EFFICACY OF MIRAZID IN COMPARISON WITH PRAZIQUANTEL IN EGYPTIAN SCHISTOSOMA MANSONI–INFECTED SCHOOL CHILDREN AND HOUSEHOLDS

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Abstract. This trial investigated the anti-schistosomal activity of mirazid in comparison with that of praziquantel in Schistosoma mansoni–infected Egyptian patients. The sample population was composed of 1,131 individuals (459 school children and 672 household members). Screening for S. mansoni was conducted using the standard Kato Katz technique. Four slides from a single stool sample were examined before treatment, and four slides per sample from stool samples obtained on three consecutive days were examined post-treatment. All positive eligible subjects were randomly assigned into two groups, the first received mirazid at a dose of 300 mg/day for three consecutive days, and the second received praziquantel at a single dose of 40 mg/kg. All treated subjects were examined 4–6 weeks post-treatment. Mirazid showed low cure rates of 9.1% and 8.9% in S. mansoni-infected school children and household members, respectively, compared with cure rates of 62.5% and 79.7%, respectively, in those treated with praziquantel. Therefore, we do not recommend mirazid as an agent to control schistosomiasis.

INTRODUCTION

Schistosomiasis remains one of the most prevalent parasitic infections in the world. It is estimated that more than 200 million people in 76 countries are infected and approximately 600 million people are at risk of infection. The majority (85%) of those infected and at risk live in Africa. In Egypt, there is extensive documentation that the government’s efforts have been successful in reducing both the prevalence and morbidity of this disease. However, schistosomiasis is still endemic in rural areas of Egypt and in spite of the low endemicity level, transmission still occurs. Chemotherapy is the most widely advocated method of schistosomiasis control. Praziquantel is still the ideal drug for implementation of schistosomiasis control programs. The drug is safe and has a high efficacy against both trematodes and cestodes. Moreover, the drug has become significantly less expensive. According to the World Health Organization, the cost of an average treatment with this drug has decreased to less than 0.30 S$. However, the extensive reliance on just one drug is of concern, due to the possible development of drug-resistant parasites. In view of concern about the possible emergence of resistance to praziquantel, there is a need for developing novel antischistosomal drugs.

The antischistosomal drug Mirazid has been available in the local Egyptian market since 2001. Although Mirazid is not used by the Ministry of Health and Population (MOHP) for schistosomiasis control in national control programs, yet the extensive advertising efforts have encouraged physicians in private clinics to use it. Mirazid is a commercial preparation made from myrrh by Pharco Pharmaceuticals (Alexandria, Egypt). Myrrh is collected from trees in Somalia and the Arabian peninsula. For several decades, it has been used in a number of medical contexts, as well as in the perfume and incense industries. It is an oleo-gum resin obtained from the stem of Commiphora molmol Engler and probably other species of Bursearacae. The experimental activity of Mirazid has been demonstrated. In this respect, Sheir and others reported that the drug showed a 91.7% cure rate after a dose of 10 mg/kg/day for three days. Badria and others reported significant parasite reductions of 76% and 75% after treatment of Schistosoma mansoni–infected mice with 250 mg/kg and 500 mg/kg of myrrh extract twice a day for three days. They also reported that the chemistry of the resin is not fully elucidated and that myrrh is generally classified into ether-insoluble and ether-soluble portions. Moreover, nothing has been reported concerning the exact species, source, and season of collection of myrrh when Mirazid is prepared, although these can determine the activity of any compound of plant origin. Independent studies concerning the antischistosomal activity of Mirazid are limited.

This study investigated the antischistosomal activity of Mirazid in S. mansoni-infected school children and household members in comparison with the classic antischistosomal drug praziquantel.

MATERIALS AND METHODS

The study protocol and patient consent procedure were reviewed and approved by the Institutional Review Board of the Theodor Bilharz Research Institute. The head of the family provided formal consent for household members, while for school children, consent was provided by the school principal, prior to participating in the study.

