CHEMOTHERAPY OF SCHISTOSOMIASIS JAPONICA IN CHINA

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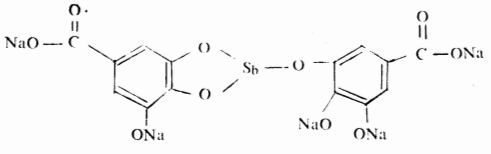
INTRODUCTION

The chemotherapy of schistosomiasis japonica in the People's Republic of China, experimental studies and clinical trials of some drugs currently used are reviewed herein.

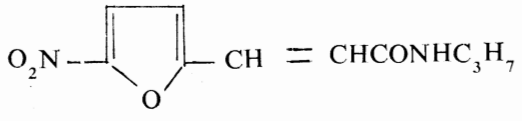
In the past trivalent antimonials, mainly potassium antimony tartrate, have been used in the treatment of schistosomiasis japonica for several decades in China. Even though the efficacy of the drugs in killing schistosomes has decreased the morbidity, their side effects were serious, especially cardiac and hepatic toxicities and the former might lead to sudden death.

Among a number of trivalent antimonials developed in China, sodium stibo-gallate with the chemical structure as follows



is an oral antimonial synthesized in China in the early sixties. It had been widely used in several million of schistosomiasis patients in selective mass treatment before 1980s. Though it had the advantages of a lower incidence of cardiac arrhythmia and easier administration, it was less potent as compared with potassium antimony tartrate.

Among several non-antimony preparations used in China, furapromidum, synthesized by Chinese scientists in the later part of the fifties, exhibited its cidal effect on both adult worm and schistosomula. But the negative



conversion rate of ova was found to be not so high when it was used alone, as compared with other effective drugs. Animal experiments revealed that the drug was rapidly degraded by enzymal activities in the liver soon after being absorbed from the intestines. As a result, the schistosomes inhabiting in the inferior mesenteric vein and its ramifications could easily escape the drug action. In order to overcome this shortcoming, the combined use of oral furapromidum with rectal dipterex suppository, or with dipterex by intramuscular injection, was developed by Chinese pharmacologists. Dipterex used herein was to expel the worms from the inferior mesenteric vein to the liver where they were subjected to the action of furapromidum. The therapeutic effect of the furapromidum-dipterex combination regime was comparable to potassium antimony tartrate, but less toxic to the heart and liver, and had been used in China for about 10 years in several hundred thousand patients before praziquantel became available in the chemotherapeutic arsenal for schistosomiasis. Other chemicals, such as niridazole, hexachloro-p-xylene, pararosaniline pamoate, and Chinese herbs were also tried in treating *S. japonicum* infections in a relatively short period.

Although all the above-mentioned drugs are effective in *S. japonicum* infections, they have the disadvantages of long treatment course, 10 days or more, inconvenient administration and, in case of antimonials, unsafety. The recent development of safe and effective oral drugs has greatly changed the situation. Now chemotherapy plays a very important role in the control of schistosomiasis japonica. Some drugs against *S. japonicum* infections currently used in China are as follows :-

PRAZIQUANTEL (BILTRICIDE, EMBAY 8440)

Experimental studies and clinical trials began in 1978 using praziquantel both supplied by Bayer AG, Federal Republic of Germany and locally manufactured product. Up till now about one million cases of schistosomiasis have been treated with praziquantel (known as Pyquiton in China).

Praziquantel has been found to possess a strong and direct action against *S. japonicum*. When the drug was given orally to infected rabbits with a single dose of 100 mg/kg, all animals were cured. When 20 mg/kg of praziquantel was administered orally to infected dogs for three times in one day, a worm reduction rate of 100% was obtained. Experimental results indicated that female worms were more susceptible to praziquantel than male ones.

Praziquantel exerted no obvious action on mature or immature eggs. However, the miracidia emerged from the ova were damaged by the drug at a concentration of 1 μg/ml. Praziquantel was also effective against invasive stage of schistosomula but the juvenile worms were less susceptible to praziquantel than adults (Shao *et al.*, 1980).

Animal treated with a curative dose of praziquantel showed no apparent side effects. No marked changes in haematology, urinalysis and in hepatic and renal functions were observed. No indication of mutagenicity and teratogenicity was seen by Ames test or in mammalian experiments (Ni *et al.*, 1982).

