Single Dose Metrifonate in the Treatment of Urinary Schistosomiasis in an Area of Low Prevalence and Intensity of Infection

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SUMMARY
Urine specimens from 638 primary school children in Gokwe Communal Land were examined for S. haematobium ova, and the 187 (29%) children who were excreting eggs were treated with a single 10mg/kg dose of metrifonate. Further urine samples were collected from all children, whether treated or not, 48 weeks later, and examined for ova.

The overall cure rate was 50.8%, and in children not cured egg excretion was reduced by an average 59.9%. Only 12.1% of children were excreting > 50 eggs per ml of urine before treatment, and after this was reduced to 3.9%.

Increased egg excretion following treatment was noted in 15 (8.0%) of the infected children, while 21 (4.7%) children with negative urines, and therefore not treated, were excreting eggs 48 weeks later.

Thus even in an area where the prevalence and intensity of infection is low, single-dose metrifonate may play a cost-effective role in the control of urinary schistosomiasis.

INTRODUCTION
The control of urinary schistosomiasis depends essentially on interrupting the cycle of transmission between the intermediate host and man. In order to achieve this, a variety of measures have been proposed, including the removal of snail populations by molluscicides, environmental modification and educational programmes to reduce contamination of the environment by excreta and restrict man–water contact, and mass treatment aimed at reducing the number of eggs being excreted into the environment by infected individuals. The use of single-dose metrifonate at 10 mg/kg has been suggested as one way of reducing delivery costs, while still significantly reducing egg excretion in the majority of infected individuals. Original studies reported an average of 96 per cent reduction in egg excretion following single-dose metrifonate, while later studies reported less optimistic results. We have previously reported our experiences in Zimbabwe on the efficacy of single-dose metrifonate in both the short and long term. In these studies, while cure rates were low, the majority of infected children showed a substantial reduction in egg excretion. These, and other reports from Africa, however, indicated that the most beneficial effect would be achieved in communities where both the prevalence and intensity of infection were high.

We here report on our experience with single-dose metrifonate in an area of Zimbabwe where the prevalence and intensity of infection with Schistosoma haematobium are low, and also present tentative data suggesting that combining such treatment with inexpensive environmental and education programmes may be an effective means of controlling urinary schistosomiasis in a community.

MATERIALS AND METHODS
Study area and subjects
The study area consisted of a rural (peasant farm)
community of about 2,000 persons, in Gokwe Communal Land, about 350 km west of the capital Harare. The economy of the community depends on subsistence farming with cattle, goats and sheep being raised. Water supplies consist of two small dams (ponds), and an intermittent stream in the immediate vicinity of the village. Domestic animals use the same water sources, which are, therefore, heavily contaminated with animal excreta. During the winter months, both the dams and the stream dry up and villagers then fetch water from a borehole some 15 km away. There were no sanitation facilities in the village.

There were two primary schools in the community, Kanwa and Nyamhara. Those included in the study were 337 boys and 301 girls, with ages ranging from 6 to 16 years; 307 children were from Kanwa school and 331 children from Nyamhara school, and the female: male ratios were 1:1.21 and 1:0.4, respectively. The age structures in the two school populations were similar, with more than one-third of children being aged 8-9 years. There were, however, fewer younger children and more older children at Kanwa than at Nyamhara (6-7 years 7.5% vs 15.1%; > 12 years 25.4% vs 15.1%, respectively).

Specimens

An initial survey was carried out to determine the prevalence of helminthiasis in the community, with stool and urine specimens being collected from 1,138 villagers (500 adults, 638 children attending the two primary schools in the community) aged 6-60 years (mean 28 years). Stool specimens were collected in pre-labelled plastic containers. Kato thick smears were prepared in the field and transported to the laboratory for microscopic examination.

Urine specimens were collected into pre-labelled plastic containers between 1100 and 1500 hours and were transported to the laboratory for examination. Because of the long distances involved, urines were stored in some cases for up to three days at 4°C before being processed for examination. Urine specimens were prepared as described previously and examined by experienced microscopists for S. haematobium ova.

Treatment and follow-up specimens

Because of the low prevalence of urinary schistosomiasis in adults during the initial screening survey, the infected adults were treated but not followed up.

A second urine specimen was obtained from each of the children in the two primary schools, and children who were found to be excreting eggs in either sample were treated with a single oral dose of metrifonate at 10 mg/kg. One child complained of slight abdominal pain following treatment, but no other side effects were reported. A third urine sample was collected from each child 48 weeks after the treatment. Processing and examination of the urines were carried out as with pre-treatment urines.

Education/environmental programmes

With community participation, the two dams serving the village were renovated and fenced to exclude animals, and vegetation along the stream bed was removed. Pupils at one school (Nyamhara) but not the other (Kanwa) received lessons on the life-cycle of schistosomiasis, with emphasis on the importance of sanitary hygiene and of reducing water contact in preventing re-infection following treatment. The lessons were supplemented with film strips, wall charts and demonstrations.