General study design. The study was conducted at El-Gezira El-Shakra village, El-Saf district, Giza governorate of Egypt. The village was selected for logistic reasons. It is relatively near the Theodor Bilharz Research Institute, and is a focus of S. mansoni infection. The study was conducted in collaboration with the MOHP.

The sample size was determined assuming that the two treatments (Mirazid and praziquantel) have equivocal effects. A one-sided upper confidence interval (CI) with a power of 90% was also assumed. A sample size of 1,131 was considered adequate, of which 459 were school children and 672 were household members. School children were composed of those in primary (fifth school year), preparatory, and secondary schools. All students in the randomly selected classes were included in the study. Their ages ranged from 12 to 18 years. Household members were sampled at random. All inhabitants of the houses selected were included in the study.
Parasitologic examination. To screen for *S. mansoni* infection, all subjects participating in the study were asked to provide stool samples. Four slides were examined per subject. For post-treatment examination, three stool samples were collected on different days and four slides per sample were examined. i.e., a total of 12 slides/patient. The Kato Katz technique using the standard weight of 41.7 mg of stool per slide was used. The local health authorities at the village were informed to stop praziquantel treatment six months before beginning the study and any of the patients giving a history of treatment of less than six months were excluded from the study.

Drug administration. All positive eligible subjects were stratified into low (<100 egg per gram [epg] of feces), moderate (100–400 epg), and heavy (>400 epg) infection strata. Each stratum was then randomly assigned into two groups. One group received Mirazid while the second group received praziquantel. All patients receiving Mirazid were asked to fast the night before treatment (300 mg/day for three consecutive days, irrespective of age and sex) and for one hour post-treatment, as recommended by the manufacturer (Pharco Pharmaceuticals). Patients were observed for 30 minutes after which they were told to come back if they had any problems. Most of the complaints were restricted to mild abdominal pain and nausea with or without vomiting. If vomiting occurred less than 30 minutes after drug intake, the dose was repeated. These complaints were rare and occurred mainly in those treated with praziquantel. Mirazid was bought from the local market at the time of the study and was given mostly to those having moderate and heavy infections.

School children were examined four weeks after treatment while household members were examined 5–6 weeks post-treatment. All parasitologists who examined the slides, the technicians who processed them, the clinicians who performed rectal snips, and those responsible for data entry were blinded to the type of treatment given.

The efficacy of Mirazid in comparison with that of praziquantel was evaluated using the percentage cure rate (those not passing eggs for three days) and the percentage reduction in egg count for uncured subjects. Rectal snips for those cured (having negative stool samples for *S. mansoni* eggs) were performed on a sample of subjects diagnosed as cured after treatment with Mirazid or praziquantel. Household members and school children positive for *S. mansoni* who did not comply with the treatment protocol were evaluated at the time of follow-up examination to obtain the spontaneous cure rate. Rectal snips were also performed on controls showing spontaneous cure.

The study was conducted from December to February, which is not high transmission season for schistosomiasis in Egypt. This was done to avoid the presence of immature stages of schistosomiasis infection and therefore to guarantee genuine treatment failures if eggs were still found after treatment.

Rectal snip procedure. A rigid proctoscope (12-cm long) was used and a punch biopsy was taken (approximately 2–3 samples), mainly from the recto-sigmoid junction, using crocodile forceps. The operator was blind for the type of treatment that was given to the patient. Samples were examined microscopically by two clinicians. A male clinician performed proctoscopy on male subjects and a female clinician performed it on female subjects.

Statistical analysis. Data were processed using Epi-Info software (Centers for Disease Control and Prevention, Atlanta, GA). The intensity of infection is expressed as the geometric mean egg count (GMEC) where log (x) was calculated for positive samples. Anti-logs were obtained for the means to obtain the GMEC. Cure rates after treatment were calculated as the percentages of individuals becoming parasitologically negative after treatment. Reduction in egg counts after treatment was calculated using the formula (1 - [GMEC/gram after treatment/GMEC/gram before treatment]) × 100.

