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# CLINICAL TRIAL WITH "CIBA 32'644-Ba" (NITROTHIAZOL COMPOUND) IN *MANSONI* SCHISTOSOMIASIS

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**SUMMARY**

The Authors have made a clinical trial in *mansoni* Schistosomiasis therapy with a new product "Ciba 32'644-Ba" (nitrothiazol compound). It was employed in 26 patients with the hepato-intestinal, hepato-splenic and cardio-pulmonary forms of the disease, in the dosage of 25 mg/kg/day during 5 to 7 days. They analysed the secondary effects having observed, in general, a good or regular tolerance. However, in 2 cases severe intolerance characterized by nervous symptoms was verified: great agitation and mental confusion and appearance of convulsive seizures. The parasitological cure was verified in more than 80% of the cases and the later clinical results were good in almost 100% of the patients. They also studied the effects of the drug on the liver function and the possible hematological and ECG modifications.

## INTRODUCTION

It is our purpose to present the preliminary results of the treatment of *mansoni* Schistosomiasis with a new product (Ciba 32'644-Ba), utilized by oral route. It is a nitrothiazol derivative, the 1 — (5 nitro-2 thiazolyl) — 2 imidazolidinone, from Ciba Laboratories, of Basle.

The well known toxicity of the antimonial compounds employed in the treatment of Schistosomiasis, as well as their parenteral route and therapeutic limitations [1, 6] have led to many tentatives of employment of new products in the treatment of this disease [4, 5, 7]. However, the majority of these trials have been unsuccessful due to intolerance or ineffectiveness of the drugs. So, when we received the Ciba product for a clinical investigation, we confess having started its employment without great enthusiasm, in spite of the preliminary good results shown by LAMBERT & FERREIRA DA CRUZ [3] in vesical bilharziasis. Nevertheless, our present initial observations in *mansoni* Schistosomiasis, as well as other investigation results [2], seem to indicate that we have now a new chemical that deserves a better interest and further extensive investigation.

## MATERIAL AND METHODS

We used the drug in twenty-six *mansoni* schistosomotic patients, 13 males and 13 females, in ages varying from 11 to 40 years (Table I). Twelve patients presented the most common complaints of the intestinal or hepato-intestinal form; the remaining 14 exhibited a more advanced clinical form — the so-called hepatosplenic syndrome with portal hypertension in its compensatory stage (without intense liver failure).

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TABLE I

*Mansoni* schistosomotic patients treated by Ciba 32'644-Ba in the dosage of 25 mg/kg/day (oral)

