Treatment of "Schistosomiasis japonica" with CIBA 32644-Ba : a preliminary report

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Treatment of *Schistosomiasis japonica* with CIBA 32644-Ba

A Preliminary Report

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Treatment of oriental schistosomiasis, the type found in the Philippines, has in the past three decades mostly been by parenteral administration of antimony preparations like tartar emetic and stibophen, and more recently Astiban. Since 1951, several oral preparations have also been tried, such as Miracil D, a thioxanthone compound, and other thioxanthone derivatives such as Win 3636, Win 3663, Win 4304, and Win 13,820 (Winthrop-Stearns, 1954, 1960) but with not too promising results (PESIGAN et al., 1951; Annual Report, BRL 1955 and 1960). In 1958, a naphthylazo derivative, CI-407 (ELSLAGER et al., 1963) was tried and gave similarly poor results (Annual Report, BRL 1958). In a more recent field trial, pamoate or CI-403-A (ELSLAGER et al., 1961) was given to over 200 subjects (Annual Report, BRL 1965) and was found to be quite effective, both as a curative and as a suppressive drug.

This brief preliminary report deals with a short-course therapy with CIBA 32644-Ba, a nitrothiazole derivative which has been found effective against the three types of schistosomal infections (CIBA, 1964), both in animal experiments and in a few human cases (LAMBERT and CRUZ FERREIRA, 1964). It is heartening to know that previous trials with this new drug have also shown its value both in experimental and clinical amoebic liver abscess (CIBA, 1964).

Materials and Methods

This study was conducted in the Bureau of Research and Laboratories, Manila, Philippines, using 22 out-patients with schisto-

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somiasis as subjects. These patients, mostly household helpers, came from endemic areas in the southern part of the Philippines, mostly from the island province of Leyte, where the prevalence of schistosomiasis is about 50% (PESIGAN et al., 1958). Out of these 22 patients, 9 were under 15 years old, 9 from 15 to 24 years old, and 4 were 25 years and above; 12 were male and 10 female patients. Our youngest patient was 10 years old while the oldest was 68 years. These patients have not received any treatment for schistosomiasis before, except two who received Astiban more than four years ago.

The patients were screened for any possible contra-indications to schistosomiasis treatment, such as lung, heart or kidney diseases, or liver pathology other than that due to schistosomiasis (these would also be contra-indications to antimony preparations), by considering the clinical history and physical findings, as well as laboratory examinations including X-ray, urine, and blood examinations. The patients included in this study were assigned to the experimental and control groups randomly as they presented, every 5th patient being designated as a control.

CIBA 32644-Ba, a nitrothiazole derivative, comes in the form of a greenish-yellow tablet containing 500 mg of the active substance. The experimental group received the drug in two dosage schedules. For purposes of this report, they will be known as Schedules A and B. A total of 16 patients were given 20 to 25 mg/kg/day for 10 days (Schedule A) while thus far only two were given the drug at a reduced dose of 15-20 mg/kg/day for five days (Schedule B). The drug was given in two divided dosages, one in the morning and the other in the evening. Patients came to the office for their supply of medicine four to five times a week under Schedule A and three times a week under Schedule B. Clinical observations especially, for drug-related signs and symptoms were made during these visits.

Laboratory examinations were made on stools, blood, and urine specimens. Later, among patients included in the Schedule B regimen, transaminase determinations were also done. The stool examination employed was the enumeration of the eggs per ml by two methods done in parallel, namely, merthiolate, iodine, formalin concentration (MIFC) and BELL's techniques (1963). Two 24-hour stool samples were examined before treatment, one week after treatment, and monthly for three months after completion of treatment.

In evaluating the efficacy of treatment, two techniques of stool counts mentioned above were used in parallel to ascertain the

variability of results and to minimise technical errors by getting averages of the two counts.

Peripheral blood studies consisted of the red and white cell counts, haemoglobin determination and leucocyte differential count. Serum glutamic-oxalacetic (SGOT) and serum glutamic-pyruvic transaminase (SGPT) determinations were done before and after treatment in patients included in Schedule B. These transaminase determinations will be routinely done in subsequent patients. The urine was examined physically and chemically as well as microscopically for cellular elements.

