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Cimetidine enhances the plasma praziquantel concentration and treatment efficacy against *Microcotyle sebastis* in cultured rockfish *Sebastes schlegeli*

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ABSTRACT: The effect of cimetidine on the praziquantel concentration in the blood of the rockfish *Sebastes schlegeli* and the consequent effect on the treatment efficacy against *Microcotyle sebastis* were investigated. Fish were divided into 7 groups and orally administered praziquantel alone (200 and 100 mg kg^{-1} body weight [BW]) or in combination with cimetidine (in doses of 200, 100 or 50 mg kg^{-1} BW cimetidine with a praziquantel dose of 100 mg kg^{-1} BW). The fish in the sixth group were coadministered 50 mg praziquantel and 200 mg cimetidine kg^{-1} BW. The fish in the control group were administered only saline. At 24 h post-treatment, the plasma was analyzed for praziquantel by reversed-phase high-performance liquid chromatography (RP-HPLC) using diazepam as the internal standard, and the gills were examined to confirm the effectiveness of each treatment. The praziquantel concentration in plasma of fish administered 100 mg praziquantel + 200 mg cimetidine kg^{-1} BW was not significantly different from that of fish treated with 200 mg praziquantel kg^{-1} BW and was significantly ($p < 0.05$) higher (about 2 times) than that of fish administered 100 mg praziquantel kg^{-1} BW. The group of fish administered 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW showed a similar plasma praziquantel concentration to that in the fish treated with 100 mg praziquantel kg^{-1} BW. The treatment efficacies of the groups of fish coadministered 100 mg praziquantel kg^{-1} BW and various concentrations of cimetidine (200, 100 and 50 mg kg^{-1} BW) were not significantly different from that of the group of fish administered 200 mg praziquantel kg^{-1} BW, but were significantly higher than those of the groups of fish fed 100 mg praziquantel kg^{-1} BW alone or coadministered 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW.

KEY WORDS: Cimetidine · Praziquantel · RP-HPLC · *Microcotyle sebastis* · Rockfish

INTRODUCTION

Cimetidine is a histamine H_2 receptor antagonist and has been shown to differentially inhibit a variety of P_{450} isoforms (Knodell et al. 1991). Administration of cimetidine has been reported to result in clinically significant pharmacokinetic interactions with a variety of drugs, including praziquantel (Dachman et al. 1994, Ebeid et al. 1994, Metwally et al. 1995, Jung et al. 1997). 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*.

Although Kim et al. (2001a) have reported that coadministration of cimetidine with praziquantel led to a significantly increased treatment efficacy of the latter drug against *Microcotyle sebastis*, there are no experimental data on the pharmacokinetic interactions between praziquantel and cimetidine in fish. Therefore,

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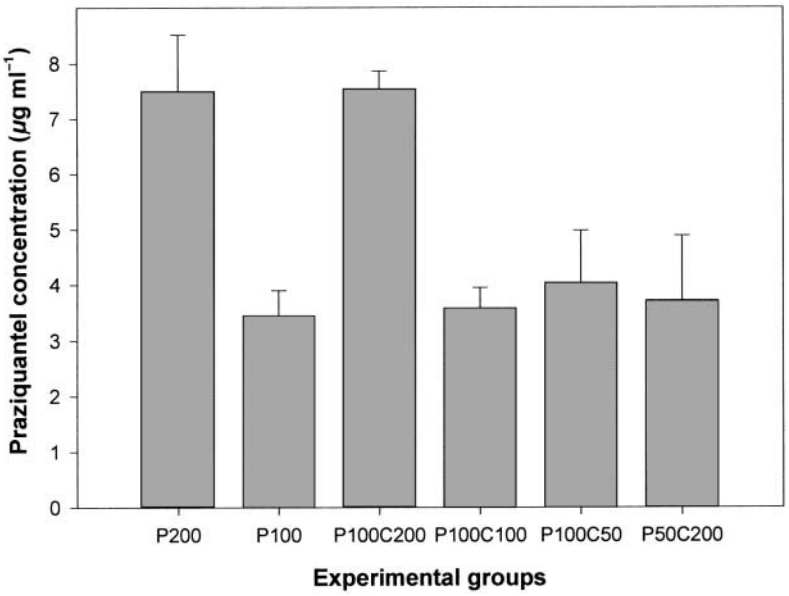

Fig. 1. Plasma concentrations (mean ± standard error) of praziquantel (P) in rockfish *Sebastes schlegeli* 24 h after oral administration of P (mg kg^{-1} BW) alone or coadministered with cimetidine (C, mg kg^{-1} BW) in various combinations

the present study was undertaken to examine the effect of cimetidine on the praziquantel concentration in the blood of rockfish and the consequent effect on the treatment efficacy against *M. sebastis*.

