Zeitschrift: Acta Tropica

Herausgeber: Schweizerisches Tropeninstitut (Basel)

Band: 23 (1966)

Heft: (9): Thérapeutique nouvelle de la Bilharziose et de l'amibiase : Symposium de Lisbonne 2 au 4 Juin 1965

Artikel: Preliminary report : treatment of eleven cases of "Schistosomiasis japonica" with CIBA 32644-Ba

Autor: Liboro, O.L. / Pineda, F.M. / Yogore, M.G.

DOI: https://doi.org/10.5169/seals-311381

Preliminary Report: Treatment of Eleven Cases of *Schistosomiasis japonica* with CIBA 32644-Ba

O. L. LIBORO *, F. M. PINEDA *, and M. G. YOGORE, Jr. **

The standard chemotherapeutic agent used for the treatment of *schistosomiasis japonica* in the Philippine General Hospital is an intramuscularly administered antimonial preparation. The common occurrence of undesirable side reactions, sometimes severe, as well as the failure to achieve parasitologic cure in a not inconsiderable proportion of cases, leave much to be desired.

The use of CIBA 32644-Ba as an experimental drug for *schistosomiasis japonica* among patients in this hospital was started in February, 1965; to date, the drug has been tried in eleven patients. Table 1 summarizes some of the general data on these patients, including some of the pertinent physical findings. It may be noted from this table that the majority of our patients were in the late chronic stage of the disease with portal hypertension.

The pre-treatment parasitologic work-up to establish the diagnosis of schistosomiasis included a series of at least three stool examinations (utilizing the acid-ether centrifugation and egg-hatching techniques) for all patients; in addition, rectal and/or liver biopsy was performed in all. The intradermal and circumoval tests were also performed.

All eleven patients reacted positively to the intradermal test for schistosomiasis and showed circumoval precipitins in their pre-treatment sera. In nine patients (exceptions are patients Nos. 4 and 11), pre-treatment stools revealed *S. japonicum* ova; patients Nos. 4 and 11 were stool-negative but ova were demonstrated in liver and rectal biopsy material. All patients were positive for hookworm and *Trichuris* ova; in addition, *E. histolytica* cysts and *Ascaris* ova were found in the stools of patient No. 1.

* College of Medicine, University of the Philippines, Manila.

** Institute of Hygiene, University of the Philippines, Manila. (Paper presented by Dr. M. G. Yogore, Jr.)

TABLE 1

General data and some physical findings of 11 subjects treated with CIBA 32644-Ba

Patient No.	Sex	Age (Years)	Clinical Diagnosis	Hepato-megaly	Spleno-megaly	Prominent Abd. Veins	Ascites
1	M	23	Schistosomiasis, hep.-int. Amoebiasis, int.	+ (1 cm)	(−)	(−)	(−)
2	M	36	Schistosomiasis, hep.-int. and cerebral (?)	(−)	(−)	(−)	(−)
3	M	27	Cirrhosis, parasitic with portal hypertension	(−)	+ (to iliac crest)	+	(−)
4	F	19	Schistosomiasis, hep.-int.	+ (2 cm)	+ (2 cm)	+	+
5	F	20	Schistosomiasis, hep.-int. PTb	+ (3 cm)	(−)	(−)	(−)
6	M	17	Cirrhosis, parasitic with portal hypertension Cor pulmonale 2° to pulmonary schistosomiasis	+ (1–2 cm)	+ (12–16cm)	+	(−)
7	M	19	Cirrhosis, parasitic with portal hypertension	+ (7.5 cm)	+ (8 cm)	+	+
8	F	17	Cirrhosis, parasitic with portal hypertension	+ (3 cm)	+ (10 cm)	+	+
9	M	14	Cirrhosis, parasitic with portal hypertension PTb minimal	+ (7 cm)	+ (9 cm)	+	(−)
10	M	14	Cirrhosis, parasitic with portal hypertension PTb	+ (6 cm)	+ (3 cm)	+	(−)
11	M	25	Schistosomiasis, hep.-int.	(−)	(−)	(−)	(−)

