DOSE FINDING DOUBLE-BLIND CLINICAL TRAIL WITH PRAZIQUANTEL IN SCHISTOSOMIASIS JAPONICA PATIENTS

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INTRODUCTION

Clinical studies on praziquantel in treating patients with *Schistosoma japonicum* infections have been carried out since 1978 in the People's Republic of China. Dosages of and over 60 mg/per kg body weight of praziquantel in divided doses over one or two days gave very promising therapeutic effects with only mild and transient adverse reactions (Anon, 1980; Fu *et al.*, 1984). The oneday regimen with a total of 60 mg/kg was also used in the Philippines with 80% and 89.2% parasitological cure six months after treatment (Santos *et al.*, 1979; 1983).

However, only a few studies have been published (Santos *et al.*, 1979; Fu *et al.*, 1983; Hua *et al.*, 1984) concerning lower total dose of praziquantel in the treatment of *S. japonicum* infections. To investigate further the suitable dosage of praziquantel for mass treatment of schistosomiasis, a dose finding double-blind clinical trial was designed and carried out among 400 cases of schistosomiasis japonica in a heavily endemic area in Dongzhi County, Anhui Province from April to October 1984.

MATERIALS AND METHODS

All the patients came from an endemic area named Qili Lake Administrative Region in the south of the Yangzi River bank. Inhabitants living in this area were screened parasitologically for *S. japonicum*. Miracidia were positive in 634 among 2,901 inhabitants upon single stool examination. 400 of them were hospitalized in Dongzhi Antischistosomiasis Station and subjected to the trial. They included 250 males and 150 females, in ages ranging from six to 64; 85 of them were children under 15 years of age. Most of the adults were farmers who were able to continue to work in the fields. Of the 400 cases, 14 were advanced schistosomiasis patients including schistosomal liver cirrhosis and splenomegaly in 12, of whom six had had their spleen removed, and schistosomal dwarfism in two; 37 had concurrent chronic cardiovascular, gastrointestinal, respiratory, renal or other disorders. Not included in the trial were those who had had other treatment within the previous six months, had been suffering from acute coexistant diseases, under five years of age, and in case of female, either pregnant or lactating.

Praziquantel with the Chinese name pyquiton and placebo tablets manufactured in 1984 were supplied by Shanghai No. 11 Pharmaceutical Factory. Firstly, entrants were stratified into two strata according to their ages, namely, children under 15 years of age and those over 15 years. Then, from within these strata, patients were randomized from a table of random number made before the start of the studies to one of the four treatment groups whose dosage and pretreatment variables are shown in Table 1. Two

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Table 1

Pretreatment variables in different dosage groups.

Group	Dose (mg/kg)	No. treated	Mean age (Years ± SD)	Proportion of	
				Males	Children*
A	2×30	100	27±14	58/100	21/100
B	2×25	101	24±13	64/101	22/101
C	2×20	100	26±14	65/100	21/100
D	2×15	99	25±12	63/99	21/99

*Under 15 Years of age.

Table 2

Results of parasitological follow-up in schistosomiasis japonica patients with regard to different villages (institution).

Name of village	No. of patients examined	Negative	
		No.	%
Office workers and teachers	12	12	100
Yanwo	60	57	95.0
Shunfengju	40	37	92.5
Qiaodong	10	9	90.0
Laozha	47	39	83.0
Bianzhai	41	34	82.9
Jiangyao	16	11	68.8
Shahe	54	35	64.8
Lingfeng	104	57	54.8
Xianghe	10	5	50.0
Total	394	296	75.1

doses were given at interval of six hours within one day. Placebo tablets of identical appearance were used to make up a total of 60 mg/kg for every patient in the four groups. The trial was a double-blind assessment of the efficacy and tolerance in schistosomiasis patients.

Efficacy was assessed by parasitological examination of three consecutive daily stools of patients using hatching test about six months after treatment. Before hatching, a nylon tissue bag method (Yu *et al.*, 1981) was used for concentrating schistosome eggs in about 30 gm of stool specimen. The frequency and severity of side effects after the drug administration were assessed by direct questioning. Electrocardiograms were recorded in 11 patients of each treatment group before medication and 24 hours after the first dose.