RESULTS

School children. Of 459 school children, 144 were positive for *S. mansoni*, giving a prevalence of 31.4% (95% CI = 27.2–35.8%). The prevalence was 37.9% in males and 18.0% in females (odds ratio [OR] = 2.8, 95% CI = 1.7–4.6). Of 44 *S. mansoni*-infected children, 66 received Mirazid, 51 received praziquantel, and 27 did not comply with full treatment protocol. Those who did not comply with the three-day follow-up stool examination were not included in our calculation for the cure rate and percentage reduction in egg count. The eligible number who completed their three days of treatment with Mirazid was 55. The eligible number of those receiving praziquantel was 32, while the eligible number of controls was 16 (Table 1). Of the 55 school children treated with Mirazid, 28 (50.9%) had light infections, 22 (40.0%) had moderate infections, and 5 (9.1%) had heavy infections. Of the 32 school children receiving praziquantel, 28 (87.5%) had light infections, 3 (9.4%) had moderate infections, and 1 (3.1%) had a heavy infection (Table 1).

Cure rates and baseline GMEC among treated school children. Four weeks after treatment, Mirazid-treated school children showed a cure rate of 9.1%, while praziquantel-treated school children showed a cure rate of 62.5%. The GMEC ± SD was 72.4 ± 3.0 for uncured subjects of controls at time before treatment (those not complying with the treatment protocol) and 56.2 ± 3.9 for the same group four weeks later. For the Mirazid-treated group, the GMEC ± SD was 93.3 ± 3.4 before treatment and 85.1 ± 4.4 after treatment. For praziquantel-treated school children, it was 38.0 ± 5.4 before treatment and 13.8 ± 2.8 after treatment. The percentage reduction in egg count was 8.8% and 63.7% in the Mirazid- and praziquantel-treated school children, respectively. Comparison of cure rates at each degree of intensity of infection showed that at a low-degree intensity of infection, cure rates were 17.9% (5 of 28) for the Mirazid-treated group, 71.4% (20 of 28) for the praziquantel-treated group, and 0.0% (0 of 10) for the control group ($P < 0.001$). At moderate and heavy intensities of infection, the cure rates for the three groups were 0.0%.

Household members. Of 672 villagers, 235 were positive for *S. mansoni*, giving a prevalence of 35.0% (95% CI = 31.4–38.7%). The prevalence was 47% in males and 25.4% in females (OR = 2.6, 95% CI = 1.9–3.7). Those individuals 10–20 years old showed the highest prevalence (43.8%). The results of eligible subjects (those receiving a full dose of drugs and supplying stool samples for three days post-treatment) for assessment of drug effects are shown in Table 1. Of the 79 household members treated with Mirazid, 61 (77.2%) had light infections, 16 (20.3%) had moderate infections, and 2 (2.5%) had heavy infections. Of the 74 individuals receiving
praziquantel, and 0.0% (0 of 3) for the untreated control treated with Mirazid, 71.4% (10 of 14) for those treated with Mirazid, 82.5% (47 of 57) for those treated with praziquantel, and 33.3% (4 of 12) for the untreated control group (*P < 0.01)*. At a heavy degree intensity of infection, cure rates were 0.0% (0 of 2) for those treated with Mirazid, 66.7% (2 of 3) for those treated with praziquantel, and 0.0% (0 of 0) for the untreated control group.

A statistical comparison of the cure rates between those treated with Mirazid and those treated with praziquantel showed that praziquantel had a statistically significant higher cure rate (*P < 0.001*) than Mirazid in both household members and school children. A comparison of cure rates between the Mirazid-treated group and the controls showed no significant difference (*P = 0.13* for household members and *P = 0.49* for school children).

There was no statistically significant difference between pre-treatment and post-treatment intensity of infection for each of the three groups (Mirazid treated, praziquantel treated, and controls) in school children (*P > 0.05*). For household members, the Mirazid-treated group had statistically significant higher intensity of infection after treatment than before treatment (*P < 0.001*), while the other two groups showed no statistically significant difference.

