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Efficacy and side effects of praziquantel in the treatment of *Schistosomiasis mansoni* in schoolchildren in Shesha Kekele Elementary School, Wondo Genet, Southern Ethiopia

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ABSTRACT

Objective: To evaluate the efficacy and side effects of praziquantel (PZQ) in the treatment of schistosomiasis in Ethiopia. **Methods:** In a cross-sectional study, stool specimens were collected from randomly selected 299 school children in Shesha Kekele Elementary School, Wondo Genet, Southern Ethiopia, in April 2010. Stool specimens were examined using a single Kato-Katz thick smear for *Schistosoma mansoni* (*S. mansoni*) ova. Children who were found positive for *S. mansoni* were treated with a single oral dose of PZQ at 40 mg/kg bw and interviewed for treatment-related symptoms 24 hours after drug administration. Four weeks post-treatment, stool specimens were collected from the same children and examined following the same procedure as in the pre-treatment. Drug efficacy was determined based on cure and egg reduction rates. **Results:** Pre-treatment prevalence of *S. mansoni* infection was 74.9% with geometric mean egg count of 268. The evaluated generic PZQ produced an overall cure rate of 73.6% (P<0.000 1, OR: 8.33, *CI*: 5.3-13.1) and egg reduction rate of 68.2% (P=0.03, F=0.64). The cure rate showed significant association with age (χ^2=11, P=0.004), the highest rate being observed in the 15-22 age group. 83% of *S. mansoni* infected children showed various treatment-related symptoms, the most frequent being headache, nausea, and abdominal pain. These symptoms were associated with age (P<0.001) and pre-treatment intensity of infection (P<0.05). **Conclusions:** The present observations revealed relatively lower cure and egg reduction rates of the PZQ evaluated as compared to previous reports for other PZQ brands in Ethiopia. Hence, in depth studies are recommended to clarify whether the present relatively lower cure rate is the actual cure rate of the praziquantel evaluated, treatment failure, or reduced susceptibility of the parasite. Treatment-related side effects observed were transient and tolerable.

1. Introduction

Schistosomiasis is a chronic disease caused by blood flukes, and it has been estimated to affect 207 million people globally, about 85% of which live in sub-Saharan Africa alone[1]. In Ethiopia, the endemicity of both intestinal and urinary schistosomiasis has long been established. Although there has been no recent national survey, estimates made in the 1980s documented that the number of people infected and at risk of infection with *Schistosoma mansoni* (*S. mansoni*) were 2.5 and 18 million, respectively, whereas the number of people at risk of *Schistosoma haematobium* infection would be about 4 million[2].

The control of schistosomiasis has hitherto involved the use of measures such as snail control, chemotherapy, basic sanitation and clean water supply and health education, either in isolation or in combination[3]. Nevertheless, chemotherapy has been the most widely advocated methods of control[4]. The obvious benefits of chemotherapy would be a decrease in individual patient morbidity and a diminution of transmission by reducing schistosome egg contamination of snail habitat[5].

Recently, schistosomicidal compounds such as artemether and mefloquine have been studied for their efficacy against schistosomes[6-9]. However, praziquantel (PZQ) remains the drug of choice in the treatment of schistosomiasis since the 1970s[10-12]. Nevertheless, few recent reports on low cure rate of praziquantel have raised some concern about its current

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efficacy[13-21]. In addition, the expiry of patent protection for the major anthelminthic drugs[10, 22] and international competition that has substantially reduced the price of the drug[23] have made several low-cost brands and generic formats of PZQ available on the market. This has caused another concern about efficacy of the drug. In this study, therefore, it was proposed to assess the efficacy and side effects of the Medochemie Ltd manufactured PZQ currently in use in the treatment of schistosomiasis in Ethiopia.

