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# Treatment of *Schistosomiasis mansoni* with a New nitrothiazole Derivative, CIBA 32644-Ba

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CUCKLER, KUPFERBERG and MILLMAN (2) demonstrated that certain nitrothiazole derivatives have activity against schistosomes. These investigators treated *Schistosoma mansoni* infection in mice and demonstrated that 2-acetamido-5-nitrothiazole killed most of the adult worms and inhibited egg production in the worms that remained alive. However, 2-amino-5-nitrothiazole was completely ineffective. AMATO NETO and PRATA (1) treated 10 patients with 2-acetamido-5-nitrothiazole in a dose of 600 mg daily for 10 days. Although the drug was well tolerated, all of the patients continued to pass stool positive for ova of *S. mansoni*.

1-(5-nitro-2-thiazolyl)-2-imidazolidinone (CIBA 32644-Ba) was synthesized by WILHELM and SCHMIDT (3). The chemistry, pharmacology and activity against *S. mansoni* have been determined, and some preliminary clinical trials have been completed (3, 4, 5, 6).

The purpose of this paper is to present preliminary results in the treatment of human schistosomiasis with CIBA 32644-Ba.

## *Materials and Methods*

Ten patients were treated with CIBA 32644-Ba in January, 1965 and 35 were treated in May, 1965. All of the patients were males, 16-19 years of age, who were attending the Naval School in Bahia, Brazil. There were 11 whites, 25 mulattoes and 9 negroes. They were restricted to the grounds of the school on weekdays and were free to leave only at weekends. The admission requirements for the school include a complete physical examination and all of the men had been found to be in good health.

The patients ranged in height from 161-182 cm and from 45 to

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TABLE 1

*Symptomatology before treatment in 45 patients*

| Patients | Occasional complaints |
|---|---|
| 4 | Asthenia, anorexia, diarrhoea |
| 5 | Headache, heartburn |
| 6 | Diarrhoea |
| 7 | Diarrhoea, streaks of blood in the stools, dyspepsia |
| 8 | Asthenia, light-headedness, diarrhoea, nausea, abdominal pain |
| 9 | Diarrhoea |
| 14 | Light-headedness. Fatty food intolerance |
| 16 | Hemicrania |
| 17 | Diarrhoea |
| 18 | Epistaxis |
| 19 | Diarrhoea |
| 20 | Anorexia, tonsillitis |
| 21 | Streaks of blood in the stools |
| 28 | Diarrhoea |
| 29 | Diarrhoea, streaks of blood in the stools, dyspepsia |
| 30 | Light-headedness |
| 33 | Headache |
| 34 | Headache, diarrhoea, abdominal pain |
| 37 | Constipation |
| 38 | Dysentery |
| 40 | Diarrhoea, streaks of blood in the stools, abdominal pain |
| 42 | Asthenia, light-headedness |
| 43 | Asthenia, light-headedness |
| | Twenty-two patients had no symptoms |

68 kg in weight. The liver was enlarged in only one patient and was felt 4 cm below the right costal margin. The spleen was palpable in three patients only on deep inspiration.

All of the patients had ova of *S. mansoni* in the stool. The incidence of other ova in the stool was *Ascaris lumbricoides* 98%, *Trichuris trichiura* 93%, hookworm 77% and *Strongyloides stercoralis* 27%. Twenty-two of the 45 patients were asymptomatic and the other 23 complained of the symptoms listed in Table 1.

The patients were divided into the following four groups:

I. Patients 1-10 who received CIBA 32644-Ba in a dose of 30 mg/kg daily for 10 days in January, 1965.
II. Patients 11-20 who received 20 mg/kg for 5 days in May, 1965.
III. Patients 21-30 who received 30 mg/kg for 10 days in May, 1965.
IV. Patients 31-45 who received 40 mg/kg for 5 days in May, 1965.

The drug was taken by mouth, two times a day (before breakfast and before supper) in the presence of a nurse. The patients continued their normal daily activities during the period of treat-

ment and each day they were questioned for manifestations of toxicity.

Group I had the following laboratory examinations before and after therapy: haemoglobin, red blood cell count, white blood cell count and differential, urine analysis, cephalin flocculation test, thymol turbidity and thymol flocculation. The other groups had daily determinations of weight, pulse rate and axillary temperature during therapy; urine analysis before and after; non-protein nitrogen determinations after; and electrocardiograms during and after completion of treatment.

Rectal biopsies were performed on five different patients each day during the second to eighth days of therapy, and 16 days after initiation of treatment in order to determine the time of cessation of oviposition in the rectum and the effect of CIBA 32644-Ba on the ova.

An evaluation of cure could be made only in Group I and consisted of 4-16 examinations of stool for ova performed 2-4 months after completion of therapy, and one rectal biopsy done 4 months after completion of therapy.

## *Results*

Table 2 demonstrates the results of serial rectal biopsies. Ova of the first stage began to diminish in number after the third day of therapy and disappeared completely from the rectal wall after the fifth day. It is of interest that during the initial days of therapy small, deformed and infertile eggs were present in the rectal biopsies. Rectal biopsies performed on the sixteenth day after initiation of therapy revealed few mature viable ova but immature ova were not present.

