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Autor: Coutinho, Amaury / Lima, Ciro A. / Alves, Carmencita

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A Clinical Trial of CIBA 32644-Ba in Patients with *S. mansoni* bilharziasis

AMAURY COUTINHO *, CIRO A. LIMA **, and CARMENCITA ALVES ***

I. Introduction

In the Recife area of Brazil many patients are seen in an advanced state of bilharziasis due to infection with *Schistosoma mansoni,* which is the only species responsible for the disease in this country. Severe hepatosplenic lesions complicated by bleeding from such sites as oesophageal varices, by pulmonary hypertension, by cor pulmonale and nanism are often associated with chronic malnutrition and intercurrent infestations by other types of parasite. Following the publication by LAMBERT and FERREIRA (1965) of their successful clinical trial of CIBA 32644-Ba in vesical bilharziasis it was decided to investigate the use of this new schistosomicide in patients seen at our hospital with *S. mansoni* infection, including a number in an already advanced stage of the disease whose treatment would represent a more severe challenge.

II. Material and Methods

The contra-indications to classical antimonial therapy, namely old age, pregnancy, cardiac failure, renal insufficiency, severe anaemia or malnutrition, advanced hepatic failure, acute or chronic pulmonary infection, and the acute form of schistosomiasis, were also taken into account on the present occasion.

A group of 20 patients, comprising 11 males and 9 females of ages ranging from 11 to 40 years, was selected for trial. Among these were 8 with the intestinal or hepato-intestinal form of the disease, which is that commonly seen in ambulant patients. The other 12 cases (see details in Table 1) were in the most advanced stage, the hepatosplenic, but in a compensatory phase without severe

* Professor of Internal Medicine, ** Assistant, *** Resident, Medical School, University of Recife, Recife, Brazil.

TABLE 1

Summary of patients and treatment schedules – all received CIBA 32644-Ba in a dose of 25 mg/kg daily by mouth over the periods indicated. Clinical types of S. mansoni infestation are abbreviated as follows:

HS = hepatosplenic form; HI = hepato-intestinal form;
CP = cardio-pulmonary form

Case no.	Initials	Sex	Age in years	Clinical type	Treatment schedule doses/day: no. of days	Date therapy initiated
1	L.M.S.	F	34	HS	2: 7 days	20. 11. 64
2	I.U.F.	M	24	HS	2: 7 days	21. 11. 64
3	W.A.S.	M	33	HS	2: 7 days	24. 11. 64
4	V.F.B.	M	28	HI	2: 7 days	16. 12. 64
5	A.M.C.	F	40	HS	2: 7 days	10. 2. 65
6	M.I.S.	F	30	HS	2: 7 days	19. 2. 65
7	I.F.J.S.	M	11	HS	3: 7 ½ days	19. 3. 65
						6. 4. 65
8	M.I.Q.	F	22	HS	3: 5 days	6. 4. 65
9	A.I.S.	F	21	HI	3: 5 days	6. 4. 65
10	O.S.D.	M	14	HS	3: 5 days	9. 4. 65
				CP	3: 5 days	
11	N.J.S.	M	14	HS	3: 5 days	13. 4. 65
12	E.Q.B.	M	12	HS	3: 5 days	13. 4. 65
13	A.P.S.	M	35	HI	3: 5 days	22. 4. 65
14	J.E.B.	M	31	HS	3: 5 days	24. 4. 65
15	L.F.P.	F	27	HI	3: 5 days	29. 4. 65
16	O.G.S.	M	19	HI	3: 5 days	30. 4. 65
17	M.L.E.	F	30	HI	3: 5 days	1. 5. 65
18	M.E.B.S.	F	22	HI	3: 5 days	3. 5. 65
19	L.B.S.	M	31	HI	3: 5 days	8. 5. 65
				HS		
20	A.A.S.	F	14	CP	3: 5 days	8. 5. 65

hepatic failure. Among these were 2 patients with cardio-pulmonary involvement and pulmonary hypertension. The less advanced cases were treated on an ambulatory basis, the more advanced as hospital in-patients.

Prior to starting the trial, general supportive measures were provided, such as improved diet, protein, vitamin and iron supplements, and specific treatment of intercurrent intestinal helminth infestation where indicated.

The daily dose of CIBA 32644-Ba for all patients was 25 mg/kg body weight. This was administered as divided doses by mouth

2 or 3 times during the day according to the individual schedules shown in Table 1. Case 7 received treatment during 2 periods of 2½ and 5 days respectively, dosage being omitted on the 3rd consecutive treatment day because of gastric bleeding. No concurrent specific medication was given except on occasion an anti-emetic.