2. Materials and methods

2.1. Study area and population

The study was carried out in Shesha Kekele Elementary School, Wondo Genet, located approximately 217 Km south of Addis Ababa, Ethiopia. Wondo Genet is located southeast of Shashemene in Oromia Region State, with latitude and longitude of 7 ° 1′N 38 ° 35′E, and an elevation of approximately 1 723 m above sea level. The study area represents a high risk community for intestinal schistosomiasis due to *S. mansoni* with a prevalence of 80.6%[24]. The study population included a random sample of 299 children, drawn from Shesha Kekele Elementary School in April and May, 2010. The mean age of the study population was 11.4 years (range: 6-22 years).

2.2. Stool collection and examination

A cross sectional study was carried out in which 304 children were randomly selected from 8 sections (grade 3 to 8) in the study in Shesha Kekele elementary school in April 2010. However, only 299 children volunteered to take part in the study. The selected children were supplied with small plastic sheet and applicator stick, and requested to bring about 2 grams of stool sample. On submission of stool samples, details on age and sex were recorded for each child. The specimens were processed for microscopic examination using Kato-Katz technique (one slide per stool specimen) employing a template delivering a plug of 41.7 mg of stool[25]. The Kato slides were transported to the Aklilu Lemma Institute of Pathobiology where they were quantitatively examined for *S. mansoni* and concurrent soil transmitted helminth infection by experienced technician within one week of preparation. The number *S. mansoni* eggs were counted and recorded. The intensity of infection for positive individuals was then categorized as light, moderate and heavy infections according to WHO[10]. Quality assurance was done by randomly examining 10% of the Kato slides by independent experienced laboratory technician. There were no discrepancies observed between the original *S. mansoni* egg counts and those obtained from the senior technicians.

2.4. Treatment and assessment of side effects

Before treatment, children who were found positive for *S. mansoni* infection were told to eat and come for treatment. The children were then treated with a single oral dose of PZQ (Medochemie Ltd, Limassol) at 40 mg/kg of body weight under supervision to ensure proper consumption of the drug. 24 hours post drug consumption, the children were interviewed about treatment-related symptoms.

2.5. Efficacy study

For efficacy study, stool samples were collected from the same children and examined following the same procedure as in the pre-treatment 4 weeks post-treatment. Drug efficacy was determined based on cure and egg reduction rates.

2.6. Statistical analysis

Data was entered into Microsoft Excel and exported to SPSS (version 15) for analysis. The proportion of children infected with *S. mansoni* was expressed as prevalence. Individual egg count of *S. mansoni* was multiplied by 24 and expressed as eggs per gram of faeces (EPG) while mean group egg counts were computed as the geometric mean for positive children. Chi-square and one way ANOVA were used to test for difference in prevalence of infections or side effects, and geometric mean egg counts, respectively. P values < 0.05 were considered statistically significant. Cure rate was calculated as the proportion of individuals found negative for *S. mansoni* egg among those examined 4 weeks after treatment. Egg reduction rate was calculated as 1- EPG (geometric mean) after treatment/EPG before treatment $\times$ 100.

2.7. Ethical considerations

The study was conducted after obtaining ethical clearance from the Institutional Review Board (IRB) of Aklilu Lemma Institute of Pathobiology, Addis Ababa University. Permission to conduct the study was also granted by West Arsi Zone Health Bureau and the Director of Shesha Kekele Elementary School after providing clear explanation about the study objective. Stool specimens were collected only from those children who volunteered to take part in the study during their break time. Furthermore, children who were found positive for schistosomiasis on stool examination were treated with praziquantel in a single dose at 40 mg/kg body weight. Children who were found positive for STHs during stool examination were also treated with a single dose of 400 mg ALB.

