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EFFICACY OF OXAMNIQUINE AND PRAZIQUANTEL IN SCHOOL CHILDREN FROM TWO *SCHISTOSOMA MANSONI* ENDEMIC AREAS
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EFFICACY OF OXAMNIQUINE AND PRAZIQUANTEL IN SCHOOL CHILDREN FROM TWO *SCHISTOSOMA MANSONI* ENDEMIC AREAS

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ABSTRACT

Objective: **To determine the relative susceptibility of *Schistosoma mansoni* infections to treatment with the oxamniquine (OXA) and praziquantel (PZQ).**

Design and setting: **Three separate cross sectional studies were performed in six primary schools located in two *Schistosoma mansoni* endemic areas in Eastern Kenya: Kangundo (low morbidity) and Kibwezi (high morbidity).**

Subjects: **One thousand two hundred and fourteen infected children aged 6-20 years were involved.**

Intervention: **Each child received either 15-mg OXA/kg body weight twice within an interval of six hours or a single dose of 40 or 60 mg PZQ/kg body weight. Three duplicate Kato stool examinations were done before and four or five weeks after treatment to assess treatment efficacy.**

Results: **The cure rates in different schools with OXA were 71.7 - 79.7% in Kangundo and 56.7 - 61.9% in Kibwezi. In children treated with PZQ, the 40-mg/kg-dose regimen achieved cure rates of 77.6 87.2% in Kangundo and 67.1 - 81.1% in Kibwezi, whereas the 60-mg/ kg dose regimen attained cure rates of 93.2% in Kangundo and 76.3% in Kibwezi. Both OXA and PZQ efficacy declined significantly with age in Kangundo, whereas the age effect was not seen in Kibwezi.**

Conclusion: **The poorer cure rates in Kibwezi than in the Kangundo children were not due to known previous drug exposure to either OXA or PZQ. The varying efficacy may be attributed to innate low drug susceptibility, possibly related to schistosome strain differences between the two areas.**

INTRODUCTION

Differences in morbidity patterns in *Schistosoma mansoni* in the Kangundo and Kibwezi Divisions have been amply demonstrated, while several hypotheses have been put forward to explain them(1,2). One such determinant of morbidity includes the possible existence of *Schistosoma mansoni* strains of different relative pathogenicity(3). The realisation that morbidity is related to heavy infections that can be rapidly detected, and that the reduction of morbidity can be achieved through chemotherapy, has changed attitudes to schistosomiasis control(4). However, differences in relative susceptibility of *S. mansoni* infections to treatment with presently available antischistosomal drugs have been demonstrated repeatedly(5-7). In Kenya, differences in susceptibility of *S. mansoni* to treatment with oxamniquine (OXA) have been described by Coles *et al*(8). Given the history of resistance/tolerance of schistosomes to drugs(4,7), it is vital that there be a monitoring programme for the presence of such resistance/tolerance to OXA and praziquantel (PZQ). This is considered especially important in view of the recent observation that the efficacy of PZQ, the current drug of choice, appeared lower than initially expected in several situations(6,9). The decreasing drug efficacy is the final effect of many complex factors, among which parasite sensitivity *sensu stricto* is one.

The present study was carried out to assess the relative susceptibility of *S. mansoni* infection in school children of Kangundo, Machakos district (low morbidity area) and Kibwezi, Makueni district (high morbidity area) of Kenya to treatment with OXA or PZQ.

MATERIALS AND METHODS

Three separate studies were performed. One addressed the efficacy of OXA only (I), the second one compared the efficacy of both OXA and PZQ (II) and the third compared the PZQ dose regimens of 40 and 60-mg/kg-body weight (III). Three stool samples were collected from each pupil and examined for *S. mansoni* infections using the Kato technique(10) with duplicate 50 mg smears for each stool sample. S. *mansoni* egg counts were expressed as the number of eggs/gm of faeces. The selected children were asked to have a proper meal at home before coming to school. Further,

to ensure that all children dosed had a full stomach, each was provided with 250 ml of milk prior to taking the drug. Three further stool examinations (2 Kato smears/stool) were made four or five weeks after treatment to assess treatment efficacy. However, in order to avoid too many dropouts, some children providing only two samples after treatment were included in the study.

Study I: This study was carried out from March to July, 1990, in Kawauni Primary School (n=99), Kangundo area and in Kamulalani Primary School (n = 97) in Kibwezi area. Infected children were matched for sex and age. The matching for age was difficult, with the mean age of Kangundo children (12.4 years) greater than Kibwezi children (10.7 years). Each child was given 15 mg OXA/kg body weight twice with an interval of six hours in between doses (total dose = 30mg/kg).