**Rectal snip results.** The rectal snip procedure was performed in 27 cases who were negative for *S. mansoni* eggs for three days. Four cases were treated with Mirazid and 20 were treated with praziquantel, while the remaining three subjects were controls. All cases were either free of *S. mansoni* eggs or had dead, calcified *S. mansoni* eggs in their samples. Only one patient showed a single living *S. haematobium* egg.

**Table 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mirazid</th>
<th>Praziquantel</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number screened</td>
<td>93</td>
<td>103</td>
<td>39</td>
</tr>
<tr>
<td>Eligible subjects†</td>
<td>79</td>
<td>74</td>
<td>15</td>
</tr>
<tr>
<td>Age in years</td>
<td>27.6 ± 16.4</td>
<td>28.9 ± 15.7</td>
<td>24.6 ± 8.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13.5 ± 1.3</td>
<td>13.4 ± 1.5</td>
<td>14.0 ± 0.9</td>
</tr>
<tr>
<td>Range</td>
<td>7–67</td>
<td>12–73</td>
<td>13–40</td>
</tr>
<tr>
<td>Intensity of infection</td>
<td>51.3 ± 2.8</td>
<td>35.5 ± 3.5</td>
<td>35.5 ± 2.6</td>
</tr>
<tr>
<td>GMEC ± SD</td>
<td>87.5 ± 3.3</td>
<td>23.5 ± 3.3</td>
<td>72.8 ± 3.0</td>
</tr>
<tr>
<td>Range of eggs/gram</td>
<td>6–618</td>
<td>6–1,014</td>
<td>6–132</td>
</tr>
<tr>
<td>Low, &lt;100 epg</td>
<td>61/79 (77.2%)</td>
<td>57/74 (77.0%)</td>
<td>12/15 (80.0%)</td>
</tr>
<tr>
<td>Moderate, 100–400 epg</td>
<td>16/79 (20.3%)</td>
<td>14/74 (18.9%)</td>
<td>3/15 (20.0%)</td>
</tr>
<tr>
<td>High, &gt;400 epg</td>
<td>2/79 (2.5%)</td>
<td>3/74 (4.1%)</td>
<td>0/15 (0.0%)</td>
</tr>
</tbody>
</table>

† Complying to treatment dose and three days follow-up.

* GMEC = geometric mean egg count; epg = eggs per gram (of feces).

**Table 2**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mirazid</th>
<th>Praziquantel</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>79</td>
<td>74</td>
<td>15</td>
</tr>
<tr>
<td>Number cured</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cure rate</td>
<td>8.9%</td>
<td>79.7%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Baseline GMEC ± SD</td>
<td>25.1 ± 3.0</td>
<td>34.7 ± 3.4</td>
<td>21.4 ± 2.8</td>
</tr>
<tr>
<td>Number not cured</td>
<td>72</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Percent not cured</td>
<td>91.1%</td>
<td>20.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Baseline GMEC ± SD</td>
<td>55.0 ± 2.7</td>
<td>37.2 ± 4.2</td>
<td>42.7 ± 2.4</td>
</tr>
<tr>
<td>GMEC after treatment</td>
<td>95.5 ± 3.2</td>
<td>22.4 ± 3.1</td>
<td>47.9 ± 2.9</td>
</tr>
<tr>
<td>Rate of reduction</td>
<td>+++++</td>
<td>39.8%</td>
<td>63.7%</td>
</tr>
</tbody>
</table>

* GMEC = geometric mean egg count; +++++ = increase in egg count.
DISCUSSION

In the present study, the efficacy of the new antischistosomal drug Mirazid was assessed in comparison with the conventional antischistosomal drug praziquantel. The area of investigation, in addition to being near the Theodor Bilharz Research Institute, which carried out the investigation, has a moderate prevalence of schistosomiasis mansoni. Although the intensity of infection was not high (epg < 400), the prevalence was 31.4% in school children and 35.0% among household members. This may be attributed to immunologic or ecologic factors. This is because S. mansoni is relatively new in Giza (Upper Egypt) since the building of the Aswan High Dam, when the epidemiology and relative distribution of Schistosoma species was changed. In general, prevalence was higher among males and among those 10–20 years old. These findings were consistent with those of a previous study. The study area can be considered a new focus of S. mansoni because all control programs were concerned mainly with S. haematobium, which is less prevalent than S. mansoni.