| No. | Identity | Sex | Age (years) | Clinical form | Treatment schedule | Date |
|---|---|---|---|---|---|---|
| 1 | L.M.S. | ♀ | 34 | H.E. | 2 dosis, 7 days | November 20-26, 1964 |
| 2 | I.U.F. | ♂ | 24 | H.E. | 2 dosis, 7 days | November 21-27, 1964 |
| 3 | W.A.S. | ♂ | 33 | H.E. | 2 dosis, 7 days | November 24-30, 1964 |
| 4 | V.F.B. | ♂ | 28 | H.I. | 2 dosis, 7 days | December 16-22, 1964 |
| 5 | A.M.C. | ♀ | 40 | H.E. | 2 dosis, 7 days | February 10-17, 1965 |
| 6 | M.I.S. | ♀ | 30 | H.E. | 2 dosis, 7 days | February 19-25, 1965 |
| 7 | I.F.J.S. | ♂ | 11 | H.E. | 3 dosis, 7½ days | March 19-21 and April 6-10, 1965 |
| 8 | M.I.Q. | ♀ | 22 | H.E. | 3 dosis, 5 days | April 6-10, 1965 |
| 9 | A.I.S. | ♀ | 21 | H.I. | 3 dosis, 5 days | April 6-10, 1965 |
| 10 | O.S.D. | ♂ | 14 | H.E. / C.P. | 3 dosis, 5 days | April 9-13, 1965 |
| 11 | N.J.S. | ♂ | 14 | H.E. | 3 dosis, 5 days | April 13-17, 1965 |
| 12 | E.Q.B. | ♂ | 12 | H.E. | 3 dosis, 5 days | April 13-17, 1965 |
| 13 | A.P.S. | ♂ | 35 | H.I. | 3 dosis, 5 days | April 22-26, 1965 |
| 14 | J.E.B. | ♂ | 31 | H.E. | 3 dosis, 5 days | April 24-28, 1965 |
| 15 | L.F.P. | ♀ | 27 | H.I. | 3 dosis, 5 days | April 29-May 3, 1965 |
| 16 | O.G.S. | ♂ | 19 | H.I. | 3 dosis, 5 days | April 30-May 4, 1965 |
| 17 | M.L.E. | ♀ | 30 | H.I. | 3 dosis, 5 days | May 1- 5, 1965 |
| 18 | M.E.B.S. | ♀ | 22 | H.I. | 3 dosis, 5 days | May 3- 7, 1965 |
| 19 | L.B.S. | ♂ | 31 | H.I. | 3 dosis, 5 days | May 8-12, 1965 |
| 20 | A.A.S. | ♀ | 14 | H.E. / C.P. | 3 dosis, 5 days | May 8-12, 1965 |
| 21 | L.A.N. | ♂ | 30 | H.I. | 3 dosis, 7 days | August 4-10, 1965 |
| 22 | A.F.S. | ♀ | 28 | H.I. | 3 dosis, 5 days | August 9-13, 1965 |
| 23 | C.M.N. | ♀ | 21 | H.I. | 3 dosis, 7 days | August 9-15, 1965 |
| 24 | E.B.A. | ♂ | 18 | H.E. | 3 dosis, 7 days | August 11-17, 1965 |
| 25 | M.T.O. | ♀ | 28 | H.E. | 3 dosis, 7 days | August 17-23, 1965 |
| 26 | J.G.S. | ♀ | 33 | H.I. | 3 dosis, 7 days | August 17-23, 1965 |

H.E. — Hepato-splenic form
H.I. — Hepato-intestinal form
C.P. — Cardio-pulmonary form

Among these later, 2 patients (no. 10 and 20) had also pulmonary arterial hypertension or the cardio-pulmonary form. The majority of cases were treated with inwarded patients; only a small number, with few complaints, were out-patients. All subjects received the drug, by oral route, in the same daily dosage — 25 mg/kg/day, in two or

three dosis during 5 to 7 days (see Table I). Only case no. 7 was treated during 2 periods of 2 ½ and 5 days respectively, due to a small gastric hemorrhage on the third day, which obliged the suppression of the drug temporarily. When necessary, many patients were submitted during 4 to 6 weeks to a previous general treatment, consisting of a diet improvement, protein and vitamin supplements, and iron containing medicaments against the associated intestinal parasites.

During the experimental therapy each patient was followed daily and every symptom was recorded on a special chart. No other drug was employed in this period, except a few symptomatic drugs (anti-emetic, sedative, anti-allergic) with some patients.

After a week of specific treatment every subject was invited to return to the Clinic 2 and 4 weeks later and monthly thereafter for a check-up, but a few of them did not come back regularly. The six last cases (no. 21-26) were treated very recently, and thus only the side effects and the immediate therapeutic results were so far observed in same.

Before the treatment and in almost all those periodical checking-ups the following laboratory tests were carried out: 1) feces examination for schistosome eggs, by Hoffman technic; 2) liver tests: cephaline cholesterol, thymol turvation, zinc sulphate, serum proteins including electrophoresis, prothrombin activity, bilirubin, transaminases (SGOT, SGPT), alkaline phosphatase, B.S.P.; 3) hematologic routine. In 7 patients, indicated below, rectal biopsy was performed, in one of those post-treatment visits. In only 6 patients an electrocardiographic study was made before and soon after the use of the drug. An electroencephalographic study was undertaken in 2 patients (no. 10 and 22) at the end of their treatment.

## RESULTS

Our observations can be unfolded into the following aspects: 1) toxicity or secondary effects during and soon after treatment; 2) clinical results, from 1 to 8 months after treatment; 3) parasitological cure; 4) liver function; 5) hematologic modifications; 6) ECG alterations.

