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Trial of CIBA 32644-Ba in the Mass-treatment of Urinary Bilharziasis

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Introduction

Although according to some epidemiologists, chemotherapy has a minor role among currently recommended methods of control of bilharziasis in many endemic areas, the presence of the following conditions in the status of bilharziasis in Iran indicates that a mass-treatment method can play an important part in the control of bilharziasis in this country:

1. The presence of isolated foci of infection, comprising one or only a few villages.
2. The limitation in area of the sites of transmission (snail habitats), mostly small barrow pits and ditches.
3. Various climatic factors, and the sudden disappearance of the snail intermediate host in some areas with the result that transmission has ceased for some years.
4. The feasibility of snail control in many breeding places, thus reducing the chance of reinfection to a minimum.
5. The absence of any other reservoir host besides man for *S. haematobium*.

Because of the above circumstances, drug screening trials with different anti-bilharziasis preparations have been started during

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the past few years in the W.H.O.-assisted Bilharziasis Project in Iran, in an attempt to find a more effective and less toxic compound. Any schistosomicidal drug which is effective in *S. haematobium*, harmless to man, and easy to administer, will obviously change the picture of bilharziasis control, especially in areas where transmission can easily be interrupted. Mass-treatment studies have been carried out in the villages where no transmission has occurred for at least three consecutive years. Up to now various antimony and thioxanthone derivatives have been tried but only one antimony compound, i.e. sodium antimony dimercaptosuccinate, has proved to be satisfactory with a high rate of cures (ARFAA, 1962). The use of sodium antimony dimercaptosuccinate, although very effective, was accompanied by severe side reactions, especially among adults.

Materials, Method, and Results

The effect of CIBA 32644-Ba on *S. haematobium* in Iran was evaluated in the following two trials:

Trial 1. In the first trial it was decided to use CIBA 32644-Ba in the treatment of a more educated group of patients, who could describe and would report side reactions encountered more precisely than the farmers, who usually attribute almost all symptoms observed to the drug used. Thus, 15 male students at a high school in Khoramshahr, a city in the south-west of Iran where most probably no transmission has occurred for the last 7 or 8 years, were chosen for treatment. These students were examined prior to the treatment, with regard to their weight, pulse rate, blood pressure, general status, subjective complaints and the number of schistosoma eggs in 20 ml of an afternoon urine specimen. They were all from two different classes, with ages between 16 and 20 years and weighing between 44 and 77 kg (average 59.8 kg). None of them had special complaints apart from haematuria and pain on micturition, which were common to almost all of them, pain in the renal area (in three cases) and myalgia.

CIBA 32644-Ba was administered *per os* in a daily dose of about 28 mg/kg of body-weight for 7 consecutive days. It was taken in two portions daily in the form of 500 mg tablets. The highest total dose given was 15 g for a 77 kg student. Tablets given to each patient were swallowed in the presence of the physician.

Urine examinations and egg counts were undertaken each day after the first daily dose was given and all side reactions and complaints were recorded. All urine samples were collected after 11 a.m.

TABLE 1

Daily changes in range, mean, and median numbers of eggs found in 20 ml of urine during treatment

| | Before treatment | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day | 7th day |
|----------|------------------|-----------|---------|----------|---------|----------|---------|---------|
| Range | 1-3,800 | 50-10,000 | 0-1,000 | 10-1,000 | 0-3,000 | 10-1,000 | 0-600 | 0-500 |
| Mean No. | 473.3 | 2407 | 240.6 | 610.6 | 661.3 | 210.3 | 177.3 | 13.8 |
| Median | 23 | — | 100 | 200 | 300 | 150 | 50 | 20 |

and eggs were counted in 20 ml of urine. Table 1 shows the range, mean, and the median number of eggs found in the 20 ml urine samples collected from the 15 students during the period of treatment.

None of the side reactions were severe, except headache, which almost all of the treated cases complained of for one or more days during treatment. Other slight complaints observed were abdominal pain, vertigo, anorexia, pain in bones and muscles, and some other very occasional complaints.

TABLE 2

Results of follow-up surveys made on 15 patients after the treatment

| Days after treatment ended | No. of patients examined | No. of patients with viable eggs | No. of patients presumptively cured | | Presumptive cure rate % |
|---|--------------------------|----------------------------------|-------------------------------------|------------------------|-------------------------|
| | | | Only dead eggs found in urine | No eggs found in urine | |
| Immediately after last tablet was given | 15 | 11 | — | 4 | 36 |
| 33 | 15 | 0 | 4 | 11 | 100 |
| 57 | 13 | 1 ¹ | 4 | 8 | 92 |
| 87 | 15 | 0 | 3 | 12 | 100 |
| 114 | 14 | 0 | 2 | 12 | 100 |

¹ Hatching test negative.

