บทความปริทัศน์

ความเป็นพิษ และการตกค้างของกรดออกโซลินิค
Toxicity and residues of oxolinic acid

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Oxolinic acid is a quinolone derivative. It is a synthetic antimicrobial agent which used to treat bacterial urinary tract infections, especially gram negative bacteria. It has been used in veterinary medicine for the control of furunculosis, vibriosis and enteric redmouth diseases. The mechanism of action of oxolinic acid inhibited bacterial DNA synthesis by effecting on bacterial DNA gyrase. Toxicity of oxolinic acid occured mainly to the central nervous system and gastrointestinal tract. Most of studies of residues of oxolinic acid were found in aquaculture animals such as fish and shrimp because oxolinic acid is used worldwide in aquaculture industry. The studies found that the absorption of oxolinic acid in rainbow trout depended on the temperature of water. And the residue time of oxytetracycline in sediment was longer than oxolinic acid. In addition, oxolinic acid in hepatopancreas of shrimp had more higher concentration than haemolymph and muscle and it also persisted in hepatopancreas longer than muscle.

Key words : Toxicity, Residues, Oxolinic acid

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กรดออกโซลินิคเป็นอนุพันธ์ของสารกลุ่มควิโนโลน ซึ่งเป็นสารต้านจุลชีพที่สังเคราะห์ขึ้นมาเพื่อใช้รักษาโรคติดเชื้อของระบบทางเดินปัสสาวะ โดยมีผลต่อแบคทีเรียแกรมลบ ต่อมานำมาใช้เป็นยารักษาโรคสัตว์ โดยเฉพาะโรคสัตว์น้ำ เช่น Furunculosis, Vibriosis และ Enteric redmouth diseases กลไกการออกฤทธิ์ของสารนี้คือไปยับยั้งการสังเคราะห์ดีเอ็นเอของแบคทีเรีย โดยมีผลกับเอนไซม์ DNA gyrase ความเป็นพิษของกรดออกโซลินิคจะมีผลต่อระบบประสาทส่วนกลาง และระบบทางเดินอาหาร การศึกษาการตกค้างของกรดออกโซลินิคพบว่า มีการศึกษามากในสัตว์น้ำประเภทกุ้งและปลา เนื่องจากมีการนำกรดออกโซลินิคมาใช้กันอย่างแพร่หลายในอุตสาหกรรมสัตว์น้ำ พบว่าอุณหภูมิของน้ำมีผลต่อการดูดซึมกรดออกโซลินิคในปลา rainbow trout การตกค้างออกซีเตตร้าซัยคลินในดินตะกอนจะมีระยะเวลานานกว่ากรดออกโซลินิค ส่วนการตกค้างของกรดออกโซลินิคในกุ้งจะพบในส่วน hepatopancreas มากกว่าส่วน haemolymph และกล้ามเนื้อ นอกจากนี้ระยะเวลาในการตกค้างของกรดออกโซลินิคในส่วน hepatopancreas นานกว่าส่วนกล้ามเนื้อ

คำสำคัญ : ความเป็นพิษ การตกค้าง กรดออกโซลินิค

Introduction

Oxolinic acid is a quinolone derivative. It is a synthetic antimicrobial agent which similar to nalidixic acid in chemical structure, mechanism of action, spectrum of activity and profile of toxicity. Oxolinic acid was approved by the Food and Drug Administration for the treatment of adults with established bacterial urinary tract infections (Gleckman *et al.*, 1979). It has been used in veterinary medicine for the treatment of disorder arising from gram negative infections. However, the major use of this drug is in aquaculture field, both as a chemotherapeutic and prophylactic agent in fish. It has broad spectrum of activity against fungi, protozoans and helminths (Wells, 1994).

