Vol. 44: 133–136, 2001 | DISEASES OF AQUATIC ORGANISMS
Dis Aquat Org | Published March 9

Treatment of *Microcotyle sebastis* infestation in cultured rockfish *Sebastes schlegeli* by oral administration of praziquantel in combination with cimetidine

Ki Hong Kim*, Eun Hae Lee, Se Ryun Kwon, Jae Bum Cho

Department of Aquatic Life Medicine, College of Fisheries Science, Pukyong National University, Pusan 608-737, Korea

ABSTRACT: The effect of cimetidine on the treatment efficacy of praziquantel against *Microcotyle sebastis* infestation in cultured rockfish *Sebastes schlegeli* was investigated. Juvenile rockfish were divided into 7 groups, and orally administered praziquantel alone (50, 100 and 200 mg kg^{-1} body wt, BW) or in combination with cimetidine at a dose of 200 mg kg^{-1} BW for each praziquantel dose. The fish in the control group were administered only saline. The results clearly showed that coadministration of cimetidine with praziquantel led to a significantly increased treatment efficacy of the latter drug, and consequently would lead to a lowering of the total dose of praziquantel, and a reduction in the administration times and costs for the treatment of *M. sebastis* infestation in cultured rockfish.

KEY WORDS: Praziquantel · Cimetidine · *Microcotyle sebastis* · *Sebastes schlegeli* · Treatment efficacy

Resale or republication not permitted without written consent of the publisher

INTRODUCTION

Praziquantel chemotherapy has been employed to control various internal helminth infections in mammals and has recently been used to control monogenean diseases in fish by bath treatment (Schmahl & Melhorn 1985, Buchmann 1987, Buchmann et al. 1990, Szekely & Molnar 1990, Thoney 1990). Recently, Kim et al. (1998) and Kim & Cho (2000) reported that oral administration of praziquantel was effective in treating *Microcotyle sebastis* infestations in cultured rockfish *Sebastes schlegeli*.

Because *Microcotyle sebastis* is a blood-sucking polyopisthocotylean, the parasite inevitibly absorbs praziquantel in the blood of treated fish in the process of blood feeding. However, all *M. sebastis* worms on the gills of a rockfish would not feed blood at the same time and the levels of praziquantel in the blood would decline with the lapse of time. When praziquantel was administered in a single oral dose in mammals, the drug disappeared in the plasma within 3 h (Bittencourt et al. 1990, Jung et al. 1991). Although little work has been done on the pharmacokinetics of praziquantel in fish administered orally, the highest residue level of praziquantel in the blood of rainbow trout which were given a single oral dose (10 mg kg^{-1} body wt, BW) of praziquantel was obtained 7 h after treatment, and no residues were found 48 h after medication according to the preliminary study of Rogstad et al. (1987). Considering this fast drop in praziquantel levels in the blood, maintaining high levels of praziquantel in blood during the treatment period and therefore increasing the amount of time to which the parasite is exposed to parasiticidal doses of the drug is essential for increasing treatment efficacy.

Cimetidine is widely used for the treatment of gastric hyperacidity syndrome in humans. Numerous studies have shown that cimetidine may interact with coadministered drugs by influencing absorption, metabolic clearance and/or renal clearance (Shaheen & Branch 1986, van Crugten et al. 1986, Somogyi & Murihead 1987, Schmidt et al. 1998). Recent reports have de-

*E-mail: khkim@dolphin.pknu.ac.kr

© Inter-Research 2001

scribed an increase in praziquantel levels in plasma of mammals when cimetidine is simultaneously administered (Dachman et al. 1994, Ebeid et al. 1994, Metwally et al. 1995, Jung et al. 1997).

In the present study, we investigated the treatment efficacy of praziquantel against *Microcotyle sebastis* infestation in cultured rockfish when administered simultaneously with cimetidine.