The evaluation of the effectiveness of the drug administration was based on the percentage of patients that became negative for schistosome eggs and on the percentage of egg reduction after treatment.

Results

In spite of the very few patients so far treated with CIBA 32644-Ba in this series and the meagre co-operation given by the patients during follow-up examinations of the stools, the results of our clinical trial thus far will be presented for the purpose of this symposium.

Follow-up Examinations of Stools

Of the 16 patients treated under Schedule A, 10 of them completed the 10-day treatment and the results of the follow-up examinations on stools are presented in Table 1.

It will be noted that all of the 10 patients were found positive for schistosoma ova at least once during the periods of follow-up from one week to three months post-treatment, although instances of negative stools were noted. The mean pre-treatment egg count of 48.3/ml of stools, however, showed a marked reduction even as early as one week after treatment (4.3 eggs/ml) up to the end of the three months follow-up (0.2 eggs/ml), the percentage egg reduction being 91% to 99%. Table 2 shows that those patients whose treatment was incomplete also had a good egg reduction of 89% and 76% for one and two months of follow-up respectively, even among patients who received the drug for a period as short as two to four days. Also two patients whose treatment was interrupted (7½ to 8 treatment days were actually spread over 14 and 16 days respectively) showed reductions of egg counts of 90% to 98%.

The two patients that received a lower dose under Schedule B both completed the treatment. They had a pre-treatment egg count

TABLE 1

Egg counts/ml of 10 Schistosomiasis japonica patients completely treated with CIBA 32644-Ba under Schedule A

Patient No.	Pre-Treatment	Post-Treatment Follow-Up One-Week	One-Month	Two-Month	Three-Month
Experimental					
1 *	8.25	1.25	0.5	0.25	0
2 **	23.25	2.25	0	3.25	0
3	60.25	6.0	0.66	1.0	0.25
7	19.25	1.0	0.0	1.25	0.50
8	64.5	12.50	0.70	0.25	
9	64.0	1.75	0.25	0	
11	15.50	0	0.25	0	
12	16.50	0.50	0.25	10.25	
13 ***	110.50	11.25			
14 ***	100.75	6.0			
Average	48.3	4.3	0.3	2.0	0.2
% Reduction		91.1	99.4	95.8	99.6

* Patients Nos. 4 and 6 did not complete the treatment (see Table 2) while patients Nos. 5 and 10 were not treated to serve as control.

** Total dose for 10 days was received in 9 days.

*** No further follow-up because of fictitious address or patient left for the province.

TABLE 2

Egg counts of 6 patients incompletely treated with CIBA 32644-Ba under Schedule A

Patient No.	Pre-Treatment	Post-Treatment Follow-Up One-Week	One-Month	Two-Month	Three-Month
a) Treatment given for 7-8 days					
4	3.75	0	0.75	1.0	0
6	6.75	–	0	0	0.25
Average	5.3	0	0.4	0.5	0.1
% Reduction		100.0	95.5	90.6	98.1
b) Treatment given for 2-4 days					
16	59.20	–	6.50	13.25	–
17	13.75	–	0.50	1.0	–
18	3.25	–	0.50	1.75	–
19	3.50	–	0.75	3.0	–
Average	19.9	–	2.1	4.7	–
% Reduction			89.4	76.4	–

of 4.75-5.0/ml and both were found negative on the first week of follow-up.

Clinical Observations

As mentioned above, the patients were treated as out-patients and reported to the office three to four times a week for clinical observations and to get the supply of drug during the treatment period. All the 18 patients that were treated with CIBA 32644-Ba complained of one or a combination of side effects to the drug, which was considered on the whole to be moderately toxic. Objectively, it was observed that they became haggard and lost their usual vitality; some became unaware of their environment and looked puzzled. Subjectively, the patients complained of vomiting, headaches, dizziness, general body weakness, nausea, anorexia, and salivation (Table 3) while the less frequently encountered side effects were skin eruptions, insomnia, tremors, etc. For a better appraisal of the side effects, details of some of the important observations are given below.

