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DOUBLE-BLIND CLINICAL TRIAL COMPARING PRAZIQUANTEL WITH OXAMNIQUINE IN THE TREATMENT OF PATIENTS WITH SCHISTOSOMIASIS MANSONI

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SUMMARY

A total of 101 patients having active schistosomiasis mansoni were randomly allocated into three treatment groups, one received praziquantel (41.2 to 51.6 mg/kg), one oxamniquine (12.8 to 17.3 mg/kg) and one placebo. The drugs were administered as single oral dose in conformity to a double-blind technique. Twenty-four hours after the drug intake the occurrence of untoward effects was investigated. Subsequently, it was disclosed whether the patients were treated with an active drug or with placebo. Those who received placebo were retreated either with praziquantel or oxamniquine, in accordance again with a randomized double-blind administration. Seventy-three cases, 36 in the praziquantel group 37 in the oxamniquine group, have concluded the six month period of parasitological follow-up. Monthly stool examination according to quantitative Kato-Katz and spontaneous sedimentation methods was performed. There was no statistical significant difference between the parasitological cure rates achieved with praziquantel (61.1%) and oxamniquine (54.0%). The main adverse reactions observed with the two active drugs were dizziness and gastrointestinal distress. The nature, intensity and duration of side-effects were similar for both praziquantel and oxamniquine as well as their frequency, 59.2% and 55.8% respectively, in contrast to the placebo group 20.6%. The clinical and laboratorial examinations performed on the next day following the drug intake did not reveal any abnormality in comparison to the findings prior to the treatment. This clinical trial has demonstrated the similarity between praziquantel and oxamniquine at the administered doses in regard to tolerance, toxicity and therapeutical efficacy in the treatment of schistosomiasis mansoni.

INTRODUCTION

Inspite of recent advances in the therapy of schistosomiasis, there are many unsolved questions like the availability of highly efficaceous, tolerable and unexpensive drugs suitable for mass treatment. The evidence of resistant strains of **S. mansoni** to antischistosome drugs means another drawback that is deserving the concern of investigators in this field [1,3,8,13].

Amongst the drugs used for treating schistosomiasis mansoni oxamniquine represents the main currently available chemotherapeutic agent. However, it does not entirely fulfil all requirements of an ideal antischistosome drug [4,5,14,17]. Consequently, it is necessary to continue the pursuit of further schistosomicide agents.

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Therein a new isoquinoline-pyrazine derivative, praziquantel, has shown low toxicity and activity against **S. mansoni** and other schistosome species pathogenic to man in several experimental investigations [9,10,18,21]. Moreover, such findings are being confirmed by promising results obtained in clinical trials on schistosomiasis haematobium, mansoni and japonicum [7,15,19].

In order to evaluate the therapeutical efficacy, tolerance and toxicity of praziquantel in comparison to oxamniquine we have designed this randomized, double-blind clinical trial, having a placebo control group to assess side-effects, with the ultimate scope of defining the prospects of this new drug in the therapy of schistosomiasis mansoni.

PATIENTS AND METHODS

A total of 101 patients coming from endemic areas and presenting chronic schistosomiasis mansoni, free from previous treatment, were included in the trial. Their age range varied from 10 to 65 years old (mean 29.7, median 31 and mode 26) and the bodyweight from 25 to 76 kg (mean 51.5, median 50 and mode 55). The diagnosis was based on positive stool examination for mature eggs of **Schistosoma mansoni** according to spontaneous sedimentation [11] and quantitative KATO-KATZ [12] methods — three slides for each method from three stool samples —. The number of eggs per gram of faeces was represented by the geometric mean.

On the day of treatment the patient was admitted to the hospital during 48 hours for clinical and laboratorial evaluation. Physical examination, complete blood count, fast glucose, creatinine, bilirubins, SGOT, SGPT, alkaline phosphatase, urinalysis and ECG were performed prior to and 24 hours after treatment to assess the drug toxicity.