### SECONDARY EFFECTS

Concerning the toxicity of the drug, we may analyse the side effects in relation to the system involved and principally to their magnitude: mild or severe. The most common mild side-effects found in our cases are listed, with their frequency, on Table II. They may be further separated into the following groups: I) general symptoms: muscular pain (21 times), headache (18), weakness (14), loss of weight (5); II) gastro-intestinal: anorexia (18 times), nausea (17), dry mouth (8), vomiting (7), abdominal pain (6); III) neuro-psychical: insomnia (13 times), dizziness (10), hot-flushes (10), palpitation (9), ocular pain (6), nervousness (5), depression (3); IV) allergic: itching (8 times), rash (3), eye burning (3).

Other mild symptoms were verified in rare occasions. In the majority of cases, those collateral effects were of little or moderate intensity and lasted for only a few days. In some patients, however, these symptoms were of a greater intensity, and the use of some palliative drugs, specially "Neozine" and "Novalgine", was prescribed. But in none of these patients the suppression of the Ciba drug was necessary.

TABLE II

Side-effects observed during the treatment with Ciba 32'644-Ba in 26 *mansoni* schistosomotic patients

| No. of patients | 26 |
|---|---|
| Muscular pain | 21 times |
| Anorexia | 18 times |
| Headache | 18 times |
| Nausea | 17 times |
| Weakness | 14 times |
| Insomnia | 13 times |
| Dizziness | 10 times |
| Hot flushes | 10 times |
| Palpitation | 9 times |
| Itching | 8 times |
| Dry mouth | 8 times |
| Vomiting | 7 times |
| Ocular pain | 6 times |
| Abdominal pain | 6 times |
| Bad taste | 5 times |
| Nervousness | 5 times |
| Weight loss | 5 times |

It seems to us that there was a higher frequency of side-effects in our casuistic than in others [7]. Perhaps this frequency is related to the greater incidence of more advanced clinical cases and associated undernourished condition prevailing in the group studied.

In 3 patients (11.5%) severe symptoms were noticed as follows: 1) Patient no. 7, with the hepatosplenic form of the disease, presented on the 3rd day of treatment a little episode of hematemesis (about 50 ml of blood) which determined the discontinuation of the treatment. As he did well afterwards, the medicament was reinstituted 15 days later and during 5 days. The patient referred having had a smaller hematemesis (about 10 ml of blood) again on the last day. It is interesting to note that a few weeks before the treatment was started, this patient had had a large blood vomit (400 ml) as well as a melena episode many months earlier. In his last appointment, 4 months after the treatment, the patient has shown to be doing well, without reference to any other gastro-intestinal hemorrhage. 2) Patient no. 22 with the hepato-intestinal form, presented on the first day of treatment headache, muscle pain and nausea soon followed by hot flushes, anorexia and cutaneous rash with itching, nervousness and insomnia. In the following days these symptoms became increasingly worse with generalized rash, great anxiety, mental desorientation and psycho-motor agitation, which rendered necessary the administration of anti-histaminics, sedatives and tranquilizers. Later on, the patient had to be immobilized in bed, because she tried to jump through a window in an attempt of suicide. Therefore the drug was discontinued on the 5th day of treatment (the schedule was for 7 days). Besides the extensive rash with some purpura and great agitation, muscular hipotony and generalized symetrical tendinous hyperreflexia were also observed. No convulsive were noticed. On the day following the discontinuation of treatment all those symptoms began to subside very fastly. An electroencefalography study, made some days later, showed no alterations. 3) Patient no. 10, a 14 years old boy with hepatosplenic plus cardio-pulmonary forms, on the last day of treatment (5th) was suddenly taken by a crisis of loss of consciousness, convulsions and cyanosis of rapid duration. His family denied previous attacks. The EEG, taken on the following day, demonstrated dysrhythmia with focal activation. At present, 5 months after treatment, this patient is much better as regards his original complants (see later) and a new EEG study failed to demonstrate any alteration.

## LATER CLINICAL RESULTS

The later clinical results (1 to 8 months of follow-up) have been good or excellent in the great majority of patients, with disappearance or great attenuation of the previous symptoms related to the disease. Only the spleen and liver dilation, when present, did not show any modification after treatment. The three examples described below correspond almost exactly to the other cases.

