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TREATMENT OF PATIENTS WITH SCHISTOSOMIASIS MANSONI: A DOUBLE BLIND CLINICAL TRIAL COMPARING PRAZIQUANTEL WITH OXAMNIQUINE

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SUMMARY

A double-blind clinical trial involving 120 patients with chronic schistosomiasis was carried out to compare the tolerability and efficacy of praziquantel and oxamniquine. The patients were randomly allocated into two groups. One was treated with praziquantel, 55 mg/kg of body weight (BWT), and the other one with oxamniquine, 15mg/kg bwt, administered in a single oral dose. The diagnosis and the parasitological follow-up was based on stool examinations by quantitative Kato-Katz method and on rectal biopsies. Side-effects — mainly dizziness, sleepness, abdominal distress, headache, nausea and diarrhea — were observed in 87% of the cases. Their incidence, intensity and duration were similar for both drugs but abdominal pain was significantly more frequent after praziquantel intake and severe dizziness was more commonly reported after oxamniquine. A significant increase of alanine-aminotransferase and γ-glutamyltransferase was found with the latter drug and of total bilirubin with the former one. A total of 48 patients treated with praziquantel and 46 with oxamniquine completed with negative findings the required three post-treatment parasitological controls — three slides of each stool sample on the first, third and sixth month. The achieved cure rates were 79.2% and 84.8%, respectively, a difference without statistical significance. The non-cured cases showed a mean reduction in the number of eggs per gram of feces of 93.5% after praziquantel and of 84.1% after oxamniquine. This diference also was not significant. Five patients retreated with praziquantel were cured but only one out of three treated a second time with oxamniquine. These findings show that both drugs — despite their different chemical structures, pharmacological properties and mechanisms-of-action — induce similar side-effects as well as a comparable therapeutical efficacy, in agreement with the results reported from analogous investigations.

KEY WORDS: **Schistosomiasis mansoni** — Treatment — Praziquantel — Oxamniquine

INTRODUCTION

Chemotherapy in a single-dose schedule with potent drugs represented a breakthrought in the treatment of schistosomiasis mansoni [9]. The first one was hycanthone, mainly administered

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by intramuscular route. Unfortunately, some cases of fatal toxic hepatitis [4,6] and drug resistance [1,5] were reported.

With the appearance of oxamniquine, hycanthone was rapidly withdrawn and it is no longer available in Brazil.

Over the last 10 years oxamniquine, a tetra hydroquinoline derivative, has been extensively used in our country, not only for individual treatment [28] but also as mass treatment [18]. Interesting enough this drug showed a greater efficacy against the Brazilian strain of **Schistosoma mansoni** than against the African strain [18].

Despite its good tolerability oxamniquine may cause unwanted side-effects such as: severe dizziness, mostly in fasting conditions [28]; neurological disturbances in animals [15] and in humans [18] and occasionaly seizures [2,25]. Moreover, elevation of serum activity of aminotransferases a few days after treatment has been reported in some patients with schistosomiasis [28]. On the other hand, cases of resistance to oxamniquine have been published [10,16,29], and finally its efficacy in humans was recently disputed in our country [8].

These findings justified further investigations with new antischistosome agents. Praziquantel, a heterocyclic pyrazino-isoquinoline compound, is a relatively new drug jointly developed by E. Merck — Darmstadt and Bayer AG — Leverkusen. It was found to be particularly active against **Schistosoma mansoni, S. haematobium** and **S. japonicum**, the three main species pathogenic to man [19,24,26,32].

In order to compare the tolerability and efficacy of praziquantel and oxamniquine, this double-blind clinical trial was carried out.

MATERIAL AND METHODS

One hundred and twenty patients with chronic intestinal or hepato-intestinal forms of schistosomiasis were included in the trial.

The selection of patients was based on age (older than 14 years), clinical form (hepatosplenic cases were not included) and worm burden established by three pre-treatment excretal egg counts according to Kato-Katz method [17]. Patients with associated acute and/or serious diseases and those who were pregnant or who have been treated within the previous 6 months with any anti-schistosomal drug were excluded.

After parasitological diagnosis, the 120 patients were randomly allocated into two groups having an equal number of cases. One received praziquantel 55 mg/kg bwt and the other group oxamniquine 15 mg/kg bwt. Both drugs were given in a single oral dose in accordance with a double-blind technique.

