

STUDIES ON THE CHEMOTHERAPY OF HUMAN OPISTHORCHIASIS : EFFECTIVE DOSE OF PRAZIQUANTEL IN HEAVY INFECTION

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INTRODUCTION

Human liver fluke infection caused by *Opisthorchis viverrini* is common in Thailand. Preuksaraj (1982) estimated over 7 million of the Thai population suffered from this infection. In Northeastern Thailand the prevalence of opisthorchiasis in some areas were as high as over 90% (Harinasuta and Vajrasthira, 1960, Upatham, 1982). The intensity of infections varied from light to heavy infection. Many of Northeastern Thais are heavily infected. The faecal egg output over 10,000 eggs per gramme of faeces (EPG) is commonly found in the age group of 40 and over. The pathological changes are more or less related with the intensity and the duration of the infection (Harinasuta *et al.*, 1984).

Bunnag and Harinasuta (1980, 1981) carried out clinical trials of praziquantel on patients with *Opisthorchis viverrini* infection, using 25mg per kilogramme body weight three times daily for one or two days, and obtained a cure rate of 100%. At dosage of 25mg per kg body weight twice in one day, 25mg per kg body weight single dose, and 40mg per kg body weight single dose, the cure rates were 88.5, 44.4 and 90.9% respectively.

In those studies, the patients had a wide range of EPG. There seems to be some correlation between dosage of praziquantel and intensity of infection. Therefore, a clinical trial of praziquantel, using 50 mg per kilogramme body weight which has been tried in human schistosomiasis, and well tolerated

(Katz, 1979) was conducted to establish an effective dose in opisthorchiasis.

MATERIALS AND METHODS

This study was carried out from October 1982 to April 1983 at the Hospital for Tropical Diseases, Bangkok on 96 patients infected with *O. viverrini*. The egg count was more than 10,000 per gramme of faeces. They had mild symptoms and had no other serious diseases. There were 72 males and 24 females, age ranging from 16 to 73 years (mean 39.0). Their weight ranged from 34 to 74 kg (mean 52.8) and their height ranged from 149 to 173 cm (mean 159.6).

Symptoms and signs before treatment were recorded. Laboratory investigations included complete blood count, liver function tests, blood urea nitrogen, serum creatinine and blood sugar were performed.

Faecal examination and egg count were carried out at pretreatment period and on day 60. One stool specimen was collected and examined by concentration technique and by Stoll's method and recorded as egg per gramme of faeces (EPG).

Praziquantel was given at dosage of 50 mg per kilogramme body weight after a morning meal. The patients were observed in the hospital for 48 hours after the drug administration. The side effects were recorded and their intensity was graded as previously described by Bunnag and Harinasuta (1980).

On follow up at day 60, clinical improvement, beneficial or adverse effect of treatment were obtained from the patients and from physical examination. One stool specimen was examined by concentration method (Ritchie, 1948). If eggs were not found Stoll count was omitted.

RESULTS

Sixty-eight patients completed the follow up period of 60 days. The pretreatment egg count ranged from 10,800 to 139,000 EPG (mean 26,044.3). The effect of praziquantel on day 60 is shown in Table 1; 66 patients were cured. The cure rate was 97.0%. Two patients had positive *Opisthorchis viverrini* eggs in their stools.

Failure case no. 1 was a male, aged 25 years. He weighed 49 kilogrammes. He had 28,800 EPG before treatment. He took praziquantel 4 $\frac{1}{4}$ tablets (2,550 mg) single dose without any side-effect. On day 60, *O. viverrini* eggs were recovered from one stool specimen. The count was 3,200 EPG, and the egg reduction was 88.8%.

Failure case no. 2 was a male, aged 32 years. He weighed 60 kg. He had 33,200 EPG at pretreatment period. He took praziquantel 5 tablets (3,000 mg) single dose

successfully. On day 60, the stool examination was positive for *O. viverrini* eggs, (1,600 EPG). The egg reduction was 95.8%.

These two patients denied retaking raw fish food after treatment. Both showed clinical improvement.

Side-effects occurred in 61 of 68 patients (89.7%). Diarrhoea was the most common, observed in 37 of 68 patients (54.4%). The other side-effects were dizziness in 25 (36.4%) and sleepiness in 19 (27.9%). Epigastric pain, headache, nausea and anorexia occurred in 17 (25%), 11 (16.2%) and 9 (13.2%) respectively.

