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EFFICACY OF OXAMNIQUINE, PRAZIQUANTEL AND A COMBINATION OF BOTH DRUGS IN SCHISTOSOMIASIS MANSONI IN BRAZIL

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SUMMARY

A randomized clinical trial was carried out to compare the efficacy of a low-dosage combination of oxamniquine (7.5 mg/kg) plus praziquantel (20 mg/kg) against either agent, oxamniquine (15 mg/kg) or praziquantel (40 mg/kg) alone, in the treatment of schistosomiasis mansoni in the Brazilian north-east.

The drugs were randomly administered per os to 91 patients. Six and twelve months after treatment 89% of those admitted to the trial were reexamined by Kato-Katz method (ten slides) and MIF technique (one gram of stool)

The achieved cure rates, as defined by absence of **S. mansoni** eggs in the faeces of individual patients at all points during the parasitological follow-up, were 81.8%, 81.2% and 67.6% for praziquantel, oxamniquine and the combination respectively. The reduction of eggs excretion in non-cured patients six months after therapy ranged from 93.8-96.8% with praziquantel, 32.5-97% with oxamniquine and 76.9-99.5% with the combination.

It is concluded that, at the used dosages, the three therapeutical regimens give similar and satisfactory results in the treatment of uncomplicated **S. mansoni** infection in Brazil.

KEY-WORDS: Schistosoma mansoni; Oxamniquine; Oxamniquine resistance; Praziquantel.

INTRODUCTION

Two compounds are currently recommended for the treatment of schistosomiasis mansoni[52]. Oxamniquine has been used in large scale mass treatment in Brazil, in an attempt to curtail the transmission of this helminthiasis and to achieve eradication[30, 45, 48, 51]. The drug was advantageous from the point of view of cost-effectiviness, since satisfying cure rates have been accomplished in this country with a single oral dose of 15 mg/kg body weight[33, 40]. In contrast, doses up to 60 mg/kg are required in Africa to attain similar therapeutical efficacy in schistosomiasis mansoni[39]. Oxamniquine is usually well tolerated[35, 42] and clinical improvement has been observed in advanced cases of this parasitosis[3, 23]. Nevertheless serious central nervous adverse

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reactions have been reported following its administration[5, 16, 36, 37, 47]. Unfortunately it also became apparent already at early stages of the eradication campaign in Brazil that **S. mansoni** strains resistant to oxamniquine exist[32]. Such resistance has been confirmed by other investigators[2, 19, 28, 41].

Praziquantel is a novel antihelminthic agent active against all schistosome species pathogenic to man[1, 26, 49] as well as a variety of other human trematode[50] and cestode[27] infections. It proved to be a safe drug[24, 25, 38] which has been administered to schistosomiasis patients with hepatosplenomegaly without inducing any severe untoward effects[11, 13]. Moreover, it has been successfully used in oxamniquine-resistant cases of schistosomiasis mansoni[4, 9, 20].

Recently it has been suggested that the combination of oxamniquine and praziquantel, even at low dosages, produces a synergistic action against **S. mansoni**[8, 18, 29, 44]. These preliminary findings have not yet been clinically investigated in northeastern Brazil. Thus we have carried out a field trial at this endemical region in order to compare the efficacy of a half-dose combination on these two drugs against each one alone.

PATIENTS AND METHODS

A total of 93 subjects living at an area endemic for schistosomiasis in the municipality of Crato, situated in the interior of Ceara state, Brazil, were diagnosed as infected by **S. mansoni** in a parasitological survey. All of them, 70 males and 23 females, presented the uncomplicated form of the disease. The median age was 21 ranging from 10 to 62 years. Only 20% were younger than 16 or older than 30 years. Two females allocated to the praziquantel group were exempted from treatment at the beginning of the study because of pregnancy. They received therapy post-partum but were excluded from the evaluation.

The worm burden was quantified on the basis of faecal egg counts using the Kato thick smear technique as modified by KATZ et al.[31]. The number of eggs per gram of faeces prior to treatment was calculated from five slides (equivalent to 210 mg of stool). Parasitological follow-up examinations performed on a single specimen obtained three, six and twelve months post-treatment, comprised a minimum of ten slides (corresponding to 420 mg of stool) per patient. In addition, approximately 1 g of stool sample was examined by the merthiolate-formol (MIF) concentration technique[6]. This methodology was based on the rationale that a single Kato thick smear reliably indicates the intensity of infection only if egg excretion is higher than 50 ova per gram of faeces, whereas below this level false-negative results are frequent[46].

Subjects with previous history of seizures were excluded from the trial. The patients were then randomly allocated to one of the following treatment group: (a) oxamniquine 15 mg/kg in a single dose; (b) praziquantel 40 mg/kg in two split doses, taken 4 hours apart; and (c) a combination of oxamniquine 7.5 mg/kg plus praziquantel 20 mg/kg, taken simultaneously. Tablets of both drugs were used in adults; in children, oxamniquine was administered in the form of syrup. Thirty-two individuals were treated with oxamniquine, 24 with praziquantel and 35 received the combination. The unequal number of patients within the three groups was due to the non-prefixed limitation in the amount of cases entering the trial. In such event it may occur that at a certain moment the open random allocation brings about a disproportional distribution of patients amongst groups.