Follow-up surveys were undertaken by urine egg counts, hatching tests, and enquires about the general health of the patients, at intervals of 33, 57, 87, and 114 days after the completion of treatment. During the last two follow-up surveys, urine samples were collected from the students after at least 5 minutes of exercise. Two patients were absent at the 2nd, and one at the last follow-up. The results of the follow-up surveys are summarised in Table 2.

The dead eggs observed in all urine samples were degenerated and black and the hatching tests were negative. It is interesting to note that during the last two follow-up surveys (on days 87 and 114 following treatment) all the students except two reported the total absence of haematuria and painful micturition, and a general improvement in their health.

Trial 2. The second trial was designed to test the effect of CIBA 32644-Ba in different sex and age groups, as well as its effect on the reduction of the total prevalence of bilharziasis infection in small and isolated communities where transmission had evidently been interrupted. Two villages, Hossein Kaluli and Sabzevar, situated about 12 km north-west of Dezful, were chosen for this study. These two villages were established about 8 years ago, after the emigration of the inhabitants of a distant and highly infected village, Abe Koweit.

No snail habitat exists near the two new villages. The epidemiological survey carried out prior to the start of chemotherapy showed that of the 92 and 49 people of Hossein Kaluli and Sabzevar examined, 33 (30.6%) and 12 (30%) persons respectively had bilharziasis.

Table 3 shows the age and sex distribution of infected people in these two villages.

Egg counts undertaken in the afternoon prior to the first day of treatment showed that in Hossein Kaluli 33 patients had between

TABLE 3

The sex and age distribution of 35 bilharziasis patients in Hossein Kaluli and Sabzevar villages

| Age | Sex | | Total |
|--------------|---------------------|---------|-------|
| | Number of patients: | | |
| | Males | Females | |
| 0-10 | 0 | 2 | 2 |
| 11-20 | 4 | 3 | 7 |
| 21 and above | 17 | 9 | 26 |
| Total | 21 | 14 | 35 |

1 and 250 eggs in 20 ml of their urine, with an average of 60.1. The range of the number of eggs in Sabzevar was 4-1000, with an average of 107.

Dosage and method of administration of the drug were similar to those used in the first trial (28 mg/kg daily), except that, since the age groups and the weights were different in this trial, the total dose calculated was given in 6-8 days. All bilharzia cases detected in the two villages (35) were included in the treatment, except for two patients from Sabzevar village: one, a pregnant woman, was excluded to avoid any severe side reactions, and the other, a girl, was absent during the treatment. In all, 33 patients underwent the treatment and 31 completed the course. Because of severe anorexia, abdominal pain, myalgia and dyspnoea, the treatment of two patients, an old man with the clinical symptoms of tuberculosis and a very anaemic woman, was stopped on the 4th and 3rd days of treatment, i.e. when they had taken a total dose of 5.25 and 4.5 g of drug respectively.

Urine examinations and egg counts were made on the last day of treatment and at intervals of 32 and 45 days after the treatment. Two, three, and five patients were absent during the first, second, and last follow-up examinations respectively. The results are summarised in Table 4.

Almost all the eggs found in the last two follow-up surveys were degenerated and black and none hatched when the hatching test was performed.

The side reactions encountered in the second trial were more

TABLE 4

Results of follow-up surveys made on 33 patients after the treatment

| Days after treatment ended | No. of patients examined | No. of patients presumptively cured | | Presumptive cure rate ¹ % |
|---|--------------------------|-------------------------------------|------------------------|---|
| | | Only dead eggs found in urine | No eggs found in urine | |
| Immediately after last tablet was given | 31 | — | 8 | 20 |
| 32 days | 30 | 7 | 23 | 100 |
| 45 days | 28 | 22 | 26 | 100 |

¹ Cure rate among patients examined.

severe than those observed among the students. The most important ones were intense headache, anorexia, vertigo, abdominal pain, and lumbago. These side reactions became more severe on the 4th day of treatment and the days following, and disappeared a few days after the end of treatment.

Discussion and Conclusions

The results so far obtained from the present study indicate that CIBA 32644-Ba has a very promising effect in the treatment of urinary bilharziasis in Iran. The simplicity of administration, the high cure rate, and the absence of severe side reactions are important features of this drug. Patients treated in the first trial, who did not pass a single viable egg 114 days after treatment, may be considered completely cured according to the standard agreed upon by the W.H.O. Expert Committee on Bilharziasis (1957). The presence of dead eggs 114 days after treatment confirms the findings of other authors (VOGEL, 1942; MAEGRAITH et al., 1964) indicating that their passage from the body may take a long time. It should also be noted that the treatment was successful in the two patients in whose case drug administration was stopped on the 3rd and 4th days because of their physical condition, so that they only received half of the calculated dose. The recovery of these patients with a smaller dose is promising and should be further investigated, particularly in relation to intense infections. It would be highly desirable to find out whether total recovery can be obtained by giving a still smaller dose, thus minimizing the length of treatment needed and the incidence of side reactions.

