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ASSESSMENT OF OLTIPRAZ IN SCHISTOSOMIASIS MANSONI CLINICAL TRIAL

Naftale KATZ, Roberto S. ROCHA and Adelú CHAVES

SUMMARY

Seventy three children (6-15 years) and 75 adults (18-47 years) with active schistosomiasis mansoni were treated with oltipraz. All cases had at least 100 eggs per gram of feces as determined by the Kato-Katz technique. Children and adults were divided in two groups receiving respectively 25 or 30 mg/kg, as a single oral dose. Clinical examination, laboratories tests (haemogram, urinalysis, hepatic and kidney functions tests, glycemia, cholesterol, triglicerides, lipoprotein — HLD and LDL) and ECG were performed before, 3 or 7 days and 1 month after treatment. Parasitological control with 3 daily coprological examinations, was done on the 1st, 3rd, 6th month after drug administration. Giddiness, somnolence, headache, nausea, vomiting and abdominal distress were the most frequent side effects. Pain in the finger tips that need further investigations also occurred. No significant alteration in complementary tests were observed, whereas eosinophilia 1 month after treatment was detected, probably indicating worm death. The cure rate in children was 81.8% and 74.2% with 25 and 30 mg/kg respectively, and in adults 75.0% and 81.2% of the patients. No statistical significant difference was observed between cure rate and side effects at different dosages employed, neither between adults nor children. In all groups the percentage of egg reduction in feces in the non cured patients was higher than 96.0%. Further investigation with this new compound is necessary to accomplish the real value of oltipraz in the schistosomiasis chemotherapy.

INTRODUCTION

Oltipraz [4-methyl-5-(2-pyrazinyl)-3H-1,2-dithiole-3-thione] synthetized at Rhone Poulenc Laboratories has shown good tolerance and efficacy in the treatment of **Schistosoma mansoni, S. haematobium** and **S. intercalatum** infection [1,2,3,7].

Preliminary clinical trials in schistosomiasis mansoni infection carried out in Brazil by KATZ et al. [6] demonstrated that oltipraz was well tolerated and active. In fact, side-effects presented by patients treated with different dosages (10, 20, 25 or 30 mg/kg) were unfrequent and of light intensity. Laboratory tests showed only eosinophilia 1 month after treatment, and no significant alterations has been found in haemogram, urinalysis, liver function tests, blood urea nitrogen (BUN), creatinine, glycemia, ECG's and EEG's tracings. The cure rate increased with the dosage, and it has been 80% and 100% with 25 and 30 mg/kg, respectively.

In this paper further data from clinical and laboratory follow-up of chronic **S. mansoni** patients (adults and children) treated with oltipraz (25 and 30 mg/kg) are presented.

Work carried out at Centro de Pesquisas "René Rachou" — FIOCRUZ and supported in part, by grant from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil. Address for reprints: NAFTALE KATZ, Caixa Postal 1.743, 30.000 — Belo Horizonte, MG, Brasil

MATERIAL AND METHODS

Patients and treatment — Seventy-three children and 75 adults with active schistosomiasis mansoni were treated as out-patients.

Number of treated cases, schedule of treatment, age, sex, arithmetical mean of **S. mansoni** eggs and clinical form of the disease are shown in Table I.

TABLE I

Schedule of treatment, number of patients, AGE, arithmetical mean of **S. mansoni** EGGS before treatment, sex and clinical form in patients treated with single oral dose of oltipraz

Schedule	Number of treated cases	Mean age (range)	Arithmetical mean of **S. mansoni** eggs before treatment	Sex		Clinical form	
				Male	Female	Intestinal	Hepatointestinal
25 mg/kg	37	12 (08 — 15)	460	28	9	32	5
	40	24 (16 — 47)	488	34	6	38	2
30 mg/kg	36	13 (08 — 15)	490	26	10	30	6
	35	24 (17 — 47)	362	28	7	37	2

The cases were diagnosed by three quantitative Kato-Katz technique[5] and all cases had at least 100 eggs per gram of feces.

Oltipraz (500 mg and 100 mg tablets) was administered with some milk, coffee and bread as a single oral dose.

In all patients the following laboratory examinations were carried out before, 3 days (in 60% of the patients) or 7 days (in the others 40%), and 1 month after treatment: haemogram, urinalysis, hepatic-function tests [bilirubin, serum asparte aminotransferase (SGOT), serum alanine aminotransferase (SGPT), alkaline phosphatase], blood-urea nitrogen (BUN), creatinine and glicose.

In at least 10 patients of each group, cholesterol, triglicerides, lipoprotein HLD an LDL were performed before and 3 or 7 days after treatment.

Electrocardiogram was performed before and 3 or 7 days after drug administration.

Assessment of drug activity — The evaluation of chemotherapeutic activity was based on 3 daily consecutive stool examination (2 slides from each stool sample), performed on the 1st, 3rd and 6th month after drug administration. The coprological examinations were performed according to the quantitative Kato-Katz technique.

Patients were considered as cured when no eggs were found in their feces in the follow-up period.

Statistical analysis — The chi-square (X^2) test was performed and the significance level of 5% was considered.

RESULTS

The main side effects reported or observed are shown in Table II. They were of light to moderate intensity and disappeared 24-48 hours after drug ingestion. No significant difference was observed between side effects at different dosages employed, neither between adults nor children. In the data provided by laboratory tests, no alteration but eosinophilia at 1 month after treatment, were found.

Inversion or flattening of T waves were the alterations found always in isolated leads, in electrocardiograms, and probably with no clinical significance.

The therapeutical activity of oltipraz was good with the two dosages as can be seen in Table III.

