

DOSE-RANGING CLINICAL TRIAL WITH OLTIPRAZ IN SCHISTOSOMIASIS MANSONI

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SUMMARY

There has been performed a dose-ranging trial with oltipraz in *S. mansoni* infected patients. Four groups of 6 patients each received 10, 20, 25 or 30 mg/kg, single oral dose, of oltipraz, and another group of 7 patients received oxamniquine, 15 mg/kg, as a single oral dose. Side effects with oltipraz were rare and of light intensity. Laboratory tests showed only eosinophilia 1 month after treatment. No significant alterations has been found in haemogram, urinalysis, liver function tests, creatinine, urea, glycemia, ECG's and EEG's tracings. Parasitological control (quantitative stool examinations by the Kato-Katz technique) performed 1 and 4 months after treatment showed a cure rate of 16.7%, 40.0%, 80.0% and 100% with the dosages of 10, 20, 25 and 30 mg/kg of oltipraz, respectively. Oxamniquine (15 mg/kg) produced 66.7% of cure. With all schedules, the percentage of egg count reduction in the non-cured patients was around 90%. Further clinical trials with oltipraz, this very promising drug, should be persued.

INTRODUCTION

Oltipraz (35.972 R.P.) is a synthetic drug (4-methyl-5-(2-pyrazinyl)-3H-1, 2-dithiole-3-thione) (Fig. 1), synthesized at Rhone-Poulenc Laboratories, whose antischistosomal properties were determined in mice and monkeys (*Maca-ca mulatta*) infected with *Schistosoma mansoni*^{4,5}. Toxicological studies in laboratory animals, reveal oltipraz to be a low toxic drug, and preliminary teratogenic, embriotoxic, and mutagenic studies giving negative results⁵.

Clinical trials in *S. mansoni*, *S. haematobium* and *S. intercalatum* infections performed in France and in some African countries by GENTILINI et al.² showed oltipraz to be very active. In fact, using 2 to 7.5 g (over 1 to 5 days) in human *S. haematobium* infection the percentage of cure in 86 patients was about 90%; in *S. intercalatum* in 72 patients (1.25 to 4.5 g over 3 days) the cure rate was 87%, and

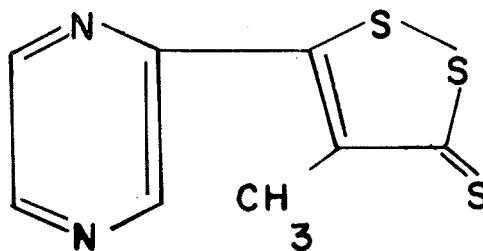


Fig. 1 — Chemical structure of oltipraz

in *S. mansoni* in 47 patients who received a total dose, ranging from 3 to 5 g over 2 to 5 days, 100% cure. The most frequent side effects were nausea, vomiting, abdominal pain, headache and extremity parestesias. Laboratory tests showed increased eosinophilia, and transient slight elevations of transaminases and alkaline phosphatase levels. Similar results were obtained by WOEHRLE et al.⁶ in 77 patients infected

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either with *S. mansoni*, *S. intercalatum* or *S. haematobium* after treatment with doses of 1.0 or 1.5 g three times daily.

This paper presents the data from clinical and laboratory follow-up of chronic *S. mansoni* patients in Brazil treated with oltipraz in a dose-ranging trial.

PATIENTS AND METHODS

Patients and treatment — Thirty-one adults with active schistosomiasis mansoni were treat-

ed as in-patients at the Hospital Evangélico, Belo Horizonte. The number of patients, age, sex, clinical forms of the disease and schedules of treatment are shown in Table I. In all cases, viable *S. mansoni* eggs were detected by quantitative Kato-Katz technique.

Only those patients with a mean egg excretion rate of at least 100 eggs per gram of feces were accepted for inclusion in the trial.

Oltipraz was orally administered with food, as a single dose, in the form of 100 mg ta-

T A B L E I

Schedule of treatment, number of patients, age, sex and clinical form in patients treated with single oral dose of oltipraz or oxamniquine

| Drug | Schedule (mg/kg) | Number of treated patients | Mean AGE (range) | Sex | | Clinical form | |
|-------------|------------------|----------------------------|------------------|------|--------|---------------|------------------|
| | | | | Male | Female | Intestinal | Hepatointestinal |
| Oltipraz | 10 | 6 | 39 (32-43) | 6 | 0 | 6 | 0 |
| | 20 | 6 | 36 (30-48) | 6 | 0 | 4 | 2 |
| | 25 | 6 | 37 (31-43) | 6 | 0 | 5 | 1 |
| | 30 | 6 | 31 (22-46) | 6 | 0 | 3 | 3 |
| Oxamniquine | 15 | 7 | 23 (18-32) | 5 | 2 | 7 | 0 |

blets. Oxamniquine was orally administered, in the form of 250 mg, capsules.

