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# Preliminary Observations on the Use of CIBA 32644-Ba in *S. mansoni* at Mwanza, Tanzania

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The trials reported here are incomplete in that although 76 patients have been treated, 2 month follow-up results are available at the present time for only 37 patients and 4-month results for only 15 patients. However, it is thought that the results which are available are sufficient to obtain some idea of the effectiveness of CIBA 32644-Ba in the treatment of *S. mansoni* in East Africa.

Mwanza, where these trials are being carried out, is a township at the southern end of Lake Victoria; *S. mansoni* is endemic in the lake-shore area with the prevalence rate falling only slightly amongst the adult population. Transmission is mainly consequent on contact with Lake Victoria, seasonal streams running into it or backwaters near the lake-shore.

In the present trials, children and adults of both sexes were treated with CIBA 32644-Ba in a dose of 25 mg per kilogramme body-weight daily for five days, given in a morning and evening dose. Adults were unselected and were either referred from the Government Hospital for treatment or attended the Institute Research Ward for examination. Children at a Primary School were initially screened for infection; those found infected were treated. All patients were treated as in-patients in the Research Ward of the East African Institute for Medical Research, Mwanza, Tanzania.

## *Methods*

Patients were given a general clinical examination and, following admission, a 24-hour collection of stool was made which was processed by the quantitative method devised by BELL (1963). In some cases blood was taken for haematological study.

In accordance with the W.H.O. recommendation, assessment of

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cure was to be made 4 months after treatment. At this time (and also at 2 months for comparison with other results) patients were readmitted to the ward for the collection of a 24-hour stool for quantitative assessment of any remaining infection and a further complete stool on which 3 separate concentration tests were done (AMS III technique) involving the removal of approximately 3 grammes of faeces, the rest being subjected to a hatching test. Invariably, 3 or 4 stools were therefore involved in each of the 2 and 4 month follow-up examinations.

In a few cases stools were also obtained for examination at the end of treatment and 14 days after commencement of treatment.

## *Results*

### *General acceptance of drug*

Generally the drug was well tolerated. No details of the incidence of subjective side effects were kept as it has been found that these may be misleading when all patients in a small ward are having the same treatment. Vague abdominal pain was noted in a few cases as was headache, but these were not severe enough to warrant stopping therapy. Nausea occurred in a few cases but troublesome vomiting in only one patient—an Arab who insisted on having his own food (presumably highly spiced) sent to him.

The general absence of nausea, vomiting and anorexia, so frequently seen in patients being treated with antimonial drugs—including TWSb—is reflected in the data on weight loss recorded

TABLE 1

*Comparison of change in weight of primary school children treated with TWSb and CIBA 32644-Ba*

| | | | |
|---|---|---|---|
| | | *TWSb* | |
| No. losing weight | 90 | Average weight lost | 1.1 kg |
| No. gaining weight | 11 | Average weight gained | 0.6 kg |
| | | % losing weight 90% | |
| | | *CIBA 32644-Ba* | |
| No. losing weight | 13 | Average weight lost | 0.6 kg |
| No. gaining weight | 16 | Average weight gained | 0.5 kg |
| No change | 4 | | |
| | | % losing weight 39% | |

in 2 similar groups of school children, one of which was treated with CIBA 32644-Ba, and the other with TWSb for *S. haematobium*.

One patient developed a maculopapular rash, another an apparent paroxysmal tachycardia. One further, an adult, showed signs suggestive of a temporary mental disturbance. This patient also had TB for which treatment was being given. On the 5th day of treatment he had a fit of some kind, but on questioning later he admitted he was an epileptic. However, it must be considered possible that CIBA 32644-Ba precipitated the fit.

Two other cases of what might have been mental confusion were encountered—also in adults. One patient—the morning after completion of treatment—woke at 4.30 a.m. and insisted on discharging himself from the ward, believing he was being killed. When seen at 7.30 a.m., he appeared rational and agreed he had been dreaming. Since fear of witchcraft and dreams is not unusual in these parts, the case is probably of little importance. The second occurrence was in an English-speaking laboratory assistant who, on the second day of treatment, was found at night to be perspiring profusely and in a semi-comatose state from which he could not be roused. He eventually woke suddenly and was quite rational. He was apparently normally a light sleeper and had had one fit the previous year.