Clinical trials

Dosage schedules: The drug is given orally. Different dosage schedules have been used in China. They included 1×40, 1×60, 2×15, 2×20, 2×25, 2×30, 3×15, 3×20 mg/kg in one day, and 4×15, 6×10, 6×15 mg/kg in two days for latent cases with or without complications, 6×10, 9×8 mg/kg in three days for chronic or advanced cases and 18×5 mg/kg in six days for advanced cases or latent cases with coexistent serious illness, and 9×10 mg/kg in three days and a total of 120 mg/kg divided into 12 or 18 doses over four or six days for acute schistosomiasis. For selective mass chemotherapy, the total dose of 60 mg/kg divided into three (one day) or six doses (two days) has been used widely. However, since 1984, a single dose of 40 mg/kg or a total of 40 mg/kg divided into two doses with six hours apart has been preferred in some endemic areas.

Side effects: Most of the cases tolerated the drug well and their normal activities were not hindered during and after the treatment course. About 30% to 50% of the cases were free from any reactions and more than 98% of the cases completed the regimes on schedule. Severe drug reactions necessitating the interrruption of treatment occurred only in a very few cases. Side effects involved mainly the nervous, digestive and cardiovascular systems.

Dizziness, headache and fatigue were the chief complaints. Insomnia, muscular tremor, sweating, vertigo, drowsiness were also recorded in some patients. Usually they were mild in degree and transient. Abdominal pain and diarrhoea in tolerable degree were experienced by a few cases. Other complaints

included nausea and abdominal distension. Abdominal cramps followed by passing bloody stools were occasionally seen. Palpitation, premature beat, bradycardia were noted in some patients and tachycardia in children. Pain in limbs, skin rash, fever, chest tightness were encountered in some cases (Anonymous, 1980a; Fu *et al.*, 1983; 1984).

A retrospective survey involving 25,693 persons was carried out in four provinces and the city of Shanghai to document relatively serious side effects of praziquantel used in a mass treatment programme for schistosomiasis japonica. Only 122 or 0.47% of those participating in the study had experienced relatively serious side reactions to the drug. However, most of the side effects were transient and reversible and no fatality could be directly associated with the drug (Chen *et al.*, 1983).

Some of the cases had increased blood eosinophil count after treatment. Almost no significant pathological findings were recorded in various laboratory examinations such as haematological, biochemical, hepatic and renal function tests.

Electrocardiographic changes were noted in a few cases. Depressed, diphasic or slightly inverted T waves were recorded. Other changes included arrhythmia, for example, premature beats, escape beats and paroxysmal supraventricular tachycardia, as well as first degree auriculoventricular block. Generally, these changes were not serious and eventually returned to normal within a short period after drug cessation.

Electroencephalographic tracings in 105 cases were examined after treatment and most of them failed to show any marked changes. The increase of θ wave associated with elevation of the amplitude and extended duration was noticed in eight of them after treatment. Improvement was recorded when they were re-examined later.

Therapeutic effects

Parasitologic cure: In the early stage of clinical studies for praziquantel, stool of 199 cases treated with a total of 60 mg/kg divided into three or six doses given in one or two days were examined daily by hatching test to see the dynamic change of miracidia in patients' stool. All became persistently negative nine to 19 days after the beginning of praziquantel treatment. In acute schistosomiasis cases, the negative change of stool hatching for miracidia took place in all 49 cases 10 to 20 days after the beginning of a six-day treatment course of praziquantel with a total of 120 mg/kg (Chen *et al.*, 1981).

Follow-up results by three consecutive hatching tests three and six months after treatment with different dosage schedules in different endemic areas reported by several authors are shown in Table 1.

The total dosage of 60 mg/kg divided into three to six portions over one to two days were recommended and the overall stool miracidum negative rate was over 97% six months after treatment. However, after comparing with a total of 40 mg/kg in two divided doses, no significant difference in hatching tests was seen between the former and the latter (Hua *et al.*, 1984). Now praziquantel with a lower total dose (40 mg/kg), single or divided into two, is also recommended for selective mass treatment. A higher dosage (90 mg/kg) in two days, although being tried in quite a few cases and the cure rate being 100%, seemed to be unwarranted because of the relatively higher side effects, and higher cost (Anonymous, 1980a). However, in acute cases with heavier infections, Chinese clinicians preferred to use the dosage schedule of 120 mg/kg over six days after comparing different regimes.