Evaluation of symptoms and physical examination were performed on the same day and 24 to 48 hours after the drug administration. Report of side-effects was attained through the spontaneous information of the patients.

Blood was collected just before, 24 to 48 hours and on the 7th. day after treatment. The following tests were accomplished: alanine-aminotransferase (ALT); aspartate-aminotransferase (AST); gammaglutamyl-transferase; and bilirubin.

One patient was not included in the evaluation of tolerance and toxicity as he was inadvertently treated with oxamniquine at the beginning of an assymptomatic viral hepatitis. The evolution was uneventful.

The assessment of drug efficacy was based on three slides of each stool sample obtained prior to as well as one, three and six months after tretment [21]. In 73 out of 77 patients with negative stool examinations up to the sixth month, 4 to 6 biopsies were taken from the valves of Houston during rectoscopy, always performed by the same investigator.

Patients with less than three negative post-treatment parasitological controls were not included in the assessment of efficacy but all cases who eliminated viable eggs in any stool examination from the first month on after treatment were considered as noncured; whenever feasible they were retreated with the same drug. The shortest period between both treatments was four months.

For the statistical analysis [14,31] of side-effects tables of contingency 2x3 were constructed, and the hypothesis of homogeneity between the two

groups was tested by the Pearson's statistic. A "one-sample profile analysis" was utilized to evaluate the biochemical data; for comparing the therapeutical efficacy it was applied the chi-square test and the Mann-Whithney test to confront the reduction of eggs eliminated by the non-cured cases. Calculations were done by using the software Statistical Analysis System.

RESULTS

Clinical and parasitological findings

Sex, age, body-weight and egg counts from patients of the two groups were compared and no significant difference ($p > 0.05$) was found (Table I). All but three patients had more than 100 S. mansoni eggs per gram of stools.

TABLE I

Clinical and parasitological findings on 120 patients with chronic schistosomiasis mansoni treated with praziquantel or oxamniquine

Drugs / Patients	Praziquantel		Oxamniquine	
	No.	(%)	No.	(%)
Male	30	50.0	27	47.0
Female	30	50.0	33	55.0
	Mean ± SD		Mean ± SD	
Age (*)	25.55 ± 7.82		25.71 ± 8.19	
Weight (*)	57.31 ± 10.90		58.40 ± 8.90	
Egg counts (*)	312.66 ± 237.15		346.86 ± 356.57	

(*) $p > 0.05$ (N.S.)

Tolerability

Side-effects following the administration of praziquantel or oxamniquine were observed in 53 out of 60 patients (88.3%) and in 51 out of 59 (86.4%), respectively. The main complaints were dizziness, sleepness, abdominal pain or disconfort, headache, nausea and diarrhea. (Table II). Abdominal pain was significantly more frequent ($p < 0.001$) after praziquantel intake. A severe degree of dizziness occurred in 13 out of 59 cases (22.0%) after oxamniquine, and in 5 out of 60 (8.3%) after praziquantel but this difference was not significant ($p > 0.1$). Most of the symptoms disappeared without additional medication within a few hours.

Biochemical data

TABLE II

Occurrence of side-effects after praziquantel and oxamniquine treatment

Drugs / Dose	Praziquantel 55 mg/kg		Oxamniquine 15 mg/kg	
Side-effects	No.	(%)	No.	(%)
None	7	11.7	8	13.6
Dizziness (*)	36	60.0	38	64.4
Abdominal distress (**)	29	48.3	10	16.9
Sleepness (*)	21	35.0	16	27.1
Nausea (*)	14	23.3	11	18.6
Headache (*)	12	20.0	15	25.4
Diarrhea (*)	12	20.0	4	6.8
Vomiting	7	11.7	9	15.3
Itching	4	6.7	2	3.4
Anorexia	1	1.7	3	5.1
Myalgia	—	—	3	5.1
Asthenia	1	1.7	—	—

(*) $p > 0.05$ (NS)
(**) $p < 0.001$

Table III displays the data obtained before T_0, two days (T_2) and 7 days (T_7) after chemotherapy.