3. Results

3.1. Pre-treatment S. mansoni infection

Among children randomly selected from Shesha Kekele Elementary School (grades 3 to 8) in Wondo Genet, southern Ethiopia, 299 children volunteered and provided stool sample. The mean age of the study population was 11.4 (age range: 6 to 22 years) with the highest proportion of individuals lying in the 10-14 age group (56.5%). Pre-treatment prevalence of *S. mansoni* infection was 74.9% (95% confidence interval (CI) =0.696-0.79). This prevalence of infection had sex-related pattern (χ^2=4.63, P=0.03). 42.4% of the infected children had heavy infection intensity, followed by moderate (31.1%) (χ^2= 9.12, P=0.01) (Table 1). Infection intensity showed significant association with age (χ^2= 10.9, P=0.027), but not with sex (χ^2= 3.29, P=0.193). The majority of infected children younger than 10 years and those in the 10-14 age group (χ^2=11.1, P=0.004) had heavy infection followed by moderate infection. Slightly high proportion (48.6%) of children in the 15-22 age group were lightly infected with *S. mansoni* (χ^2=3.65, P=0.16) (Table 2).

3.2. Post-treatment S. mansoni infection

Among the 224 children who were found positive for *S. mansoni* infection and received PZQ treatment at baseline survey, only 144 children were re-examined and 38 of them were still found infected 4 weeks post-treatment. The drug showed an overall cure rate of 73.6% and produced significant reduction in prevalence (from 74.9% to 26.4%) of *S. mansoni* infection (P<0.0001, OR: 8.33, CI: 5.3-13.1). Cure rate showed significant association with age (χ^2= 6.35, P=0.04). The highest cure rate was observed among individuals in the 15-22 age group (Table 1). Slightly higher cure rate (82.4%, 28/34) was observed among individuals with light infection intensity as compared to those with moderate (67.4%, 31/46) and heavy (73.4%, 47/64) infection intensities.

Most of the *S. mansoni* infected children were either cured or the intensity of infection became significantly reduced. The geometric mean egg count of *S. mansoni* infected children declined from 268 to 85 (egg reduction rate of 68.2%) 4 weeks after treatment in those who were not-cured (P=0.03, F=4.64). This percent in egg reduction was also significant for each age group and sexes (Table 1). Nevertheless, there are exceptional situations where mean egg count increased from light to heavy infections after treatment (egg reduction rate of -17.3) (data not shown).

3.3. Side effects

Treatment-related symptoms in children in relation to pre-treatment intensity and age group are presented in Table 3. Out of 224 treated children, 218 showed up for the interview 24 hours post-treatment about treatment-related symptoms they experienced. 83% (181/218) of the children interviewed responded that they experienced two or more manifestations suggestive of side effect of the drug. On

Table 1
Pre- and post-treatment prevalence (%) and intensity (EPG) of *S. mansoni* infection by age group and sex among schoolchildren in Shesha Kekele Elementary School in Wondo Genet, southern Ethiopia, 2010.

Age Group	Pre-treatment		Post-treatment		% reduction in prevalence	% reduction in EPG
	% positive (No. Pos./No. Exam)	EPG	% positive (No. Pos. /No. Exam)	EPG		
<10	74.4 (58/78)	298	28.1 (9/32)	96	62.2	68.0
10-14	77.5 (131/169)	296	31.8 (27/85)	87	59.0	71.0
15-22	67.3 (35/52)	164	7.4 (2/27)	42	89.0	75.0
Total	74.9 (224/299)	268	26.4 (38/144)	85	64.8	68.2
χ^2/ F (p)	2.22 (0.329)	1.6 (0.21)	6.35 (0.04)	0.28 (0.76)		
Female	72.5 (87/120)	267	26.8 (15/56)	102	63.0	62.0
Male	76.5 (137/179)	263	26.1 (23/88)	76	65.9	71.0
χ^2/F (p)	4.63 (0.03)	0.149 (0.7)	2.25 (0.324)	0.11 (0.75)		

Table 2
Proportion of pre-treatment classes of *S. mansoni* infection intensity by age group in Shesha Kekele Elementary schoolchildren in Wondo Genet, southern Ethiopia, 2010.

