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CLINICAL TRIALS WITH PRAZIQUANTEL IN SCHISTOSOMIASIS MANSONI

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SUMMARY

One hundred and thirty-eight individuals with active schistosomiasis mansoni were treated as out-patients with praziquantel. In all cases, viable **Schistosoma mansoni** eggs were obtained by quantitative Kato-Katz technique and hatching test. The trial was conducted as a single randomized blind study. The stratification was based on the geometric mean value of 3 pre-treatment egg counts, the patients being assigned to one of the following strata: Stratum I = 95-500 eggs per gram; Stratum II = 501-1,000; Stratum III = over 1,000. To each stratum, the following 3 dosage schemes were equally alloted at random: 30 mg/kg body weight as single dose; 40 mg/kg, single dose and 25 mg/kg, twice a day at a 6-hour interval. The main side effects were from the gastro-intestinal (abdominal distress, diarrhoea, nauseas) and the psychoneurological fields (dizziness, headache, somnolence), and the intensity was from mild to moderate with a duration from 24 to 48 hours. No difference was observed between adults and children, nor with the three different therapeutical schemes employed. Complementary tests performed before and 24 hours later, did not reveal any important toxicity effects of the drug. The parasitological cure rate was of 56.1% with the dosage of 30 mg/kg, and 78.0 and 75.0% with 40 mg/kg and 50 mg/kg in two doses, respectively. Children presented lower cure rates than adults, although the difference was only statistically significant at 0.10 level. The cure rate in the three strata was similar. Praziquantel seems to have high schistosomal activity and low toxicity; nevertheless, further increase in the number of treated patients is necessary before final conclusion can be reached of its real value as a schistosomicidal drug.

INTRODUCTION

Praziquantel (Embay 8440), a new schistosomicidal drug, is a derivative of a new heterocyclic system, an isochinolin-pyrazin derivative (2-Cyclohexilcarbonyl-1,3,4,6,7, 11b (hexahydropyrazino 2,1-a isoquinolin-4-one).

Laboratory studies conducted on many animal species demonstrated praziquantel to be highly effective against all schistosome species pathogenic to man [1-4].

After pharmacological and toxicological studies (including teratogenicity, embryotoxicity and mutagenicity), as well as experiments carried out on healthy volunteers by the drug manufacturers [5], KATZ et al. [6] performed the first clinical trials on adult patients with **Schistosoma mansoni** infection. A hundred and sixteen individuals were treated with praziquantel or placebo (double-blind test) at different schedules: one, two or three doses of 20 mg/kg and a single dose of 50 mg/kg. The side effects induced by the highest doses were especially observed in the gastro-intestinal and psychoneurological

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fields, such as nausea, epigastric distress, headache, dizziness, drowsiness, etc. They varied in intensity from mild to moderate, and disappeared 24 to 48 hours after drug administration. Complementary tests did not show significant alterations, except those regarding electroencephalographic tracings, which led to no conclusion. Over 90% of the patients treated with the higher doses were considered as cured.

This paper presents further data from clinical and laboratory follow-up of chronic **S. mansoni** patients treated with praziquantel.

PATIENTS AND METHODS

Patients and treatment — One hundred and thirthy-eight individuals with active schistosomiasis mansoni were treated as out-patients in the Parasitosis Section of the Municipal Secretary of Health, Belo Horizonte. The number of patients, the age groups, sex, clinical form of the disease and schedules of treatment are shown in Table I. In all cases, viable **S. mansoni** eggs were obtained by quantitative Kato-Katz technique [7] and hatching test [8]. The trial was conducted as a single randomized blind study. The stratification was based on the geometric mean value of 3 pre-treatment egg counts, the patients being assigned to one of the following strata: Stratum I = 95-500 eggs per gram; Stratum II = 501-1,000; Stratum III = over 1,000. To each stratum, the following 3-dosage schemes were equally alloted at random: 30 mg/kg body weight as single dose, 40mg/kg, single dose, and 25 mg/kg, twice a day. The drug was orally administered in the form of 400 mg tablets. A 6 hour interval was observed between the doses, and the tablets were swallowed down with some liquid and food.