Table 1

Results of post-treatment stool examinations in schistosomiasis japonica.

Praziquantal Regimen (days/total dose)	Months post-treatment	Cases re-examined	Negative	%
1 day 40 mg/kg	3	86	78	90.7
1 day	3	39	38	97.4
45 mg/kg	6	41	40	97.6
1 day 50 mg/kg	6	131	131	100
1 day	3	147	146	99.3
60 mg/kg	6	187	183	97.9
2 days	3	682	677	99.3
60 mg/kg	6	787	776	98.6
2 days	3	85	85	100
90 mg/kg	6	84	84	100
3 days 72 mg/kg	6	128	127	99.2
6 days	3	16	16	100
90 mg/kg*	6	21	21	100
6 days 120 mg/kg**	6	36	35	97.2

Note: * for schistosomiasis liver cirrhosis and/or with co-existent serious illness.
** for acute schistosomiasis.

Clinical improvement: In acute cases, generally, three to five days since the beginning of praziquantel therapy without using any antipyretics, subsidence of fever was noted in association with marked improvement in general condition. The body temperature fell to normal within an average of 9.5 days. Immunological function tests for γ-globulin, IgG, IgM and lymphoblastic transformation rate showed marked improvement in most of the treated cases. The average percentage of positive eggs in circumoval precipitin test (COPT) dropped down noticeably from 34% before treatment to 9% six months after (Chen *et al.*, 1981). Heavily infected patients and acute schistosomiasis cases showed noticeably favorable turn upon follow-ups. Their health and working capacity improved markedly.

A four year follow-up observation was made in an area where schistosomiasis was practically eradicated in Zhejiang province, China. 287 cases treated by praziquantel with a total dosage of 60 to 90 mg/kg in one or two days were followed up by physical examination and stool hatching test. Before treatment 110 cases had hepatomegaly below the right costal margin, 193 below xyphoid process and 96 had splenomegaly. Physical examination four years later revealed hepatomegaly in 35 and 78 cases, and splenomegaly in 19 cases. The negative hatching rate was 99%. Negative conversion rates of 84% with ELISA and 89% with COPT were also observed (Zhou *et al.*, 1983).

The drug has been recommended as the first choice in the treatment for schistosomiasis in China because of its high efficacy, low toxicity, easy administration and not very expensive cost: for local-made praziquantel, one treatment course costs about an equivalent of 1.0 to 1.5 US dollars.

NITHIOCYAMINE (AMOSCANATE)

The drug has been used in China since 1975. More than one million cases of schistosomiasis japonica have so far been treated.

When a daily oral dose of 40 mg/kg was given for three consecutive days to infected rabbits, a total hepatic shift of schistosomes was observed and all animals were cured (Huang *et al.*, 1980). The suckers of the male worm were paralyzed shortly after the administration and the paired worms were carried down to the liver and killed there. The reproductive organ of the worms changed no-

ticeably and finally the ovaries and testes were completely degenerated. The therapeutic efficacy was directly related to the particle size of the drug.

The effect of nithiocyamine on *S. japonicum* was observed through pathological, histochemical, indirect immunofluorescence and *in vitro* culture technique. It was found that the minimum lethal concentration was 1 μg/ml. After having shifted from mesenteric vein to the liver, the worms have their surface membrane destroyed and the metabolism disturbed. Loss of glycogen phosphorylase phosphatase, succinate dehydrogenase and ATPase were observed (Yu, 1981). Experiments show that the schistosomicidal effect of nithiocyamine may involve several factors, the important ones being the damage of the protective function of the membrane and disturbance in glucose metabolism.

Nithiocyamine exerts less effect to the juvenile worms, especially to the worms under 14 days of age (Huang *et al.*, 1980). The acute LD_{50} could not be determined because all the tested mice survived after an oral administration of the drug even with a dose as high as 5 g/kg (Quan *et al.*, 1982).