MATERIALS AND METHODS

Fish. Netpen-reared juvenile rockfish *Sebastes schlegeli* (body length: 13 to 16 cm) were obtained from a local rockfish farm in Tongyoung, Korea. The presence of *Microcotyle sebastis* on the gills was confirmed by examination of 10 fish. After 1 wk acclimation, a total of 70 fish was randomly divided into 7 groups of 10 fish in each group. The volume of each experimental aquarium was 50 l, the water temperature was 20 ± 1°C, and salinity was 33‰. Fish were not fed throughout the experiment.

Treatment regime. Fish were anaesthetized with MS222 (Sigma) and were intubated directly onto the stomach with varying concentrations of praziquantel and cimetidine. The first group was given 200 mg praziquantel (Shinpoong Pharm. Co. Ltd.) kg^{-1} BW, the second group 100 mg praziquantel kg^{-1} BW, and the third group 50 mg praziquantel kg^{-1} BW. The fourth group was coadministered 200 mg praziquantel and 200 mg cimetidine kg^{-1} BW, the fifth group 100 mg praziquantel and 200 mg cimetidine kg^{-1} BW, and the sixth group 50 mg praziquantel and 200 mg cimetidine kg^{-1} BW. The fish in the seventh group (control group) were given 0.7% saline. At 84 h post-treatment, the gills of all fish in each group were examined to confirm the effectiveness of each treatment. Abundance and prevalence were determined according to the methods given in Margolis et al. (1982).

Statistical analysis. All data were analyzed using Mann-Whitney's *U*-test (SPSS for Windows, SPSS Inc.).

RESULTS

Prevalence and intensity of *Microcotyle sebastis* in the fish sampled randomly before the start of the treatments were 100% and 21.9 ± 16.8 (mean ± SD), respectively. All treated groups, except the group fed 50 mg kg^{-1} BW praziquantel, showed significantly lower abundances of *M. sebastis* than the control group (Tables 1 & 2). When cimetidine was administered together with praziquantel, the treatment efficacy was significantly elevated. Maximum efficacy was recorded when both drugs were given simultaneously at 200 mg kg^{-1} BW, and this regime completely eradicated all *M. sebastis*. The treatment efficacies of 100 mg praziquantel + 200 mg cimetidine kg^{-1} BW and 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW were not significantly different from those of 200 mg praziquantel kg^{-1} BW and 100 mg praziquantel kg^{-1} BW, respectively.

DISCUSSION

The present results clearly show that coadministration of cimetidine with praziquantel leads to a significantly increased treatment efficacy of the latter drug against *Microcotyle sebastis* infestation in rockfish *Sebastes schlegeli*. Cimetidine is known to be a non-selective inhibitor of cytochrome P_{450} isozymes, and it has been found to impair the hepatic oxidative metabolism of a wide variety of drugs (Somogyi & Gugler 1982, Sedman 1984, Gerber et al. 1985, Somogyi &

Table 1. Efficacy of oral administration of praziquantel alone and coadministration with cimetidine against *Microcotyle sebastis* infestation in juvenile rockfish. BW: body weight

Experimental group	Praziquantel (mg kg^{-1} BW)	Cimetidine (mg kg^{-1} BW)	Prevalence (%)	Abundance (mean ± SD)	No. of parasites
Praziquantel alone	200	0	40	1.4 ± 1.8	0–4
	100	0	90	6.0 ± 5.8	0–19
	50	0	100	15.3 ± 6.8	6–30
Praziquantel + Cimetidine	200	200	0	0	0
	100	200	100	1.7 ± 0.9	1–3
	50	200	100	8.6 ± 3.5	3–13
Control	Only saline		100	18.3 ± 11.2	7–39

Table 2. Values of significance among experimental groups calculated using the Mann-Whitney's *U*-test. P: praziquantel; C. cimetidine

Group	P200	P100	P50	P200 + C200	P100 + C200	P50 + C200	Control (saline)
P200	–	0.016	0.000	0.000	0.377	0.001	0.000
P100		–	0.007	0.000	0.034	0.083	0.004
P50			–	0.000	0.000	0.022	0.820
P200 + C200				–	0.000	0.000	0.000
P100 + C200					–	0.001	0.000
P50 + C200						–	0.023