Patient no. 1, a female of 34 years of age, with the hepatosplenic form has shown, 5 months after treatment, a negative feces examination and an accentuated improvement of her previous general and digestive complaints, such as: anorexia, headache, insomnia, dizziness, fatigability, epistaxis, nausea, vomiting once in a while, stomach fullness, intolerance to many foods, abdominal pain (colics), diarrhea alternating with constipation. But the increased volume of the liver and spleen continued the same. Patient no. 4, a man of 28 years of age, with the hepato-intestinal form, presented a great improvement 6 months after the treatment. The following symptoms had almost disappeared, from the first month on: abdominal pain, flatulence and frequent diarrhea, and the patient had a slight weight increase. The liver enlargement, however, remained the same. Patient no. 10, a boy of 14 years of age, in a very advanced stage of the disease (hepatosplenic plus cardio-pulmonary form) showed, 1 month after treatment, a good improvement of many symptoms, including the cough, dyspnea and palpitation following physical effort. He also gained weight, but the liver and the spleen enlargements did not show any alteration. In our opinion it is of great interest to stress the clear improvement observed in such a patient, with the very advanced cardio-pulmonary form of the disease.

PARASITOLOGICAL CURE

So far, the evaluation of the parasitological cure could be carried out in only 16 of the 26 patients who received the drug. The last 6 (no. 21 to 26) were treated very recently, and the 4 other patients unfortunately did not return for reexamination.

From the 16 cases evaluated, 12 were followed for a period between 4 and 8 months later. A rectal biopsy performed 3 ½ months. All but one of the 16 patients had a negative feces examination. Only patient no. 12 after showing 2 negative stools, 1 and 2 months post-therapeutics, presented some viable schistosomal eggs 3 months later. A rectal biopsy performed during the first 2 months had still shown a few viable eggs. Clinically, this patient had shown a great improvement in this complaints.

In 6 of the 15 patients with stool negativation a rectal biopsy was also made, with a negative result in four. In one patient (no. 4), some viable eggs were found 4 months after treatment and in another (no. 8), many inviable and calcified eggs as well as a granulomatous lesion were detected, at the same period of time.

So, in the present small casuistic the parasitological cure was observed in almost 80% of the patients treated. In the other 20% there was certainly a reduction of the degree of infestation demonstrated by the clinical improvement and the scarcity of parasite eggs in stools or rectal biopsy.

LIVER FUNCTION

Through the tests indicated above and at different intervals post-treatment, we searched to find out any modifications of the liver function. On Tables III, IV, V, VI and VII some examples of these observations are included. We can see that, in general, the liver function remained almost unaltered or, in a few instances, a slight improvement was revealed by the majority of the tests.

A clear damage of the liver physiology was never observed.

TABLE III

Modifications of the liver tests after treatment. Patient no. 1

| Type of tests | Before treatment | Post-treatment | | | |
|---|---|---|---|---|---|
| | | 1 month | 4 months | 5 months | 7 months |
| Hanger test | +++ | ++ | +++ | +++ | +++ |
| Zinc sulphate | 14.9 | 12.2 | 7.4 | 8.8 | 7.7 |
| Thymol turvation | 7.6 | 7.2 | 4.3 | 4.0 | 4.1 |
| Thymol flocculation | +++ | + | — | + | ++ |
| Albumin | 3.16 | 3.03 | 3.63 | 3.43 | 3.91 |
| Globulins | 3.13 | 2.82 | 2.38 | 3.17 | 2.45 |
| A/G ratio | 1 | 1.08 | 1.52 | 1.08 | 1.5 |
| γ globulin | 1.31 | 1.53 | — | 1.32 | — |
| Total Bilirubin | 0.54 | 0.24 | 0.75 | 0.96 | 0.75 |
| Alk. phosphatase (U.B.) | 7 | 6.6 | 6.6 | 4.7 | 6.5 |
| S.G.O.T. | 23 | 27 | — | 22 | — |
| S.G.P.T. | 22 | 23 | — | 20 | — |
| Prothrombin | 68 | 60 | 71 | 86 | 50 |

