STUDIES ON THE CHEMOTHERAPY OF HUMAN OPISTHORCHIASIS: III. MINIMUM EFFECTIVE DOSE 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). Praziquantel has been found to be an effective drug on human opisthorchiasis, at 25 mg per kilogramme body weight three times daily for one or two days (Bunnag and Harinasuta, 1980). The purpose of this study is to find the minimal effective dose of praziquantel for the treatment of opisthorchiasis.

MATERIALS AND METHODS

A clinical trial of praziquantel was carried out from April 1979 to May 1980 on 97 patients infected with *Opisthorchis viverrini* who came from the Northeastern part of Thailand and were admitted to the Hospital for Tropical Diseases, Bangkok. There were 66 males and 31 females, 13 to 70 years of age. Most of them had mild clinical manifestation, including from occasional to constant pain at the right costal, left costal and epigastric regions, low back pain and lassitude. None of them had jaundice or fever. The diagnosis and the methods for evaluation were the same as those described previously (Bunnag and Harinasuta, 1980). Two regimens, I and II were reported earlier. Three more regimens III, IV and V were used in this trial. In group III, there were 30 patients, 18 males, and 12 females whose age ranged from 17 to 64 years (mean 38.6), body weight ranged from 41 to 71 kg (mean 51.9) and height ranged from 149 to 197 cm. (mean 160.8). In group IV there were only 12 patients, because the efficacy was low, the allocation of patients was interrupted. There were 5 males, and 7 females aged from 19 to 63 years (mean 42.8), body weight ranged from 40 to 77 kg (mean 50.6) and height ranged from 148 to 172 cm. (mean 158.6); while in group V there were 55 patients, 43 males, and 12 females age ranging from 13 to 70 years (mean 37.6), body weight ranged from 29 to 72 kg (mean 52.3) and height ranged from 139 to 173 cm. (mean 159.8). Searching for worms in stool after praziquantel administration was carried out in patients with high egg count, by sedimentation.

Dosages

Three regimens were used:

Group III : Praziquantel tablets 25 mg/kg body weight, twice in one day after meals at 8.00 and 17.00 hr.

Group IV : Praziquantel tablets, 25 mg/kg boy weight, single dose after morning meal.

Group V : Praziquantel tablets, 40 mg/kg body weight, single dose after meal.

RESULTS

Efficacy

In group III, IV and V, 26, 9 and 44 patients respectively completed the follow-up period

of 30 and 60 days. The results of stool examination, pre and post treatment are shown in Table 1. On day 60, cure rates of 88.5%, 44.4% and 90.9% were obtained in group III, IV and V respectively. The efficacy of the drug regimen of group III and V showed no significant difference (Chi square test).

Side effects

The side effects from each patient were observed for at least three consecutive days or until the symptoms and signs disappeared, The duration was recorded and the intensity was also graded. Grade I the side effects were very mild; grade II mild; grade III moderate,

Table 1

Therapeutic effect of praziquantel in patients with *Opisthorchis viverrini* infection.

Group	No. of patients	Pre Rx GM·EPG (range)	No.neg/No.exam.		Cure rate%
			Day 30	Day 60	on Day 60
III	30	15,504 (679-77,573)	24/26	23/26	88.5
IV	12	13,510 (1,184-43,468)	4/10	4/9	44.4
V	55	12,858 (929-97,380)	39/44	40/44	90.9

GM = geometrical mean; EPG = eggs per gramme of faeces.

Table 2

Side effects, (intensity and duration) following praziquantel administration.

Group: Dosages	III : 25 mg/Kg b.d.					IV : 25 mg/Kg					V : 40 mg/Kg*				
Pt.with side effect	21/30 (70%)					5/12 (42%)					26/55 (47%)				
Grades of intensity	I	II	III	IV	No. Pt.	I	II	III	IV	No. Pt.	I	II	III	IV	No. Pt.
Abdominal pain	5	4			7		2			2		2			2
Anorexia							1			1		1			1
Nausea		2			2							1			1
Diarrhoea	1	1			2						21	1			21
Headache			1		1		1			1		4			4
Dizziness	3	2			3										
Lassitude		4			3	1	1			1	1	6			6
Myalgia		3			3										
Tachycardia		3			2										
Sleepiness		2			2										
Hot sensation						3				1		4			2
Skin rash	1	2			1										

* Saturated magnesium sulphate was given.
Grade of intensity I, II, III and IV = very mild, mild, moderate, severe.

+ Figures in the column under the grades are symptom-days i.e. number of pt. experiencing the symptom x duration of symptom in days.

appropriate medication was prescribed, and in grade IV, severe, requiring both medication and bed rest. There were side effects in 52 of 97 patients (54%); highest in group III (70%). Apart from diarrhoea the frequent symptoms were generalised abdominal pain in 11 patients (11%), lassitude in 10 (10%) and headache in 6 (6%). All of these were mild and transient (Table 2).

The other complaints were : in group III, one patient, complained of pain below the left costal margin for one hour after the second dose; one, an urge to defaecate lasting one day; two, abdominal rumbling on day 0 and day 1 and one, fine papular rash on the trunk for three days; this patient gave a past history of maculo-papular rash and fixed drug eruption on penis so the skin rash may not have been due to praziquantel. In group IV, one patient complained of heaviness in both legs for one day, one had chest pain 15 hours after drug administration. The ECG was normal and the pain was not relieved by nitroglycerine, the pain lasted 20 minutes. In group V, it should be noted that saturated magnesium sulphate was given to some patients in this group, so it was difficult to evaluate whether the gastro-intestinal symptoms as well as lassitude were due to praziquantel or to magnesium sulphate.