Murihead 1987, Paller & Jacob 1994). Masimirembwa & Hasler (1994) reported that praziquantel was metabolized by phenobarbitone-inducible isoforms of cytochromes P_{450}, and cimetidine was an effective inhibitor of the metabolism of praziquantel. Diekmann et al. (1989) also reported that cimetidine was an effective inhibitor of praziquantel metabolism at a dose of 200 mg kg^{-1} in rats. In the treatment of human neurocysticercosis, an increase in praziquantel's bioavailability by coadministration of cimetidine and consequently an increase in treatment efficacy have been well demonstrated by many studies (Overbosch 1992, Dachman et al. 1994, Jung et al. 1997, Sotelo & Jung 1998, Al-Khodairy et al. 1999).

In this study, we applied cimetidine as a potentiator of praziquantel to treat fish monogenean infestations for the first time. Treatment efficacy increased about 2-fold at each praziquantel dose with joint administration of cimetidine. This suggests that coadministration of cimetidine may suppress the metabolism of praziquantel and raises the bioavailability and levels of praziquantel in the blood in treated fish. This is also common in mammals.

Dachman et al. (1994) reported that concurrent cimetidine administration increased not only maximum concentration but also the elimination half-life of praziquantel in humans. According to the present and the previous studies (Kim et al. 1998), a dose of 200 mg praziquantel kg^{-1} BW was enough to kill *Microcotyle sebastis* parasitizing on the gills of rockfish. In the present study, however, the differences in feeding times or intervals among *M. sebastis* individuals in fish which were administered 200 mg praziquantel kg^{-1} BW alone might have afforded some parasites an opportunity to avoid parasiticidal concentrations of praziquantel in the blood. On the other hand, the complete eradication of *M. sebastis* in fish treated with 200 mg praziquatel + 200 mg cimetedine kg^{-1} BW suggested that the addition of cimetedine increased the length of time that parasiticidal levels of praziquantel were maintained enough to surmount the problem of the parasite's feeding intervals.

The present results suggest that the coadministration of cimetidine with praziquantel would lead to a lowering of the total dose of praziquantel needed, as well as a reduction in administration times and costs (considering the high cost of praziquantel for aquaculturists) of *Microcotyle sebastis* infestation treatment. Further investigation on the pharmacokinetics of praziquantel in orally administered fish when coadministered with cimetidine is needed to explain the present results explicitly.

Acknowledgements. This study was supported in part by a grant from the Ministry of Maritime Affairs and Fisheries, Republic of Korea.

LITERATURE CITED

Al-Khodairy AT, Annoni JM, Uebelhart D (1999) Parenchymatous cerebral neurocysticercosis in a quadriplegic patient. Spinal Cord 37:142–146

Bittencourt PRM, Gracia CM, Gorz AM, Oliveira TV (1990) High-dose praziquantel for neurocysticercosis: serum and CSF concentrations. Acta Neurol Scand 82:28–33

Buchmann K (1987) The effects of praziquantel on the monogenean gill parasite *Pseudodactylogyrus bini*. Acta Vet Scand 28:447–450

Buchmann K, Szekely C, Bjerregaard J (1990) Treatment of *Pseudodactylogyrus* infestations of *Anguilla anguilla*. II. Trials with bunamidine, praziquantel and levamizole. Bull Eur Assoc Fish Pathol 10:18–20

Dachman WD, Adubofour KO, Bikin DS, Johnson CH, Mullin PD, Winograd M (1994) Cimetidine-induced rise in praziquantel levels in a patient with neurocysticercosis being treated with anticonvulsants. J Infect Dis 169:689–691

Diekmann HW, Schneidereit M, Overbosch D (1989) Inhibitory effects of cimetidine ketoconazole and miconazole on the metabolism of praziquantel. Acta Leiden 57:217–228

Ebeid FA, Metwally A, Botros SS, Bennett JL (1994) Treatment of experimental schistosomiasis mansoni with praziquantel alone and combined with cimetidine. Arzneimforsch 44:1268–1270

Gerber MC, Tejwani GA, Gerber N, Bianchine JR (1985) Drug interactions with cimetidine: an update. Pharmacol Ther 27:353–370