Patients were hospitalized for at least 72 hours, and general medical examinations were performed before treatment and on several occasions after drug administration.

Laboratory monitoring tests, haemogram, serum bilirubin, serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glycemia, urinalysis, electrocardiography (ECG) and electroencephalography (EEG) were all performed once, before treatment and, then 24 hours, 1 and 4 months after drug administration. EEG was performed only once before and 24 hours after treatment.

Assessment of drug activity — The evaluation of oltipraz activity was based on 2 consecutive daily stool examination by Kato-Katz

quantitative² technique (two slides from each stool sample), performed before treatment and after 1 month. On the 4th month, 6 consecutive daily stool examinations were performed. Patients were considered as cured when no *S. mansoni* eggs were detected in their feces for a 4-month period of follow-up.

RESULTS

Tolerance — The side effects regarding the different schedules employed are shown in Table II. The side effects with oltipraz were rare, and appeared on the first day of drug ingestion. With 30 mg/kg, 2 patients presented nausea and/or somnolence. With oxamniquine 3 out of 7 patients claimed somnolence.

Complementary tests — The data provided by laboratory test are shown in Tables IV to VII. Significant alteration has been observed only in the eosinophile count: a sharp increase

has been observed 1 month after treatment with oltipraz (20 to 30 mg/kg) and with oxamniquine, returning to pre-treatment level by the 4th-month.

Electrocardiographic and electroencephalographic tracings did not reveal any significant alterations.

T A B L E II
Side-effects observed in patients treated with single oral dose of oltipraz or oxamniquine

| Side-effects | Oltipraz | | | | Oxamniquine | | | | | |
|---|------------|-------|------------|-------|-------------|-------|------------|-------|------------|-------|
| | 10 mg/kg | | 20 mg/kg | | 25 mg/kg | | 30 mg/kg | | 15 mg/kg | |
| | on the day | 24 hs | on the day | 24 hs | on the day | 24 hs | on the day | 24 hs | on the day | 24 hs |
| Skin eruption | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asthenia | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 0 |
| Abdominal distress | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Giddiness | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 0 |
| Anorexia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Nausea | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 |
| Somnolence | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 3 | 0 |
| Number of patients with side-effects/ treated | 2/6 (33.3) | | 0/6 (0.0) | | 3/6 (50.0) | | 3/6 (50.0) | | 4/7 (57.1) | |

Therapeutic results — The therapeutic results provided by oltipraz and oxamniquine are shown in Table VIII. Oltipraz at 10 mg/kg cured 16.7% of the treated patients, with 20 mg/kg 40.0%, with 25 and 30 mg/kg, 80.0% and 100%, respectively. Oxamniquine at 15 mg/kg cured 66.7%. In the non-cured patients it was observed a decrease in the number of *S. mansoni* eggs from 85.6 to 99.6%.

DISCUSSION

In this first trial of oltipraz in schistosomiasis mansoni infected patients in Brazil, good tolerance and therapeutic activity were found. With 10 mg/kg, one patient present skin eruption, but, in his past history, allergic reaction to merthiolate was reported. It is a possibility that in the hospital his skin eruption could be related to merthiolate contact. The main side effects were observed with the highest dosage of oltipraz (30 mg/kg) where nausea and/or somnolence were found in 2 out of 6 patients treated. With oxamniquine (15 mg/kg), those side-effects were observed in 1 and 3 out of 7 patients, respectively. The side-effects were mild and disappeared before 24 hours.

Laboratory test changes after treatment were not detected with the exception of an increase of eosinophile counts one month after

treatment, and this probably is a good indication of the schistosomicidal activity of oltipraz. Paired electrocardiograms and electroencephalograms did not display any significant abnormalities of clinical importance.

It must be pointed out, that in this present trial, tolerance was better than in the other two trials already published^{1,6}. This difference could be afforded to the lower dosage employed by us. First of all, the dosage was calculated per patients on a mg/kg basis, instead of using the same total amount of drug; and second, the highest total dose that was administered in the present trial, was 2,300 mg instead of 3,000 or 7,500 mg used by the previous Authors.

Although the dosage was lower, the antischistosomal activity was very high. In fact, using 25 mg/kg, or 30 mg/kg, single oral dose of oltipraz the cure rate were 80.0% and 100.0%, respectively. With all schedules, the percentage of egg count reduction in the non-cured patients was higher than 85%.