The 101 patients were randomly allocated into three paralell groups, one received praziquantel — 45.4 mg/kg (41.2 to 51.6 mg/kg) —, one oxamniquine — 13.8 mg/kg (12.8 to 17.3 mg/kg) — and, one placebo. The drugs were administered as a single oral dose in conformity to a double-blind technique.

On the next day following the drug intake the patients were investigated for the occurrence of untoward effects. This investigation was carried out by the same physician in all cases. Subsequently, it was disclosed whether the patients have taken placebo or an active drug. Those who received placebo were retreated, either with praziquantel or oxamniquine, in accordance again with a randomized double-blind administration.

At the end 34 patients were treated with placebo, 49 with praziquantel and 52 with oxamniquine.

The criterion established for controlling the parasitological cure was based upon monthly stool examinations — Kato-Katz and spontaneous sedimentation methods (three slides for each method) — during a minimum period of six consecutive months following the treatment. A single positive finding meant a therapeutical failure.

The chi-square test was applied for the statistical analysis of the results accepting 5% as the limiting level of significance.

RESULTS

Therapeutical efficacy

A total of 73 patients, 59 adults and 14 children, have concluded the six month follow-up period of parasitological control and were evaluated regarding therapeutical efficacy. Their distribution between the two active drugs as to age range, sex and clinical form of the disease is shown in Table I.

The parasitological cure rates obtained with both drugs are demonstrated in Tables II and III. There was no statistical significant difference between the therapeutical efficacy of praziquantel, 61.1% (22/36) and oxamniquine 54.0% (20/37). All non-cured cases treated with praziquantel had a marked decrease in the number of **S. mansoni** eggs eliminated per gram of faeces whereas such reduction did not ocurred in two cases treated with oxamniquine.

The results concerning the age range and the worm burden also did not reveal any significant difference either within or in between the two treatment groups although there was a tendence to observe lower therapeutical efficacy amongst children. The parasitological cure achieved with praziquantel at different dose le-

TABLE I

Distribution of patients with schistosomiasis mansoni between the two treatment groups

Treatment group			Sex		Age		Clinical form		
Drugs	No. of cases	Dose (mg/kg)	M	F	C	A	I	HI	HE
Praziquantel	36	41.2 — 51.6	16	13	7	29	16	12	8
Oxamniquine	37	12.8 — 17.3	18	12	7	30	13	15	9
Total	73		34	25	14	59	29	27	17

M = male; F = female

C = children ($\leq$ 14 years old); A = adults ($>$ 14 years old)

I = intestinal; HI = hepatointestinal; HE = hepatosplenic

TABLE II

Parasitological cure rates according to the age groups

Age Groups	Praziquantel			Oxamniquine		
	Treated	Cured		Treated	Cured	
	No. of cases	No. of cases	(%)	No. of cases	No. of cases	(%)
Adults	29	19	**65.5**	30	17	**56.7**
Children	7	3	**42.8**	7	3	**42.8**
Total	36	22	**61.1**	37	20	**54.0**

TABLE III

Parasitological cure rates according to the number of eggs (geometric mean) per gram of faeces

No. of eggs per gram of faeces	Praziquantel			Oxamniquine		
	Treated	Cured		Treated	Cured	
	No. of cases	No. of cases	(%)	No. of cases	No. of cases	(%)
24 to 500	28	17	**60.7**	24	12	**50.0**
$>$ 501	8	5	**62.5**	13	8	**61.5**
Total	36	22	**61.1**	37	20	**54.0**

vels in adult patients, Table IV, (53.3% and 78.5% with 41.2 to 45.0 and 45.1 to 51.6 mg/kg respectively) was not statistically significant. Consequently no conclusion about dose levels could be reached with this limited number of cases.