TABLE I

Schedule of treatment, number of patients, age groups, sex and clinical forms in patients treated with praziquantel

Schedule (mg/kg X dose)	Number of treated patients	Age		Sex		Clinical form		
		Adults	Children	Male	Female	Intestinal	Hepatointestinal	Hepatosplenic
30 x 1	47	18 (15-40)	29 (08-14)	42	5	45	2	0
40 x 1	45	7 (15-42)	38 (08-14)	41	4	43	1	1
25 x 2	46	16 (15-48)	30 (05-14)	38	8	41	4	1

( ): range of age

Laboratory monitoring tests, haemogram, serum bilirubin, serum aspartate aminotransferase (SGOT), serum alamine aminotransferase (SGPT), serum alkaline phosphatase, urea and creatinine, urinalysis and electrocardiography were all performed once, before treatment and, then, 24 hours after drug administration.

Assessment of drug activity — The evaluation of praziquantel activity was based on 3 consecutive daily stool examination by Kato-Katz quantitative technique (two slides from each stool sample) plus 3 hatching tests on daily stools. Follow-up examinations were performed at 1, 3 and 6 months after treatment. Patients were considered as cured when no **S. mansoni** eggs or miracidia were detected in their feces for a 6-month period of follow-up.

Statistical analysis — X^2 test was performed taking into consideration a 0.05 significance level.

RESULTS

Tolerance — The main side effects (reported or observed) regarding the different schedules employed are shown in Tables II, III and IV. In general, the side effects were of mild-to-moderate intensity, most of them having disappeared 24 hours later and, others, within 48 hours after drug ingestion. No differences were observed between the side effects in the 3 groups of patients nor between tolerance by adults and children.

Complementary tests — The data provided by laboratory tests are shown in Tables V, VI and VII. Two the patients treated with a single dose of 30 mg/kg presented a significant increase in the total number of leucocytes (from 8,400 to 13,700 and from 8,100 to 12,000 cells/mm^3). In one patient there was also detected an increase of indirect bilirubin (from 0.3 to 1.2).

T A B L E II

Side-effects observed in patients treated with praziquantel, single oral dose of 30 mg/kg

Side-effects	Adults		Children		Total	
	On the day	24 hs	On the day	24 hs	On the day	24 hs
Abdominal distress	6 (33)	0 (0)	14 (48)	1 (3)	20 (43)	1 (2)
Diarrhoea	6 (33)	0 (0)	5 (17)	0 (0)	11 (23)	0 (0)
Headache	3 (17)	2 (11)	7 (24)	4 (14)	10 (21)	6 (13)
Giddiness	4 (22)	0 (0)	3 (10)	0 (0)	7 (15)	0 (0)
Drowsiness	2 (11)	0 (0)	1 (3)	0 (0)	3 (6)	0 (0)
Nausea	0 (0)	0 (0)	2 (7)	0 (0)	2 (4)	0 (0)
Bitter taste	1 (6)	0 (0)	1 (3)	0 (0)	2 (4)	0 (0)
Asthenia	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (2)
Number of patients with side-effects/treated	15/18 (83)		22/29 (76)		37/47 (79)	

( ): percentage

T A B L E III

Side-effects observed in patients treated with praziquantel, single oral dose of 40 mg/kg

Side-effects	Adults		Children		Total	
	On the day	24 hs	On the day	24 hs	On the day	24 hs
Abdominal distress	3 (43)	0 (0)	17 (45)	5 (13)	20 (44)	5 (11)
Giddiness	1 (14)	0 (0)	11 (29)	0 (0)	12 (27)	0 (0)
Diarrhoea	2 (20)	0 (0)	2 (5)	0 (0)	4 (9)	0 (0)
Headache	1 (14)	0 (0)	1 (3)	3 (8)	2 (4)	3 (7)
Drowsiness	0 (0)	0 (0)	2 (5)	0 (0)	2 (4)	0 (0)
Urticariform reaction	1 (14)	0 (0)	1 (3)	0 (0)	2 (4)	0 (0)
Vomiting	0 (0)	0 (0)	2 (5)	0 (0)	2 (4)	0 (0)
Bitter taste	1 (14)	0 (0)	1 (3)	0 (0)	2 (4)	0 (0)
Anorexia	0 (0)	0 (0)	1 (3)	0 (0)	1 (2)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (2)
Number of patients with side-effects/treated	4/7 (57)		28/38 (74)		32/45 (71)	