According to Wilks (W) and Fisher-Snedecor's (F) statistics, significant changes were observed with alanine-aminotransferase ($p < 0.05$) and gammaglutamyltransferase ($p < 0.01$) after oxamniquine and with total bilirubin ($p < 0.05$) after praziquantel. In order to study the influence of time on these changes, the above-mentioned liver function tests were further submitted to statistical analysis with the same methods. The results are shown in Table IV. A significant difference was observed between T_0 and T_7 and T_2 and T_7 for ALT and GGT after oxamniquine. For TB after praziquantel a significant difference was observed between T_2 and T_7.

Efficacy

The parasitological follow-up examinations were completed in 94 patients. In the praziquantel group 38 out of 48 (79.2%) were considered as cured; and in the oxamniquine group 39 out of 46 (84.8%). The difference was not statistically significant ($p > 0.1$).

Rectal mucosa biopsies in 73 out of 77 patients with three negative stool examinations did not show viable eggs.

TABLE III

Biochemical data from schistosomotic patients before and after oxamniquine and praziquantel

Blood tests (*)	No. of patients	Time (days)	Range		Mean	SD
			Oxamniquine group			
AST	52	0	2.00	27.00	9.98	4.92
		2	2.00	24.00	9.92	4.45
		7	2.00	51.00	11.29	8.16
ALT	52	0	4.00	47.00	12.00	8.52
		2	4.00	52.00	12.17	8.74
		7	4.00	61.00	15.04	11.49
GGT	52	0	6.00	159.00	25.46	26.87
		2	7.00	152.00	25.69	28.32
		7	7.00	210.00	30.60	35.08
TB	49	0	20.00	138.00	62.69	25.63
		2	15.00	149.00	59.76	24.66
		7	18.00	140.00	56.35	23.84
			Praziquantel group			
AST	53	0	4.00	37.00	11.38	6.32
		2	3.00	27.00	10.40	5.58
		7	3.00	29.00	10.60	5.40
ALT	53	0	4.00	62.00	16.23	13.61
		2	3.00	71.00	16.00	14.96
		7	3.00	49.00	14.68	10.80
GGT	52	0	8.00	193.00	26.62	28.26
		2	7.00	176.00	28.71	28.71
		7	6.00	197.00	28.21	27.88
TB	49	0	22.00	107.00	55.96	20.37
		2	24.00	195.00	60.76	29.01
		7	20.00	110.00	51.08	20.83

(*) AST, ALT, GGT, TB = aspartate and alanine aminotransferases, gammaglutamyltransferase and total bilirubin

TABLE IV

Results of statistical analysis comparing blood tests obtained before (T_0) and two days (T_2) and seven days (T_7) after chemotherapy

Blood tests	Hypothesis	W (*)	F (*)	p
ALT (**)	$T_0 = T_2$	0.9979	0.1058	0.7463
	$T_0 = T_7$	0.8741	7.3468	0.0091
	$T_2 = T_7$	0.9003	5.6504	0.0212
GGT (**)	$T_0 = T_2$	0.9979	0.1098	0.7417
	$T_0 = T_7$	0.8935	6.0785	0.0171
	$T_2 = T_7$	0.8036	12.4659	0.0009
TB (**)	$T_0 = T_2$	0.9772	1.1189	0.2955
	$T_0 = T_7$	0.9633	1.8274	0.1828
	$T_2 = T_7$	0.8715	7.0778	0.0106

(*) Wilks and Fisher-Snedecor's statistics

(**) Alanine aminotransferase, gammaglutamyltransferase and total bilirubin

Considering the non-cured cases, except for one who received oxamniquine, all of them had a marked decrease in the mean number of eggs eliminated per gram of feces. The average reduction after praziquantel was 93.5% and after oxamniquine 84.1% (Table V), a difference without statistical significance ($p > 0.1$).

Six out of the non-cured patients with praziquantel were treated again with the same drug. Five were followed up for six months and all were considered as cured.

Retreatment with oxamniquine was carried out in four out of seven non-cured patients. Three completed the follow-up and only one was cured. A non-cured case was retreated once more but with praziquantel achieving parasitological negativation.

DISCUSSION

These data show that praziquantel and oxamniquine produce similar side-effects, despite their different chemical structures and pharmacological properties. Only abdominal pain was more frequently observed with praziquantel. Most of the post-chemotherapy symptoms, although being frequent, were of slight or moderate intensity and did not require symptomatic medication.