TABLE IV

Parasitological cure rates obtained with praziquantel in adult patients according to the administered dose

Dose range (mg/kg)	Praziquantel		
	Treated	Cured	
	No. of cases	No. of cases	(%)
41.2 — 45.0	15	8	**53.3**
45.1 — 51.6	14	11	**78.5**
Total	29	19	**65.5**

Tolerance

The main adverse drug reactions in the three groups are presented in Table V. They were mostly of mild to moderate severity and subsided spontaneously within 6 to 12 hours after the drug intake. The occurrence of side-effects followed a similar pattern for both active drugs whilst the placebo group was practically devoided of adverse reactions. The physical examination performed in all patients on the next day following the treatment did not disclose any change in comparison to the initial examination.

Laboratorial data

No relevant alterations were detected on the laboratorial values in both treatment groups. As pointed out in Table VI the complete blood count and the serum biochemical determinations, before and 24 hours after drug administration, failed to demonstrate any abnormal findings, below or above the normal range, besides those already altered prior to the treatment. The electrocardiogram elicit only slight ventricular repolarization changes in one patient treated with praziquantel and in two with oxamniquine.

TABLE V

Side-effects observed within 24 hours following the administration of praziquantel, oxamniquine and placebo

Side-Effects	Praziquantel		Oxamniquine		Placebo	
	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)
Dizziness	23	46.9	23	44.2	6	17.6
Abdominal pain	12	24.5	6	11.5	—	—
Diarrhea	6	12.5	2	3.8	—	—
Nausea	4	8.2	3	5.8	—	—
Borborigmus	3	6.1	4	7.7	1	2.9
Vomiting	2	4.1	1	1.9	—	—
Headache	2	4.1	—	—	—	—
No side-effects	20	40.8	23	44.2	27	79.4
Total	72	100.0	62	100.0	34	100.0

TABLE VI

Laboratorial findings before and 24 hours after praziquantel and oxamniquine administration

Laboratorial findings	Number of patients			
	Praziquantel		Oxamniquine	
	Before	24 hours after	Before	24 hours after
Hemoglobin (g %)				
≤ 11	7	7	3	3
11.1 - 20.0	42	42	49	49
Hematocrit (%)				
≤ 36	2	2	5	4
37 - 54	47	47	45	48
≥ 55	0	0	2	0
Total leukocytes (mm^3)				
< 5 000	35	34	38	39
5 000 - 10 000	12	13	12	11
> 10 000	2	2	2	2
Eosinophiles (mm^3)				
< 100	12	15	14	14
100 - 400	5	4	4	1
> 400	32	30	34	37
Fast glucose (mg %)				
< 70	5	8	9	5
70 - 110	43	40	42	46
> 110	1	1	1	1
Creatinine (mg %)				
≤ 2	49	49	52	52
Total bilirubin (mg %)				
≤ 1.2	47	47	49	49
> 1.2	2	2	3	3
SGOT (U/ml)				
≤ 40	46	47	49	48
> 40	3	2	3	4
SGPT (U/ml)				
≤ 35	43	44	48	50
> 35	6	5	4	2
Alk. Phosphatase (mU/ml)				
15 - 69	39	39	40	42
> 69	10	10	12	10

DISCUSSION

Randomized double-blind comparative trials offer the most appropriate methodological design for providing reliable and consistent data on the therapeutical usefulness of drugs having same indications. At the current phase of the development of praziquantel for the treatment of schistosomiasis mansoni such clinical trial design in comparison to oxamniquine, a drug already extensively used in this indication, is fully justified.

Concerning the occurrence of adverse reactions to treatment, the side-effects were similar with regard to their nature, frequency, severity and duration for both active drugs. In the control group, initially treated with placebo, 79.4% of the cases had no complaint in contrast to 40.8% and 44.2% of those who received praziquantel and oxamniquine respectively. Dizziness and gastrointestinal distresses, like diarrhea and vomiting, were the most common untowards effects. These findings are in agreement with those refered by the medical literature [6,15,16,20]. Under praziquantel administration abdominal pain and diarrhea were two and three times more frequent than with oxamniquine but without statistical significance.