In addition to a clinical history, physical examination and laboratory examinations, the pre-treatment clinical work-up of each patient included studies for evaluating liver dysfunction. The results of tests for liver profile are given in Table 2. While evidence of liver-function impairment was found in each subject, no consistent pattern of abnormality was observed. The most consistent abnormality found was an elevation of serum globulin (8/11) in the presence of normal total serum proteins; this abnormality resulted in reversal of the A/G ratio to a figure of less than 1 in 5/11 subjects and a ratio approaching 1 in another two patients. Other findings were: abnormal CCF (cephalin-cholesterol flocculation) and TFT (thymol flocculation test) in eight patients; elevated TTT (thymol turbidity test) values in five; elevated total serum bilirubin

TABLE 2

Liver profile of the 11 cases before treatment

	CCF	TTT	TFT	Alk. Phos.	SGOT	Pro Time (diff.)	Total Serum Bilirubin	Alb.	Glob. 2	Total	A/G ratio	BSP
Normal values	(–) to +	6–10	(–)	14 KA	35	5 sec or less	1 mgm or less	3.5 to 4	2 to 2.5	6–8		5 % or less
Patient No.												
1	(–)	4.4	+	28.3	60	0	0.1	3.8	3.3	7.2	1.1	22
2	(–)	2.9	(–)	17.6	23	1.5	1.0	4.1	2.35	6.5	1.8	10
3	++	8.6	(–)	8.4	44	6.5	3.2	3.2	3.2	6.4	1.0	25
4	++	9.4	+	10.0	25	1.0	5.3	4.4	2.8	7.2	1.6	4
5	(–)	4.4	(–)	7.6	81	1.0	5.0	4.8	2.25	7.0	2.1	8
6	++++	14.0	++	12.5	36	5.5	3.8	3.75	4.1	7.8	0.9	11
7	++++	12.6	+++	17.7	1	3.0	13.0	3.0	4.15	7.15	0.7	3
8	++++	16.0	+++	24.0	82	2.0	0.6	2.35	3.65	6.0	0.6	13
9	+++	12.5	++	30.9	76	4.0	0.7	3.05	4.3	7.5	0.7	4
10	+++	10.1	++	13.8	38	4.0	2.85	3.05	4.3	7.35	0.7	4
11	+++	17.0	++	7.3	36	3.5	1.4	4.7	2.5	7.2	1.9	4
No. with abnormal or elevated values	8	5	8	5	5	1	7		8	0		6

TABLE 3

Dosage schedule and actual amount of CIBA 32644-Ba taken by each of the 11 subjects

Patient No.	Sex	Age (Years)	Weight (kg)	Dosage (mg/kg/day)	Total dose prescribed (7 days) (grams)	Actual Amt. Taken (grams)
1	M	23	57	25	9.8	2.8
2	M	36	53	25	8.4	8.4
3	M	27	50	25	8.4	2.4
4	F	19	50	15	5.25	5.25
5	F	20	45	15	4.9	4.4
6	M	17	45	15	4.9	1.2
7	M	19	50	15	4.9	4.9
8	F	17	29	15	2.8	2.8
9	M	14	22	15	2.1	2.1
10	M	14	26	15	2.8	2.2
11	M	25	42	15	4.2	2.4

in seven; elevated alkaline phosphatase in five but an abnormal prothrombin time only in one subject. Elevated SGOT values were found only in five patients, the highest reading being 82. Delayed BSP retention was observed in six subjects.

The first three subjects were placed on a regimen of 25 mg/kg/day for seven days while the next eight patients were treated with 15 mg/kg/day. Table 3 gives the dosage schedule and the actual amount of CIBA 32644-Ba taken by each patient. It will be seen from this table that two subjects (patients Nos. 1 and 3) at the 25 mg level and two (patients Nos. 6 and 11) at the 15 mg level actually took an amount of the drug very much less than the total prescribed amount. All four of these patients had severe untoward reactions which made termination of the drug administration imperative.