TABLE IV

Modifications of the liver tests after treatment. Patient no. 2

| Type of tests | Before treatment | Post-treatment | | |
|---|---|---|---|---|
| | | 1 month | 4 months | 8 months |
| Hanger test | ++ | +++ | + | +++ |
| Zinc sulphate | 8.5 | 11.5 | 14.6 | 17.3 |
| Thymol turvation | 3.8 | 4.5 | 6.1 | 5.8 |
| Thymol flocculation | + | — | — | +++ |
| Albumin | 4.39 | 3.91 | 4.03 | 4.32 |
| Globulins | 2.17 | 3.91 | 3.72 | 3.84 |
| A/G ratio | 2.02 | 1.00 | 1.08 | 1.1 |
| γ globulin | 0.99 | — | 1.78 | 2.45 |
| Total Bilirubin | 0.90 | 0.90 | 0.78 | 0.60 |
| Alk. phosphatase (U.B.) | 8.9 | — | 5.2 | 15 |
| S.G.O.T. | 38 | 26 | 40 | 40 |
| S.G.P.T. | 37 | 30 | 20 | 40 |
| Prothrombin | 59 | 40 | 44 | — |

TABLE V

Modifications of the liver tests after treatment. Patient no. 6

| Type of tests | Before treatment | Post-treatment | | |
|---|---|---|---|---|
| | | 2 months | 3 months | 5 months |
| Hanger test | ++++ | +++ | — | ++++ |
| Zinc sulphate | 18.9 | 15.3 | 17.5 | 18.9 |
| Thymol turvation | 3.96 | 3.24 | 5.0 | 5.9 |
| Thymol flocculation | + | — | + | + |
| Albumin | 3.56 | 3.23 | 3.23 | 3.44 |
| Globulins | 3.85 | 3.77 | 3.23 | 4.04 |
| A/G ratio | 0.92 | 0.85 | 1 | 0.85 |
| Bilirubin | 0.30 | 0.84 | — | 1.2 |
| Alk. phosphatase (U.B.) | 6.6 | 6.1 | 8.6 | — |
| S.G.O.T. | 45 | 30 | 30 | — |
| S.G.P.T. | 37 | 41 | 31 | — |
| Prothrombin | 42 | 50 | 34 | — |

TABLE VI

Modifications of the liver tests after treatment. Patient no. 10

| Type of tests | Before treatment | Post-treatment | | |
|---|---|---|---|---|
| | | 6 days | 1 month | 4 months |
| Hanger test | +++ | +++ | +++ | +++ |
| Zinc sulphate | 26.0 | 22.3 | 17.1 | 19.4 |
| Thymol turvation | 11.8 | 9.7 | 7.9 | 9.4 |
| Thymol flocculation | ++++ | +++ | ++ | ++++ |
| Albumin | 3.46 | — | 3.78 | 4.01 |
| Globulins | 4.00 | — | 3.36 | 3.95 |
| A/G ratio | 0.86 | — | 1.12 | 1.01 |
| Total Bilirubin | — | 0.96 | 0.90 | 1.02 |
| Alk. phosphatase (U.B.) | 12.9 | 15.4 | 16.2 | 14.3 |
| S.G.O.T. | — | — | 48 | 50 |
| S.G.P.T. | — | — | 32 | 50 |
| Prothrombin | 70 | 50 | — | 71 |

TABLE VII

Modifications of the liver tests after treatment. Patient no. 11

| Type of tests | Before treatment | Post-treatment | | | | |
|---|---|---|---|---|---|---|
| | | 4 days | 13 days | 23 days | 1 month | 4 months |
| Hanger test | +++ | +++ | — | — | +++ | + |
| Zinc sulphate | 19.8 | 19.8 | — | — | 22.5 | 24.3 |
| Thymol turvation | 9.4 | 9.9 | — | — | 10.6 | 7.2 |
| Thymol flocculation | — | ++ | — | — | ++ | + |
| Albumin | 2.24 | — | 2.72 | 2.79 | 3.05 | — |
| Globulins | 4.62 | — | 5.64 | 7.07 | 4.97 | — |
| A/G ratio | 0.40 | — | 0.48 | 0.39 | 0.61 | — |
| γ globulin | 2.57 | — | — | — | 2.97 | — |
| Total Bilirubin | 0.50 | 0.48 | — | — | 0.30 | — |
| Alk. phosphatase (U.B.) | 9.9 | 9.0 | — | 16.4 | 9.13 | 13.2 |
| S.G.O.T. | 35 | — | 35 | 36 | 35 | 50 |
| S.G.P.T. | 35 | — | 40 | 20 | 20 | 44 |
| Prothrombin | 71 | 60 | — | 57 | 32 | 44 |

