The Central African Journal of Medicine

Editor:
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Volume Nineteen

JANUARY - DECEMBER

1973

SALISBURY : RHODESIA

Suppressive Therapy in the Control of Bilharziasis: A Comparative Trial in African School Children

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INTRODUCTION.

One of the major problems facing the health service in any country which has a high prevalence of bilharziasis is the shortage of medical personnel required for the successful treatment of the large numbers of people who show infection. However, if a totally safe regime involving the administration of relatively innocuous drug at low dosages over long periods of time to control or suppress the level of infection in the person, the administration of the drug could then be left to the teachers or to other responsible members of the community. It is in this context that the policy of suppressive therapy or management of schistosome infections shows its greatest attraction.

The original concept of "suppressive management" in the control of bilharziasis as suggested by Friedheim and de Jong (1959), by Davis (1961) and by Jordan and Randall (1962) made use of the drug TWSb-antimony di-mercapto-succinate (Astiban) which required parental administration. McMahon (1966) investigated the suppressive effect of niridazole (Ambilhar, CIBA) and lucanthone hydrochloride (Nilodin, B.W. and Co.). He concluded that the latter named drug was ineffective in the doses given, but that niridazole was more promising. The dose of lucanthone hydrochloride given was only 250 mg in the group in which he was able to obtain adequate follow-up results. Niridazole was given at a dose of 25 mg/kg at weekly intervals for eight weeks and he obtained a 45 per cent. reduction in urine egg output. Kilala (1966) also used niridazole at a dose rate of 25 mg/kg per week for only five weeks and he obtained a 20 per cent. reduction in urine egg output, and noted that the reduction was more noticeable in children with heavier egg loads.

McMahon (1967) compared niridazole at a dose of 35 mg/kg twice weekly for six weeks with a group treated with lucanthone hydrochloride at a dose of 500 mg once weekly for 10

weeks. He obtained a reduction of 72 and 89 per cent. respectively, in the excretion of *Schistosoma mansoni* eggs in the stool. He considered drug resistance not to be a problem in bilharziasis and no evidence that suppressive therapy affected the immune response. In his opinion suppressive therapy is a justifiable form of treatment in endemic areas with high infectivity in that it would reduce tissue damage in the human host.

The most encouraging results were those reported by Lees (1968) following his trial of lucanthone hydrochloride in suppressive treatment of *S. mansoni* infections in school children in St. Lucia. Giving 500 mg of the drug once weekly for 10 weeks he obtained a mean reduction of egg output of virtually 90 per cent., 26 and 36 weeks after the end of the treatment. He obtained an overall parasitological cure in 37 per cent. of the patients, these being children with light infections who were excreting less than 10 000 eggs. The drug was administered by a qualified nurse and no significant side effects were noted.

It is accepted that *S. haematobium* infections are more easily cured than those caused by *S. mansoni* and this seems to be so whatever drug is used. If Lees' results could be confirmed under African conditions, a programme of suppressive management would have wide application in the treatment of vast numbers of school children showing both *S. haematobium* and *S. mansoni* infections. With these indications in mind, it was decided to attempt a comparative trial of lucanthone hydrochloride (Nilodin, B.W. and Co.), niridazole (Ambilhar, CIBA) and oral hycanthone (Win — 24, 933-2) in the suppressive management of *S. haematobium* and *S. mansoni* infections in a locality of high transmission of bilharziasis.

Programme for the Trial.

An African primary school in the Mazoe Valley, 30 miles north-west of Salisbury, was selected for the trial. The school, which has an enrolment of nearly 500 pupils, is situated on the banks of the Mazoe River and is near a system of irrigation canals. Although the school has a purified piped water supply and adequate sanitary facilities, the children have ready access to the river and other infected waterways, and transmission of bilharziasis to this community would be high before, during and after the period of the drug trial. In February, 1969, a stool and urine survey was carried out on all the children attending the school. All material was examined by the methods advocated by Blair *et al* (1969a and b); urine egg counts, stool egg estimations and hatching of miracidia were done on urine and stool specimens to determine the viability of the infection in each subject. A full record of names, sex, age and weight was made so that each child could be confidently identified at each of the subsequent drug administrations which were given weekly for 10 weeks from 24th February to 28th April, 1969.

The pre-treatment parasitological survey showed 442 children infected with either *S. haematobium, S. mansoni* or with both parasites and, in fact, only 29 children in the whole school were found free of parasitological evidence of bilharziasis.