The main characteristics of the patients enrolled in the three groups are shown in Table I. They did not differ in age or sex composition, and there was no significant difference in pre-treatment worm burden. The overall median number of eggs per gram of stool prior to therapy was 168, range 42-964. Fewer than 100 eggs per gram were encountered in 27% of the individuals, whereas in 26%, egg excretion exceeded 300 per gram.

Statistical evaluation was performed according to Fisher's exact test for comparison of relative frequencies, and Mann-Whitney signed-rank test to compare reductions in egg excretion.

TABLE I

Characteristics of the patients within the three drug groups (OXM = oxamniquine, PZQ = praziquantel, EPG = number of **S. mansoni** eggs per gram of faeces)

Drug groups		Praziquantel	Oxamniquine	OXM & PZQ
Dosages (mg/kg)		40*	15	7.5 + 20
Treated cases		24	32	35
Sex	Male/female	16/8	25/7	29/6
Age	Median	22 ys.	21 ys.	20 ys.
	Range	12 - 50 ys.	10 - 62 ys.	12 - 54 ys.
	< 16 ys.	22%	21%	18%
	16 - 30 ys.	56%	61%	61%
	> 30 ys.	22%	18%	21%
Worm burden	Median	132 EPG	156 EPG	176 EPG
	Limits**	100 - 216 EPG	132 - 236 EPG	120 - 216 EPG
	< - 100 EPG	32%	28%	25%
	100 - 300 EPG	45%	44%	50%
	> 300 EPG	23%	28%	25%

* Twice 20 mg, four hours apart.
** 95% confidence interval.

RESULTS

Clinical tolerability to all three medications was uneventfull as no difference was noticed in regard to the usual side-effects already reported in Brazil with praziquantel, oxamniquine, and inclusively with the combination[10, 15, 21].

Table II shows the number of examined patients, positive cases and eggs excreted per gram of faeces at different points of the follow-up period. Seventy-two percent, 89% and 89% respectively, of the treated patients could be reexamined three, six and twelve months after theraphy. The cure rates, i. e., failure to detect ova

TABLE II

Parasitological findings 3, 6 and 12 months after treatment (for negative stool samples by Kato-Katz but positive by MIF concentration, an EPG of 5 was assumed in order to calculate the reduction in ova excretion)

Follow-up Controls	Findings	Dose groups		
		Praziquantel	Oxamniquine	OXM & PZQ
3rd. Month	Examined patients*	18 (71%)	26 (81%)	21 (61%)
	Positive cases**	0	2 (8%)	1 (5%)
	EPG in non-cured cases — range		24 — 186	48
	Reduction of EPG — range		46.1 — 67.6%	87.7%
6th Month	Examined patients*	20 (83%)	30 (94%)	32 (91%)
	Positive cases**	3 (15%)	6 (20%)	8 (25%)
	EPG in non-cured cases - range	5 — 10	5 — 230	5 — 25
	Reduction of EPG — range	93.8 — 96.8%	32.5 — 97.0%	76.9 — 99.5%
12 th. Month	Examined patients*	22 (92%)	30 (94%)	28 (80%)
	Positive cases**	2 (9%)	4 (13%)	4 (14%)
	EPG in non-cured cases — range	5 — 85	10 — 25	15 — 25
	Reduction of EPG — range	39.2 — 96.9%	72.2 — 94.0%	82.5 — 93.7%

* In brackets, the percentage of reexamined cases in relation to treated patients.
** In brackets the percentage of positive cases in relation to reexamined patients.

in the faeces, corresponding to these control intervals were: 100%, 85%, 91% for praziquantel; 92%, 80%, 87% for oxamniquine; and 95%, 75%, 86% for the combination, according to the Kato-Katz method. Taken into account the findings of the MIF concentration in addition to the results by Kato-Katz, and embraceing the whole twelve months of parasitological follow-up, cure rates of 81.8%, 81.2% and 67.6% were achieved with praziquantel, oxamniquine and the combination respectively, as shown in Table III. The relative frequencies of parasitological cures did not differ statistically between the groups.

TABLE III

Overall results of the parasitological examinations by Kato-Katz and MIF methods, during the entire 12-month follow-up.

Drug groups	Praziquantel	Oxamniquine	OXM & PZQ
Negative cases	18	26	23
Positive cases*	4	6	11
Cure rates	81.8%	81.2%	67.6%

* One patient in the oxamniquine and one in the combination group was found positive by the MIF concentration only.

In those patients still excreting eggs after treatment, considerable reductions in egg counts were observed. They also did not differ significantly between the three groups, and the number of remaining positive cases was too small to allow statistical comparison of persisting excretion of **S. mansoni**. It is visualized in Figure 1, however, that the reincrease of egg excretion in non-cured patients appears to be steeper in those treated with oxamniquine than in those who received praziquantel.