Study II: This study was carried out between September and November, 1991, in Kikombi Primary School (n = 237), Kangundo area and in Mbetwani Primary School (n = 187), Kibwezi area. Children were subsequently matched for age and sex within and between the schools. Nearly half of the children in each school received two doses each of 15 mg OXA/kg body weight six hours apart. The rest of the children were given 40 mg PZQ/kg body weight once.

Study III: The study was a randomised clinical trial done between October and November, 1990 in Kitwii Primary School (n=267), Kangundo area and in Kambu Primary School (n=325), Kibwezi area. The main objective was to compare the efficacy of a single dose PZQ treatment of 40 or 60-mg/kg-body weight in school children. The children were randomly allocated the 40 or 60 mg dose regimen. Each regimen group was subsequently matched for age and sex within and between the schools.

Statistical methods: Egg counts were not normally distributed and were logarithmically transformed after adding 1. Comparisons of these transformed egg counts between groups were made by either Student's t-test or one or two factor analysis of variance(11). Treatment was considered effective only if no eggs were found during the 4 or 5-week post treatment stool examinations. Treatment effect in relation to various factors such as age, sex and school was assessed on basis of $\chi 2$–values(11) or by logistic regression analysis(12). P values <0.05 were considered to indicate significant effects. Reduction in egg counts was calculated as the percentage reduction in the geometric mean egg count.

RESULTS

Study I efficacy of oxamniquine: Table 1 sumarises the effects of treatment with OXA by area and age group. Overall, there was a significant lower cure rate ($p<0.05$) in the Kibwezi School (56.7%) than in Kangundo School (71.7%). In the Kangundo School, cure rates differed significantly between age groups ($p<0.001$), but this was not seen in Kibwezi School. In both areas, the overall percentage egg count reduction was similar.

Logistic regression analysis (data not shown) revealed a significant interaction between age and area ($p<0.01$), the decline in treatment failure by age occurring only in the Kangundo School. The age effect should be interpreted with caution since the mean age distribution was lower in Kibwezi by 1.7 years. When adjustment for age was made, there were no significant differences in the treatment failure between schools. Pre-treatment egg counts did not differ significantly between the two schools.

However, pre-treatment egg counts differed between age groups in Kangundo School but not in Kibwezi School. Sex had no effect on treatment failure but pre-treatment egg counts were important ($p<0.05$). There was no interaction between either of these two variables and area, and the area effect remained significant after adjustment for sex and pre-treatment egg counts.

Table 1

Efficacy of Oxamniquine (15mg/kg body weight) on Schistosoma mansoni infections 5 weeks after treatment in children of Kawauni school, Kangundo area of Machakos District and Kamulalani school, Kibwezi area of Makueni Districts.

Age group (years)	No. treated	Cure rate (%)	Egg count (egg/g Pre-treatment	% egg reduction
Kawauni school, Kangundo area				
4-8	8	50	62.0	96.3
9-11	30	50	45.5	97.7
12-14	35	77.1	38.0	99.7
15 and above	26	96.2	27.5	100.0
P=value		<0.001	<0.05	n.s.
Overall	99	71.7‡	38.3	96 3†
Kamulalani school, Kibwezi area				
4-8	21	52.4	25.3	97.9
9-11	42	52.4	25.7	97.0
12-14	24	75.3	48.3	99.9
15 and above	10	40.0	54.7	98.4
P=value		n.s.	<0.01	n.s.
Overall	97	56.7‡	32.3	95.4†

‡-χ=4.81, P<0.05; significance level of cure rates between schools
†-χ=0.11, P>0.05; significance level of percentage egg reduction between schools

Table 2

Efficacy of oxamniquine (15 mg/kg body weight) and praziquantel (40 mg/kg body weight) on S. mansoni infections in school children of Kangundo area of Machakos district and Kibwezi areas of Makueni district

Age group (years	No. treated	Oxaminiquine Cure rate (%)	Pre-treatment (epg)	% egg reduction	No. treated	Praziquantel Cure rate (%)	pre-treatment (epg)	% egg reduction
Kikombi, Kangundo area								
5-9	27	63.0	162.4	98.9	28	59.3	192.9	99.2
10-12	39	74.4	358.0	99.8	38	77.8	286.3	99.8
13-15	34	91.2	455.4	99.9	29	81.5	431.1	99.9
16+	23	91.3	375.2	99.9	27	92.3	506.2	100
P-value		<0.05	<0.01	n.s.		n.s.	<0.05	n.s.
Overall	123	79.7	324.6	99.8†	116	77.6	327.0	99.8†
Mbetwani, Kibwezi area								
5-9	14	50.0	485.1	99.0	11	72.7	314.6	99.3
10-12	36	61.1	763.8	99.7	33	81.8	572.7	99.9
13-15	31	71.0	475.4	99.4	33	84.8	632.3	99.9
16+	16	56.2	635.4	98.9	14	78.6	476.0	99.9
P value		n.s	ns	n.s.		n.s.	ns	n.s.
Overall	97	61.9‡	596.4	99.6†	91	81.1	536.7	99.9†

‡-$\chi 2$=8.51, P<0.05; significance level of cure rates between schools (oxamniquine).
†-$\chi 2$=0.43, P>0.05; significance level of cure rates between schools (praziquantel).