Oxamniquine, a highly active and well tolerated antischistosomal drug in Brazil³, has been used as a control drug, and although only a few patients has been treated in each group, it can be concluded that oltipraz at the schedule of 25 to 30 mg/kg is comparable, as far as

T A B L E III
Laboratory tests performed in patients treated with oltipraz (10 mg/kg single oral dose)

| LABORATORY TEST | Before treatment | | After treatment | |
|----------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | Mean (range) | 24 hs | 1 month | 4 months |
| HEMATOLOGY | | | | |
| HEMOGLOBIN | 15.9 (14.4-18.0) | 16.1 (15.0-18.0) | 15.7 (14.4-16.8) | 16.1 (15.0-17.0) |
| HEMATOCRIT | 50 (46-56) | 51 (48-60) | 47 (41-52) | 49 (46-53) |
| ERYTHROCYTE COUNT | 5500000 (5000000-6100000) | 5683000 (5400000-6600000) | 5183000 (4500000-5700000) | 5431000 (5100000-5800000) |
| LEUCOCYTE | 7050 (4500-9500) | 7083 (5000-10000) | 7141 (5300-8700) | 6400 (3400-9500) |
| NEUTROPHILE | 48 (35-58) | 52 (39-61) | 42 (35-61) | 48 (31-61) |
| EOSINOPHILE | 12 (9-20) | 10 (5-19) | 16 (13-21) | 8 (6-11) |
| LYMPHOCYTE | 34 (25-42) | 30 (16-50) | 28 (16-43) | 38 (30-49) |
| MONOCYTE | 4 (3-8) | 6 (4-9) | 5 (4-7) | 5 (3-9) |
| BIOCHEMISTRY | | | | |
| SGPT | 22 (12-40) | 18 (11-30) | 14 (10-24) | 16 (12-20) |
| SGOT | 19 (16-28) | 18 (14-22) | 14 (10-20) | 15 (14-20) |
| BILIRUBIN TOTAL | 0.7 (0.6-0.9) | 0.9 (0.6-1.5) | 0.6 (0.5-0.9) | 0.6 (0.6-0.7) |
| ALKALINE PHOSPHATASE | 2.6 (1.3-4.0) | 3.4 (2.2-5.0) | 3.4 (1.7-5.0) | 3.6 (2.6-4.6) |
| BUN | 14 (10-20) | 18 (15-21) | 22 (16-25) | 28 (20-34) |
| CREATININE | 0.8 (0.8-1.0) | 0.9 (0.7-1.1) | 0.8 (0.6-1.1) | 0.7 (0.5-1.0) |
| GLYCOSE | 79 (64-92) | 83 (66-96) | 89 (79-103) | 77 (64-95) |

() : range

T A B L E IV
Laboratory test performed in patients treated with oltipraz (20 mg/kg single oral dose)

| LABORATORY TEST | Before treatment | | After treatment | |
|----------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | Mean (range) | 24 hs | 1 month | 4 months |
| HEMATOLOGY | | | | |
| HEMOGLOBIN | 15.5 (13.8-16.8) | 15.8 (13.8-16.8) | 15.2 (13.8-16.0) | 15.1 (13.2-17.0) |
| HEMATOCRIT | 47 (40-50) | 47 (40-51) | 47 (40-50) | 48 (43-53) |
| ERYTHROCYTE COUNT | 5158000 (4400000-5500000) | 5200000 (4400000-5600000) | 5141000 (4400000-5500000) | 5360000 (4800000-5800000) |
| LEUCOCYTE | 8850 (7300-11000) | 8550 (7300-9800) | 8633 (6250-13500) | 8200 (6000-10000) |
| NEUTROPHILE | 54 (49-63) | 50 (42-57) | 43 (24-55) | 55 (42-63) |
| EOSINOPHILE | 8 (2-14) | 8 (3-23) | 20 (9-53) | 11 (3-30) |
| LYMPHOCYTE | 30 (24-43) | 33 (20-45) | 31 (20-39) | 31 (25-45) |
| MONOCYTE | 6 (4-11) | 7 (3-12) | 5 (3-8) | 5 (3-9) |
| BIOCHEMISTRY | | | | |
| SGPT | 20 (12-40) | 22 (11-46) | 16 (12-22) | 18 (16-34) |
| SGOT | 21 (16-28) | 22 (16-34) | 18 (12-24) | 20 (16-24) |
| BILIRUBIN TOTAL | 0.7 (0.6-1.0) | 0.8 (0.6-1.0) | 0.9 (0.6-1.2) | 0.6 (0.6-0.7) |
| ALKALINE PHOSPHATASE | 3.2 (1.3-5.0) | 2.4 (1.5-3.7) | 4.4 (3.1-8.4) | 3.4 (2.9-4.5) |
| BUN | 16 (10-23) | 21 (15-29) | 22 (19-24) | 24 (15-38) |
| CREATININE | 0.7 (0.6-0.9) | 0.8 (0.7-0.9) | 0.8 (0.7-1.2) | 0.7 (0.6-0.8) |
| GLYCOSE | 91 (84-100) | 78 (71-86) | 86 (76-96) | 70 (60-86) |