Oxolinic acid has *in vitro* activity against most gram negative aerobic coccobacilli bacteria. The majority of *Escherichia coli, Klebsiella* sp., *Enterobacter* sp. and *Proteus* sp. are susceptible to oxolinic acid (Guyer, 1974). Although oxolinic acid is similar to nalidixic acid, oxolinic acid has more broad spectrum against pathogen and active than nalidixic acid. In addition, it shows good activity against *Staphylococcus aureus* (Ringel *et al.*, 1967). Furthermore, oxolinic acid proved to be efficacious in the prevention and cure of plant diseases caused by bacterial such as *Pseudomonas* sp. and *Erwinia* sp. in agricultural fields. Oxolinic acid was developed as an agricultural antimicrobial agent by Sumittomo Chemical Co. Ltd. (Hikichi *et al.*, 1989). Oxolinic acid is used in many countries in the treatment of fish diseases. It has been used successfully for the control of furunculosis, vibriosis and enteric redmouth disease (Endo *et al.*, 1973a; 1973b). General information and properties of oxolinic acid are as follows : (Wells, 1994; Kaminsky and Meltzer, 1968)

Chemical names:	5-ethyl-5, 8-dihydro-8-oxo-1, 3-dioxolo [4,5-g] quinoline-7-carboxylic acid 1-ethyl-1, 4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolone carboxylic acid
Synonyms:	W 4565, Emyrenil, Nidantin, Ossian, Ozoboi, Pietil, Urinox, Uritrate, Uro-Alvar, Urotrate, Uroxin Von Boch, Uroxol, Utibid, Prodoxol
Molecular formular:	$C_{13} H_{11} NO_5$
Molecular weight:	261.24

Appearance:	Colourless powder or crystals
Melting point:	314-316 ^{o}C
Solubility:	Soluble in base solution and non-soluble in water
Mechanism of action:	Inhibit DNA synthesis in bacteria which it has effect on bacterial DNA gyrase and suppress protein synthesis but no effect on RNA synthesis

Toxicity of oxolinic acid

Oxolinic acid is a quinolone derivative with antimicrobial activity, effectively used in the clinical treatment of urinary tract infections in human. The mechanism of action is involved with deoxyribonucleic acid (DNA) synthesis in bacteria. It has a ten fold greater ability to inhibit DNA replication than nalidixic acid. Side-effects observed in patients after therapeutic doses of mainly to the central nervous system and gastrointestinal tract. Central nervous system toxicity has included insomnia (the most frequent), restlessness, dizziness, headache, drowsiness and visual disturbances. In contrast to nalidixic acid, oxolinic acid has not been implicated as causing intracranial hypertension and an association with seizures has not been clearly established. Gastrointestinal disturbances include nausea (the most frequent), vomiting, abdominal discomfort and diarrhea. These can be minimized by concurrent administration of food or antacids. Less frequent miscellaneous reactions attributed to oxolinic acid have included fever, skin eruptions, photosensitivity, palpitations, dyspnea and a sense of chest tightness (Gleckman *et al.*, 1979). It showed low levels of toxicity in animal studies (Angelo and Monti, 1981).

After oral administration to human, the absorption of oxolinic acid was rapid from the gastrointestinal tract (Mannisto, 1975). They could detect oxolinic acid and its metabolites from daily urinary accounts for only 43 - 49 % of administered drug. Fecal excretion accounts for 16 - 20 % which could represent either incomplete absorption or biliary excretion (Gleckman *et al.*, 1979). In human metabolism, oxolinic acid is converted into at least 8 metabolites which are principally excreted as glucuronides. The mechanism of formation of the urinary metabolite may be considered to proceed as shown in Figure 1 (Di Carlo *et al.*, 1968a; 1968b).