All patients were observed daily during therapy and all symptoms were recorded on a special chart. Clinical and laboratory examinations were carried out before the start of treatment and, as far as possible, 15, 30, 60, 90 and 120 days after its completion. Up to the time of writing, only cases 1 to 4 had been followed up for an adequate period, i.e. 4 months. Cases 5 and 6 were followed up for 3 months, and 7 to 12 for 1 month only. As the remaining 8 cases were treated only a short time prior to writing, only their immediate post-treatment results and incidence of side effects can be recorded here.

Before and on most occasions after treatment the following laboratory investigations were made:

1. Examination of faeces for ova of *S. mansoni* by the Hoffman technique.
2. Liver function tests: cephalin-cholesterol (Hanger), thymol turbidity and flocculation, zinc sulphate flocculation, serum protein profiles (electrophoresis), prothrombin time, bilirubin, transaminases (SGOT, SGPT), alkaline phosphatase, BSP retention.
3. Routine haemogram.

Electrocardiographic records before and after treatment were made of 5 patients and rectal biopsies 1, 2 or 4 months after treatment were taken from a few cases as detailed below.

III. Results

The results of our trial are considered under the headings of 1. Clinical picture, 2. Parasitological status, 3. Tolerability. In group 3 are included symptomatic side effects, as well as changes in liver function and haematological and ECG data.

1. Clinical picture

As far as observed at the time of writing, a follow-up period of between 1 and 5 months, all the patients showed a very satisfactory clinical result. The following three cases may be taken as representative of the general picture.

Case 1. Female, 34 years, hepatosplenic form. After 5 months a marked improvement in her previous complaints of anorexia, nausea with occasional vomiting, sensation of fullness in the stomach and intolerance of many foods, abdominal colic, alternating constipation and diarrhoea; headache, insomnia, dizziness and ready fatigability, epistaxis. On clinical examination the general condition was improved but there was no modification in the size of liver and spleen.

Case 4. Male, 28 years, hepato-intestinal form. Continuing clinical improvement after 4 months. By the end of the first month after treatment the following symptoms had almost disappeared: bad taste in mouth, sense of fullness in stomach with flatulence, abdominal pain, frequent diarrhoea; weakness, muscular pains in the legs, insomnia. The patient gained several kilos in weight but the liver enlargement remained unchanged.

Case 10. Male, 14 years, hepatosplenic complicated by cardio-pulmonary forms, very advanced. After 1 month a most satisfactory improvement of many symptoms including cough and palpitations and dyspnoea on exertion. Some weight gain but no modification of the liver or splenic enlargement.

2. *Parasitological status*

As a period of 4 months is generally accepted as the minimum follow-up observation time necessary to judge whether schistosomicidal therapy has produced a "parasitological cure" our data will be considered in two groups.

Cases 1 to 4 were followed up for at least 4 months while Cases 5 to 12 inclusive were observed after an interval of between only 1 and 4 months after completing treatment.

Group 1

Case 1. Stools negative for ova 15, 30, 60, 90 and 120 days after treatment. Rectal biopsy negative at day 120.

Case 2. Stools negative for ova 15, 30, 60, 90 and 120 days after treatment. No rectal biopsy made as this would have entailed a risk of repeated haemorrhage from rectal varices.

Case 3. Periodical stool examinations negative up to 60 days after which he returned to his home in the hinterland.

Case 4. Stool negative for ova 15, 30, 60, 90 and 120 days after treatment but rectal biopsy on day 120 revealed some viable eggs. (Clinical results, however, were as good as in the first 3 patients.)

Group 2

Cases 5 and 6. Stools and rectal biopsies negative up to the last examination at 90 days.

Cases 7 to 12. Treated 1 month previously, 5 patients had negative stools and the 6th continued to eliminate a few eggs. Rectal biopsy after 30 days in 1 case was negative, in a second revealed a few viable immature ova.

In summary, in addition to good clinical improvement, the majority of these 12 patients, as far as they had been followed up, showed a reduction or absence of egg elimination following therapy with CIBA 32644-Ba, and 2 of the 3 followed up for a full 4 months showed parasitological cure.

3. Tolerability

a) Symptomatic side effects

The complaints reported by the group of 20 patients during their treatment period are summarised in Table 2.