Age Group (years)	No. Exam.	No. Post.	Light % (*n*)	Moderate % (*n*)	Heavy % (*n*)	χ^2 (*P*)
<10	78	58	22.4 (13)	32.8 (19)	44.8 (26)	4.39 (0.1120)
10-14	169	131	22.1 (29)	32.1 (42)	45.8 (60)	11.10 (0.0040)
15-22	52	35	48.6 (17)	25.7 (9)	25.7 (9)	3.65 (0.1600)
Total	299	224	26.3 (59)	31.3 (70)	42.4 (95)	9.12 (0.0105)

Table 3
Percentage treatment-related symptoms in relation to pre-treatment intensity level and age group among schoolchildren in Shesha Kekele Elementary School in Wondo Genet, southern Ethiopia, 2010

Symptoms	Pre-treatment infection intensity					Age group			
	Light	Moderate	Heavy	% total for specific symptom (*n*= 218)	χ^2(*P*)	<10	10-14	15-22	χ^2((*P*)
Headache	23.1	31.7	45.2*	47.7 (104)**	7.8 (0.02)	29.8	57.7	12.5	32.4 (<0.001)
Nausea	20.2	35.1	44.7	43.1 (94)	8.6 (0.01)	25.5	57.4	17.1	25.6 (<0.001)
Abdominal pain	36.8	58.6	73.6	39.9 (87)	10.6 (0.01)	26.4	52.9	20.7	48.3 (<0.001)
Bloody stool	19.2	32.1	48.7	35.8 (78)	10.2 (0.01)	28.2	64.1	7.7	38.1 (<0.001)
Drowsiness	23.0	38.5	38.5	35.8 (78)	3.7 (0.158)	23.1	61.5	15.4	28.6 (<0.001)
Vomiting	19.2	32.9	47.9	33.5 (73)	9.1 (0.01)	39.7	53.4	6.9	25.1 (<0.001)
Fever	24.6	34.8	40.6	31.7 (69)	2.7 (0.259)	20.3	68.1	11.6	38.4 (<0.001)
Fatigue	27.0	23.8	49.2	28.9 (63)	7.2 (0.03)	27.0	52.4	20.6	10.7 (0.005)
Diarrhea	24.2	35.5	40.3	28.4 (62)	2.6 (0.279)	32.3	53.2	14.5	14.0 (<0.001)
Straining	23.3	30.0	46.7	27.5 (60)	5.2 (0.07)	16.7	66.7	16.6	30.0 (<0.001)
Dysuria	25.7	28.6	45.7	16.1 (35)	2.5 (0.292)	14.3	68.6	17.1	19.6 (<0.001)
Itching	32.1	25.0	42.9	12.8 (28)	1.4 (0.507)	17.9	67.9	14.2	15.1 (<0.001)

* Percentage values for treatment-related symptoms at each class of intensity was calculated in relation to total number of individuals experienced specific symptom.
** Total percentage values for specific symptom for the three classes of intensity were calculated in relation to total number examined (n = 218).

the other hand, 17% (38/218) of the children reported no complaint or symptoms at all. Most of the side effects were transient and mild, lasting only 30 minutes to 4 hours after treatment. The most commonly reported symptoms were headache (47.7%), nausea (43.1%), and abdominal pain (39.9%).

Most (80.7%) children reported 3 or more side effects. The manifested symptoms showed significant association with age ($P<0.001$), the highest frequency being observed in the 10-14 age group, followed by children younger than 10 years. The reporting of abdominal pain ($\chi^2=10.6$, $P=0.005$), vomiting ($\chi^2=9.08$, $P=0.01$), nausea ($\chi^2=8.57$, $P=0.01$), bloody stool ($\chi^2=10.23$, $P=0.006$), headache ($\chi^2=7.75$, $P=0.02$), dizziness ($\chi^2=6.86$, $P=0.032$) and fatigue($\chi^2=7.24$, $P=0.027$) were significantly associated with pre-treatment intensity level.