Jung H, Vazquez ML, Sanchez M, Penagos P, Sotelo J (1991) Clinical pharmacokinectics of praziquantel. Proc West Pharmacol Soc 34:335–340

Jung H, Medina R, Castro N, Corona T, Sotelo J (1997) Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. Antimicrob Agents Chemother 41:1256–1259

Kim KH, Cho JB (2000) Treatment of *Microcotyle sebastis* (Monogenea: Polyopisthocotylea) infestation with praziquantel in an experimental cage simulating commercial rockfish *Sebastes schlegeli* culture conditions. Dis Aquat Org 40:229–231

Kim KH, Park SI, Jee BY (1998) Efficacy of oral administration of praziquantel and mebendazole against *Microcotyle sebastis* (Monogenea) infestation of cultured rockfish (*Sebastes schlegeli*). Fish Pathol 33:467–471

Margolis L, Esch GW, Holmes JC, Kuris AM, Schad GA (1982) The use of ecological terms in parasitology (report of an ad hoc committee of the American Society of Parasitologists). J Parasitol 68:131–133

Masimirembwa CM, Hasler JA (1994) Characterisation of praziquantel metabolism by rat liver microsomes using cytochrome P450 inhibitors. Biochem Pharmacol 48:1779–1783

Metwally A, Bennett JL, Botros S, Ebeid F (1995) Effect of cimetidine, bicarbonate and glucose on the bioavailability of different formulations of praziquantel. Arzneim-forsch 45:516–518

Overbosch D (1992) Neurocysticercosis. An introduction with special emphasis on new developments in pharmacotherapy. Schweiz Med Wochenschr 122:893–898

Paller MS, Jacob HS (1994) Cytochrome P-450 mediates tissue-damaging hydroxyl radical formation during reoxygenation of the kidney. Proc Natl Acad Sci USA 91: 7002–7006

Rogstad A, Hormazabal V, Yndestad M (1987) Extraction of praziquantel from fish tissue and its determination by high-performance liquid chromatography. J Chromatogr 391:328–333

Schmahl G, Mehlhorn H (1985) Treatment of fish parasites. 1. Praziquantel effective against Monogenea (*Dactylogyrus vastator*, *Dactylogyrus extensus*, *Diplozoon paradoxum*). Z Parasitenkd 71:727–737

Schmidt EK, Antonin KH, Flesch G, Racine-Poon A (1998) An interaction study with cimetidine and the new angiotensin II antagonist valsartan. Eur J Clin Pharmacol 53:451–458

Sedman AJ (1984) Cimetidine-drug interactions. Am J Med 76:109–114

Shaheen O, Branch RA (1986) Pharmacokinetic drug interaction with cimetidine. J Pharmacol Exp Ther 20:1–6

Somogyi A, Gugler R (1982) Drug interactions with cimetidine. Clin Pharmacokinet 7:23–41

Somogyi A, Murihead M (1987) Pharmacokinetic interactions of cimetidine 1987. Clin Pharmacokinet 12:321–366

Sotelo J, Jung H (1998) Pharmacokinetic optimisation of the treatment of neurocysticercosis. Clin Pharmacokinet 34: 503–515

Szekely C, Molnar K (1990) Treatment of *Ancylodiscoides vistulensis* monogenean infestations of the European catfish (*Silurus glanis*). Bull Eur Assoc Fish Pathol 10:74–77

Thoney DA (1990) The effects of trichlorfon, praziquantel and copper sulphate on various stages of the monogenean *Benedeniella posterocolpa*, a skin parasite of the cownose ray, *Rhinoptera bonasus* (Mitchill). J Fish Dis 13:385–389

van Crugten J, Bochner F, Keal J, Somogyi A (1986) Selectivity of the cimetidine-induced alterations in the renal handling of organic substrates in humans. Studies with anionic, cationic and zwitterionic drugs. J Pharmacol Exp Ther 236:481–487

Editorial responsibility: Wolfgang Körting, Hannover, Germany

Submitted: October 16, 2000; Accepted: November 21, 2000
Proofs received from author(s): February 12, 2001