TABLE 2

Summary of secondary effects reported by 20 patients during treatment with CIBA 32644-Ba

Complaint	No. of times reported
a) *of regular occurrence*	
passage of dark urine	15
muscular pains	15
nausea	13
anorexia, headache	12 each
weakness	8
hot flushes, insomnia, dizziness	7 each
bad taste, dry mouth, vomiting, ocular pain	5 each
abdominal pain, weight loss	4 each
flatulence, itching, palpitations	3 each
b) *of sporadic occurrence*	
fullness of stomach, formication in hands, nervousness, depression, somnolence, fainting, dark vision, burning in eyes	2 each
burning or pain on micturition, lumbar pain, testicular pain, joint pain, oedema, rash, sialorrhea, muscle tremor	1 each
small haematemesis	1
loss of consciousness, convulsions, cyanosis	1

TABLE 3. *Liver function tests before and at various*

Test	Normal	Case 1				Case 2			
		Before	Days after therapy			Before	Days after therapy		Before
			30	120	150		30	120	
Total bilirubin	0.5	0.54	0.24	0.75	0.96	0.90	0.90	0.78	0.30
Prothrombin	100	68	60	71	86	59	40	44	42
Thymol turbidity	?	7.6	7.2	4.3	4.0	3.8	4.5	6.1	3.96
Thymol flocculation	0	+++	+	0	+	+	0	0	+
Hanger	0	+++	++	+++	+++	++	+++	+	++++
$ZnSO_4$	<40	14.9	12.2	7.4	8.8	8.5	11.5	14.6	18.9
Albumin	4.04	3.16	3.03	3.63	3.43	4.39	3.91	4.03	3.56
Globulin	2.34	3.13	2.82	2.38	3.17	2.17	3.91	3.72	3.85
A/G ratio	1.73	1.00	1.08	1.52	1.08	2.02	1.00	1.08	0.92
γ-globulin	0.74	1.31	1.53	—	1.32	0.99	—	1.78	0.30
S.G.O.T.	8–40	23	27	—	22	38	26	40	45
S.G.P.T.	5–35	22	23	—	20	37	30	20	37
Alkaline phosphatase	3–13	7	6.6	6.6	4.7	8.9	—	5.2	6.6

We may immediately eliminate the passing of dark urine as a side effect since it merely demonstrates the presence of the drug or its metabolites in the urine. Of the other complaints, muscular pain or discomfort was reported 15 times, nausea 13, anorexia and headache each 12 times, weakness 8, hot flushes, insomnia and dizziness each 7 times, bad taste, dry mouth, vomiting and ocular pain each 5 times. Numerous other minor symptoms as listed in Table 2 were reported sporadically. The intensity and duration of the above symptoms were never so great as to necessitate discontinuation of the therapy except in 1 patient (in whom treatment was later completed). The frequency of symptoms we believe may be related to the number of advanced cases of schistosomiasis that were included in our series.

More serious side effects occurred in two patients. The first of these (case 10), a boy of 14 years with advanced hepatosplenic and cardio-pulmonary manifestations, lost consciousness during his final day of treatment. This episode was followed by convulsions and cyanosis of brief duration. Although his family denied any

intervals after treatment with CIBA 32644-Ba

Case 6		Case 10			Case 11				
Days after therapy		Before	Days after therapy		Before	Days after therapy			
60	90		6	30		4	13	23	30
0.84	—	—	0.96	0.90	0.50	0.48	—	—	0.30
50	34	70	50	—	71	60	—	57	32
3.24	5.00	11.8	9.7	7.9	9.4	9.9	—	—	10.6
0	+	++++	+++	++	0	++	—	—	++
+++	—	+++	+++	+++	+++	+++	—	—	+++
15.3	17.5	26.0	22.3	17.1	19.8	19.8	—	—	22.5
3.23	3.23	3.46	—	3.78	2.24	—	2.72	2.79	3.05
3.77	3.23	4.00	—	3.36	4.62	—	5.64	7.07	4.97
0.85	1.00	0.86	—	1.12	0.40	—	0.48	0.39	0.61
0.84	—	—	—	—	2.57	—	—	—	2.97
30	30	—	—	48	35	—	35	36	35
41	31	—	—	32	35	—	40	20	20
6.1	8.6	12.9	15.4	16.2	9.9	9.0	—	16.4	9.13

previous history of such attacks, an EEG demonstrated a pattern of dysrhythmia associated with focal activation which, in the opinion of the consultant neurologist, was not directly associated with the administration of the drug. As stated above, 1 month after treatment this boy showed marked clinical improvement including a decrease of dyspnoea and palpitations on exertion and had gained 2 kilos in weight. The second patient (case 7), a boy of 11 years, produced a haematemesis of about 50 ml during the third day of treatment, which had thus to be temporarily discontinued. A few weeks previously he had lost about 400 ml of blood from a haematemesis and on another occasion had had melaena. As he continued to improve, therapy with CIBA 32644-Ba was reinstated 15 days after the latest haematemesis and continued for 5 days, at the end of which the patient vomited a further quantity of about 10 ml of blood. At the time of writing, 1 month after the end of treatment, this boy was continuing to improve clinically, his symptoms were decreasing, and he had had no further episodes of gastro-intestinal haemorrhage.