Clinical trials

The side effects were as follows:

Neuropsychiatric: Dizziness, veritgo, headache, asthenia, insomnia, dreaminess and unstable gait were the chief complaints. Failing memory, blurred vision, sweatiness, muscular tremor and listlessness were also recorded in some patients. The side effects appeared at the end of, or soon after treatment course and they usually lasted for several days to one week. However, in a few cases, the symptoms persisted for more than one month, and hysteria or psychosis was encountered in some patients after nithiocyamine treatment.

Digestive system: Loss of appetite, nausea, abdominal distension, abdominal pain and jaundice were recorded. Jaundice is related to hepatobiliary toxicity caused by the drug. It usually happened one to two weeks after the treatment and faded within an average of 12 days. Rarely, jaundice can persist for two to three months. The incidence of jaundice is closely related to the dosage of the drug. In early trial nithiocyamine was used in a large dosage of 1,500 mg over seven days and high incidence of jaundice was recorded in six out of 22 patients. As the dosage was reduced to 500 and 350 mg for adults in three days, the incidences were 15.9% and 6.6% respectively. SGPT was elevated in all the icteric patients and also in some of those without jaundice. Liver biopsy showed acute inflammatory lesion with degeneration and necrosis of the hepatic cells, indistinct structure of the mitochondria and vacuole formation on the expanded endoplasm reticulum. However, some of the biopsy specimens also revealed cholestasis in liver, and hypersensitive phenomena were seen in some patients with jaundice. It has been considered that pathological mechanism of jaundice is mainly hepatic injury, while in some cases hypersensitivity may also play a role (Miao *et al.*, 1981).

Cardiovascular system: Bradycardia, premature beat and depression of T wave in ECG tracing were recorded in a few cases. Adams-Stokes syndrome induced by serious arrhythmia after the drug administration was seen in three cases among 192,000 schistosomiasis patients in Hubei province of China and one of them died (Wang *et al.*, 1981).

Therapeutic effects

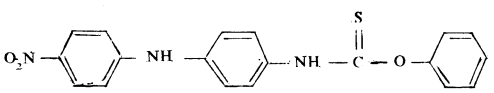
The therapeutic effects were quite satisfactory. In one clinical trial of 4,022 cases of *S. japonicum* by using fine particles of 3-6 μm in diameter and with the total dosage of seven mg/kg in three days, the negative rates for stool hatching were 92.2%, 87.6% and 85.3%, respectively three, six and 12 months

after treatment (Anonymous, 1980b). In treating acute schistosomiasis nithiocyamine also manifested its efficacy in the subsidence of fever and improvement of symptoms, and in most of the cases, stool negativation for miracidia as well.

The drug has the advantage of good efficacy and very low cost: one treatment course costs only an equivalent of 12 US cents. However, its untoward side effects remain a problem for mass treatment.

PHENITHIONATE

Phenithionate (phenyl-4-nitrodiphenylamine-4'-thionocarbamate) is a now derivative of nithiocyamine synthesized in China. The chemical formula is as follows:



Phenithionate exhibited cidal effect on *S. japonicum* in experimental animals. The infected rabbits became free from schistosomes after oral use of phenithionate with a daily dose of 16 mg/kg for five days. Mice tolerated phenithionate well even when higher dose of 5 g/kg was given. Results obtained by the subacute toxicity test on dogs and rats, liver and renal function tests, haematological test, ECG as well as pathological examination, in comparison with those by nithiocyamine, showed that phenithionate possessed milder toxic effects (Quan *et al.*, 1982).

Clinical trials have been carried out on 526 cases in two different endemic areas. One trial using the drug with the dosage of 18, 20, 22, 24 and 26 mg/kg in three days showed that stool negative conversion rate for hatching test increased proportionately with the dosage. In the group of the highest dosage, 26 mg/kg, the negative rates three and six months after treatment were 93.8% and 85.7% (Liu *et al.*, 1983). However, in another trial, using the same dosage schedule, 26 mg/kg in three days, only 63.9% of the patients became stool negative three months after treatment (Zhou *et al.*, 1983). The side effects were similar to nithiocyamine but milder in degree. 0.6% of the treated cases had complicating jaundice. The drug is undergoing further clinical trial in schistosomiasis japonica.

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