*Parasitological results*

At the end of treatment, 24-hour stool samples in 8 cases showed no decrease in the number of eggs being passed. Hatching tests

TABLE 2

*Preliminary results with CIBA 32644-Ba in S. mansoni*

| | 2 months | 4 months |
|---|---|---|
| Number of patients in whom counting, concentration and hatching tests used | 22 | 15 |
| Number of patients with all tests negative | 5 | 7 |
| "Cure rate" | 23% | 47% |
| Number of patients with eggs | 17 | 8 |
| Demonstrable viable eggs | 11 | 5 |
| Viable eggs not demonstrated | 6 | 3 |
| | (2 pos. on count, with neg. conc. test 4 pos. on conc. test) | (2 pos. on count, with neg. conc. test 1 pos. on conc. test) |
| Number of patients in whom counting technique used | 37 | 15 |
| Number of patients showing eggs | 22 | 6 |
| "Cure rate" | 40.5% | 60% |
| % reduction in egg load (mean reduction per individual) | 82.5% | 96.0% |

at this time were also positive. By 14 days after the commencement of treatment the egg output had dropped considerably, but eggs were still hatchable.

At two months the 24-hour stool output of 37 patients was examined quantitatively and 15 were negative to this technique. The drop in egg count at this time was 82.5%.

Of the above 37 patients, 22 were also examined by the hatching and AMS III technique, and 11 were found to give a positive hatch. Of those with negative hatch tests, 5 were completely negative to counting, concentration and hatching tests, and of the remaining 6 with a negative hatch, 4 were positive for eggs in the concentration test performed on the same stool. It seems likely therefore that these 4 represent the only cases in which non-viable eggs were being passed.

At the 4-month follow-up, only 15 cases have so far been examined. With the quantitative technique 9 were negative, having a total egg-output reduction of 96%. With the counting concentration of hatching tests only 7 were negative. Of the 8 cases in which eggs were demonstrated, 5 had viable eggs. One stool in which eggs were present in the concentration test failed to show a positive hatch test, and in this case it seems likely that non-viable eggs were being passed.

*Haematological results*

Differential and total white cell counts were made in a number of patients. It was found that an absolute increase in eosinophils occurred, reaching a maximum at the 14-day follow-up, and generally dropping 2 months after treatment.

SGOT levels were dertermined in a number of cases, and levels at the end of treatment compared with those at the end of treat-

TABLE 3

*Comparison of change in SGOT levels in patients given TWSb and CIBA 32644-Ba*

| | TWSb | | CIBA 32644-Ba | |
|---|---|---|---|---|
| | Pre-therapy | Post-therapy | Pre-therapy | Post-therapy |
| Number of patients | 37 | 37 | 21 | 21 |
| Mean SGOT level (S.F. units) | 16.5 | 50.1 | 23.7 | 33.4 |
| Number above 40 S.F. units | 2 | 14 | 2 | 4 |

TWSb patients treated for *S. haematobium.*
CIBA 23644-Ba patients treated for *S. mansoni.*

ment in a series of *S. haematobium* cases treated with TWSb. Although there was a slight rise in level after treatment, this was generally dropping a week later.

## *Discussion*

In view of low numbers of eggs being present after treatment, their irregular distribution in the stool, and their complete absence from some stools, it is recognised that the examination of a small part of a stool or even the whole of a single stool may not demonstrate eggs, and the cure rate will vary inversely with the number of stools and/or the amount of stool examined.

A 24-hour specimen will probably contain more eggs than a single stool specimen (but not necessarily so), and certainly hatching of eggs in a large volume of faeces is more likely to be positive than the examination of only 3 grammes even when concentrated.