The serum enzymatic changes observed after oxamniquine intake deserve some comments. It is a well-known fact that following chemotherapy there is a worm shift from the terminal mesenteric veins to the liver. Thus, the significant elevation of alanine-aminotransferase and of gammaglutamyltransferase found with oxamniquine might be due to worm embolization. As a matter of fact, an experimental study in infected and non-infected mice, undertaken in our laboratories has demonstrated that oxamniquine leads to worm embolization, focal hepatic necrosis and a significant increase in serum aminotransferase activity in the infected mice but no changes were seen in the control animals [27]. The absence of serum enzimatic alterations [7,30] and the elevation of serum total bilirubin after praziquantel remain to be elucidated.

Parasitological negativation occurred in 38 out of 48 patients (79.2%) under praziquantel

TABLE V

Reduction of the number of S. mansoni eggs per gram of feces after praziquantel and oxamniquine treatment in non-cured patients

Drugs	Praziquantel			Oxamniquine		
No. of Cases	Mean egg counts Before	After	Reduction (%)	Mean egg counts Before	After	Reduction (%)
1	120	32	73.3	112	24	78.6
2	144	24	83.3	216	8	96.3
3	152	56	63.2	344	456	0.0
4	200	32	84.0	344	104	69.8
5	264	24	90.9	704	112	84.1
6	264	16	93.9	846	104	87.7
7	344	24	93.0	2 552	8	99.7
8	544	8	98.5	—	—	—
9	880	16	98.2	—	—	—
10	1 132	32	97.2	—	—	—
Mean	404	26	93.5(*)	731	117	84.1(*)

(*) $p > 0.05$ (NS)

administration and in 39 out of 46 (84.8%) under oxamniquine. Other investigators also have reported no significant difference between the efficacy of both drugs [3,13,20,21]. However, some of them referred a lower [3] whereas others a higher [13] cure-rate. For children, higher doses of praziquantel, 70 mg/kg, as well as of oxamniquine, 20 mg/kg, are necessary for achieving a cure-rate of about 70% [12,23].

The results of retreatment are worth to be mentioned. Though the number of non-cured patients submitted twice to the same drug therapy is rather small, there was a tendency for the appearance of resistant cases to oxamniquine and apparently such occurrence does not influence the sensitivity of **S. mansoni** to praziquantel [11].

RESUMO

Estudo clínico duplo cego comparando praziquantel com oxamniquine

Com objetivo de se compararem a tolerabilidade e eficácia do praziquantel e oxamniquine, procedeu-se a um estudo prospectivo duplo-cego envolvendo 120 pacientes com esquistossomose intestinal ou hepatintestinal.

Os pacientes foram randomizados em dois grupos. Um foi tratado com praziquantel, na dose de 55 mg/kg de peso, o outro com oxamniquine, 15 mg/kg de peso, sempre administrados em dose única por via oral. O diagnóstico e seguimento parasitológicos basearam-se no exame de fazes pelo método de Kato-Katz. Em 73 de 77 casos negativos após tratamento, executaram-se biopsias retais.

Efeitos colaterais, principalmente tontura, sonolência, dores abdominais, cefaléia, náuseas e diarréia foram observados em 87% dos casos. Sua incidência, intensidade e duração foram semelhantes em ambos os grupos, mas a dor abdominal foi significativamente mais freqüente após praziquantel, havendo maior tendência para tontura intensa após oxamniquine. Observou-se aumento significante de alamina-aminotransferase e gama-glutamiltransferase após oxamniquine e de bilirrubina total após praziquantel.

Um total de 48 pacientes tratados com praziquantel e 46 com oxamniquine completaram os exames de controle até o sexto mês. As percentages de cura foram de 79,2% e de 84,8% respectivamente, diferença não significativa. Os pacientes não curados mostraram redução média do número de ovos de 93,5% e de 84,1%, diferença não significativa. Cinco pacientes retratados com praziquantel curaram-se, mas somente um de três retratados com oxamniquine.

Estes resultados mostram que ambas as drogas-apesar de diferentes propriedades farmacológicas — provocam reações colaterais semelhantes e apresentam eficácia terapêutica comparável.

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