Table 3

Effect of treatment on S. mansoni in school children of Kitwii and Kambu Primary Schools by age groups, five weeks post-treatment with praziquantel (40mg or 60mg kg-).

Age group (years)	No. treated	40mg kg^{-1} Cure rate	Pre-treatment (epg)	% reduction	No. treated	60mg kg^{-1} Cure rate	Pre-treatment (epg)	% egg reduction
Kitwii school, Kangundo area								
6-9	10	80.0	86.9	92.9	13	76.9	109.1	89.3
10-14	77	84.6	166.3	92.2	78	93.6	176.6	96.3
15+	46	93.5	229.1	98.1	42	97.6	180.7	99.5
P-value		n.s.		n.s.		<0.05		n.s.
Total	133	87.2‡	177.0	94.3t	133	93.2†	169.8	96.6T
Kambu school, Kibwezi area								
6-9	27	51.9	118.6	74.9	27	63.0	194.5	80.9
10-14	87	64.4	217.8	83.3	78	71.8	221.8	89.0
15+	59	78.0	171.0	90.5	47	91.5	184.9	95.0
P-value		<0.05		n.s.		<0.01		n.s.
Total	173	67.1‡	182.4	84.4t	152	76.3†	205.1	89.4T

‡ - $\chi 2$ = 6.94, P<0.01, significance level of cure rates between schools for 40 mg/kg.
†- $\chi 2$ = 4.72, P<0.05, significance level of cure rates between schools for 60 mg/kg.

t - $\chi 2$ = 6.83, P<0.01, significance level of egg reduction between schools for 40 mg/kg.
T- $\chi 2$ = 4.76, p<0.05, significance level of egg reduction between schools for 60 mg/kg.

Study II treatment with oxamniquine and praziquantel: Table 2 summarises the cure rates of OXA and PZQ by school and drug analysed separately. The overall cure rate in Kibwezi children (61.9%) treated with OXA was statistically lower (p<0.05) than that of Kangundo children (79.7%). However, the difference in overall cure rates in PZQ treated children between Kibwezi and Kangundo was not significant. Treatment effects of OXA and PZQ were similar in Kangundo children, but OXA was less efficient than PZQ in the Kibwezi school. Treatment failure in Kangundo children declined with age, both for OXA and PZQ, but this age effect was not seen in either OXA or PZQ treated children in the Kibwezi School. The overall percentage egg count reduction for OXA and PZQ in the two areas was similar.

Logistic regression analysis was performed for each drug separately (data not shown). For OXA treatment, sex, age group and pre-treatment egg counts had a significant

effect on treatment failure, when entered separately ($p<0.05$), but the effect of area alone was more pronounced ($p<0.01$). The effect of area remained significant ($p<0.05$) after adjusting for the other three factors. For PZQ treatment, only age had a significant effect on treatment failure ($p<0.05$).

Study III treatment with 40 or 60 mg/kg of praziquantel: The overall mean pre-treatment egg counts were comparable as regards age in the two dosage groups, but the Kangundo children were slightly older (mean age for Kangundo 13.3 versus Kibwezi 12.6). The drug response was better in Kangundo school than the Kibwezi school for both treatment doses ($p<0.001$ for both doses), Table 3. In the Kangundo school, cure rates differed significantly among age groups in the 60mg/kg treatment regimen ($p<0.05$), but not in the 40mg/kg group.

In Kibwezi, cure rates differed significantly between age groups for both treatments with 40mg/kg ($p<0.05$) and 60 mg/kg ($p<0.01$). Within the schools, the overall cure rate and the percentage egg reduction did not differ significantly between the 40 and 60 mg regimen ($p>0.05$).

There were, however, significant differences of the overall cure rates between the schools for the 40 mg regimen ($\chi 2 = 6.94$, $p<0.01$) and the 60 mg dose ($\chi 2 = 4.72$, $p<0.05$). Using a logistic regression model with sex, age, area and dose entered as independent variables, a significant association was demonstrated between cure rates, sex, age, dose and school. No two way interactions were significant (data not shown).