After 2.1 g of the drug in the first two days of treatment, patient No. 1 developed nausea with severe vomiting and such marked weakness as to result in almost complete prostration. The drug was therefore withdrawn. On the third day of drug withdrawal these reactions cleared up and an attempt was made to resume treatment on the sixth day. A single dose of 700 mg (one-half the daily prescribed amount) however resulted in the same severe and alarming reactions and the drug was discontinued entirely.

In the regimen of 25 mg/kg/day, patient No. 3 received a total of 2.4 g in two days. Late on the second day the patient became disoriented, would not respond to external stimuli and suffered a convulsive seizure. The drug was immediately withdrawn. The

TABLE 4

Some reactions observed in 11 patients with schistosomiasis japonica treated with CIBA 32644-Ba

R_x Day	Pt 1 (25)	Pt 2 (25)	Pt 3 (25)	Pt 4 (15)	Pt 5 (15)	Pt 6 (15)	Pt 7 (15)	Pt 8 (15)	Pt 9 (15)	Pt 10 (15)	Pt 11 (15)
1			D V+			N W	D H N	V	D	D N	H
2	M N+ V++ W++ –	D M N	* –			N W++ –	H N	D H N V	D H N W	A D+ H N V++	H
3	M N W++	D++ M N				N W+ **	H N V		D H N W	D	H
4	M W	D M N		D	A D H N V W	**	H M W		D W	D	A H++ W++ ***
5		D+ N		D W	A D H N W	W+	H		D N V W	D N	A H++ W++
6		D		D W	A D H N V W+	W	H		D N W	D N V	A H W++
7		D		D	D W		H		D N W	D	H W++

* = disoriented, convulsion, coma
** = disoriented, coma
*** = marked dyspnoea and wheezing respiration
++ = severe
+ = moderate
no+ = slight

A = anorexia
D = dizziness
H = headache
M = myalgia
N = nausea
V = vomiting
W = weakness

patient remained disoriented for the next four days, occasionally becoming violent, sometimes comatose, and he developed gum bleeding and subconjunctival hemorrhage. The slight icterus observed prior to treatment appeared to deepen. The patient regained his faculties on the fifth day of drug withdrawal but recovered slowly from the marked weakness occasioned by the crisis he went through.

In the regimen of 15 mg/kg/day, patient No. 6 had received only 1.2 g when he developed an attack of profuse sweating accompanied by marked weakness. Although administration of the drug was immediately stopped, the patient became disoriented the next day and comatose the day after that. He was partly conscious on the third day of drug withdrawal but had a residue of moderate weakness. He became fully conscious on the fourth day of withdrawal.

Patient No. 11 had a history of asthmatic attacks occurring almost every month since he was five years old. On the third day of treatment (after 1.8 g), the patient developed marked sweating and a wheezing respiration. The drug, however, was continued on the fourth day for a total of 2.4 g. The patient became dyspneic with marked weakness and the drug was stopped. The patient remained very weak and markedly dyspneic for the next 11 days, even developing crepitant rales and fever. Recovery was a very slow process.

Of the other seven patients, five (patients Nos. 2, 4, 7, 8, and 9) completed the prescribed course of treatment while the other two (patients Nos. 5 and 10) took almost the whole prescribed amount of the drug, but missed a few doses because of anorexia and vomiting. The reactions in these patients consisted of anorexia, dizziness, headache, myalgia, nausea, vomiting and weakness. A summary of the reactions observed in these subjects in their time sequence is given in Table 4.

We are not prepared at this time to give any results on changes in the liver profile of these patients following treatment with CIBA 32644-Ba.