The difference in the therapeutical efficacy between praziquantel (61.1%) and oxamniquine (54.0%) was not statistically significant at the administered doses. BERTI [2], in Venezuela, reached the same conclusion on an open comparative trial.

The 61.1% cure rate achieved with praziquantel in our trial was lower than those refered by other Brazilian investigators administering 40 to 50 mg/kg: COUTINHO et al. [6] reported 82.9% in patients presenting the hepatosplenic form of the disease; KATZ et al. [16] 76.5% and SILVA et al. [20] 94.4% also in hepatosplenic cases.

Such discordance probably is due to the more strict parasitological control adopted in this trial (monthly stool examinations according to two different methods) because the majority of our patients had a relatively low worm load and were free from reinfection.

The same comments are applicable to the equally low cure rate, 54.0%, reached with oxamniquine but dosage could also have played a role since we have attained better therapeutical efficacy with this drug on a previous trial but using doses higher than 15 mg/kg [17].

The laboratorial evaluation did not reveal any relevant alterations with the two drugs confirming their low toxicity [4,5,6,14,16,17,20]. Concerning the slight increase in the SGOT, SGPT and alkaline phosphatase found in a few cases it was not possible to reach a conclusion about its meaning since in other cases these enzymes already augmented before treatment have either decreased or remained unchanged.

Taking into consideration these results we conclude that praziquantel and oxamniquine, at the administered doses, have low toxicity, good tolerance and reasonable cure rates. Perhaps the therapeutical efficacy of both drugs can be improved by using higher doses. Praziquantel, having different chemical, pharmacological and antiparasitic properties than oxamniquine and other schistosomicide agents represents an alternative for treating schistosomiasis mansoni, particularly the resistant cases to oxamniquine [1,8]. Further clinical trials, inclusively with higher doses, are still required for a more definitive conclusion about the real position of praziquantel in the treatment of schistosomiasis mansoni.

RESUMO

Estudo duplo-cego comparando praziquantel e oxamniquine no tratamento de pacientes com esquistossomose mansônica

Cento e um pacientes, portadores de esquistossomose mansônica em fase ativa, foram distribuídos, aleatoriamente, em três grupos: um recebeu praziquantel (41,2 a 51,6 mg/kg), um oxamniquine (12,8 a 17,3 mg/kg) e um placebo. Os medicamentos foram administrados em dose única por via oral, segundo técnica duplo cega.

A avaliação da ocorrência de efeitos colaterais era realizada 24 horas após o tratamento. Em seguida identificava-se se os pacientes haviam recebido medicação ativa ou placebo. Os tratados com placebo retornaram ao estudo, sendo retratados com praziquantel ou oxamniquine, novamente, segundo uma administração duplo-cega.

Setenta e três pacientes, 36 no grupo medicado com praziquantel e 37 com oxamniquine, completaram o período de seis meses de controle parasitológico. Exames mensais de fezes, pelos métodos quantitativo de Kato-Katz e sedimentação espontânea. Não houve diferença estatisticamente significativa entre as porcentagens de cura parasitológica obtidas com praziquantel (61,1%) e com oxamniquine (54,0%).

Os principais efeitos colaterais observados nos pacientes que receberam medicação ativa foram: tonturas e distúrbios gastrintestinais. A natureza, intensidade e duração dos paraefeitos foram semelhantes com praziquantel e oxamniquine, bem como a freqüência, respectivamente, 59,2 e 55,8%, contrastando com 20,6% no grupo placebo.

Os resultados do exame clínico e das provas laboratoriais, no dia seguinte após o tratamento, não evidenciaram, em ambos os grupos que receberam medicação ativa, alterações, quando confrontados com os achados anteriores à terapêutica.

O presente estudo demonstrou semelhança entre o praziquantel e a oxamniquine, nas doses empregadas, em relação à tolerância, toxicidade e eficácia terapêutica.

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