, Björklund and Bylund (1991) used very high dose whereas Kleinow et al. and our study used much lower doses of the drug.

The time required for drug absorption (TDA) is defined as the time for absorption to reach 90% of the maximum level. TDA, calculated by the Wagner-Nelson method, was 96 h (Fig. 2). The TDA for OA in rainbow trout was 72 h (Ueno and Tatsuno, 2003), indicating that OA is absorbed in black tiger shrimp slower than in rainbow trout.

We examined the intake of OA in shrimp by giving the commercial shrimp pellet feed coated with OA, starch and fresh minced fish, respectively. The Cmax was obtained between 3-5 h during a single free feeding. By using the AUC values of the data, the intake of OA was calculated to be 12.4%. In this experiment, the binder (starch) used may have reduced bioavailability for OA as Rigos et al. (2002) reported. Further study is needed to improve the formula of medicated feed, in order to get an attractive appetizer to shrimp.

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กรมประมง
7-9 กรกฎาคม 2547
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