Parasitologic Evaluation

Table 5 shows the stool follow-up, to the time of the preparation of this report, in the seven patients who received the complete or almost complete prescribed dosages of the drug. It is evident that patient No. 4 cannot be evaluated by stool examination because she was originally stool-negative; moreover, she was lost from observation two weeks after the end of therapy. So far, only one patient (patient No. 2) has been followed up for two months;

TABLE 5

Pre-treatment and post-treatment stool examinations of 7 schistosomiasis japonica patients treated with CIBA 32644-Ba

Numerator = results of acid-ether centrifugation technique
Denominator = results of egg-hatching technique

	Pt No. 2	Pt No. 4	Pt No. 5	Pt No. 7	Pt No. 8	Pt No. 9	Pt No. 10
Pre-treatment	0 to + / 0 to ++	0 / 0	++ to +++ / +++	0 to + / 0 to +	0 to + / + to ++	0 to + / 0	+++ / +++
Post-treatment							
Within one week	+ / +	0 / 0	0 / 0	0 to + / 0	0 to + / +	0 to + / 0 to +	0 to ++ / 0 to +
Within two weeks	0 to + / 0	0 / 0	0 / 0	0 / 0	0 to + / 0 to +	0 to + / 0 to +	0 to + / 0 to +
At about one month	0 / 0		0 / 0	0 / 0	0 to + / 0 to +	0 / 0	0 to + / 0 to +
At about two months	0 / 0						

Note: Results for each period are based on 3 stool samples obtained on successive days whenever possible.

0 = negative; + = few; ++ = moderate; +++ = large numbers.

the other five (patients Nos. 5, 7, 8, 9, and 10) have been followed up for only a month. Within one week after the end of treatment, *S. japonicum* ova were seen in the stools of five of the six patients, although hatchable eggs were seen only in four. At about two weeks after the end of treatment, ova were demonstrated in the stools of four patients, with hatchable eggs in three. At one month, ova were detected in the stools of two and these included hatchable ones. We may therefore say that at least two (patients Nos. 8 and 10) of the six have already turned up as probable treatment failures, both of these having been given 15 mg/kg/day for 7 days. Patient No. 2, although stool-positive at one week and two weeks after treatment, has been stool-negative at one month and two months of follow-up.

Before treatment, immediately after treatment and as the patients return to us for stool follow-up, we have been collecting sera

from them for possible evaluation of the effect of treatment by immunoelectrophoresis, utilizing saline extracts from lyophilized adult *S. japonicum* and lyophilized *S. japonicum* ova as antigens. In most patients who have been treated with the antimony compound and in whom parasitologic cure has been obtained. LEWERT and YOGORE (1) have shown that there is an increase in the number and titer of anti-adult somatic precipitins within two weeks to one month after the end of therapy. In addition, there is a decrease in anti-egg precipitins within two to three months after treatment. We have run only a few of the antisera collected from the CIBA-treated patients so far and we have not found the changes that we have come to associate with death of worms and cessation of oviposition, as brought about by the antimony compound. We hope to give more definitive results in this aspect as we gather more sera from CIBA-treated patients.

Summary

This preliminary report describes the observations made during treatment with CIBA 32644-Ba in 11 patients with *S. japonicum* infections, most of whom were at the advanced, chronic stage of the disease and had portal hypertension.

The findings with regard to tolerability, side effects, antiparasitic action, and immunology are reported. Although the results are of a preliminary nature, they show how different and how much more difficult to cure splenohepatic schistosomiasis is in comparison with *S. haematobium* or *S. mansoni* infections.

Résumé

Ce rapport préliminaire relate les observations faites lors du traitement par le CIBA 32644-Ba de 11 malades infestés par *S. japonicum,* dont la majorité était dans une phase chronique avancée de la maladie, avec hypertension portale.

Les observations sur la tolérance, les effets secondaires, l'action antiparasitaire, l'immunologie sont rapportées. Bien que préliminaires, elles montrent à quel point la situation de la bilharziose splénohépatique est différente et plus difficile à résoudre que celle des bilharzioses à *S. haematobium* et *S. mansoni.*

Reference

1. LEWERT, R. M. & YOGORE, M. G., Jr.: Alterations in immunoelectrophoretic reactions following chemotherapy of human *schistosomiasis japonica* and *paragonimiasis.* (Manuscript in preparation.)