Mild side-effects such as lassitude, abdominal discomfort, hot sensation, low back pain, myalgia, and palpitation occurred in less than 10% (Table 2).

All of these side-effects were mild and transient. Only one patient had severe diarrhoea, epigastric pain and dizziness. He needed intravenous fluid replacement and recovered on the following day. Many of them observed that the side-effects of dizziness and sleepiness subsided after they had a good sleep.

Clinical improvement : general health, parasitological cure and clinical assessment on day 60 were followed up 62 patients

Table 1

Therapeutic effect of praziquantel in opisthorchiasis patients with heavy infection.

No. of patients	Pre-treatment GM EPG (range)	Post-treatment		Cure rate
		No. negative	No. positive	
68	26,044.3 (10,800-139,000)	66	2	97.0%

GM = geometrical mean.

EPG = egg per gramme of faeces.

Table 2
Number of patients with side-effects following praziquantel treatment.

Side-effects	Grading*				Total	Percent
	I	II	III	IV		
Diarrhoea	7	29	1	0	37	54.4
Dizziness	24	1	0	0	25	36.4
Sleepiness	16	3	0	0	19	27.9
Epigastric pain	10	7	0	0	17	25.0
Headache	9	2	0	0	11	16.2
Nausea	8	1	0	0	9	13.2
Lassitude	4	2	0	0	6	8.8
Abdominal discomfort	5	0	0	0	5	7.4
Hot sensation	3	0	0	0	3	4.4
Low back pain	3	0	0	0	3	4.4
Myalgia	1	1	0	0	2	2.9
Palpitation	1	0	0	0	1	1.5

* I = very mild, II = mild. III = moderate, appropriate medication was prescribed, IV = severe, requiring both medication and bed rest.

Table 3
Clinical improvement evaluated on day 60 post-treatment.

Clinical change	No. of patients	Percent
No improvement	2	2.9
Improved	62	91.2
Improved less than 50%	10	14.7
Improved over 50%	32	47.1
Improved 100%	20	29.4
Not assessable	4	5.9
Total	68	100

(91.2%) showed clinical improvement; in ten patients clinical improvement was less than 50%; symptoms improved over 50% in 52 patients while 20 patients were completely cured. (Table 3).

DISCUSSION

Praziquantel at dosage of 50 mg per kilogramme body weight in heavy infected patients, attained a cure rate of 97%. This

result was similar to previous studies using 40 mg per kilogramme body weight (Bunnag and Harinasuta, 1981; Supanvanich *et al.*, 1982; Vivatanasesth *et al.*, 1982). However, in this study the intensity of infection was high.

Side-effects in this study were higher (80.7%) than in other studies (Bunnag and Harinasuta 1981). These side-effects were mild and transient; it appeared to be dose related.

Clinical improvement on day 60 was 91.2% which was comparable with the cure rate. Two patients had positive *Opisthorchis viverrini* eggs in stool on day 60, eventhough, they denied consuming raw food. They had returned to endemic area during the follow up period. The prepatent period of *O. viverrini* is known to be less than 8 weeks. They might have eaten infective metacercaria from contaminated utensils, and reinfection might occur. Another possibility was the residual of previous infection. The flukes were affected by praziquantel, though most of them died but some were injured and may have recovered. Sirisinha (1984) studied *in vitro* exposure of the flukes with various concentration of praziquantel. Some flukes remained alive.

Praziquantel tablet preparation of 600 mg could easily be quartered and the dose could be rounded to the nearest 150 mg. To prescribe 40mg per kg body weight with tablets could not be made exactly, for in most cases it turn out to be nearly 50 mg per kg body weight. Since, the efficacy of praziquantel at dosage of 40mg per kg body weight is similar to 50mg per kg body weight, the drug regimen chosen for treatment opisthorchiasis should be a single dose of 40-50mg per kilogramme body weight of praziquantel.

SUMMARY

Ninety-six patients who had heavy *Opisthorchis viverrini* infection were studied. Egg

count per gramme of faeces ranged from 10,800 to 139,000 (mean 26,044.3). Praziquantel 50 mg per kg body weight was given after a morning meal. 68 patients completed the follow up period of 60 days. The cure rate was 97.0%. The side-effects occurred in 61 patients (89.7%). The common side effects were diarrhoea, dizziness, sleepiness, epigastric pain, headache, nausea and anorexia. These side-effects were mild and transient. 62 patients (91.2%) showed clinical improvement, and 20 patients were symptom free on day 60.

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