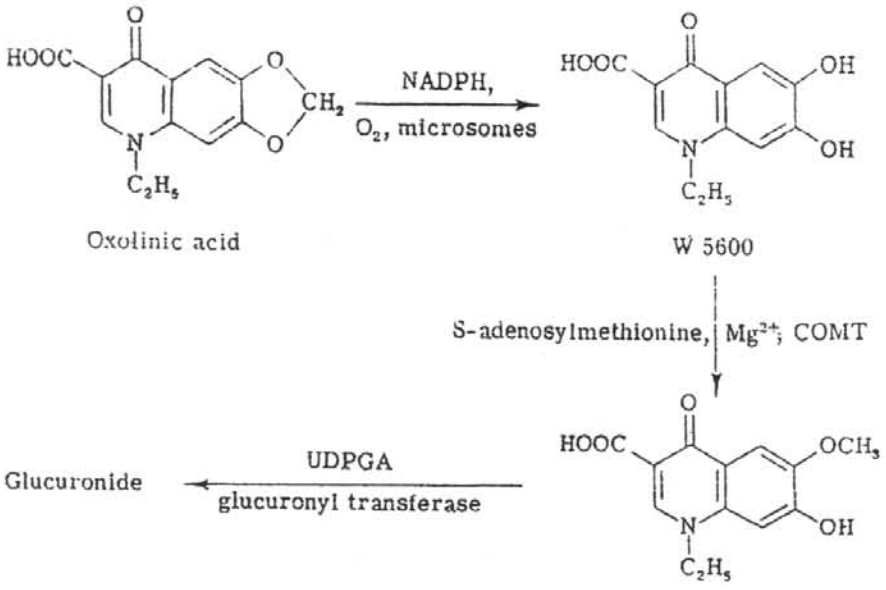

Figure 1 Mechanism proposed for formation of urinary metabolite from oxolinic acid

Guyer (1974) studied the acute toxicity of oxolinic acid in mice, rats, hamsters and dogs by oral administration. The LD_{50} is > 6000 mg/kg in mice and hamsters, > 2000 mg/kg in rats and more than 1000 mg/kg in dogs. In new-born mice and rats the LD_{50} is 128-136 mg/kg. Sub-acute toxicity, dogs were given oxolinic acid 500 mg/kg by mouth for five weeks. A moderate weight loss of about 15 %, body weight was observed and was related to anorexia and emesis. There appeared to be some muscle weakness and loss of visual-depth perception. Chronic toxicity, rats were treated with oral doses of oxolinic acid at 200 mg/kg for six months. They lose weight to one-third body weight but no animal died on this treatment. All animals showed signs of CNS stimulation. Dogs were treated with oral doses of oxolinic acid at 500 mg/kg for six months. There was no mortality and no evidence of organ pathology or alteration in haematological or biochemical parameters. All animals showed signs of hyperactivity.

The study of effect of oxolinic acid on reproduction and teratology found that there was no influence on reproductive performance in rats after oral administration at doses of oxolinic acid up to 80 mg/kg and no teratological changes in the offspring. There was an increased mortality in the offspring because of toxic effects of the drug on new-born rats. There was no effects on cardiovascular or respiratory function in dogs after intraduodenal oxolinic acid administration.

The study of oxolinic acid in human was found that maximum serum levels of 2.7-3.2 μg/ml being found three to four hours after a single oral dose of 750 mg. The serum half-life of oxolinic acid is in the range six to seven hours. The study of 1400 patients with urinary tract infection had been treated with oxolinic acid 750 mg, twice daily, for 14-28 days. The result showed that 21 % of patients had side-effects. They were mainly referable to the central nervous system and gastrointestinal tract. Side-effects were general of mild nature and necessitated withdrawal of treatment in only 4.8 % of cases.

Mannisto (1975) studied the pharmacokinetics of oral administration of oxolinic acid (750 mg, two times a day) for 7 days in the same 10 healthy women on the first, third and seventh days of the treatment. The result showed that the oxolinic acid concentration in serum was very low (1.4μg/ml) on the first day of the treatment but it increased to 4-5 folds on the third and seventh days. The oxolinic acid concentration in urine varied from 120 to 580 μg/ml on the first day and was 570 μg/ml in the steady state. The oxolinic acid concentration in urine was still 18 μg/ml on the third day after last dose. The study of pharmacokinetics of oxolinic acid in man have less than the study in animals. The absorption of oxolinic acid was rapid and serum concentration peak was achieved at 3 hours. The low concentration peak of oxolinic acid was found after a single dose and rather higher concentration was found during the chronic treatment. The oxolinic acid concentration in urine was higher than that in plasma.