No attempt was made to prevent the dissemination of information from one school population to the other, and children from both schools continued to use the same water sources, supplemented with two wells dug by villagers and accessible to the whole community.

It should also be noted that no attempt was made to authenticate the origin of the samples submitted for analysis.

RESULTS

Intestinal helminths

No S. mansoni eggs were found in the stool specimens, and eggs of other intestinal helminths were infrequent. Ascaris sp. ova were detected in 1.2%, Hymenolepis nana ova in 2.5%, Taenia sp. ova in 0.4% and hookworm ova in 1.2% of specimens.

Prevalence and intensity of urinary schistosomiasis

S. haematobium eggs were detected in pre-treatment urine samples from 12 (2.4%) adult and 187 (29.3%) children. Because of the very low prevalence in adults, they were excluded from the study, and subsequent data refers only to children at the two primary schools.

The prevalence in boys (30.0%) was similar to that in girls (28.6%). Younger children were more commonly infected than older children, as shown in Fig. 1, with 32.9% of six to seven year-olds excreting eggs compared with 24.7% of children aged more than thirteen years.

The majority of infections were classified as light with 58.3% of infected children excreting 50 eggs per ml of urine. Of the detected infection...
10.8% were classified as moderate (51-150 eggs/ml) 14.4% as heavy (151-500 eggs/ml) and 7.5% as severe (> 500 eggs/ml). There was no apparent relationship between age of children and intensity of infection.

TABLE 1— Cure rates and reduction in egg excretion 48 weeks after single-dose metrifonate.

<table>
<thead>
<tr>
<th>Initial Infection</th>
<th>No.</th>
<th>Eggs/ml urine*</th>
<th>Cured</th>
<th>Mean reduction in egg excretion of children not cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>109</td>
<td>7.2</td>
<td>68.8%</td>
<td>38.2%</td>
</tr>
<tr>
<td>Moderate</td>
<td>37</td>
<td>83.5</td>
<td>35.1%</td>
<td>61.3%</td>
</tr>
<tr>
<td>Heavy</td>
<td>27</td>
<td>307.5</td>
<td>25.9%</td>
<td>83.4%</td>
</tr>
<tr>
<td>Severe</td>
<td>14</td>
<td>1 058.0</td>
<td>0%</td>
<td>74.3%</td>
</tr>
</tbody>
</table>

*Geometric mean

TABLE II— Effect of single-dose metrifonate on egg excretion of children not cured.

<table>
<thead>
<tr>
<th>School</th>
<th>Mean % reduction in egg excretion</th>
<th>% children with ≥ 90% reduction in egg excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanwa</td>
<td>42.3%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Nyamhara</td>
<td>81.1%</td>
<td>62.8%</td>
</tr>
<tr>
<td>Total</td>
<td>59.9%</td>
<td>34.7%</td>
</tr>
</tbody>
</table>

FIG 1—Prevalence of urinary schistosomiasis in different age groups. Bars show the % of children infected, with shaded area denoting the % of children with light infections. Peak prevalence in Kanwa school (●) occurred in children aged 6–7 years, while in Nyamhara school (□) peak prevalence occurred in children aged 8–9 years.

The pattern of prevalence and intensity of infection in the two schools was similar, with 29.0% of Kanwa children and 29.6% of Nyamhara children excreting eggs in pre-treatment urines. In Kanwa school the highest incidence of infection (39.1%) occurred in six-seven year old children, while at Nyamhara it occurred in eight-nine year olds (also 39.1%). In both schools the incidence in older children was lower (23.7% and 26.3% in >13 year-olds from Kanwa and Nyamhara, respectively). The majority of initial infections were classified as light in both schools (73.0% at Kanwa, 45.3% at Nyamhara), though significantly more of the infected children at Nyamhara were excreting >50 eggs per ml of urine ($X^2=10.7, P <0.01$).

Cure following single dose metrifonate

With cure being defined as the absence of eggs in the 48 week post-treatment sample, the overall cure rate was 95/187 (50.8%). The majority of cures occurred in children with an initially light infection, while none of the children with severe infections were cured (Table I).

The cure rate at Nyamhara was significantly greater than Kanwa 59.2% vs 41.6% ($X^2=5.8, P > 0.05$). Thirteen (6.0%) of Kanwa and 8 (4.9%) of Nyamhara children with negative pre-treatment samples were excreting eggs by 48 weeks post-treatment and in each case the infection was classified as light.

Reduction of egg excretion

In children who were not cured egg excretion was reduced by an average of 59.9%, and a reduction of ≥ 90% was recorded in 33 (34.7%) of these
children. In 15 (8.0%) children's egg excretion had increased at the post-treatment examination with the majority (91/15) of such children having initially light infections. The change in the pattern of infection intensity is shown in Fig. 2, with the proportion of children excreting > 50 eggs per ml urine being reduced from 12.1% pre-treatment to 3.9% post-treatment. The effect of treatment on egg excretion by children not cured is shown in Table II, with significantly more children at Nyamhara showing a > 90% reduction in egg excretion (Χ² = 29.8, P > 0.001).