Vomiting

Vomiting occurred among 12 of 16 patients that received the drug and it appeared as early as the first day of treatment, about

TABLE 3

*Types and frequency of toxic reactions observed among 16 Schistosomiasis patients * treated with CIBA 32644-Ba under Schedule A*

Vomiting	12
Headache	12
Dizziness	12
General body weakness	11
Nausea	8
Anorexia	8
Salivation	8
Insomnia	5
Tremors	3
Joint pains	3
Unawareness of environment	3
Skin eruptions	2
Abdominal pain	2
Convulsions	2
Psychosis	1
Others **	9

* All had one or more toxic reactions; in 4 patients, treatment had to be discontinued because of the severity of the toxic reactions.

** This includes different complaints which may or may not be drug-related such as herpes labialis, tachycardia, dyspnoea, phobia of drug, epistaxis, epigastric fullness, bitter taste and diarrhoea.

two to three hours after drug ingestion. It occurred intermittently or from one to six times a day for a period of seven days. When vomiting occurred several times a day, as in the case of two adult females with early schistosomiasis, they complained of associated abdominal pain and because of general weakness they preferred to be in bed. Vomitus consisted of ingested food or occasionally of bitter-tasting fluid, when vomiting was severe. In two cases, excessive vomiting and marked general body weakness were the main causes for the discontinuation of the drug. In one case, the vomiting provoked the rupture of oesophageal varices which seriously aggravated the condition of the patient.

Dizziness

This was also frequently experienced and occurred throughout the whole course of treatment in two patients, but it was usually associated with a change in posture or exposure to the sun.

General Body Weakness

One of the frequent causes of irregular intake of the drug was general body weakness. This started as early as the first day of treatment, although it was more common on the second or third day and persisted up to the 10th day of treatment in a few cases. Vomiting, dizziness and anorexia were found to aggravate this condition.

Acute Psychosis

This was observed in a young adult female patient with marked splenomegaly. On the fourth day of treatment (7th dose), she became queer in her behaviour, as manifested by shouting, incoherent speech, and purposeless movements, whereupon she was hospitalised. At different times, signs of mental depression were also noted, as well as the above signs of excitation. The symptoms, however, disappeared four days after drug withdrawal upon treatment with sedatives.

Convulsions

Two boys, aged 12 and 15, developed convulsive seizures with tonic fits, rolling of the eyes and frothing at the mouth, accompanied by cold clammy perspiration. This was preceded by a feeling of warmth, severe epigastric pain, and marked dizziness. No

localised tremors or sensory disturbances (such as the numbness frequently found in cerebral schistosomiasis) were observed prior to the convulsive seizures. Neither patient had a history of previous epileptic attacks or convulsions such as were observed this time. The younger child had hepatomegaly and was erroneously given an overdose (33.6 mg/kg) on the first two days of treatment. This patient was hospitalised while the older patient was treated at home. Both were given dilantin sodium which improved their condition. Both boys had convulsions twice, the younger boy on two successive days (the 4th and 5th days of drug intake). This patient, however, was able to complete treatment. The older boy had the first attack on the 10th day of treatment. Five days after treatment, a much milder attack was observed.

Tremors of Extremities

These were experienced by four patients in the form of uncontrolled, fine or coarse tremors of the hands and legs developing towards the end of treatment. This condition was associated with general body weakness.

Skin Eruptions

Observed in two patients, these appeared on the second day. In one patient, the lesions were papulomacular and non-itchy and were found on exposed areas of the face and extremities. The rash lasted for 8 days. However, the eruption was more severe in another patient, whose lesions were small macules scattered on the face and extremities. These gradually coalesced into a generalised, intense erythema, with a slight thickening of the skin. The bulbar and palpebral conjunctivae were also involved on the 4th day and at this time the drug had to be discontinued. There was no pruritus, but intense bulbar pain occurred, giving a sensation of "eyes popping out". The eruption persisted for seven days (three days after discontinuation of the drug).