There was no evidence of toxic effect on the heart, the kidneys, the liver, the brain and/or blood forming organs in any patient in all groups.

Clinical improvement

As shown table 3, a high percentage of clinical improvement was observed in all groups by day 30 and at day 60 follow up, total relief of symptoms was observed in 33% of them.

In the non assessable group, the symptoms, such as low backache, lassitude, myalgia of back and legs, were not directly related to the biliary system, the liver or to the gastro-intestinal tract.

Flukes recovered from stool

Stools were collected for 3 days after administration of praziquantel. Flukes were searched for in the stools using sedimentation technique. Many dead and disintegrated flukes, some with irregular and punched out lesions were recovered. In order to obtain flukes in good condition and to facilitate the searching, 45 ml of saturated magnesium sulphate with 2-4 glasses of warm water were given four hours after the drug administration. The patients passed watery stools on 1-5 occasions. Numerous flukes came out alive. There were flukes in the first motion passed 1-2 hours after magnesium sulphate or 5-6

Table 3

Clinical improvement after praziquantel therapy, follow up.

	Group III	Group IV	Group V
Number of patients	26	9	44
No.Pt.not assessable	10	5	8
No.Pt.no improvement	2	0	3
No.Pt. clinical improvement, day 30	14(88%)	4(100%)	33(92%)
Pain RCM, LCM, etc.	11	3	26
Pain epigastrium	3	1	7
Total relief, day 60	3(21%)	1(25%)	13(39%)

RCM, LCM = Right Costal Margin, Left Costal Margin.

hours after administration of praziquantel. All the liver flukes recovered were identified as *Opisthorchis viverrini*. The highest number recovered from one patient was 2,822.

DISCUSSION

Rim (1980) and Rim *et al* (1981) carried out a clinical trial of praziquantel on *Clonorhcis sinensis* infection in Korea using 25 mg per/kg body weight three times a day for one day, 25 mg per kg body weight twice daily for two days and a single dose of 40 mg per kg body weight. Cure rates of 86.8%, 80.0% and 25% were obtained respectively.

The cure rate in our studies on opisthorchiasis were higher than those of Rim's with clonorchiasis; 100% cure rate was obtained with 25 mg per kg body weight three times for one day (Bunnag and Harinasuta, 1980) and in this trial, group III with 25 mg per kg body weight twice in one day, and group V with a single dose of 40 mg/kg yeilded cure rates of 88.5% and 90.9% respectively. Ambroise-Thomas (1980) used 75 mg per kg body weight in three divided doses on opisthorchiasis in 46 Loatian immigrants. The results were excellent.

It should be mentioned that patients included in our studies were heavily infected, the geometric mean of egg counts per gramme of faeces in the groups mentioned above were 15,504, 11,676, and 12,858. It could therefore be concluded that praziquantel is more effective against opisthorchiasis than clonorchiasis. This may be due to the difference in the structure of the integument and hence the vulnerability to praziquantel.

Opisthorchis viverrini were recovered in the stool 5-6 hours after praziquantel administration confirming the rapid action of the drug on the flukes. The dead flukes appeared to have similar lesions to those described by Mehlhorn (1980).

The side effects were similar to other studies and those reported earlier (Bunnag and Harinasuta, 1980) but were milder and of shorter duration that no symptomatic treatment was needed by any patient. The side effects appeared to be dose related.

Opisthorchis viverrini live in the bile ducts; after treatment with praziquantel, the dying or the dead worms are expelled with the bile into the intestines and come out with the stool. Allergic reaction to foreign protein of the dead worms such as fever and skin rash were not observed in our patients.

There was no evidence of biliary obstruction following praziquantel treatment, the dying or dead worms seen in stool did not stick together to form a bolus.

Opisthorchiasis is common among poor people in the rural areas of Thailand. The drug regimen chosen for the treatment and control of the disease, apart from being very effective and tolerable, must be easy to administer and not expensive. The authors recommend a single dose of 40 mg per kg body weight of praziquantel.

SUMMARY

A clinical trial of praziquantel was carried out in patients with opisthorchiasis using low dosages with 30 and 60 days follow-up. In group III, 30 patients treated with praziquantel 25 mg per kg body weight bid, for one day yielded a cure rate of 88%. In group IV, 12 patients received 25 mg per kg body weight in a single dose and gave a cure rate of 44%. In group V, 55 patients received 40 mg per kg body weight in a single dose and yielded a cure rate of 91 %. Mild and transient side effects were present in 54 %, these included abdominal pain, lassitude, headache, dizziness, nausea, diarrhoea, myalgia and tachycardia.

Clinical improvement was observed in most of the patients after one month and 33% of them were clinically cured in two months.

The recommended dose of praziquantel for the treatment and control of opisthorchiasis in the endemic area is a single dose of 40 mg per kg body weight after meals.

ACKNOWLEDGEMENTS

The authors wish to thank the Dean, Professor Chamlong Harinasuta for his encouragement, Messrs Bayer AG, West Germany for partial financial support and providing the drugs for this clinical trial, the technical and nursing staff of the Bangkok Hospital for Tropical Diseases for their assistance and Mr. Prayong Radomyos for his enthusiasm in searching for the flukes.

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