4. Discussion

In this study, an overall schistosomiasis mansoni cure rate of 73.6% and egg reduction rate of 68.2% were observed for the PZQ (Medochemie Ltd, Limassol) administered in a single oral dose at 40mg/kg body weight and evaluated 4 weeks post-treatment. These values are in general within the usual cure rate ranges (63-95%) of PZQ against *S. mansoni* reported in different epidemiological settings[4, 26-28]. Some previous studies have reported efficacy higher than 85% for PZQ[29-34], while others have reported lower (<63%) efficacy for the drug[13-21,35,36]. Such variations might be attributable to differences in the number of treatment, factors related to the host, parasite, and drugs or to the methodology.

The efficacy of the PZQ observed in the present study was relatively lower and this is partially explained by a single administration of the drug. Unlike a single administration in the present study, most of the previous studies that have reported high efficacy of PZQ administered two or three treatments spaced at certain time intervals[16,21,31,37,38]. In areas with heavy transmission of schistosomiasis, it has been suggested that people might have been infected in the previous 3-5 weeks. Hence, such patients would harbor immature schistosomes that are less susceptible to PZQ [7,39-41]. These immature stages have the high chance to survive a single treatment and mature to deposit eggs in the subsequent weeks. Also, high percent of *S. mansoni* infection (74.9%) in general and heavy infection cases (42.4%, 95/224) in particular before treatment in our study population might have decreased the cure rate of the drug. Unlike the present study, previous studies which documented higher efficacy (>85%) for PZQ were conducted in areas of lower *S. mansoni* prevalence (<51%) and light intensity infection[30-32].

Assessment of *S. mansoni* infection using a single Kato-Katz slide per individual collected on a single day could be a limitation of this study as some light infections could have been missed[35,42].

In this study, pre-treatment infection intensity and cure rates showed significant association with age. Accordingly, infected children younger than 10 years and in the 10-14 age group showed high percent of heavy and moderate infection and low cure rate after treatment as compared to those in the 15-22 age group. This agrees with similar previous studies [16,36,43] in which significant association between classes of intensity and age groups was observed. The present study area is an area of intense transmission where school age children acquire heavy infection. In the 15-22 age group, lower intensity and prevalence of *S. mansoni* infection and high cure rate after treatment may be explained by reduced exposure to cercariae infested water and maturing acquired immunity with age. The difference in the drug efficacy among the different age groups could also be due to absence of linear relationship between body weight and dose of PZQ[21]. However, adjusting for the effect of age and sex, cure rate was found to be independent of pre-treatment infection level.

Although most are mild and transient, 83% of the treated children complained that they experienced two or more treatment-related symptoms suggestive of side effects of the drug. The most frequent of these were headache, nausea, and abdominal pain. These observations were in agreement with previous studies in Ethiopia and other countries[21,29,31,37,44]. Nevertheless, there are variations in the overall prevalence and frequency of the different symptoms observed. Yeneneh *et al*[29] reported an overall side-effect prevalence of 70%, the most frequent being headache (64.4%), followed by abdominal pain (46.5%). On the other hand, Berhe *et al*[44] reported an overall side-effect prevalence of 91.5%, with a high frequency of abdominal cramp (86.9%), followed by diarrhea (49.7%). These variations might be due to variations in parasite, host or drug factors.

A number of treatment-related symptoms reported by the children 24 hours post-treatment had significant association with age, *i.e.*, children in the 10-14 and 15-22 age groups experienced high and low proportion of side effects, respectively. This agrees with a report by Kabatereine *et al*[21], and perhaps has to do with heavy intensity infection in the 10-14 age group and low intensity infection in the 15-22 age group. The former might be explained by increased amount of chemicals released from the dying schistosomes[37].

In conclusion, the present findings revealed relatively lower cure (73.6%) and egg reduction (68.2%) rates of the PZQ (Medochemie Ltd, Limassol) evaluated as compared to most previous reports for the Biltricide® , Distocide® and other brands[29, 32, 44]. Hence, in depth studies are recommended to clarify whether the present low cure rates are due to treatment failure or the actual efficacy of the drug. With regard to treatment-related side effects, an overall prevalence of 83% frequent headache, nausea and abdominal pain were observed which were mild, transient and tolerable.

Conflict of interest statement

We declare that we have no conflict of interest.

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