For practical reasons the infected children in the two senior grades of the school were set aside for treatment with intramuscular hycanthone (Etrenol, Winthrop). A total of 60 boys and girls were given a single intramuscular injection of this drug at a level of 3 mg/kg on 10th March, 1969. The remaining infected children were allotted to one of four groups, selected so that each group contained an equal proportion of children of each sex and the various age groups and to obtain as even a spread as possible of heavy *S. mansoni* infections, light *S. mansoni* infections, heavy *S. haematobium* infections, light *S. haematobium* infections and double infections in each group. Allocation of children to receive oral medication into four groups was arranged because it was originally hoped to have two groups receiving lucanthone hydrochloride, both groups for the first term of 1969 (10 weeks) and one of these to receive the same course of treatment in the third term of the year. In the event, the results were so disappointing that in the analysis of the results, the two lucanthone hydrochloride groups have been amalgamated and the second group not re-treated in the third term. A few children were lost to the trial after the initial survey so that when drug administration on a weekly basis started Group A comprised 181 children each receiving two 250 mg tablets of uncoated lucanthone hydrochloride as a single dose each week for 10 weeks; Group B consisted of 92 children who were to receive two 500 mg tablets of niridazole as a single dose each for 10 weeks, and Group C contained 92 children who were to have been given two 50 mg enteric coated tablets of hycanthone (Win 24, 933-2) as a single dose each week for 10 weeks. Side effects and serious absenteeism after the administration of the first dose of oral hycanthone prompted a reduction of the weekly dose to one 50 mg tablet. Follow-up surveys were carried out at 5, 12 and 19 weeks after the administration of intramuscular hycanthone and at 6 and 13 weeks after the completion of the 10 weeks of treatment for children receiving oral drugs.

Table I.

BILHARZIASIS PREVALENCE SURVEY.
Mazoe Citrus Estates African Primary School.
February, 1969.

	Age Group in Years				
	7-9	10-12	13-15	16-20	Total
S. haematobium					
Males:					
Number examined	100	119	76	7	302
Number positive	61	95	50	5	211
Percentage positive	61	80	66	—	70
Females:					
Number examined	79	68	20	2	169
Number positive	60	53	15	1	129
Percentage positive	76	78	75	—	76
Total:					
Number examined	179	187	96	9	471
Number positive	121	148	65	6	340
Percentage positive	68	79	68	—	72
S. mansoni					
Males:					
Number examined	103	120	77	7	307
Number positive	73	91	58	5	227
Percentage positive	71	76	75	—	74
Females:					
Number examined	70	71	20	2	163
Number positive	54	58	15	2	129
Percentage positive	77	82	75	—	79
Total:					
Number examined	173	191	97	9	470
Number positive	127	149	73	7	356
Percentage positive	73	78	75	—	76
Distribution of S. mansoni infections:					
Cases *S. mansoni* only	43	31	25	3	102
Double infections *S. haematobium* and *S. mansoni*	85	119	48	4	256

RESULTS.

The analysis of the pretreatment survey is set out in Table I. Boys outnumbered the girls, but the latter had slightly higher prevalence of both forms of bilharziasis. It is unusual in Rhodesia to have a higher prevalence of *S. mansoni* infections as is the case in this trial. The majority of the children were in the age groups 7 to 15 years and only nine children were 16 years and over.

Efficiency of drug dosing:

Not all the children took the full course of ten doses of the oral drugs. The main reason for this was that because of the time expended in carrying out the initial prevalence survey and in arranging the allocation groups, the last two doses had to be administered during the school holidays. During the first eight weeks the number of children treated each Monday morning ranged from 364 on the first round to

Table II.

PERFORMANCE OF CHILDREN IN TAKING THEIR DOSE OF DRUGS ADMINISTERED.

	Number of Doses Taken						Gone away from school	Total
	All 10	9	8	7	6	less than 6		
A	35	40	52	32	15	5	2	181
B	20	18	32	11	6	5	1	93
C	26	11	27	19	9	0	2	94
	81	69	111	62	30	10	5	368
% taking six doses or more (353 pupils)	23,0	19,5	31,4	17,6	8,5			

Table III.

IMMEDIATE PATIENT REACTION TO DOSING.

Group	No. of children affected	No. of doses vomited or rejected	Children who vomited or rejected				No. of tablets not taken
			One dose	Two doses	Three doses	Five doses	
A	31	54	18	7	5	1	99
B	5	8	4	—	1	—	13
C	4	5	3	1	—	—	5

318, while on the ninth and tenth dosing days only 157 and 123 children were treated, respectively. Over the 10-week period the maximum number of doses for the four oral drug groups was 3 680, but only 3 012 were administered — 82 per cent. Considering only the first eight weeks of drug administration which took place in term-time, 2 732 out of a possible 2 944 (93 per cent.) were administered. There was no difference between the performance of the children in one group as compared with the others, and considering the first eight weeks of treatment the percentage efficiency of dose taking for Groups A, B and C was 92, 94 and 93, respectively. Thus the foul taste of lucanthone hydrochloride did not seem to have discouraged children from coming to school and taking the next dose. Table II shows the number of children in each group who took six or more doses. The proportions are roughly the same for each drug.