Angelo and Monti (1981) studied the effects of oxolinic acid on the sleep-wakefulness cycle of the rat. Oxolinic acid (8.32 mg/kg) induced a significant and dose-related increase of waking EEG, while slow wave and rapid eye movement (REM) sleep were decreased. The effects of oxolinic acid on waking, slow wave and REM sleep were antagonized by ∝- methyl-p-tyrosine (AMPT) (50-100 mg/kg).

Residues of oxolinic acid

Oxolinic acid is used in many countries in the aquaculture both as a chemotherapeutic and prophylactic agent. It is possible to find the residues of oxolinic acid in the aquaculture products such as shrimp and fish. Therefore, the amount of residues of oxolinic acid that can be found depending on absorption, distribution, elimination and half-life of oxolinic acid.

Jacobsen (1989) studied the absorption of oxolinic acid in whole gutted, skin, muscle, kidney and blood of rainbow trout, *Salmo gairdneri* Richardson, at 6, 12 and18°C. Any concentrations in rainbow trout feed were found to be stable during the pelleting process and storage up to 81 days after pelleting (Table 1). The absorption of the drug in rainbow trout showed different temperature dependencies. The result of recovery and absorption of oxolinic acid in various tissues was shown in table 2. The residual concentration of oxolinic acid at 12 °C in skin and muscle of trout could not be detected 8 days after treatment of oxolinic acid, whereas the residual concentration of oxolinic acid in blood was 0.1 mg/kg blood after 4 days.

Table 1 Recovery of drug (g/kg feed) before and after the pelleting process

Storage (days)	Oxolinic acid
0	0.66
1	0.68
7	0.68
15	0.67
24	0.68
51	0.69
81	0.68

Table 2 Absorption of the drug in various tissues at 6, 12 and 18°C measured 24 hours after cessation of treatment

Sample	Gutted rainbow trout	Skin	Muscle	Kidney	Blood	Gutted rainbow trout
Temperature (°C)	6	12	12	12	12	18
Absorption of oxolinic acid (mg/kg)	2.8	4.13	4.04	4.79	1.44	2.5

Hustvedt *et al.* (1991) studies the absorption, distribution and elimination of oxolinic acid in Atlantic salmon after intravascular, intraperitoneal and oral administration. Oxolinic acid is increasingly used due to its high antibacterial potency and to its shorter withdrawal period. The result showed that the elimination half-life of oxolinic acid in Atantic salmon was estimated to be 60.3 hr after a single rapid intravascular (IV) injection of 20 mg of oxolinic acid/kg body weight through a cannula into the dorsal aorta. Apparent volume of distribution and total clearance were 1.8 l/kg and 0.7 l/kg.24 hr, respectively. Serum concentration peak was achieved within 1 hr after injection 20 mg of oxolinic acid/kg body weight into the peritoneal cavity and peak was achieved 3.9 hr after oral administration 10 mg of oxolinic acid/kg body weight.

Hustvedt and Salte (1991) studied elimination half-life, apparent volume of distribution and total clearance of oxolinic acid after a single intravascular injection of oxolinic acid in rainbow trout. The fish was given a single rapid injection 10 mg of oxolinic acid/kg body weight through the cannula. (Table 3)

Table 3 Oxolinic acid concentration in serum of rainbow trout

Time	mean concentration (μg/ml ± s.d., among fish)	
	Fresh water	Sea water
15 min	15.0 ± 0.6	18.5 ± 3.9
45 min	9.5 ± 1.2	9.8 ± 2.5
90 min	5.7 ± 2.4	6.4 ± 2.8
3 hr	3.4 ± 0.6	3.3 ± 2.0
6 hr	3.0 ± 1.6	3.4 ± 1.9
9 hr	2.4 ± 0.5	2.7 ± 1.7
12 hr	2.5 ± 1.0	2.4 ± 1.7
24 hr	1.8 ± 0.2	1.4 ± 1.0
48 hr	1.5 ± 0.3	0.7 ± 0.5
73 hr	1.2 ± 0.2	not determined
96 hr	1.0 ± 0.4	0.34 ± 0.4
144 hr	0.7 ± 0.2	0.14 ± 0.1
192 hr	not determined	0.05 ± 0.02

The terminal elimination half-life for oxolinic acid in rainbow trout was estimated to be 52.6 hr in freshwater and 29.1 hr in seawater. This considerable difference in elimination half lifes was mainly due to the increase in total clearance; their values were 1.2 and 2.0 l/kg.24 hr in freshwater and seawater, respectively. The apparent volume of distribution was estimated to be 2.9 and 2.6 l/kg in freshwater and seawater, respectively.