Only Group I has been followed long enough to evaluate results of therapy. As demonstrated in Table 3, 7 of the 10 patients have continued to have stools free of ova of *S. mansoni*. In 3 patients ova of *S. mansoni* reappeared in the stool 57, 75 and 76 days after completion of therapy.

Table 4 lists the toxicity and side effects of the drug. The most common side effects were headache, asthenia, anorexia, abdominal pain, light-headedness, nausea, vomiting and diarrhoea. These symptoms were minor and appeared after the second or third day. It is important to note that generalized convulsions occurred on the fifth day of therapy in two patients who were receiving a daily dose of 40 mg/kg of CIBA 32644-Ba. These patients each had 2 typical epileptiform seizures.

TABLE 2

*Disappearence of immature eggs during treatment with CIBA 32644-Ba*
*(5 rectal biopsies each day)*

| Days of treatment | First Stage | | Second Stage | | Third Stage | | Fourth Stage | | Mature | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Positive biopsies | Total eggs | Positive biopsies | Total eggs | Positive biopsies | Total eggs | Positive biopsies | Total eggs | Positive biopsies | Total eggs |
| 1 | — | — | — | — | — | — | — | — | — | — |
| 2 | 3 | 45 | 4 | 126 | 4 | 58 | 0 | 0 | 5 | 51 |
| 3 | 1 | 35 | 2 | 47 | 2 | 2 | 1 | 2 | 4 | 55 |
| 4 | 0 | 0 | 1 | 20 | 3 | 12 | 1 | 1 | 5 | 104 |
| 5 | 1 | 5 | 1 | 6 | 2 | 25 | 1 | 1 | 3 | 34 |
| 6 | 0 | 0 | 1 | 1 | 3 | 35 | 0 | 0 | 3 | 116 |
| 7 | 0 | 0 | 3 | 3 | 4 | 22 | 4 | 30 | 5 | 201 |
| 8 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 2 | 35 |

TABLE 3

*Stool examinations and rectal biopsy following therapy*

| Patient | Stool Examinations | | | | | | | | | | | | | | | | | | | Rectal Biopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | |
| 1 | — | + | + | + | — | + | + | — | — | + | — | + | + | + | + | | | | | — |
| 2 | — | — | — | — | | | | | | | | | | | | | | | | — |
| 3 | — | — | — | — | — | — | + | + | + | — | — | — | — | — | | | | | | — |
| 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | | | — |
| 5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | | | | | | — |
| 6 | — | — | — | — | | | | | | | | | | | | | | | | — |
| 7 | — | — | — | — | — | — | — | — | — | — | + | — | + | — | — | — | — | — | — | — |
| 8 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | | | — |
| 9 | — | — | — | — | — | — | — | — | — | — | | | | | | | | | | — |
| 10 | — | — | — | — | — | — | — | — | — | — | — | — | | | | | | | | — |

TABLE 4

*Toxicity and side-effects with CIBA 32644-Ba*

| Manifestations | Daily dose per kg | | |
|---|---|---|---|
| | 20 mg | 30 mg | 40 mg |
| | 10 patients | 20 patients | 15 patients |
| | n. | n. | n. |
| Headache | 2 | 10 | 7 |
| Abdominal pain | 3 | 6 | 6 |
| Light-headedness | 2 | 4 | 8 |
| Nausea | 1 | 8 | 4 |
| Vomiting | 1 | 2 | 4 |
| Anorexia | 1 | 9 | 0 |
| Excess salivation | 0 | 2 | 2 |
| Constipation | 0 | 2 | 0 |
| Asthenia | 0 | 8 | 1 |
| Convulsions | 0 | 0 | 2 |
| Diarrhoea | 0 | 1 | 2 |
| Increase in appetite | 0 | 1 | 0 |
| Heartburn | 1 | 0 | 0 |
| Sore throat | 1 | 3 | 0 |
| Somnolence | 0 | 1 | 0 |
| Bitter sensation in the mouth | 0 | 1 | 0 |
| No complaints | 3 | 1 | 2 |

n = Number of patients

During the course of therapy, 19 of the 35 patients in Groups II, III, and IV had axillary temperatures of 37°C or higher on at least one occasion. In one patient the temperature was elevated to 38°C. There was no abnormality in the pulse rate during therapy. Fourteen of the 35 patients lost weight and 13 gained weight during treatment. The maximum change in weight was 3 kg.

In the 10 patients in Group I, red blood cell counts and haemoglobin values were not altered by treatment. It is apparent that the total white blood cell count and the percentage of eosinophils increased during the course of therapy. The cephalin flocculation, thymol flocculation and thymol turbidity tests were not altered except in one patient in whom the cephalin flocculation changed from negative to 3 +.

Soon after the initiation of treatment the colour of the urine became red. During therapy traces of protein appeared in the urine of 8 of the 10 patients. There were 6 red blood cells per high-powered field in the urine of one of these patients and another had 50 white blood cells per high-powered field. Determinations of blood urea nitrogen were normal in these 8 patients.

