STUDIES ON THE CHEMOTHERAPY OF HUMAN OPISTHORCHIASIS IN THAILAND: I. CLINICAL TRIAL OF PRAZIQUANTEL

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INTRODUCTION

Opisthorchiasis is common in the Northeastern part of Thailand where people commonly eat raw or undercooked fish (Harinasuta, 1969). It has been estimated that over 4 million of Thai people suffered from this infection (Wykoff *et al.*, 1965). Although there has been no effective and safe drug for the treatment of opisthorchiasis (Sadun *et al.*, 1955; Plengvanit and Harinasuta, 1961; Wykoff *et al.*, 1967; Bunnag *et al.*, 1970; Muangmanee *et al.*, 1974; Bunnag *et al.*, 1980), drug companies have continued to search for a preparation that would be effective yet non-toxic. The most promising of the new compounds is praziquantel synthesized by E. Merck, and evaluated for antiparasitic activity by Bayer AG, West Germany. Praziquantel is an isochinolin-pyrazine derivative of a new heterocyclic system. It is a colourless, almost odourless, crystalline powder with a bitter taste and stable under normal conditions. The tablets disintegrate in gastric juice (37°C) in approximately 5 minutes.

MATERIALS AND METHODS

A clinical trial of praziquantel was carried out from November 1978 to September 1979. Fifty-eight patients infected with *Opisthorchis viverrini* were admitted to the Hospital for Tropical Diseases, Bangkok. All patients 21 females and 37 males, 17 to 67 years of age (mean 36.2 years) came from the northeastern part of Thailand. Their weights ranged from 41 kg to 86 kg (mean 54.05 kg) and their heights from 144 cm to 181 cm (mean 158.9 cm). The diagnosis of opisthorchiasis was based on detection of *O. veverrini* in stool, dietary habits, history and residence from an endemic area. Most had mild gastrointestinal symptoms, including pain at the right costal margin, dyspepsia and epigastric discomfort which persisted for months to years. Other symptoms were lassitude, aches and pain in the back and legs. Most of the patients were farmers who were able to continue to work in the paddy fields and tapioca plantations.

Patients were divided into two groups of 29 each; Group I consisted of 10 females and 19 males, and Group II consisted of 11 females and 18 males.

Routine physical examination were performed on admission and patients were observed for three days after drug administration. The various laboratory investigations were performed prior to treatment, within 36 hours after the last dose, on days 30, 60, and at subsequent visits, including serum glutamic oxaloacetic and pyruvic transaminases, serum creatinine, and blood urea nitrogen. Electrocardiogram was performed daily for three days (D0, D1, D2). If and when there was any deviation from normal values, the test concerned was monitored daily.

During the pre-treatment period five stool specimens were collected and from each, two aliquots were made and the eggs counted by Stoll's method (Stoll, 1923). The geometrical mean was calculated from ten counts and recorded as pre-treatment eggs per gramme

of faeces (EPG). During the follow-up period, at days 30, 60 and others, the same protocol were followed. When the egg counts became negative, two examinations using a concentration method (Ritchie, 1948) were made from each of the five stool specimens.

The side effects were recorded daily and graded from 0 to 4 (nil, very mild, mild, moderate and severe). Grades 3 and 4 required symptomatic treatment and management.

Dosages:

Two regimens were used:

Group I : Praziquantel tablets, 25 mg/kg body weight, three times daily after meals for two consecutive days.

Group II : Praziquantel tablets, 25 mg/kg body weight, three times daily after meals for one day.

RESULTS

Twenty-nine patients were treated in each group. In Group I, 26 patients completed the follow-up period of 30 and 60 days, while 18 attended for further follow-up from 4 to 8 months. In group II, 23 patients completed the follow-up. The results of stool examination pre and post treatment are shown in Table 1.

All stool specimens were negative for egg during the entire follow-up period except one. From this patient only one specimen (first of five) contained eggs, with two counts of 800 EPG at day 30 follow-up; on subsequent follow-up the stools were negative on day 60, 4 months and 6 months.

Mild transient side effects were common in group 1, include anorexia, nausea, vomiting, abdominal pain, epigastric pain, rumbling in the abdomen, diarrhoea, lassitude, myalgia, headache, dizziness, sleeplessness, sleepiness, "hot sensation", shortness of breath, hyperaesthesia of the back, and complaints about the strong odour of the drug. Headache was the commonest symptom (30.7%). One patient had severe diarrhoea with seven bowel movements on day 0.

The side effects in group II were milder and of a shorter duration, but 3 patients experienced mild tachycardia and 2 patients profuse sweating. One patient also had severe diarrhoea with ten bowel movements on day 0.

There was no objective evidence of toxicity from the results of laboratory tests carried out on the patients.

DISCUSSION

Praziquantel has been found to be an effective drug for opisthorchiasis even though in one patient, the first of five stool specimens showed two positive egg count of 800 EPG on day 30 of the follow-up period. This suggests that some flukes may take up to a month to stop producing eggs and perhaps die. Many drugs including quinacrine hydrochloride

Table 1

Therapeutic effects of praziquantel against *Opisthorchis viverrini* infection.

	No. of cases	Pre Rx	No. of positive cases in follow up (days)				Cure rate%
		mean EPG range	30	60	120	180	
Group I	26	1932-93211	0	0	0	0	100.0
Group II	23	1282-57322	0	0	0	0	100.0

(Sadun *et al.*, 1955) entobex (Plengvaint and Harinasuta, 1961), propoquine (Wykoff *et al.*, 1967), Hetol (Bunnag *et al.*, 1970) Niclofolan (Bunnag *et al.*, 1980), have been tried in human opisthorchiasis but none were found to be highly effective and some produce toxic effects.

The results of this present clinical trial with praziquantel indicate that it seems to be the drug of choice in the treatment of opisthorchiasis. Clinical trails with this drug has been carried out in cases of schistosomiasis (Chou Hsüeh-Chang, 1980), taeniasis (Rim *et al.*, 1979) and has shown excellent activity against all species of schistosomes and cestodes in man and animals. The effect on *Opisthorchis viverrini* is a great advance in the treatment of opisthorchiasis as evidenced by the cure rate in 4-8 months follow-up. At these dosages the drug was evaluated in Vietnamese refugees in France, and the findings were similar (Wegner, pers. comm., 1979). Based on the results obtained so far, it appears that praziquantel is the first drug found to be effective in the treatment of human opisthorchiasis.

SUMMARY

Praziquantel (Embay 8440) was found to be effective in eliminating egg of *Opisthorchis viverrini.* from the stools of 49 patients. Two regimens were used: Group I patients received 25 mg/kg body weight three times daily after meals for two consecutive days: and Group II patients received 25 mg/kg body weight three times daily after meals for one day. In both groups eggs were not detected in the faeces by day 60 and up to 4-8 months post treatment. Mild transient side effects were present in approximately 80% of patients of Group I, with milder side effects reported in Group II. Severe diarrhoea was present on day 0 in one patient from each group. Side reactions included headache, dizziness, myalgia and lassitude, however, no laboratory evidence of toxicity was detected.

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