RESULTS

Therapeutic efficacy: At approximately six months post-treatment, 394 (98.5%) of the 400 cases were reexamined parasitologically by three consecutive stool hatchings

each. 296 (75.1%) were negative for miracidia The negative rates in group A, B, C and D, in which, patients from different villages were all randomly allocated, were 79.8% (79/99), 71.7% (71/99), 78.8% (78/99) and 70.1% (68/97) respectively. No statistically significant difference was found among the four groups ($x^2 = 2.46$, $p > 0.05$). However, when patients of various occupations and from different villages were assessed separately, the therapeutic effects were quite different as shown in Table 2. The negative rates for miracidia were as high as 100% among office workers and school teachers and as low as 50% in Xianghe village. Effects in other farming villages ranged from 54.8% to 95%. Reinfection was considered to be the reason of the lower cure rates.

According to the distribution and density of *Oncomelania* snails, the villages involved could be grouped into two categories. In Lingfeng, Shahe and Jiangyao snails were abundant, exposure of the villagers to infested water was constant and no other control measure was advocated. The stool negative rates among patients from these three villages in Groups A, B, C and D were 68.2% (30/44), 46.5% (20/43), 66.7% (30/45) and 54.8% (23/42), with overall negative rate of 59.2% (103/174).

In Lingfeng village, most of the households were situated along the Yangzi River in a highly endemic spot. Of the five inhabitants from one household in the village, all were positive by stool hatching at six-month follow-ups, three of them having been treated with a total of 60 mg/kg and two, with a total of 50 mg/kg. As these two regimens of praziquantel are usually of high efficacy in schistosome infection, the five patients from that family was considered to be the result of re-infection rather than treatment failure.

In patients from other villages where snails were scarce, the negative stool hatching rates six months after treatment in Groups A, B, C and D were 89.1% (49/55), 91.1% (51/56), 88.9% (48/54) and 81.8% (45/55) respectively, the overall negative rate being 87.7% (193/220) (Table 3). Its difference with that of patients from Lingfeng, Shahe and Jiangyao villages where re-infection was easily encountered, was statistically significant ($\chi^2 = 42.3$, $\rho < 0.01$).

The efficacy between children under 15 years of age and adults was different. The stool negative rates in Groups A, B, C and D were 84.6% (66/78), 77.9% (60/77), 83.3% (65/78) and 74.0% (57/77) in adults, and 61.9% (13/21), 50% (11/22), 61.9% (13/21) and 55% (11/20) in children. The differences

Table 3

Results of parasitological follow-up with regard to chance of reinfection.

Group	Areas where reinfection was scarce			Areas where reinfection was common		
	No. patients examined	Negative		No. patients examined	Negative	
		No.	%		No.	%
A	55	49	89.1	44	30	68.2
B	56	51	91.1	43	20	46.5
C	54	48	88.9	45	30	66.7
D	55	45	81.8	42	23	54.8
Total	220	193	87.7	174	103	59.2

Table 4

Percentages of symptoms present after treatment with praziquantel.

Symptoms	Group A (n=100)	Group B (n=101)	Group C (n=100)	Group D (n=99)
Nausea	15	7.9	9	10.1
Vomiting	4	3.0	1	3.0
Anorexia	9	4.0	2	4.0
Abdominal pain	17	22.8	17	19.2
Abdominal distension	11	5.9	7	7.1
Diarrhoea	5	5.0	6	1.0
Headache	7	6.9	5	1.0
Dizziness	25	28.7	36	30.3
Lassitude	3	7.9	4	7.1
Skin rashes	4	2.0	2	0
Free of symptoms	43	43.6	45	44.4

were of statistical significance ($x^2 = 18.5$, $p < 0.01$). Nevertheless, such difference was not observed in areas where re-infection was scarce, since the stool negative rates were 87.8% (165/188) in adults and 87.5% (28/32) in children, in contrast to areas where re-infection was easy and where rates were 68.0% (83/122) in adults, and 38.5% (20/52) in children, with significant difference ($\chi^2 = 6.94$, $\rho < 0.01$).