MATERIALS AND METHODS

Fish. Netpen-reared juvenile rockfish *Sebastes schlegeli* (average body weight [BW] 110 g) were obtained from a local rockfish farm in Tongyoung, Korea. The presence of *Microcotyle sebastis* on the gills was confirmed by examination of 5 fish. After a week's acclimation, 35 fish were randomly divided into 7 groups of 5 fish in each group. The volume of each experimental aquarium was 50 l, the water temperature was 20 ± 1°C, and the salinity was 33‰. Fish were not fed throughout the experiment.

Treatment regimen. Fish were anesthetized with MS222 (Sigma) and were intubated directly into the stomach for the administration of varying concentrations of praziquantel and cimetidine. The groups were administered as follows: the first group was fed 200 mg praziquantel (Shinpoong Pharmaceutical) kg^{-1} BW; the second group 100 mg praziquantel kg^{-1} BW; the third group was coadministered 100 mg praziquantel + 200 mg cimetidine kg^{-1} BW; the fourth group 100 mg praziquantel + 100 mg cimetidine kg^{-1} BW; the fifth group 100 mg praziquantel + 50 mg cimetidine kg^{-1} BW; and the sixth group 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW. The fish in the seventh group (control group) were given 0.7% saline. At 24 h post-treatment, all fish in each group were sampled and anaesthetized with MS222. Blood samples drawn from the caudal vein were centrifuged immediately to get plasma samples and were kept frozen at –70°C until analyzed. The gills of fish in each group were examined to confirm the effectiveness of each treatment.

Chromatographic conditions. The chromatographic analysis was performed according to the method established previously in this laboratory (Kim et al. 2001b). The instruments used were a Hewlett-Packard (HP 1100 Series) high-performance liquid chromatograph equipped with QUAT pump (HP1100 Series G1311A), an automatic gradient controller (HP1100 Series G1324A), an injection valve fitted with a 5 ml sampling loop, a variable-wavelength UV detector and a data module. Analysis was performed on an ODS2 C18 column (125 × 4 mm, Hewlett-Packard) with acetonitrile-water (45:55, v/v) as the mobile phase. The column was kept at room temperature (20 to 24°C) and the flow rate was kept constant at 1.0 ml min^{-1}. The detector wavelength was set at 217 nm. Between each 200 µl injection the column was washed for 15 min with 100% acetonitrile.

Preparation of plasma. To a 1.0 ml volume of plasma, 1.0 ml of 100% acetonitrile and 0.4 ml of the inter-

Table 1. Significance in plasma praziquantel concentrations between experimental groups calculated using Student's *t*-test 24 h after oral administrations. C: cimetidine (mg kg^{-1} BW); P: praziquantel (mg kg^{-1} BW)

Group	P200	P100	P100 + C200	P100 + C100	P100 + C50	P50 + C200
P200	–	0.022	0.969	0.062	0.067	0.071
P100		–	0.002	0.848	0.609	0.838
P100 + C200			–	0.004	0.025	0.034
P200 + C100				–	0.745	0.934
P100 + C50					–	0.846

nal standard solution were added. The sample was allowed to stand for 10 min at 4°C, then centrifuged at 10 000 × *g* for 10 min. The collected supernatant was evaporated to dryness with a speed vacuum (Heto-Holten A/S). The dry residue was dissolved in 1 ml of mobile phase, and a portion of 200 µl was injected into the high-performance liquid chromatography (HPLC) column.

Statistical analysis. The plasma praziquantel concentrations were analyzed using Student's *t*-test, and the abundances of *Microcotyle sebastis* were analyzed using the Mann-Whitney *U*-test.