b) Changes in liver function tests

Particular attention was paid to any possible changes in the liver function tests since some patients already demonstrated abnormal readings in various of these owing to their general disease status even before therapy was commenced. The data on 5 patients (cases 1, 2, 6, 10 and 11), summarising the various liver function tests made before and at different intervals after treatment, are presented in Table 3. In general there was little or no significant change in any test in these patients on any occasion after treatment and in no case was there any indication that liver function had deteriorated. In some cases indeed there was a reversion of some pre-treatment abnormal values towards more normal ones following therapy.

c) Changes in haematological data

Complete haematological data were obtained before and after treatment in cases 2, 5, 6, 7 and 10. As no consistent or significant modifications were demonstrated following therapy the detailed figures are omitted from this paper.

d) Electrocardiographic records

In the only 5 cases in our series in whom it was possible to record the ECG before and shortly after treatment with CIBA 32644-Ba, no obvious modifications of the trace related to the period of treatment were observed. In cases 10 and 20, patients with pulmonary hypertension and cor pulmonale, the ECG showed, as would be anticipated, evidence of right atrial and ventricular hypertrophy, but in no case was any special modification of the T wave verified.

4. Summary

In this clinical trial of CIBA 32644-Ba a series of 20 patients was selected deliberately to include 12 with advanced hepato-splenic disease, 2 of whom had in addition chronic cor pulmonale. The drug in a total daily oral dose of 25 mg/kg was well tolerated and gave rise in general, even in this group of relatively severe cases, only to minor or moderate side effects. Severe symptoms in 2 patients were probably related to underlying constitutional changes, in one case a tendency to haemorrhage from bleeding oesophageal varices and in the other focal cerebral dysrhythmia.

Although the period of observation was restricted so that some cases could not be followed up for the requisite time, a good clinical result associated with an improvement of the parasitological status was obtained in all cases. Parasitological cure was obtained in 2 of those 3 patients who were observed for over 4 months. The drug apparently induced no untoward changes in the liver, blood, or myocardium, and indeed there was evidence in some cases of improvement in liver function.

The good results obtained in this preliminary investigation indicate that the drug should be tested on a larger scale. If this preliminary success is confirmed CIBA 32644-Ba will offer a distinct therapeutic advance in the treatment of schistosomiasis, for the following reasons:

1. It can be administered orally.
2. The treatment period is short.
3. The side effects are only minor to moderate.
4. The compound may be administered safely even to the most advanced cases, such as those with hepatosplenic or cardiopulmonary syndromes.

Résumé

Dans l'essai clinique rapporté, 20 malades furent sélectionnés de façon que 12 d'entre eux présentent des cas avancés d'hépatosplénomégalie, dont 2 cas avec cœur pulmonaire. Le CIBA 32644-Ba donné à raison de 25 mg/kg/jour fut bien toléré et ne provoqua, même chez les malades à symptomatologie sévère, que des effets secondaires mineurs ou modérés. Des effets secondaires sévères, observés chez 2 malades, furent attribués à des altérations constitutionnelles sous-jacentes: tendance hémorragique à partir de varices œsophagiennes dans un cas, dysrythmie focale cérébrale dans l'autre.

Quoique la période d'observation soit insuffisante à un jugement définitif, un bon résultat clinique fut observé dans tous les cas et 2 sur 3 malades, suivis pendant 4 mois, ont été parasitologiquement guéris.

Le traitement n'a pas d'action toxique sur le foie, le sang et le myocarde, et la fonction hépatique a même été améliorée dans quelques cas.

Les bons résultats obtenus dans cet essai préliminaire indiquent que le CIBA 32644-Ba devrait être étudié sur une plus grande échelle. Si les résultats préliminaires sont confirmés, le CIBA 32644-Ba offrira de nouvelles perspectives du traitement de la bilharziose pour les raisons suivantes :

1. Il peut être donné par voie orale.
2. La durée du traitement est courte.
3. Les effets secondaires sont seulement mineurs ou modérés.
4. Le médicament peut être administré avec sécurité même dans les cas les plus avancés, comme les syndromes splénohépatiques ou le cœur pulmonaire caractérisé.

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