In fact, with 25 mg/kg the cure rate was 81.8% in children and 75.0% in adults. With 30 mg/kg 74.2% and 81.2% of children and adults respectively, were considered as cured, with no statistical significance between them. Moreover, the percentage of egg reduction in the feces of non cured patients was higher than 96%.

TABLE II
Side-effects observed in patients treated with different schedules of oltipraz

Side-effects	Children		Adults	
	25 mg/kg	30 mg/kg	25 mg/kg	30 mg/kg
Somnolence	11 (29.7)	10 (27.8)	9 (22.5)	7 (19.4)
Giddiness	8 (21.6)	10 (27.8)	14 (35.0)	7 (19.4)
Pain in the extremities	6 (16.2)	12 (33.3)	6 (15.0)	7 (19.4)
Nausea	4 (10.8)	8 (22.2)	9 (22.5)	5 (13.8)
Vomiting	2 (5.4)	4 (11.1)	1 (2.5)	0
Headache	2 (5.4)	7 (19.4)	6 (15.0)	3 (8.3)
Abdominal pain	1 (2.7)	6 (16.7)	7 (17.5)	7 (19.4)
Diarrhoea	0	5 (13.9)	4 (10.0)	0
Asthenia	0	3 (8.3)	5 (12.5)	0
Bitter taste	1 (2.7)	0	1 (2.5)	0
Anorexia	0	0	1 (2.5)	0
Number of patients with side-effects/treated	26/37 (70.3)	30/36 (83.3)	29/40 (72.5)	23/35 (65.7)

( ): percentagem

TABLE III
Parasitological results of patients treated with different schedules of oltipraz

Schedule (mg/kg X dose)	Age group	Number of patients			% of eggs reduction
		Treated	Followed-up	Cured (%)	
25 X 1	Children	37	33	27 (81.8)	98.6
	Adults	40	36	27 (75.0)	96.5
30 X 1	Children	36	35	26 (74.2)	96.0
	Adults	35	32	26 (81.2)	98.9

DISCUSSION

The data herein presented confirm previous results with oltipraz that showed good therapeutical activity and low toxicity.

The most frequent side effects observed were from the gastro-intestinal (nausea, vomiting, abdominal pain) or psyconeurological field (giddiness, somnolence, headache). All side effects were of mild to moderate intensity with duration of 24 to 48 hours, and associated medication was not necessary. No significant difference was found in the frequency of side effects between children and adults, nor between the two dosages employed.

Trials carried out in Africa and France by RICHARD-LENOBLE et al.[7], GENTILINI et al.[3], COULOUD et al.[2], CERF et al.[1], showed that tolerance with this drug was similar to that found in Brazil although dosages used was sometimes three to four times higher.

It is worthwhile to mention that pain in the extremities were observed in about 20% of the treated patients. It was an intense and persistent pain, most frequent in the finger tips, without visible modification of the local colour, temperature, sensitivity or morphology. This symptom was also described by KARDANAN et al.[4] in a field trial in Gezira when 32.6% of school children treated with 20 mg/

kg in a single oral dose claimed pain at finger tips. RICHARD-LENOBLE et al.[7] treating **S. intercalatum** in Gabon found that 5 cases claimed extremities paresthesia in a total of 30 persons treated. Further investigation about the mechanism of this pain is necessary for a better understanding of this undesirable effect.

An increase of eosinophilia count one month after treatment was the only alteration found in laboratory tests, and probably indicates worm death.

Electrocardiograms and other laboratory tests did not display any significant abnormality of clinical importance.

The assessment of therapeutical efficacy reveled a good activity (about 80%) in both groups of adults or children, being the percentage of egg count reduction in the non cured patients higher than 96%.

Summing up, one may conclude that oltipraz in Brazil at the dosage of 25 or 30 mg/kg presents good tolerance and efficacy. It is necessary however, further clinical trials with new compound to reach its real value in the schistosomiasis mansoni chemotherapy.

RESUMO

Avaliação do oltipraz na esquistossomose mansônica. Ensaio clínico.

Setenta e três crianças (6 a 15 anos) e 75 adultos (18-47 anos) com esquistossomose mansoni foram tratados com oltipraz. O diagnóstico foi feito através do exame parasitológico quantitativo de Kato-Katz e só os pacientes com 100 ou mais ovos por grama de fezes foram admitidos no ensaio.

Crianças e adultos foram divididos em dois grupos cada, os quais eram tratados com 25 ou 30 mg/kg em dose única oral.

Exame clínico, testes de laboratório (hemograma, urina rotina, funções hepática e renal, glicose, colesterol, triglicéridas, lipoproteínas HLD e LDL) e eletrocardiograma foram realizados antes, três ou sete dias e um mês após o tratamento. O controle parasitológico foi realizado com três exames de fezes em dias consecutivos no 1.°, 3.° e 6.° mês após o tratamento.

Tontura, sonolência, cefaléia, náusea, vômitos e dor abdominal foram os efeitos colaterais mais encontrados, bem como "dor nas extremidades" principalmente nos dedos, um sintoma que necessita novos estudos.

Não houve alterações nos exames de laboratório a não ser eosinofilia um mês após o tratamento, o que indica provavelmente, a morte de vermes.

O índice de cura nas crianças foi de 81,8% e 74,2% com 25 ou 30 mg/kg respectivamente, enquanto nos adultos com 25 mg/kg, 75,0% dos pacientes foram considerados curados e com 30 mg/kg 81,2%. Não houve diferença estatística no que se refere a cura e efeito colateral, quando comparado com as doses usadas, nem entre adultos e crianças.

Em todos os grupos a porcentagem de redução do número de ovos nas fezes foi maior que 96,0% nos pacientes não curados.

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