RESULTS

Praziquantel concentrations in plasma

After 24 h of each treatment, the praziquantel concentration in plasma of fish administered 100 mg praziquantel + 200 mg cimetidine kg^{-1} BW was not significantly different from that of fish treated with 200 mg praziquantel kg^{-1} BW and was significantly ($p < 0.05$) higher (ca. 2×) than that of fish administered 100 mg praziquantel kg^{-1} BW (Figs. 1 & 2, Table 1). Although the fish administered 100 mg praziquantel + 100 mg cimetidine kg^{-1} BW or 100 mg praziquantel + 50 mg cimetidine kg^{-1} BW showed slightly higher plasma praziquantel concentrations than fish administered 100 mg praziquantel kg^{-1} BW, there were no statistical significances. However, the group of fish administered 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW showed similar plasma praziquantel concentration to the fish treated with 100 mg praziquantel kg^{-1} BW. No praziquantel was detected in the plasma of control fish.

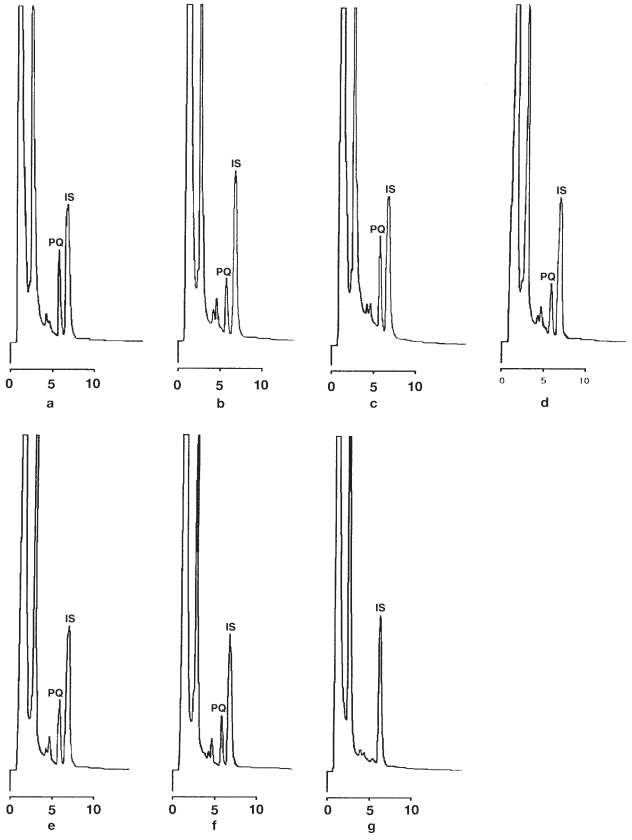

Fig. 2. Chromatograms of praziquantel (PQ) in plasma of rockfish compared with diazepam as an internal standard (IS) 24 h after each oral treatment with (a) 200 mg praziquantel kg^{-1} BW, (b) 100 mg praziquantel kg^{-1} BW, (c) 100 mg praziquantel + 200 mg cimetidine kg^{-1} BW, (d) 100 mg praziquantel + 100 mg cimetidine kg^{-1} BW, (e) 100 mg praziquantel + 50 mg cimetidine kg^{-1} BW and (f) 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW and (g) with control

Treatment efficacy

All the groups of fish administered praziquantel alone or coadministered praziquantel and cimetidine simultaneously showed significantly lower abundances of *Microcotyle sebastis* on the gills than the control fish (Fig. 3, Table 2). The treatment efficacies of the groups of fish coadministered 100 mg praziquantel kg^{-1} BW and various concentrations of cimetidine (200, 100 and 50 mg kg^{-1} BW) were not significantly different from those of the group of fish administered 200 mg praziquantel kg^{-1} BW but were significantly

Table 2. Significance in abundance of *Microcotyle sebastis* between experimental groups calculated using Mann-Whitney *U*-test 24 h after oral administrations. C: cimetidine (mg kg^{-1} BW); P: praziquantel (mg kg^{-1} BW)

Group	Control (saline)	P200	P100	P100 + C200	P100 + C100	P100 + C50	P50 + C200
Control	–	0.000	0.000	0.000	0.000	0.000	0.000
P200		–	0.020	0.346	0.791	0.143	0.111
P100			–	0.026	0.020	0.029	0.707
P100 + C200				–	0.387	0.550	0.138
P100 + C100					–	0.121	0.116
P100 + C50						–	0.153