( ): percentage

T A B L E IV

Side-effects observed in patients treated with 25 mg/kg bid of praziquantel

Side-effects	Adults		Children		Total	
	On the day	24 hs	On the day	24 hs	On the day	24 hs
Abdominal distress	7 (44)	3 (19)	15 (50)	3 (10)	22 (48)	6 (13)
Headache	4 (25)	1 (6)	8 (27)	5 (17)	12 (26)	6 (13)
Giddiness	8 (50)	0 (0)	4 (13)	2 (7)	12 (26)	2 (4)
Diarrhoea	2 (13)	1 (6)	4 (13)	1 (3)	6 (13)	2 (4)
Nausea	1 (6)	1 (6)	1 (3)	0 (0)	2 (4)	1 (2)
Urticariform reaction	2 (13)	1 (6)	0 (0)	0 (0)	2 (4)	1 (2)
Number of patients with side-effects/treated	13/16 (81)		25/30 (83)		38/46 (83)	

( ): percentage

Among the patients treated with 40 mg/kg (single dose), 6 cases showed and increase in the number of leucocytes and, 2 in the total bilirubin amount (from 0.9 to 1.2 and 1.0 to 1.5, respectively). As regards treatment with 2 doses of 25 mg/kg (total dose of 50 mg/kg), 2 patients presented an increase in the number of leucocytes and one, in the amount of indirect biliru-

T A B L E V

Laboratory tests results of patients treated with praziquantel, single oral dose of 30 mg/kg

Tests	Before treatment Mean (range)	After treatment Mean (range)
HAEMATOLOGY		
Haemoglobin	12.65 (8.90 — 17.60)	12.67 (7.60 — 18.40)
Haematocrit	43.02 (34 — 53)	43.33 (34 — 54)
Erythrocyte count	4.843.000 (4.200.000 — 5.800.000)	4.788.000 (4.200.000 — 5.900.000)
Leucocyte count	8.580 (5.000 — 15.000)	8.617 (5.000 — 18.000)
Neutrophile	47.15 (28 — 71)	56.91 (25 — 79)
Eosinophile	13.51 (3 — 28)	10.41 (2 — 33)
Basophile	0.13 (0 — 1)	0.15 (0 — 2)
Lymphocyte	33.94 (21 — 58)	27 — 59 (10 — 65)
Monocyte	5.26 (1 — 10)	4.93 (1 — 11)
BIOCHEMISTRY		
SGPT	13.11 (5 — 31)	12.80 (6 — 42)
SGOT	19.94 (8 — 47)	19.63 (7 — 47)
Bilirubin indirect	0.35 (0.10 — 0.60)	0.40 (0.20 — 1.20)
Bilirubin total	0.59 (0.20 — 1.00)	0.64 (0.40 — 1.50)
Alkaline phosphatase	7.46 (1.20 — 17.00)	7.33 (2.00 — 13.00)
BUN	20.56 (11.70 — 35.00)	20.82 (12.00 — 36.00)
Creatinine	0.61 (0.40 — 0.80)	0.71 (0.40 — 0.98)

T A B L E VI

Laboratory tests results of patients treated with praziquantel, single oral dose of 40 mg/kg

Tests	Before treatment Mean (range)	After treatment Mean (range)
HAEMATOLOGY		
Haemoglobin	12.38 (9.50 — 16.80)	12.44 (9.50 — 16.80)
Haematocrit	42.47 (35 — 54)	42.38 (36 — 51)
Erythrocyte count	4.780.000 (4.200.000 — 5.700.000)	4.779.000 (4.240.000 — 5.800.000)
Leucocyte count	8.072 (5.000 — 12.500)	9.446 (5.000 — 17.500)
Neutrophile	66.1 (27 — 72)	58.86 (17 — 75)
Eosinophile	15.22 (5 — 42)	15.32 (2 — 58)
Basophile	0.36 (0 — 2)	0.23 (0 — 2)
Lymphocyte	33.30 (16 — 46)	25.52 (11 — 43)
Monocyte	4.98 (1 — 10)	5.05 (1 — 11)
BIOCHEMISTRY		
SGPT	12.40 (5 — 26)	12.00 (5 — 30)
SGOT	19.08 (6 — 40)	18.84 (8 — 40)
Bilirubin indirect	0.34 (0.20 — 0.60)	0.38 (0.20 — 0.90)
Bilirubin total	0.57 (0.40 — 1.00)	0.62 (0.30 — 1.50)
Alkaline phosphatase	10.02 (3.1 — 19.2)	10.01 (1.8 — 19.8)
BUN	21.49 (12.0 — 42.0)	19.2 (10.0 — 36.0)
Creatinine	0.59 (0.40 — 0.90)	0.64 (0.40 — 0.98)