Reaction to the drugs: (*Immediate*) :

A study was made of the immediate patient reaction to the drugs and these are shown in Table III. It will be noted that the vomiting of drug and the rejection of the second tablet after the first had been vomited, was most obvious in Group A (lucanthone hydrochloride), and these children tended to go on vomiting on subsequent attendances. The number of children taking niridazole and hycanthone fared much better. The problem of immediate vomiting and gagging of lucanthone hydrochloride meant that after the first week drug administration had to be carried out under the shade of trees in the playground otherwise the floors of the class-rooms would have been fouled with vomit.

Drug toxicity:

Toxicity as opposed to vomiting and immediate rejection of the drug was rare, and few of the children showed little more than nausea or vomiting in the evening of the day the drug was administered. Table IV shows the later reactions to the drugs, and the effect on school attendance on the days following the administration of the drug. It is interesting to see that oral hycanthone caused more school absence and affected more children in the group than did lucanthone hydrochloride, considering that nearly twice as many children were at risk in the latter drug group.

Table IV.

LATER REACTION TO DRUG DOSING AS SHOWN BY ABSENCE FROM SCHOOL.

Drug Group	Total children in group	No. affected so as to be absent for day after dosing	Absent from school day after dosing					Total Nos. of absence incidents	Total No. of school days lost
			One Occasion	Two Occasions	Three Occasions	Four Occasions	Five Occasions		
A	181	18	9	4	1	3	1	37	44
B	93	3	2	0	1	0	0	5	5
C	94	16	2	9	2	2	1	39	60

Effect of treatment on urine egg output:

The method of examination of urine specimens for eggs of *S. haematobium* allows of the counting of the numbers of eggs seen in the terminal urine passed in the middle of the day. It is possible, therefore, in follow-up surveys conducted in the same way to measure the reduction in the number of eggs passed per urine positive case. Table V shows the effect of the treatment in not only reducing the number of urine egg excretions, but also reducing the number of eggs passed by each positive case. The group which was given intramuscular hycanthone consisted of boys and girls in the two senior classes in the school and at this age, as is usual, the number of eggs per positive case before treatment, is much less than is found in children aged 7 to 15 years. It will be seen that less than half the children in each group treated with one of the oral drugs were free of eggs twelve weeks after the completion of the suppressive course of treatment. A more encouraging reduction in the number of eggs per positive case was noted. The results in urine egg "cures" and in number of eggs per positive case is much more encouraging when intramuscular hycanthone was administered.

Cure at 12 *weeks after the end of treatment*:

The criterion of "cure" used in this series was failure to find hatchable eggs in either urine or stool. Table VI sets out the results for *S. haematobium* and *S. mansoni* infections separately even when these were occurring in the same individual. Each case was assessed at 12-13 weeks after the completion of treatment on the following criteria:—

S. haematobium infections:

C.—"cured"; less than 100 "dead" eggs in the sample and no miracidia hatch.
P.—"improved"; at least a 90% reduction in the egg count, but miracidial hatching still occurring.
F.—no change — a failure.

S. mansoni infections:

C.—"cured"; no eggs seen or miracidia hatched.
P.—"improved"; few miracidia hatched, but a great reduction in the numbers seen and in the number of eggs observed.
F.—little or no change in hatching status.

As would be expected in a trial conducted in circumstances where the children were exposed to re-infection, even some of those found to be free from bilharziasis in the pre-treatment sur-

Table V.

EFFECT OF TREATMENT ON S. HAEMATOBIUM EGG COUNTS IN URINE IN PATIENTS FOLLOWED UP 12 WEEKS AFTER THE END OF TREATMENT.

	Pre-treatment Survey			At 12 weeks after treatment		
Group	Total eggs	No. of positive cases	Average eggs per positive case	Total Eggs	No. of positive cases	Average eggs per positive case
A	73 431	139	528	11 608	86	135
B	55 956	72	777	9 583	45	113
C	43 976	75	586	3 417	43	79
Intramuscular hycanthone	8 450	44	192	45	3	15

vey were found infected at the follow-up examination. These, and children who received five doses or less have been excluded from Table VI.

The concept of suppressive therapy is not to attempt a parasitological cure of the disease but to reduce the worm load, the schistosome egg output and the tissue damage to the host. This is a combination of preventive and personal health motives which, if effective, might go a long way to reducing the infection potential in an area. Taking the "cured" and "improved" categories together; of the oral drugs hycanthone has the best performance against both infections.