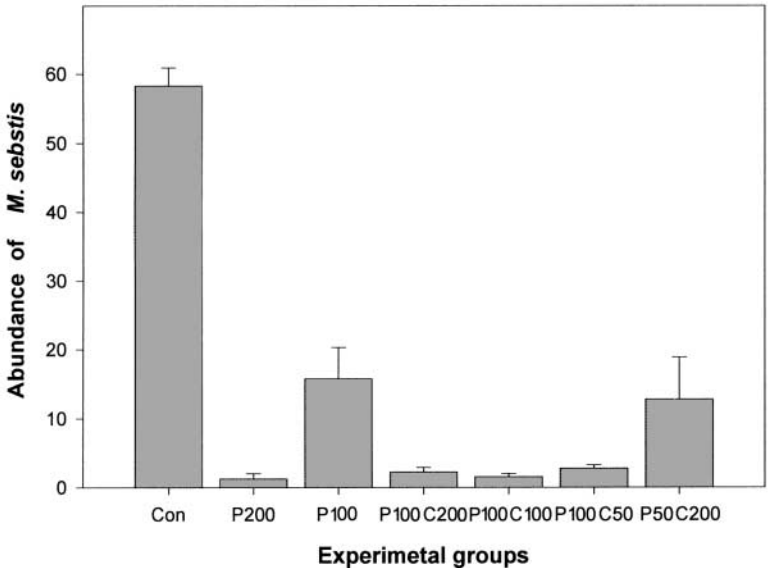

Fig. 3. Abundance (mean ± SE) of *Microcotyle sebastis* on the gills of rockfish *Sebastes schlegeli* 24 h after oral administration of praziquantel (P; mg kg^{-1} BW) alone or coadministered with cimetidine (C; mg kg^{-1} BW) in various combinations

higher than those of the groups of fish fed 100 mg praziquantel kg^{-1} BW alone. Because of large variations in treatment efficacy in the fish coadministered 50 mg praziquantel + 200 mg cimetidine kg^{-1} BW, there were no significant differences between this group and other experimental groups except the control group.

DISCUSSION

The results of the present study agree with a previous report which indicated that coadministration of cimetidine with praziquantel led to a significantly increased treatment efficacy of the latter drug against *Microcotyle sebastis* infestation in rockfish *Sebastes schlegeli* (Kim et al. 2001a). Moreover, in the present study we first demonstrated in fish that these increased treatment efficacies by cimetidine supplementation were through elevation of praziquantel concentration in the blood of treated fish. Masimirembwa & Hasler (1994) reported that praziquantel was metabolized by phenobarbitone-inducible isoforms of cytochrome 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} BW in rats. In the treatment of human neurocysticercosis, increase of praziquantel's bioavailability by coadministration of cimetidine and consequently increase of treatment efficacy were well demonstrated by many studies (Overbosch 1992, Dachman et al. 1994, Jung et al. 1997, Sotelo & Jung 1998, Al-Khodairy et al. 1999).

The present results showed that coadministration of 200 mg cimetidine kg^{-1} BW with 100 or 50 mg praziquantel kg^{-1} BW raised the plasma praziquantel level to that achieved by administration of praziquantel alone at dosages of 200 or 100 mg kg^{-1} BW, respectively. Although addition of 100 mg cimetidine or 50 mg kg^{-1} BW to 100 mg praziquantel kg^{-1} BW did not significantly affect the plasma praziquantel levels 24 h post-administration when compared with oral administration of 100 mg praziquantel kg^{-1} BW alone, the treatment efficacies against *Microcotyle sebastis* were not significantly different from those of the group coadministered 100 mg praziquantel + 200 mg cimetidine kg^{-1} BW. In mammals, cimetidine is rapidly absorbed following oral administration, peak plasma levels being attained after approximately 2 h when taken with food, or after 1 h when taken without food, and about two-thirds of the oral dose is excreted within 24 h (Kelly et al. 1995). According to the pharmacokinetic study of Kim et al. (2001b), praziquantel was also sharply decreased in plasma of rockfish after 24 h of oral administration. Therefore, the results of the present study suggest that oral administration of cimetidine at doses of 100 or 50 mg kg^{-1} BW to rockfish can inhibit praziquantel metabolism in liver and can raise plasma praziquantel levels enough to kill *M. sebastis* within 24 h.

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