Electrocardiograms performed during treatment on the 35 patients in Groups II, III, and IV demonstrated abnormalities in the T waves of 6 patients. Subsequent electrocardiograms have not yet been obtained. These electrocardiographic alterations were not related to the size of the daily dose of CIBA 32644-Ba.

## *Discussion*

It has been demonstrated (7) that the duration of the first stage of ova of *S. mansoni* is only one day. In the present study ova of the first stage seen in rectal biopsies began to diminish in number after the third day of therapy and disappeared completely on the sixth day. Therefore eggs were not deposited after the fifth day of treatment. These time relationships closely resemble those observed in previous studies in which rectal biopsies were performed on patients receiving antimonylithium thiomalate (anthiomaline) (7).

The appearance of small, deformed and infertile ova in the rectal biopsies indicates that CIBA 32644-Ba damages the genital system of the worms. However it is clear that some ova already deposited can continue to develop normally despite administration of the drug. This fact was demonstrated by the presence of mature viable ova in biopsies taken 16 days after initiation of therapy.

CIBA 32644-Ba was relatively well tolerated in doses of 20 to 30 mg/kg per day. The side effects listed in Table 4 were not constant and were generally minor. However at a dose of 40 mg/kg generalized convulsions occurred in 2 of 15 patients on the fifth day of treatment. This serious toxic side effect was reversible as the seizures did not recur after the drug was discontinued. Similarly, toxic doses of CIBA 32644-Ba have been reported to cause convulsions in animals (3). Abnormalities in the electrocardiogram have been reported before in humans receiving CIBA 32644-Ba (4).

Although the drug appears to be effective in these preliminary studies, additional groups of patients must be treated to allow a more adequate evaluation. Other interesting lines of investigation are the effect of the drug on the central nervous system and on spermatogenesis in humans.

## *Summary*

45 patients with *Schistosomiasis mansoni* were treated with CIBA 32644-Ba.

The doses were 20 mg, 30 mg or 40 mg/kg daily for 5 to 10 days. Deformed, infertile eggs appeared in rectal biopsies shortly after

initiation of therapy and oviposition stopped on the fifth day. However, some ova already deposited, continued to develop normally despite administration of the drug.

Ten patients have been followed for a period of four months. Seven apparently have been cured, but in three patients ova of *S. mansoni* reappeared in the stool.

CIBA 32644-Ba was relatively well tolerated in daily doses of 20-30 mg/kg per day. However, at a dose of 40 mg/kg generalized convulsions occurred in 2 of 15 patients.

This drug appears to be a large step forward in the therapy of schistosomiasis.

*Résumé*

45 malades infestés par *S. mansoni* ont été traités par le CIBA 32644-Ba. Les doses furent de 20, 30 ou 40 mg/kg/jour pendant 5 à 10 jours.

Des œufs altérés, stériles sont apparus tôt après le début du traitement dans les biopsies rectales et la ponte paraît arrêtée au 5e jour de traitement. Cependant quelques œufs, déjà pondus avant le traitement, continuent de se développer normalement en dépit de l'administration médicamenteuse.

10 malades ont été suivis pendant 4 mois. 7 ont été trouvés apparemment guéris, mais chez 3 malades des œufs de *S. mansoni* sont réapparus dans les selles.

Le CIBA 32644-Ba a été relativement bien toléré aux doses de 20 à 30 mg/kg/jour ; à 40 mg/kg/jour cependant, des convulsions ont été observées chez 2 des 15 malades traités.

Le nouveau médicament paraît bien être un grand pas en avant dans le traitement de la schistosomiase à *S. mansoni*.

*References*

1. AMATO NETO, V. & PRATA, A. (1958). Tratamento da esquistossomose mansoni pelo 2-acetamido-5-nitrotiazol (não publicado).
2. CUCKLER, A.; KUPFERBERG, A. B. & MILLMAN, N. (1955). Chemotherapeutic and tolerance studies on amino-nitro-thiazoles. — Antibiot. et Chemother. *5,* 540-550.
3. Introductory report on preparation CIBA 32644-Ba, a schistosomicidal and amoebicidal agent.
4. Introductory report on treatment of hepatic amoebiasis with CIBA 32644-Ba. First clinical trials.
5. LAMBERT, C. R. & FERREIRA DA CRUZ, F. S. (1965). Résultats du premier essai de traitement de la bilharziose vésicale par le CIBA 32644-Ba. — Bull. O.M.S. *32,* 73-82.
6. LAMBERT, C. R. & STAUFFER, P. (1964). Chemotherapy of experimental *Schistosoma mansoni* infections with a nitrothiazole derivative, CIBA 32644-Ba. — Ann. Trop. Med. Parasitology *58,* No. 3, 292.
7. PRATA, A. (1957). Biopsia retal na esquistossomose mansoni; bases e aplicações no diagnostico e tratamento. — Bahia, Faculdade de Medicina, pp. 107, Tese.