TABLE VIII

Hematological data after treatment. Patient no. 2

| | Before | Last day of treatment | 17 days | 4 months | 5 months |
|---|---|---|---|---|---|
| RBC | 4,875,000 | 4,100,000 | 4,355,000 | 4,225,000 | 4,500,000 |
| Hb | 14.5 | 12 | 12.5 | 14 | 14.5 |
| Ht | 44 | 41 | 41 | 42 | 44 |
| Leuk. | 3,000 | 4,000 | 2,000 | 3,500 | 5,350 |
| Eos. | 11 | 10 | 10 | 13 | 39 |
| Sed. rate | 19 | 25 | 6 | 10 | 32 |
| Platelets | 120,000 | 110,000 | — | 160,000 | — |

TABLE IX

Hematological data post-treatment. Patient no. 5

| | Before | 2 months | 3 months | 6 months |
|---|---|---|---|---|
| RBC | 4,000,000 | — | 4,400,000 | 4,225,000 |
| Hb | 14 | 13 | 14.5 | 14.5 |
| Ht | 39 | — | 41 | 39 |
| Leuk. | 2,600 | 4,500 | 3,000 | 2,100 |
| Eos. | 1 | 0 | 0 | 0 |
| Sed. rate | 39 | — | 47 | 46 |
| Platelets | 36,000 | 174,000 | 100,000 | 100,000 |

TABLE X

Hematological data post-treatment. Patient no. 6

| | Before | 8 days | 1 month | 2 months | 4 months |
|---|---|---|---|---|---|
| RBC | 2,997,000 | — | 3,960,000 | 4,000,000 | 4,100,000 |
| Hb | 8.5 | 10.5 | 11.5 | 12.5 | 12.5 |
| Ht | 25 | 32 | 38 | 39 | 40 |
| Leuk. | 1,050 | — | 1,630 | 2,600 | 2,000 |
| Eos. | 8 | — | 3 | 6 | 6 |
| Sed. rate | 27 | — | 20 | 13 | 12 |
| Platelets | 40,000 | — | — | 50,000 | 60,000 |

TABLE XI

Hematological data post-treatment. Patient no. 7

| | Before | 13 days | 1 month |
|---|---|---|---|
| RBC | 4,095,000 | 4,095,000 | 4,000,000 |
| Hb | 12.5 | 12 | 13 |
| Ht | 38 | 38 | 39 |
| Leuk. | 2,000 | 3,550 | 3,450 |
| Eos. | 18 | 22 | 21 |
| Sed. rate | 47 | 59 | 48 |
| Platelets | 125,000 | 156,000 | 130,000 |

TABLE XII

Hematological data post-treatment. Patient no. 10

| | Before | 6 days | 1 month | 4 months |
|---|---|---|---|---|
| RBC | 4,500,000 | 4,420,000 | 4,290,000 | 4,550,000 |
| Hb | 13.5 | 14.5 | 14 | 14.2 |
| Ht | 39 | 43 | 41 | 42 |
| Leuk. | 5.300 | 7,000 | 4,400 | 4,950 |
| Eos. | 11.5 | 18 | 16 | 14 |
| Sed. rate | 30 | 35 | 20 | 18 |
| Platelets | 216,000 | 125,000 | 70,000 | — |

## HEMATOLOGICAL RESULTS

There was no consistent modification of the hematological tests at any time post-treatment, as indicated in Tables VIII, IX, X, XI and XII.

## ECG MODIFICATIONS

Electrocardiographic studies could be performed in only 6 patients, before and soon after the treatment. No modification was verified in two cases (no. 10 and 20) with

pulmonary arterial hypertension and chronic *Cor pulmonale*. In these 2 cases, as expected, the ECG showed right atrial and ventricular hypertrophy both before and after treatment. No special modification of the *T* wave was verified.