DISCUSSION

The prevalence of S. haematobium infection (17.5% overall, 29.3% school children) was lower than is found in other communities north of Harare where ova may be excreted by more than 80% of children of similar age. Other studies in Africa have shown that wide variation in prevalence may occur in different geographical areas of the same country. Nevertheless, urinary schistosomiasis was identified as the major helminthic disease in this community, intestinal helminths being only infrequently diagnosed in Kato smears. This is in keeping with other surveys in rural areas of Zimbabwe. No infections with S. mansoni were found, and this could be attributed to the intermittent drying out of surface water bodies in the region which the snail host is unable to tolerate.

There is little information on the medical consequences of urinary schistosomiasis in Zimbabwe, though in other African countries the conclusion is that infection with S. haematobium is of considerable public health importance. The control of urinary schistosomiasis should, therefore, be seen as having a potentially substantial impact on the health status of African communities.

The value of single dose metrifonate mass treatment for the control of urinary schistosomiasis remains controversial. In Kenya, a mean 96.5% reduction in egg excretion following single-dose metrifonate was reported, but results of similar studies in The Gambia and Malawi were less promising. Our previous studies in Zimbabwe in a region of high prevalence and intensity of infection, demonstrated a mean of 75% reduction in egg excretion four months after treatment, while 50% of treated children maintained a > 90% reduction in egg excretion for eighteen months, even though many uninfected children became infected during this period. Many of the children included in these studies had severe infections, and while single dose metrifonate may achieve reasonable cure rates in light infections, the greatest reduction in egg excretion occurred in children carrying the highest worm burdens. In this study, we report on the effect of single-dose metrifonate in an area of Zimbabwe where both the prevalence and intensity of infection is much lower than in the north of the country. The data accumulated here is perhaps less reliable than in previous studies, in that follow-up urine samples were not collected until 48 weeks after treatment owing to the long distances between the study point and the laboratory. Previous experience has, however, been that reductions in excretion occur rapidly following treatment and are maintained for at least 18 months even in areas of high exposure. The method used for quantifying egg excretion rates is least accurate in samples containing few eggs, though any such inaccuracy would be expected to have little effect on the assignment of children to the intensity categories described here.

The overall cure rate (50.8%) was very similar to that recorded for light infections in previous studies and the highest cure rates (68.8%) were obtained in children excreting up to 50 eggs per ml of urine. None of the 14 children with severe infections had ceased excreting eggs 48 weeks after treatment. In only 34.7% of children not cured, was a > 90% reduction in egg excretion achieved compared with 65—69% children in regions of Zimbabwe of high-prevalence and intensity. It has been noted before, however, that the greatest reduction in egg excretion may be achieved in those individuals with severe infections, and the overall mean reduction of egg excretion (59.9%) was similar to that achieved in children with light infections elsewhere in the country.

Even in this region, however, the administration of a single dose of metrifonate achieved a significant change in both the prevalence and intensity of infection with moderate to severe infections being recorded in under 4% of children 48 weeks after treatment compared with 12% before treatment. Increases in egg excretion following treatment with single-dose metrifonate, which were recorded in 8.0% of these children, have been noted previously. These may represent children who were harbouring immature worms at the time of treatment or were exposed to infection after cure.

Thus, bearing in mind our reservations on the accuracy of our data, we nevertheless conclude that a single dose of metrifonate may achieve radical cure of a significant proportion of infected children, and a reduction in egg excretion can be expected in most individuals not cured, particularly those excreting large numbers of eggs into the
environment. Considering the low cost of the drug, and the virtual absence of side effects, we believe mass treatment with metrifonate should be seriously considered as a means of controlling urinary schistosomiasis in rural communities.

Our conclusions regarding the impact of environmental and educational programmes in addition to single dose therapy are more tentative, since there were differences in the age structure, age-related prevalence and the intensity of infection between the two schools we studied. Although there was evidence that both the cure-rate and reduction in egg excretion were higher in the school where an educational programme was available, it is difficult to attribute this solely to that programme. The incidence of infection, as determined by egg excretion in children with negative urines at the start of the study, showed no significant differences between the two schools as would have been expected if the educational programme had modified water-contact behaviour. The numbers of children apparently acquiring infections was, however, small, and at least some of the cases may represent maturation of juvenile worms rather than de novo infection, as discussed above.

More intensive investigations on a larger population would be needed to determine whether the apparent treatment failures result from reinfection or maturation of juvenile worms, to determine the effects of mass treatment on transmission by snails, and to determine the impact of educational programmes on water-contact behaviour. The findings in this study suggest that such investigations are warranted.

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REFERENCES