Performance of oral drugs on patients with double infections:

Table VII shows the effect of suppressive therapy on children with double infections of *S. haematobium* and *S. mansoni*. This small group of patients seems to show that there is no close relationship between the reaction of the drug on both parasites.

Intramuscular hycanthone:

The follow-up results of the group of elder children treated with a single intramuscular injection of hycanthone was the most satisfactory of all, particularly in respect of *S. haematobium* infections.

Gain in weight:

In trials of drugs for the treatment of bilharziasis it is the rule to weigh patients at each follow-up examination. It was thought that this might be a secondary indication of improvement in general health following treatment. The same procedure was followed in the present trial. The oral treatment groups followed up at six months after the commencement of treatment numbered 335, with an average weight of 27,5 kg, and they gained 10,9 per cent. in weight. The intramuscular treated hycanthone group who were, of course, older than the previous group, averaged 44,3 kg at the time of injection, and also gained 10,9 per cent. in weight, which is a more significant gain in older children. Untreated children who were also weighed numbered only 13 and had an average weight of 26,6 kg, showed an 11,1 per cent. gain in weight. It appears that the heavier children receiving intramuscular hycanthone showed a marked increase in weight gain.

Teachers' observations:

Some of the teachers said that their pupils were more attentive and alert at the end of the first term and that this improvement was maintained throughout the second term of the year when the stool and urine follow-up examinations were being carried out. One teacher said that the condition of the skin of the children in his class was very much better. A male teacher who had the duty of inspecting the cleanliness of the boys' latrines remarked that at the beginning of the term the urinals had to be washed down daily to remove the blood stains: in the latter part of the term blood staining of the urinals had ceased.

DISCUSSION.

Comparing the three drugs given orally, hycanthone (Win 24, 933-2) had the best performance; the immediate patient reaction to the tablets was good, perhaps due to the fact that only one small enteric-coated tablet had to be

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Table VI.

FOLLOW-UP AT 12 WEEKS AFTER END OF TREATMENT: NUMBER OF FAILURES, "CURED" AND "IMPROVED" AND PERCENTAGE IN EACH CATEGORY.

	Urine				Stool			
Group	C	P	F	T	C	P	F	T
A	36 39,6	22 24,2	33 36,2	91 100,0	2 1,9	13 12,3	91 85,8	106 100,0
B	12 25,0	14 29,2	22 45,8	48 100,0	2 3,6	3 5,4	50 91,0	55 100,0
C	20 40,0	11 22,0	19 38,0	50 100,0	9 19,2	12 25,5	26 55,3	47 100,0
Intramuscular hycanthone	38 90,5	3 7,1	1 2,4	42 100,0	10 21,3	9 19,1	28 59,6	47 100,0

"C" = Cured "F" = Failure
"P" = Improved "T" = Total

taken as compared with two large tablets of niridazole or lucanthone hydrochloride. The later reactions in the hycanthone tablet group was more severe than the other two drugs. It is not practical to undertake suppressive therapy in schools, with drugs administered by the school teachers once a week on a dose/weight scale and one has to accept a standard dose for all the children from the smallest child in the school upwards. It will be recalled that it was the original intention to administer two oral hycanthone tablets of 50 mg each. In fact, two tablets caused such serious absenteeism that after the first week's dose it was cut to a single tablet. Oral hycanthone has now been withdrawn and seems unlikely ever to become commercially available and therefore is not likely to be used in the future. Niridazole, at the dose stated above, was reasonably efficient in *S. haematobium,* but had a rather poor showing in *S. mansoni* infections. Lees (1968) employed lucanthone hydrochloride tablets coated with cellulose acetate phthalate which seems to have been acceptable to the children in the St. Lucia trial as no difficulties in drug administration were noted. Using plain tablets of lucanthone hydrochloride, the number vomited and second tablets refused made a mass administration of this form of the drug an unpleasant duty to be carried out by school teachers. Children in the lower class were found to have great difficulty in swallowing the large size tablets of niridazole and lucanthone hydrochloride.

SUMMARY.

Children attending a school in a bilharziasis endemic area, shown to have high infection rates of *S. haematobium* and *S. mansoni* were given a single weekly dose of an oral drug for ten weeks of a school term. The drugs used were lucanthone hydrochloride, niridazole and oral hycanthone. The latter drug had the best showing, both in urinary and stool infections, although it appears to have caused more drug toxicity and absence from school. Even in *S. haematobium* infections only half the children had their condition improved. A group of 60 older children who were given a single intramuscular injection of hycanthone showed the best results in urinary infections.

ACKNOWLEDGMENTS.

We are grateful to the Secretary for Health, Rhodesia, for permission to submit this paper for publication, and to the other members of the technical staff of the Laboratory for their assistance, and to Mrs. Thomson for her work in maintaining the records.

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