Unawareness of the Environment

One of the side effects observed and worth mentioning was unawareness of the environment, which was manifest in three patients. They were slow in answering questions and had anxious faces. One patient, a 12-year-old child, had a transient lapse of memory and could not remember his own name. It was significant

that this was observed five days after the last dose of the five-day Schedule B treatment.

It is of interest to note that three of the six patients who developed severe toxic reactions were healthy-looking females who were considered to be early cases of schistosomiasis, since no hepatomegaly was detected on palpation. Two others were the male children who developed convulsions (see above), and the last was a female patient in the chronic stage of schistosomiasis (with splenomegaly) who developed acute psychosis. In general, children, even with hepatomegaly, had transient and less severe side effects and tolerated the drug better than adults.

Blood and Urinary Findings

In spite of the toxic reactions experienced, the peripheral blood picture of the patients treated with CIBA 32644-Ba showed no apparent changes in the different cellular components and haemoglobin values, before and after treatment. This was also true of the results of routine urinalysis.

In a few patients transaminase determinations and the thymol turbidity test (TTT) were done. The SGPT level before treatment was below 50 units in four of five such patients; the other, who had marked splenomegaly, had a level of 108 units. On the other hand, all the SGOT values were elevated, ranging from 92 to 160 units. In one patient, the SGOT and SGPT values were the same before treatment and 15 days after treatment. TTT values were all elevated from 5.5 to 36 units before treatment, and in one case, it almost doubled to 70 after treatment.

Discussion

To date, there has been no satisfactory drug for the treatment of *S. japonica* because the effective drugs, such as tartar emetic, Astiban and Fuadin, always produced unpleasant side reactions, not to mention the possible occurrence of haemolytic anaemia (Harris, 1956; De Torregrosa et al., 1963). An ideal drug for mass treatment must be non-toxic, capable of being administered orally, and effective within a relatively short period of treatment.

From the preliminary results of the treatment of *S. japonicum* infections, as assessed by the criteria of (1) the number of patients found negative for schistosoma ova, and (2) the egg reduction in stools, it would seem that the nitrothiazole derivate, CIBA 32644-Ba, may not give a total cure of patients suffering from

S. japonica, even with a dose of 20-25 mg/kg/day for 10 days. However, the results also show that the drug can effect a marked reduction in the egg count even with a shorter duration of drug intake (2 to 4 days). Because of the apparent moderate toxicity of this drug, a higher dosage could not be used in an attempt to produce better results with *S. japonicum* patients in the Philippines. A lower dosage of the drug administered for a shorter period of five days is on trial. From the preliminary animal studies, the activity of this drug appears to be better against *S. japonicum* than against the other human schistosomal infections (LAMBERT, 1965). Therefore, a lower dose might be effective against *S. japonicum* in the human, but this remains to be proved clinically.

The apparent suppression of egg production for as long as three months after treatment may be attributed to the direct action of the drug on the reproductive organs both of the male and female flukes, wherein inhibition of spermatogenesis and morphological changes in the ootype and vitellaria have been observed. Moreover, it has been found, by using radioactive carbon, that the drug concentrates in the eggs lodged in the liver and walls of the large intestines and also in the vitellaria of the female worms (CIBA, 1965).

It is of special interest to note that clinical trials done among West Africans (LAMBERT and CRUZ FERREIRA, 1964) infected with *S. haematobium,* and among Siamese with hepatic amoebiasis, have shown that the drug can be well tolerated. It may be assumed that hepatic damage both in *S. japonicum* infection and hepatic amoebic abscess would be more manifest than in *S. haematobium* and *S. mansoni* infections. However, the difference between the findings among patients from Thailand and the Philippines may not be due to a racial factor, despite the apparent ethnic relationship. It should also be kept in mind that the parasitic infections and liver pathology in the two groups are not the same. Nutritional and other environmental factors may also be involved.