Bjorklund *et al.* (1991) studied the residues of oxolinic acid and oxytetracycline in fish and sediments from five fish farms. Oxolinic acid was better absorbed and faster excreted from the treated fish than oxytetracycline. The oxolinic acid sediments lost their antibacterial activity within 10 days after addition, while the oxytetracycline sediments still had a high antibacterial effect after 77 days of incubation as shown in table 4.

Table 4 The antibacterial activity of oxolinic acid and oxytetracyclne in fish farm sediments

Sample	Diameter of zone of inhibition (mm) [a]	
	Oxolinic acid	Oxytetracycline
Standard (2.5 μg)	47	37
Sediment extract [b]		
0 day	15	26
10 day	0	24
20 day	0	24
77 day	0	24

a : Obtained by adding sediment extracts to wells on Mueller-Hinton agar seeded with *Vibrio anquillarum*

b : Sediments stored at 17 °C

Horii *et al.* (1991) studied the residues of quinolones (oxolinic acid, nalidixic acid, and piromidic acid) in cultured fish and cultured prawns; and the residues of coccidiostats, nicarbazine, pyrethamine, salinomycin, monensin and lasalocid sodium in chicken tissues and eggs. These samples came from products purchased in retail shops in Tokyo in 1988-1990. Oxolinic acid was detected at 0.07 ppm. in one eel sample out of 28 samples,

nicarbazine at 0.56 ppm. in one chicken sample out of 46 samples, lasalocid sodium at 0.02-0.1 ppm. in 5 chicken liver samples out of 51 samples and pyrethamine at 0.04 ppm. in one egg sample out of 46 samples.

Steffenak *et al.* (1991) studied the reservoir of quinolone residues in salmon. Salmon tissues were treated with the quinolone : Oxolinic acid, flumequine, enrofloxacin and sarafloxacin. Residues of oxolinic acid and flumequine seem to be especially bound to bone, enrofloxacin to skin, and sarafloxacin to both bone and skin. Residues of these drugs were presented in the fish for long periods after treatment. (Table 5)

Table 5 Concentrations of oxolinic acid, flumequine, enrofloxacin and sarafloxacin in different fish tissue

Drug	Days after end of medication	Fish (n)	Average tissue conc. (ng/g)				
			Muscle	Liver	Fat	Skin	Bone
Oxolinic acid	20	3	16	35	87	336	1201
	60	3	15	47	26	253	478
	180	4	0	8	2	35	164
Flumequine	48	2	0	8	8	36	571
	70	3	0	16	27	36	465
Enrofloxacin	60	3	6	18	14	641	49
	80	3	0	10	5	284	26
Sarafloxacin	50	3	0	4	4	114	27
	80	3	0	6	6	95	60

Bjorklund *et al.* (1992) studied the absorption and elimination of oxolinic acid in serum, bile and tissue of rainbow trout at 5, 10 and 16 $^{\circ}$C after a single oral dose of 75 mg/kg. The highest oxolinic acid concentrations were measured in bile followed by liver, kidney, muscle tissue and serum. The elimination half-life in serum was 24 hr. at 16 $^{\circ}$C, 4.0 days at 10°C and 6.1 days at 5 $^{\circ}$C.

Ishida (1992) studied the concentrations of oxolinic acid in tissues of seawater acclimated rainbow trout and freshwater rainbow trout after a single oral administration at a dose 40 mg/kg. The concentrations of oxolinic acid in every tissue of freshwater trout reached a maximum value 48 hr. after treatment and high levels of the drug persisted in the tissues for up to 120 hr. The concentrations of oxolinic acid in tissue of seawater trout were much lower than those in freshwater trout. When oxolinic acid was injected at a dose 20 mg/kg into the caudal vessels of seawater and freshwater trout, serum levels of oxolinic acid decreased immediately after injection. The elimination of oxolinic acid in seawater trout was much more rapid than that in freshwater trout.