The cure rate of different schistosomicides most probably depends primarily on the load of worms in the body as manifested by the number of eggs passed per unit of time. In indicating the cure rate, the number of eggs found in the urine of patients prior to treatment must also be determined. In this connection it is noteworthy that during both our trials the urine of treated patients with both large and small numbers of eggs became negative, but in patients with small number of eggs, the urine became negative almost as soon as the last tablets were taken.

In comparing the incidence of side reactions in both groups, it was noticed that the farmers (second trial) complained more of the side reactions than the students (first trial). The difference could be attributed mainly to the greater physical activity of the farmers, but there may also be other environmental factors. Side reactions were observed less frequently in children than in adults. No sex differences were observed.

Although it is too soon to draw any definite conclusions, it is interesting to note the effect of CIBA 32644-Ba in reducing the prevalence of bilharziasis in these two villages. The percentage of infected cases among examined people has dropped from 30.5% before treatment to zero after treatment in Hossein Kaluli, and from 30% to 4% in Sabzevar.

The form of administration of anti-bilharziasis drugs for mass-treatment is important. It is mainly farmers who suffer from this disease, and in this part of the world they believe that only drugs given parenterally can cure their diseases. For this reason, and owing to other factors, such as negligence, one cannot rely on them to take their tablets regularly, unless the tablets are swallowed in the presence of the health worker. On the other hand, drugs given by injection require the presence of a physician or a nurse, which adds to the expense of mass-treatment in rural areas.

Summary

Because of the presence of different epidemiological factors in the status of bilharziasis in Iran, chemotherapy can play an important role in the control of this disease in this country.

CIBA 32644-Ba was one of the anti-schistosomal drugs tried in the W.H.O.-assisted Bilharziasis Project in Iran.

Two trials were undertaken to determine the effect of this drug in the treatment of urinary bilharziasis in the southern part of Iran, where most probably no transmission has occurred for 7 years. In these trials, 15 students and 33 infected farmers were treated with CIBA 32644-Ba, given *per os* in the form of 500 mg tablets in a daily dose of 28 mg/kg body-weight for 7 consecutive days. Clinical and urine examinations were undertaken for all patients before and after treatment. Urine samples collected during follow-up surveys were found to be negative in some patients and only dead eggs were found in others. Eggs found in the urine of patients after treatment were all degenerated and black and none hatched. The cure rate observed was therefore very high, almost 100% being presumptively cured. Recovery was also observed in two patients whose treatment was stopped on the 3rd and 4th days because of their physical condition. Side reactions were headache, anorexia, abdominal pain, vertigo, and lumbago; but only headache was severe.

CIBA 32644-Ba appears to be a promising drug in the treatment of bilharziasis due to *S. haematobium* and in reducing the prevalence of infection in infected villages.

Résumé

A cause de l'existence de différents facteurs épidémiologiques dans l'état de la bilharziose en Iran, la chimiothérapie peut jouer un rôle important dans le contrôle de la maladie dans ce pays.

Le CIBA 32644-Ba fut l'un des médicaments anti-schistosomiens essayés dans le cadre des travaux soutenus par l'O.M.S. en Iran.

Deux essais furent entrepris pour évaluer l'activité du traitement dans la bilharziose urinaire, au sud du pays, où vraisemblablement aucune réinfestation ne fut possible durant les 7 dernières années. 15 étudiants et 33 fermiers furent traités oralement, à raison de 28 mg/kg/jour pendant 7 jours consécutifs. L'examen clinique et l'examen des urines furent pratiqués avant et après le traitement.

Les échantillons d'urine collectés après traitement furent trouvés négatifs à la recherche des œufs de *S. haematobium* chez certains malades ; seuls des œufs morts furent observés chez les autres. Les œufs trouvés dans l'urine étaient tous dégénérés ou morts, et aucun n'a présenté d'éclosion. Le taux de guérison fut ainsi élevé, et pratiquement le 100 % des malades pouvait être considéré comme guéri. Il en fut de même chez 2 malades ayant arrêté le traitement au 3^e et 4^e jour en raison de leur mauvaise condition physique.

Les effets secondaires observés furent des céphalées, de l'anorexie, des douleurs abdominales, des faux vertiges, des lombalgies ; seules les céphalées furent sévères.

Le CIBA 32644-Ba apparaît ainsi un traitement prometteur de la bilharziose à *S. haematobium* ; il permettrait en outre de réduire l'incidence de l'infestation dans les villages infectés.

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