## DISCUSSION AND CONCLUSIONS

A clinical-therapeutical trial was made with the new product "Ciba 32'644-Ba" in 26 patients with *mansoni* Schistosomiasis, 12 with the hepato-intestinal form and 14 with the hepatosplenic syndrome. Among these later, two had also chronic *Cor pulmonale* due to schistosomotic pulmonary arterial hypertension. The drug was employed by oral route, in the dosage of 25 mg/kg/day during 5 to 7 days. We believe that the best schedule is 25 mg/kg/day, in two daily doses during 7 days.

Considering the small number of cases and the limited time of observation in some of them, it is still early to establish definitive conclusions about the effectiveness of this new medicament. However, these preliminary results seem to demonstrate that the present drug, in the schedule utilized, has evident schistosomicide effect in man, in the great majority of cases.

Our present experience seems also to show that its therapeutic effects is equal or perhaps better than that of the best antimony products. Disappearance of parasite eggs in stool and also in rectal biopsies (small number) resulted in almost 80% of the cases. In the other 20%, a great reduction in the degree of infestation was evidentiated. In this later group of patients, we believe a new period of treatment 6 to 12 months after the first schedule could be tried.

The later clinical results were good in almost all cases, with disappearance or great reduction of the majority of symptoms, some gain in weight and a sensation of well-being. Only the enlargements of liver and spleen did not show any modification after treatment. There was no alteration of the hematological findings and the liver function did not show any impairment, in spite of our having utilized the drug in a great number of patients with the advanced hepatosplenic form.

One important point to us is the favourable effect verified in the patients with the advanced pulmonary hypertension form and chronic *Cor pulmonale*. These good results, together with the almost complete absence of liver and heart injury due to drug, in comparison with the antimony therapy, came to enlarge the indications and possibilities of the specific treatment of bilharziasis. Another important aspect is the facility of employment of this new drug by oral route.

Nevertheless, some negative aspects in connection with the tolerance of the drug must be stressed, principally related to two items: the nervous and the reproductive system. As to the first we have observed, besides some benign symptoms such as headache, insomnia, nervousness, palpitation, dizziness, 2 cases with severe symptoms: one with a gradual intensive psychotic agitation and mental confusion and the other with a sudden attack of loss of consciousness, convulsions and cyanosis. In the later a focal dysrhythmia was demonstrated by EEG, probably related to the drug. Similar cases were observed by other investigators in trials with the same drug [2].

It is possible, perhaps, to reduce these psycho-neurological symptoms with the simultaneous use of sedative and anti-convulsive drugs, such as Amplictil and Phenobarbital. We also suggest to exclude from the treatment with this nitrothiazol compound, in the future, all the patients with previous nervous symptoms or with EEG alterations.

In relation to the reproductive system we do not have any personal experience, but there are a few statements [2] of transitory inhibition of spermatogenesis due to the drug, in animal experimentation. A few preliminary studies in man [2], by spermatogram or testicular biopsy, seem to demonstrate that there are very little functional or histological modifications, both reversible.

## RESUMO

*Ensaio clínico com "Ciba 32'644-Ba" (composto nitrotiazólico) na esquistossomose mansônica*

Os Autores realizaram ensaio clínico terapêutico na esquistossomose mansônica com um nôvo produto, "Ciba 32'644-Ba" (com-

posto nitrotiazólico). Foi empregado em 26 pacientes com formas hepatintestinal, hepatesplênica e cárdio-pulmonar da doença, na dose de 25 mg/kg/dia por 5 a 7 dias. Foram analisados os efeitos secundários imediatos, havendo em geral boa ou regular tolerância. Salientaram-se, todavia, pela sua gravidade, as alterações do sistema nervoso encontradas em 2 pacientes: grande agitação e confusão mental e aparecimento de crises convulsivas. A cura parasitológica foi verificada em mais de 80% dos casos e os benefícios clínicos tardios foram evidenciados na quase totalidade dos pacientes. Também foram estudados os efeitos sôbre a função hepática e as possíveis modificações hematológicas e electrocardiográficas.

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