The cure rate in this study for Mirazid-treated household members and school children was 8.9% and 9.1%, respectively. Irrespective of the type of treatment, all cured school children and most of the cured household members had light infections. Pre-treatment intensity of infection appeared to be a determining factor for complete cure.12,13

Although this study was conducted during the low transmission season (December–February), which minimized the possibility of pre-patent infections not susceptible to treatment, the presence of pre-patent infections cannot be ruled out. It is worth mentioning that the observed cure rate in this study could be considered the false cure rate. This is because a spontaneous cure rate of 26.7% was observed among household members defined as controls who did not comply with the treatment protocol. The controls stated that they have not received any antischistosomal drugs. This false or reverse cure rate in patients with schistosomiasis has been reported by several investigators.

Our cure rates in S. mansoni-infected household members and school children treated with Mirazid are consistent with the results of a recent study (Barakat R and others, unpublished data). These investigators showed a cure rate of 8.9% among S. mansoni-infected villagers receiving two treatments at a three-week interval (each treatment was two capsules taken on an empty stomach for three consecutive days). However, our findings do not agree with those of Sheir and others, in which a cure rate of 91.7% was observed after a dose of 10 mg/kg for three days. In their study, they did not report the method of stool analysis used to diagnose schistosomiasis and monitor cure or the number of stool samples before or after treatment. In addition, although they did report the cure rate, no mention was made of the epg or GMEC before or after treatment. Moreover, they stated that the majority of the S. mansoni-infected patients treated with Mirazid were previously treated with repeated courses of praziquantel, but they did not report the time interval between both treatments.

In our study, the reduction in egg counts in Mirazid-treated school children was very low (8.8%). Moreover, a higher percentage of eggs passed in Mirazid-treated household members was observed, denoting the inefficacy of the drug and the capability of residual worms surviving treatment to lay eggs. This increase in the percentage of eggs passed after Mirazid treatment has been reported by the MOHP of Egypt in their trial on myrrh (Abdel-Wahab Y, Wafa A, unpublished data). The increased number of S. mansoni eggs passed in the excreta of patients reported in both trials may be related to a gut stimulant activity of the drug that eases the extrusion of eggs from the gut with the excreta.

With regard to praziquantel, 79.7% of the household members who received the drug showed cure. This cure rate is within the normal range for cure stated for the drug tested during the 1980s, and also in a recent study in Kenya. Contrary to the cure rate recorded among household members, school children showed a lower cure rate of 62.5%. This low cure rate can not be related to the possibility of the presence of young schistosomes not susceptible to treatment because the study was conducted during the low transmission season and the follow-up post-treatment was conducted in a relatively short time period, which did not allow for the presence of young schistosomes that were not susceptible to the drug as a result of reinfection. All eggs found at examination after treatment were viable eggs, thus excluding the possibility of delayed passing of dead eggs from the gut. The low cure rate and the reduced percentages of egg reduction observed among praziquantel-treated school children could be related to an inappropriate immune response, which is known to act synergistically with praziquantel. It cannot be attributed to previous drug treatments because the study area has been recently identified as a region endemic for schistosomiasis mansoni. A biologic difference in strain susceptibility between different localities and/or tolerant resistant isolates cannot be ruled out. In spite of the modest percentages of egg reduction observed in patients treated with praziquantel, they are still far higher than those observed for Mirazid.

In conclusion, the clinical findings in this study show that treatment of schistosomiasis with Mirazid is of questionable value. Experimentally various doses (as high as the 50% lethal dose) of different formulations of Mirazid have been tested against different strains of S. mansoni and little to no anti-schistosomal activity was observed.

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