DISCUSSION

Our results confirm the similar efficacy of praziquantel and oxamniquine when used in conventional dosages for treating **S. mansoni** infection, as already demonstrated in double-blind comparative trials carried out in Brazil[7, 14, 22, 34]. In addition, it has been disclosed that a low-dose combination of both drugs is effective, with 67.6% of patients no longer excreting ova after the treatment and an average reduction of egg counts of 88.7% in those patients in whom no

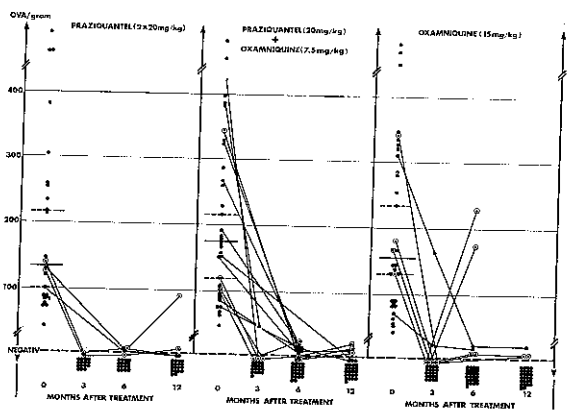

Fig. 1 — **S. MANSONI** OVA EXCRETION IN INDIVIDUAL PATIENTS (points indicate the EPG of each case, those negative at the first follow-up but positive on subsequent examinations are denoted by open circles. Medians and 95% confidence limits prior to therapy are indicated by horizontal bars. Follow-up examinations positive by MIF concentration only are not quantified).

complete parasitological cure was accomplished.

A similar dosage to the one we used in this trial has previously shown to be advantageous in a dose-finding study conducted in Malawi[43]. The children treated in this country had 2 to 4 times higher egg counts prior to treatment, and many were concomitantly infected with **S. haematobium**. In that study, the reduction of ova excretion three months after therapy was marginally lower using 7.5 mg/kg oxamniquine plus 15 mg/kg praziquantel, as compared to the group treated with 10 mg/kg oxamniquine plus 20 mg/kg praziquantel (93% vs. 97%). Six months after treatment little difference was apparent between the two dosage schemes (95% vs. 96%).

In our trial the post-treatment decrease of **S. mansoni** ova excretion and cure rate seemed more favourable for the group treated with praziquantel alone, however, the initial egg count was slightly lower than in the two remaining groups. In this connection, a statistically significant difference in the reduction of the mean numbers of eggs per gram of faeces after treatment with praziquantel in comparison to oxamniquine has been reported in a much larger sized sample[17]. A reincrease in egg counts upon reexamination six and twelve months after treatment was noted in two to three patients in each group in whom the counts had fallen to nought or 10 eggs per

gram 3 months post-therapy. This finding was most pronounced on the 6th. month after treatment in the oxamniquine group. Actually, in two cases treated with this drug the egg counts reached pre-therapeutical levels. This could be due to a diminished susceptibility of **S. mansoni** strains to this drug but the possibility of reinfection or relapse cannot be ruled out either. In regard to this, the assessment of oxamniquine efficacy by the quantitative oogram technique has been indicative of persistance of egg production four months on after treatment[12].

In conclusion, a single dose administration of oxamniquine 15 mg/kg or praziquantel 40 mg/kg or a half-dose combination of both drugs proved to be similarly effective in schistosomiasis mansoni in Brazil, as analogous cure rates and reductions of egg excretion in non-cured cases were achieved. It remains speculative whether this combination will prevent further development of oxamniquine resistance, which could turn into a serious hazard for schistosomiasis control in Brazil. Finally it should be emphasized that these are only preliminary results not to be extrapolated to large scale therapy.

RESUMO

Eficácia da oxamniquine, do praziquantel e da combinação de ambas as drogas na esquistossomose mansônica no Brasil.

Conduziu-se um ensaio clínico para comparar a eficácia de uma combinação em baixas doses de oxamniquine (7,5 mg/kg) mais praziquantel (20 mg/kg) com ambas as drogas — oxamniquine (15 mg/kg) e praziquantel (40 mg/kg) — empregadas isoladamente, no tratamento da esquistossomose mansônica em uma área endêmica do nordeste brasileiro.

Os medicamentos foram administrados, aleatoriamente, por via oral, a 91 pacientes. Seis e doze meses depois do tratamento 89% dos admitidos no ensaio foram reexaminados segundo os métodos de Kato-Katz (dez lâminas) e MIF (um grama de fezes).

Os índices de cura alcançados, representando a ausência de ovos nas fezes em todos os controles durante o acompanhamento parasitológico individualizado dos pacientes, foram de 81,8%, 81,2% e 67,6% com, respectivamente, o praziquantel, a oxamniquine e a combinação. A redução do número de ovos eliminado por grama de fezes nos casos não curados, variou de 93,8-96,8% com o praziquantel, 32,5-97% com a oxamniquine e 76,9-99,5% com a combinação.

Concluiu-se que os três regimes terapêuticos, nas doses utilizadas, dão resultados similares e satisfatórios no tratamento da esquistossomose mansônica não complicada, no Brasil.

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