Tolerance: Tolerance to the drug was very good. Only minor post-treatment symptoms being noted, all of a short duration. The types and percentages of adverse reactions within dosage groups are shown in Table 4. Dizziness, abdominal pain, nausea and abdominal distension were the main complaints, all of tolerable degree. No patients' treatment had to be interrupted because of adverse reaction. The reactions were milder in children but appeared relatively more frequently in females than in males. In comparative studies, no significant difference was observed in respect to adverse reactions among the four dosage groups. 176 cases (44%) were free from any reaction during the treatment course. However, one girl of 14 became asthmatic one hour after the first does of the drug administration and developed papule rashes over large areas of the body surface. After being treated with dexamethasone, the symptoms subsided quickly. One other patient had not taken part in physical work for six months after treatment because of headache, dizziness and loss of appetite. They had been both in good health before praziquantel administration.

No changes of clinical relevance were detected in a battery of electrocardiography in 44 cases in the four groups.

DISCUSSION

The trial showed that the differences of parasitological effects of praziquantel in the four groups of different dosage levels (60, 50, 40 and 30 mg/kg), either in adults or in children, were not statistically significant. Further analysis of the efficacy among patients from different villages, however, showed that

their parasitological cure rates six months after medication differed greatly. This is thought to be due to different natural environments with varying degrees of snail density and risk of inhabitants to contact infested water. When the ten villages were divided into two categories: one situated in areas with abundant snails and the other with fewer snails, one can see that the therapeutic effects among inhabitants from Lingfeng, Shahe and Jiangyao villages, where snails were abundant and exposure was constant, were lower than those from other villages where snails were much fewer and non-farming population who were less exposed. All patients under trial lived in schistosomiasis endemic area for about six months covering schistosomiasis transmission season. Re-exposure and reinfection were thought inevitable. This may be accountable for the lower therapeutic effects in this trial as compared with other reports in China (Anon, 1980; Fu *et al.*, 1983; Hua *et al.*, 1984; Fu *et al.*, 1984). However, as it is a double-blind randomized clinical trial, the results are comparable. A simple statistical analysis suggested little difference among failure rates at different dosages. It means that the effects of praziquantel with a total of 30 or 40 mg/kg were not significantly lower than those with commonly used regimen (60 mg/kg) in China. Since praziquantel is still rather expensive and cost effectiveness is important in mass chemotherapy programmes for schistosomiasis, the authors suggest that praziquantel with a lower total dose (30 to 40 mg/kg) may be preferable for the chemotherapy of schistosomiasis.

The efficacy of praziquantel in children in this trial was lower than that in adults Further analysis revealed that in children who lived in areas where snails were few the cure rate was no lower than that in adults; while in areas where reinfection was easy, the cure rate in children (38.5%) was significantly lower than that in adults (68.0%) It is clear that children, because of their behaviour, are more exposed to risk of reinfection However, under comparable condition, the parasitological cure rates of children in easily reinfected areas in the four dosage groups of praziquantel did not reveal statistical significance It is then suggested that in the treatment of children infected with *S japonicum*, within the dosage range used, namely, 30 to 60 mg/kg, the efficacy of praziquantel does not increase in accordance with the total dose.

SUMMARY

A double-blind clinical trial with praziquantel was carried out. A total of 400 cases was treated with four different dosages, namely, 60, 50, 40 and 30 mg/kg body weight of praziquantel. The drug was given in one day divided into two doses. Identical placebe tablets were used to make up a total of 60 mg/kg. Tolerance was good in all with the exception of one case suffering from asthmatic attack with papule rashes over large area of the body surface. 394 patients were able to be followed up parasitologically six months post-treatment. 79.8%, 71.7%, 78.8% and 70.1% of the patients were negative in the groups with the total dose of 60, 50, 40 and 30 mg/kg respectively. The cure rates as well as the side effects were similar for the four groups. The efficacy was lower than that reported by other authors and the possibility of reinfection was incriminated. In villages with few snails the negative hatching rates in aforementioned four groups were 89.1%, 91.1%, 88.9% and 81.8%, while in villages with abundant snails the rates were 68.2%, 46.5%, 66.7% and 54.8%. The difference between the two areas was statistically significant. Higher efficacy was observed in adults with an average cure rate of 80.0% than in children under 15 years of age, the average cure rate being 57.1%. Since no statistical significance was found in cure rates

with different dosages of praziquantel, either in adults or in children, the authors suggest that praziquantel with a lower total dose, namely, 30 to 40 mg/kg, might be preferable for the routine treatment of schistosomiasis japonica.

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