Somjetlertcharoen *et al.* (1993) studied the residues of oxolinic acid in *Penaeus monodon* after oral administration with oxolinic acid at a dose 2.5 g/kg in feed for 7 days. The result found that oxolinic acid persisted in hepatopancreas longer than muscle of shrimp.

Payooha *et al.* (1993) studied the residues of oxolinic acid in *Penaeus monodon* at a dose of 10, 20 and 30 mg/kg body weight. The maximum level of oxolinic acid residue was detected in the hepatopancreas. The concentration of oxolinic acid in hepatopancreas had more higher than muscle and haemolymph. The residence time of oxolinic acid in hepatopancreas, haemolymph and muscle after feeding with oxolinic acid at a dose of 10 mg/kg were 27, 10 and 7 days, respectively; after feeding with a dose of 20 mg/kg were 39, 22 and 24 days, respectively; and after feeding with a dose of 30 mg/kg were 50, 24 and 27 days, respectively.

Limpoka *et al.* (1993a; 1993b) studied the pharmacokinetics of oxolinic acid haemolymph clearance, absorption, tissue distribution and excretion in giant prawns (*Penaeus monodon*) which were treated by single intramuscular injection and oral administration of oxolinic acid at 28-32 ^{o}C. The elimination half-lifes were 4.68 and 5.37 hr following intramuscular injection of 10 mg/kg and 20 mg/kg prawn weight, respectively. Oxolinic acid was rapidly absorbed after single oral dosing. The concentrations of oxolinic acid of 0.45 ppm and 0.55 ppm in haemolymph were found in 0.87 and 0.83 hr following oral dosing of 10 mg/kg and 20 mg/kg prawn weight, respectively. The prawns were fed oxolinic acid-suplemented diets containing 0.5 and 1 g/kg feed for 5 days. The result

showed that the edible parts of prawn tissue were free of residues at 6 days and 7 days in pelleted diet trials and fish flesh diet trials, respectively.

Steffenak *et al.* (1994) studied the cooking effect of oxolinic acid residues in salmon (*Salmo salar*) by containing residues of oxolinic acid was boiling or baking in the oven. Samples of raw and cooked muscle, skin and bone, as well as of the water in which the fish being boiled and juice from the baked fish, were analysed. Oxolinic acid did not degrade at the temperatures reached when cooking the fish. (Table 6)

Table 6 Residues of oxolinic acid in fish muscle, skin and bone before and after boiling and baking in the oven, and in the boiling water and in juice exuded from the baked fish

Treatment of fish	Oxolinic acid content in tissue (ng/g)			Total amount of oxolinic acid in water or juice (ng)
	Muscle	Skin	Bone	
Raw	0	35	164	-
Boiled	6	12	46	625
Baked	7	17	57	23

Conclusion

In conclusion, oxolinic acid is active against most gram-negative aerobic bacteria such as *E. coli, Klebsiella* sp., *Enterobacter* sp. and *Proteus* sp. It was used to treat urinary tract infection in human. In agricultural industry, oxolinic acid proved to be efficacious in the preventation and cure of plant disease which caused by bacteria. It is also used in aquaculture for the treatment of fish disease for controlling of furunculosis, vibriosis and enteric redmouth disease. It is especially potent in curing or preventing diseases caused by certain species of *Yersinia, Aeromonas* and *Vibrio*. Oxolinic acid is administered orally, mixed in feed at a dose level of 12 mg/kg/day . Side effects which observed in human after therapeutic doses of oxolinic acid were generally mild in nature and mainly referable to the central nervous system and gastrointestinal tract. It shows low level of toxicity in animals.

Animals are moderate weight loss due to anorexia and emesis, some muscle weakness and loss of visual-depth perception. Oxolinic acid is faster absorbed and better treated in fish than oxytetracycline.

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