Results have been assessed therefore in two ways. In order to compare the drug with the results obtained by BELL (1964) using TWSb (and where the reduction in egg output is considered) the quantitative method has been considered, but in order to have a more accurate indication of the incidence of positive stools (i.e. those containing eggs whether viable or not) results from all three methods have been considered. The use of the concentration technique, carried out on the same stool as that processed for hatching, enables the viability of eggs to be determined.

Using these techniques, it is seen (Table 2) that a "cure" rate of only 23% was obtained at 2 months, and 47% at 4 months, and in more than half of the cases in which eggs were found they were shown to be viable. The "cure" rate when a 24-hour specimen was examined quantitatively was 40.5% at 2 months and 60% at 4 months compared with 12/38 or 32% at 3 months in Bell's series of cases treated with TWSb. At 2 and 4 months, the reduction in egg load was 82.5% and 96% respectively compared with Bell's result of 88.6% at 3 months (results from his African and Asian patients combined). If one accepts that patients with nonviable eggs be included as cured, then the figures for cure become 39% and 53%.

As pointed out by BELL (1963), a "cure" rate unqualified by data on the initial egg output may be misleading, since it may depend on the intensity of infection. Although there is some evidence that this may apply in *S. haematobium* infections (JORDAN and RANDALL, 1962; BRADLEY, 1963; JORDAN, 1965), there is little evidence in the literature that this is in fact the case with *S. mansoni*. Analysis of results in the present series, however,

TABLE 4

*"Cure rate" in relation to egg load*

| | No. treated | No. «cured» |
|---|---|---|
| Less than 10,000 eggs per 24 hours | 16 | 13 |
| More than 10,000 eggs per 24 hours | 21 | 2 |

suggest it may be, though in BELL's series there is no evidence of this.

In order therefore to get a true comparison with other drugs, or to get a true comparison of therapeutic efficiency in different areas, it is suggested that an attempt should be made, not only to use the same techniques, but also to have patients excreting similar numbers of eggs—or more practically—the intensity of infection should be indicated.

It is generally agreed, as stated by NEWSOME (1962), that adults are more readily cured than children. Results in the present trials support this view. Since, however, children may have higher egg loads than adults, this may be the explanation of lower cure rates in the younger patients. In order to investigate this, children and adults having similar egg loads in a 24-hour stool were

TABLE 5

*Comparison of 2-month results from adults and children with S. mansoni, matched for egg output per 24 hours pre-treatment*

| Adults | | | Children | | |
|---|---|---|---|---|---|
| Egg output per 24 hours (thousands) | | | Egg output per 24 hours (thousands) | | |
| Pre-therapy | Post-therapy | % reduction | Pre-therapy | Post-therapy | % reduction |
| 0.3 | 0 | 100 | 0.6 | 0 | 100 |
| 0.3 | 0 | 100 | 0.8 | 0 | 100 |
| 0.6 | 0 | 100 | 0.6 | 0 | 100 |
| 2.0 | 0 | 100 | 1.8 | 0.01 | 99.4 |
| 6.7 | 0 | 100 | 8.0 | 6 | 25 |
| 8.3 | 0 | 100 | 9.5 | 0 | 100 |
| 14.0 | 0.5 | 96.5 | 13.0 | 0.5 | 96.2 |
| 16.0 | 0.5 | 96,9 | 14.0 | 0.3 | 97.9 |
| 17.6 | 0.3 | 98.3 | 18.6 | 0.5 | 97.4 |
| 22.0 | 2.0 | 91.0 | 20.0 | 14.6 | 27.0 |
| 31.2 | 2.2 | 93.0 | 26.0 | 0.6 | 97.7 |
| 49.3 | 1.6 | 96.8 | 45.3 | 3.0 | 93.4 |
| 56.0 | 0 | 100 | 53.6 | 2.6 | 95.2 |
| 63.0 | 0 | 100 | 62.0 | 33.6 | 45.9 |

TABLE 6

*Analysis of results obtained in adults and children, matched for egg output per 24 hours pre-treatment*

| | Adults | Children |
|---|---|---|
| Number in series | 14 | 14 |
| Number "cured" | 8 | 4 |
| Reduction in egg output | 98% | 84% |
| Best results by scoring technique | 9 | 1 (4 draws) |

matched (Table 5) and the results obtained at 2 months in these matched pairs were analysed.