bin (from 0.9 to 1.4). Other biochemical tests, as well as urinalysis, did not reveal any alterations of clinical importance. Electrocardiographic tracings from some patients displayed inversion or flattening of T waves, always in isolated leads and, probably, with no clinical significance either.

Therapeutic results — The therapeutic results provided by praziquantel are shown in Tables VIII and IX. With 30 mg/kg, the cure rate was 56.1% and, with 40 mg/kg and 2 x 25 mg/kg, 78.0 and 75.0, respectively. Although with the three schedules of treatment above, children presented lower cure rates than adults, the difference between them did not prove to be statistically significant (Table VIII). In the feces of non-cured patients it was observed a decrease of more than 90% in the number of **S. mansoni** eggs.

Considering the three strata concerning the number of **S. mansoni** eggs, we can see that, as far as cure rate is concerned (Table IX), no difference is observed.

TABLE VII

Laboratory tests results of patients treated with 25 mg/kg bid of praziquantel

Tests	Before treatment Mean (range)	After treatment Mean (range)
HAEMATOLOGY		
Haemoglobin	12.65 (10.00 — 17.60)	12.59 (8.80 — 17.60)
Haematocrit	42.61 (35 — 52)	42.50 (36 — 53)
Erythrocyte count	4.875.650 (3.800.000 — 5.700.000)	4.862.610 (4.000.000 — 6.700.000)
Leucocyte count	8.300 (4.000 — 12.500)	8.549 (4.000 — 14.300)
Neutrophile	49.13 (24 — 66)	55.96 (20 — 84)
Eosinophile	12.30 (5 — 36)	11.28 (3 — 37)
Basophile	0.28 (0 — 2)	0.04 (0 — 1)
Lymphocyte	33.2 (10 — 45)	27.87 (11 — 52)
Monocyte	4.98 (1.10)	4.63 (2 — 10)
BIOCHEMISTRY		
SGPT	12.50 (6 — 30)	12.52 (6 — 50)
SGOT	21.15 (9 — 47)	19.96 (9 — 60)
Bilirubin indirect	0.39 (0.20 — 1.20)	0.41 (0.20 — 1.50)
Bilirubin total	0.65 (0.30 — 1.50)	0.66 (0.30 — 2.00)
Alkaline phosphatase	7.43 (3.00 — 15.3)	8.74 (2.80 — 13.20)
BUN	22.00 (13.0 — 34.0)	19.05 (12.0 — 35.0)
Creatinine	0.61 (0.40 — 0.88)	0.67 (0.30 — 1.00)

TABLE VIII

Parasitological results of patients treated with different schedules of praziquantel

Schedule (mg/kg X dose)	Age	Number of patients			% of eggs reduction
		Treated	Followed-up	Cured (%)	
30 x 1	Adults	18	13	9 (69.2)	98.4
	Children	29	28	14 (50.0)	93.2
	Total	47	41	23 (56.1)	92.5
40 x 1	Adults	7	7	6 (85.7)	99.7
	Children	38	34	26 (76.4)	97.3
	Total	45	41	32 (78.0)	97.7
25 x 2	Adults	16	12	11 (91.7)	99.5
	Children	30	28	19 (67.8)	93.0
	Total	46	40	30 (75.0)	95.1

TABLE IX

Parasitological results of patients treated with praziquantel and different worm burdens

Schedule (mg/kg X dose)	Stratum +	Number of patients			% of eggs reduction
		Treated	Followed-up	Cured (%)	
30 x 1	I	15	14	7 (50.0)	89.6
	II	16	13	6 (46.1)	96.6
	III	16	14	10 (71.4)	98.5
40 x 1	I	15	13	11 (84.6)	99.3
	II	15	13	12 (92.3)	99.6
	III	15	15	9 (60.0)	94.6
25 x 2	I	15	13	10 (76.9)	91.9
	II	15	12	8 (66.6)	98.9
	III	16	15	12 (80.0)	94.8

+ : I = 95 — 500 eggs per gram of feces
II = 501 — 1.000 eggs per gram of feces
III = 1.000 eggs per gram of feces

Four patients considered cured (judging from parasitological control performed 6 months after treatment) were, nevertheless, found out to be still eliminating **S. mansoni** eggs, in the lst and 3rd month follow-up examinations.