DISCUSSION

This study demonstrated that treatment with OXA and PZQ reduced significantly the intensity and prevalence of *S. mansoni* infection in school children, and that treatment with both drugs showed a lower efficacy in Kibwezi than in Kangundo children. There was also an indication of a significant difference in treatment efficacy between OXA and PZQ in Kibwezi children, but not in Kangundo children. The null hypothesis behind the study was that *S. mansoni* in the two areas would respond identically to the antischistosomal treatment. However, a recent study has shown that isolates from the two areas exhibited different patho-biological characteristics(3). Drug sensitivity is relevant because selective chemotherapy directed at school children is one of the strategies in the schistosomiasis control programme in Kenya(1). Previous studies on OXA and PZQ efficacy conducted in the Kangundo area in the late 1970s and in 1980s, showed varying cure rates with no therapeutic differences between OXA and PZQ(1). That finding was generally confirmed in the present study.

The findings also showed that the cure rates or treatment failure following PZQ and OXA treatment was age dependent. Studies on the immune dependence of chemotherapy have shown that the drug and the immune system act synergistically to kill the adult worms; antischistosomal drugs are less effective in young children who have not mounted the appropriate immune responses(13). It is not possible in man to evaluate the drug effects on worms of different ages. However, in mouse models, it has been shown that immature worms are unsusceptible to treatment with PZQ and OXA(14). Based on this finding, it is possible that the treatment failure, which was more prominent in younger children may be the result of the presence of young schistosome worms during therapy. Presumably, these immature worms could have developed into mature adults after treatment and initiated egg laying. Confirmation of this hypothesis would have been provided if a second treatment with OXA and PZQ had been dispensed some weeks later to the children who were not cured(6).

On the other hand, if the occurrence of treatment failure was due to the existence of drug tolerant worm strains, cure would not have been achieved following a second treatment(8,6). It is noteworthy that the younger age groups who frequent water contact sites are the ones at the highest risk of exposure to infection(15). Thus, the finding that treatment failure was most pronounced in the age group below ten years in both areas might indicate that the age of infection could, in part, account for the age dependent variability in drug efficiency encountered in various field studies(6).

From study II and III, the PZQ cure rates for the 60 mg/kg treatment regimen were slightly higher (93.2% in Kangundo and 76.3% in Kibwezi) than for the 40 mg/kg treatment regimen (87.2, 77.6% in Kangundo and 67.1%, 81.1% in Kibwezi). It is plausible that the low cure rates in Kibwezi area where morbidity is high could be associated with the intensity of infection and possibly an innate low drug susceptibility(16). The differences in response of OXA and PZQ between Kangundo and Kibwezi children may not be ascribed to previous and repeated drug exposure because Kibwezi was only recently identified as a schistosomiasis mansoni endemic area(2). A number of reports have been made to show that some strains of *S. mansoni* are resistant to OXA(4). In Kenya, strains of *S. mansoni* tolerant to OXA have been reported in the Mwea irrigation scheme in Kirinyaga District(8).

The results from the present study may tentatively confirm such tolerance in Kenya, since the cure rate in Kibwezi children approached the lowest limits of the usual efficacy of this drug to *S. mansoni* infection(4). The slight but significant difference in OXA efficacy between the two localities may portray a biological difference between *S. mansoni* in the two areas.

The recent finding that treatment with PZQ (40 mg/kg) showed surprisingly low efficacy in a Senegalese community (9) although re-treatment was effective (18), and also the demonstration of schistosomes in Egyptian villagers that can tolerate high doses of PZQ (6), might indicate that resistance to PZQ may sooner or later develop as in the case of OXA (17).

It should be noted that research conducted in several laboratories, has demonstrated very little variation in the efficacy of PZQ on various geographic isolates of *S.*

mansoni(5,17,18) whereas in our study we observed a significant variation in the drug response. Despite the variable cure rates between areas, the percentage egg reductions were remarkably high and stable except for one study, where a significant difference in egg reductions between the two areas was noted in the PZQ treated group (Table 3).

The finding with PZQ of varying but highly susceptible *S. mansoni* from both low and high morbidity areas, suggests that drug tolerance or resistance may not pose an immediate threat to its use in the schistosomiasis control programme in Kenya. The 60-mg/kg regimen in our study achieved cure rates of 76-93% compared to 67-87% for 40 mg/kg. Thus, the optimal PZQ dose regimen in this region remains unresolved. However, if OXA were to be used in the control programme, a higher dose as suggested by Coles *et al*(8) might be worth trying to alleviate the impending drug resistance problems(5,6,7,17). Our findings underline this necessity by pointing out a possible difference in the susceptibility of *S. mansoni* to efficacy of OXA and PZQ in the treatment of *S. mansoni* infections in school children in Kangundo-Machakos and Kibwezi-Makueni areas, and, possibly, elsewhere in Kenya.

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