Results show that when the "cure" rate and the percentage reduction in egg load are considered, the adults apparently respond better to treatment than children, and further, when the results of matched individuals are considered and the better percentage reduction given a score of one, the adults are again seen to have a better score, i.e. 9-1 with 4 draws.

Since these results are from series matched for egg output, it seems likely that apart from the intensity of infection some other factor is probably operating, and it may be that a different state of immunity in the adults may facilitate a cure. Alternatively, perhaps adults, exposing themselves less to infection than children, are less likely to be harbouring immature worms at the time of treatment (with maturation taking place in the post-treatment period) and are probably less likely to become infected immediately after treatment.

There is perhaps some evidence that one or other of the latter factors is involved from the results here (Table 5). From the results of the paired cases, in both series it is seen that in most cases the percentage reduction in egg load is in the region of 90-100%. In 3 children the figures were only 25%, 27%, 46%, and some explanation is required for the poor results obtained in these cases.

One must expect some variation in daily egg output, and it may be that either the pre-treatment 24-hour count was abnormally low, or the post-treatment count on the one day abnormally high; but the variation needed to account for these anomalous results would be very considerable. While this admittedly might be the explanation, it seems more likely that these patients harboured maturing adult worms during treatment or had become infected immediately after, and confirmation of this might be obtained by a series of 24-hour counts over a period of time, to see whether the number of eggs was increasing. If this is the explanation of these anomalous results, and these three cases are excluded, there is less evidence

that adults and children respond differently when matched for egg output.

The quantitative study of egg output in relation to drug effectiveness is comparatively new and much has yet to be learned regarding techniques and their limitations; but it is suggested that quantitative studies in therapeutic trials are worthy of investigation.

The overall picture of results suggests that CIBA 32644-Ba is an effective schistosomicide, but it seems probable that the dose given was not sufficient to cure the majority of cases treated in the present series. It is suggested that a higher total dose should be tried—perhaps a 7-day course of treatment. The low incidence of troublesome side effects suggests such a course would be generally acceptable.

## *Summary and Conclusions*

25 mg/kg body-weight of CIBA 32644-Ba was given to 76 adults and children infected with *S. mansoni*. Few serious side effects were encountered and weight loss was minimal amongst the patients.

The results were assessed 2 and 4 months after treatment. Eggs and/or miracidia (after a hatching test) in a 24-hour stool and a single stool, were demonstrated in 77% of cases at 2 months and in 53% at 4 months. The reduction in egg output was 82.5% and 96% respectively. An analysis of these preliminary results suggests that the cure rate may be related to the initial egg output, being higher when few eggs are excreted.

Results from adults and children, matched for pre-treatment egg output, suggest that adults respond to treatment better than children, though in some children there was possible evidence of maturation of worms during treatment which reduced the effectiveness of the drug.

## *Résumé et conclusions*

25 mg/kg/jour de CIBA 32644-Ba furent administrés à 76 adultes et enfants infestés par *S. mansoni*. Peu d'effets secondaires sérieux et une perte de poids minime furent observés parmi ces malades.

Les résultats furent évalués 2 et 4 mois après le traitement. Œufs et miracidies (après le test d'éclosion) furent observés, par l'examen de la totalité des selles de 24 heures et sur un seul examen, chez 77 % des cas à 2 mois et 53 % à 4 mois ; la réduction du nombre d'œufs éliminés fut respectivement de 82.5 % et 96 %. Une analyse de ces résultats suggère que le taux de guérisons pourrait être dépendant du taux d'élimination ovulaire avant le traitement ; plus le taux d'élimination est faible, plus grand est le taux de guérisons.

Les résultats comparatifs chez les adultes et les enfants, estimés sur le taux d'élimination ovulaire avant le traitement, suggèrent que les adultes répondent mieux au traitement que les enfants ; chez quelques enfants on peut penser qu'un certain nombre d'infestations récentes (parasites en voie de maturation pendant le traitement) pourraient réduire l'efficacité du traitement.

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