DISCUSSION

The data herein presented, allow the confirmation of praziquantel affording good tolerability, low toxicity and high parasitological activity.

As already mentioned in our previous paper [6], the most frequent side-effects observed were from the gastro-intestinal and psychoneurological symptoms, such as abdominal distress, diarrhoea, headache and dizziness. A significant difference, however, was that only few ambulatorially treated patients reported drowsiness, in opposition to what was reported by the in-patients. An important sign needing further studies was the occurrence of urticaria just a few hours after drug ingestion. When comparing the number of patients (adults or children) presenting side effects with the dosages employed, no significant difference could be observed.

Likewise, complementary tests did not reveal any important toxicity effects of the drug.

Good therapeutical activity has been observed especially with dosages of 40 mg/kg and 2 x 25 mg/kg, seeing that about 75% of the patients were considered as cured, and the remaining ones having presented a decrease of over 90% in the number of **S. mansoni** eggs in their feces.

In our first trial using 3 x 20 or 1 x 50 mg/kg, over 90% of cure was detected. Although being difficult to explain the less favourable results of the present trial, one can hypothetized that they may have been due to different age groups. In our preliminary trial all patients were adults whereas, in the present one, about three times more children were treated and followed up. The total percentage of cure was 81.2 for adults and 65.5 for children, such difference being only significant at $p=0.10$.

Summing up, it can be said that praziquantel is an effective drug for clinical management of schistosomiasis mansoni infection, although further increase in the number of treated patient be necessary before final conclusion can be reached.

RESUMO

Ensaios clínicos com praziquantel na esquistossomose mansoni

Cento e trinta e oito pacientes com esquistossomose ativa foram tratados com praziquantel em ambulatório. Em todos os casos, ovos viáveis de **S. mansoni** foram diagnosticados pela técnica quantitativa de Kato-Katz e pelo teste de eclosão de miracídeos. O ensaio foi "cego" e randomizado. Os pacientes foram distribuídos em 3 grupos, de acordo com a média geométrica do número de ovos de **S. mansoni** por grama de fezes obtidos em 3 exames parasitológicos de fezes, a saber: **Grupo I** — 95-500 ovos por grama; **Grupo II** — 501-1.000; **Grupo III** — mais de 1.000. Em cada grupo com o mesmo número de pacientes, os seguintes esquemas terapêuticos foram utilizados: 30 mg/kg ou 40 mg/kg (doses únicas) e 25 mg/kg, duas doses com intervalo de 6 horas (dose total: 50 mg/kg). Os principais efeitos colaterais foram da área gastrointestinal (dores abdominais, diarreia, náusea) e da área neuro-psíquica (tontura, cefaléia, sonolência) sendo de intensidade leve a moderada e de duração de 24 a 48 horas. Não foram observadas diferenças significativas na freqüência de efeitos colaterais nos esquemas terapêuticos empregados, sendo a tolerância também semelhante entre adultos e crianças. Os exames de laboratório, realizados antes e 24 horas após, não revelaram efeitos tóxicos importantes da droga.

A cura parasitológica foi de 56,1% com a dosagem de 30 mg/kg, e de 78,0 e 75,0% com as de 40 mg/kg e 50 mg/kg, respectivamente. O porcentual de cura em crianças foi menor do que em adultos, embora esta diferença só tenha sido estatisticamente significativa ao nível de 0,10. Em relação aos grupos com diferentes médias geométricas do número de ovos de **S. mansoni** nas fezes, também não houve diferença significativa quanto ao porcentual de cura.

O praziquantel parece ter boa atividade esquistossomicida e baixa toxicidade, necessitando porém de uma casuística maior, antes que se possa chegar a conclusão final acerca de seu valor no arsenal terapêutico da esquistossomose.

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