One serious toxic reaction we noted was acute psychosis. A similar case has been reported in a patient receiving both antituberculosis treatment and CIBA 32644-Ba at the same time; thus in this case, it was impossible to say which drug might have caused the psychosis (CIBA, 1965). Our patient, on the other hand, was taking no other drugs except CIBA 32644-Ba and there was no family history of mental disorders. Furthermore, the psychosis disappeared four days after drug withdrawal. No subsequent psychotic manifestation has been observed for four months since. All these points in our case favoured the impression that the psychosis was drug-induced. ZAKI et al. (1964) mentioned that

"toxic psychosis" developed among some of their patients treated with lucanthone HCl.

It is evident, therefore, that CIBA 32644-Ba affects the central nervous system, as manifested by the tremors, numbness of the extremities, insomnia, unawareness of the environment, convulsions and even psychosis which we noted.

Toxic reactions produced by CIBA 32644-Ba may be due to excessive dosage (as in one of our patients) or to the inability of the liver to metabolise the drug rapidly, due to enzymatic dysfunction, thus allowing it to circulate in abnormally high concentration in the peripheral blood. The active substance is the pure CIBA 32644-Ba and not its metabolites (CIBA, 1965). Since liver impairment is more frequently seen in *S. japonicum* than in *S.mansoni* or *S. haematobium* infections, it might be expected that the drug given at the same dosage would produce more toxic reactions among *S. japonicum* patients, as actually seems to have occurred.

It may be of further interest to know that parenchymal liver damage among our patients with no liver enlargement was possibly minimal. The relationship between elevated SGOT values and normal or borderline values of SGPT, as found among our patients, was also noted in 5 of 14 *S. haematobium* cases by LAMBERT and CRUZ FERREIRA and may be the result of Laennec's cirrhosis, myocardial infarction, and skeletal muscle necrosis (DAVIDSOHN and WELLS, 1963). However, PAUTRIZEL et al., 1963, did not find any elevation of both transaminase values in 18 *S. mansoni* patients.

These are very preliminary findings from our trials of CIBA 32644-Ba in the treatment of *S. japonicum* infection in the Philippines and they will be further elucidated when more data are available.

Summary

A new oral preparation, CIBA 32644-Ba, a nitrothiazole derivative, was tried in 16 patients with *S. japonicum* infection at a dose of 20-25 mg/kg/day for 10 days, and in two patients at a reduced dose of 15-20 mg/kg/day for 5 days.

All the patients experienced side effects which were generally moderately severe, such as vomiting, general body weakness and dizziness. Alarming symptoms, such as convulsions and psychosis, were also observed in a few cases. The drug, however, was apparently not toxic to the haematopoietic and urinary systems.

CIBA 32644-Ba, tried in a limited number of patients, apparently did not produce a parasitological cure, but it was able to effect a marked decrease in the egg count, which was maintained during

three months of post-treatment follow-up. Additional data are to be collected for a proper appraisal of this new oral drug.

Résumé

Le CIBA 32644-Ba, nouveau dérivé du groupe des nitrothiazoles, a été étudié chez 16 malades infestés par *S. japonicum* ; il a été appliqué à la dose de 20 à 25 mg/kg/jour pendant 10 jours et chez 2 malades à la dose de 15 à 20 mg/kg/jour pendant 5 jours.

Tous les malades présentèrent des effets secondaires généralement modérés, tels que vomissements, faiblesse générale et faux vertiges. Des symptômes alarmants, convulsions et psychose furent également observés dans quelques cas. Le médicament ne s'est cependant pas montré toxique pour les systèmes hématopoïétiques et urinaires.

Le CIBA 32644-Ba, essayé sur un nombre limité de malades, n'a apparemment pas produit de guérison parasitologique vraie, mais une diminution nette du nombre d'œufs éliminés ; cette diminution s'est maintenue pendant une période d'observation de 3 mois après le traitement. D'autres essais sont encore nécessaires pour pouvoir apprécier valablement l'action de ce nouveau médicament, administré par voie orale.

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