(): range

T A B L E V
Laboratory test performed in patients treated with oltipraz (25 mg/kg single oral dose)

| LABORATORY TEST | Before treatment Mean (range) | After treatment | |
|----------------------|----------------------------------|---------------------------|---------------------------|
| | | 24 hs | Mean (range) |
| | | 1 month | 4 months |
| HEMATOLOGY | | | |
| HEMOGLOBIN | 15.1 (13.8-16.8) | 15.5 (15.0-16.2) | 14.8 (12.6-17.0) |
| HEMATOCRIT | 47 (45-49) | 47 (45-50) | 49 (45-55) |
| ERYTHROCYTE COUNT | 5161000 (4950000-5400000) | 5216000 (5000000-5500000) | 5333000 (4700000-6000000) |
| LEUCOCYTE | 6658 (4500-9300) | 5891 (3500-10000) | 6816 (4900-8000) |
| NEUTROPHILE | 52 (36-65) | 47 (24-59) | 47 (21-58) |
| EOSINOPHILE | 14 (6-26) | 16 (4-41) | 12 (2-33) |
| LYMPHOCYTE | 26 (17-34) | 30 (27-43) | 35 (28-43) |
| MONOCYTE | 6 (2-11) | 4 (2-9) | 4 (3-9) |
| BIOCHEMISTRY | | | |
| SGPT | 21 (8-70) | 14 (8-22) | 35 (8-65) |
| SGOT | 20 (12-36) | 15 (10-24) | 26 (12-45) |
| BILIRUBIN TOTAL | 0.8 (0.6-1.2) | 1.0 (0.8-1.5) | 1.1 (0.9-1.5) |
| ALKALINE PHOSPHATASE | 3.9 (3.3-4.9) | 2.8 (1.2-4.4) | 4.3 (3.1-5.7) |
| BUN | 23 (16-30) | 23 (18-31) | 27 (19-40) |
| CREATININE | 0.8 (0.7-1.0) | 0.9 (0.9-1.0) | 0.8 (0.7-1.0) |
| GLYCOSE | 83 (72-100) | 78 (64-92) | 78 (60-98) |

(): range

T A B L E VI
Laboratory test performed in patients treated with oltipraz (30 mg/kg single oral dose)

| LABORATORY TEST | Before treatment | | After treatment | |
|----------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | Mean (range) | | Mean (range) | |
| | 24 hs | 1 month | 1 month | 4 months |
| HEMATOLOGY | | | | |
| HEMOGLOBIN | 15.7 (14.1-17.4) | 16.0 (14.4-17.4) | 15.0 (13.7-16.5) | 14.6 (12.0-17.0) |
| HEMATOCRIT | 49 (46-53) | 48 (42-54) | 49 (46-54) | 44 (36-48) |
| ERYTHROCYTE COUNT | 5388000 (5060000-5800000) | 5365000 (4620000-5940000) | 5260000 (5000000-5400000) | 4850000 (4000000-5300000) |
| LEUCOCYTE | 6933 (4700-10000) | 6666 (5300-8000) | 6820 (5500-8100) | 7500 (5800-8800) |
| NEUTROPHILE | 44 (23-64) | 42 (27-54) | 38 (27-53) | 49 (36-62) |
| EOSINOPHILE | 11 (4-22) | 10 (3-15) | 20 (10-37) | 10 (4-19) |
| LYMPHOCYTE | 35 (17-47) | 40 (31-50) | 36 (28-50) | 32 (22-40) |
| MONOCYTE | 8 (6-12) | 6 (5-9) | 5 (4-7) | 7 (4-9) |
| BIOCHEMISTRY | | | | |
| SGPT | 15 (8-24) | 15 (8-22) | 18 (10-28) | 23 (10-50) |
| SGOT | 16 (12-20) | 14 (12-18) | 16 (12-20) | 25 (18-45) |
| BILIRUBIN TOTAL | 0.7 (0.6-1.2) | 0.7 (0.6-0.9) | 0.7 (0.5-1.2) | 0.7 (0.2-0.9) |
| ALKALINE PHOSPHATASE | 3.2 (2.6-4.0) | 2.8 (2.3-3.3) | 2.9 (1.8-4.2) | 3.6 (2.3-4.5) |
| BUN | 23 (15-34) | 24 (18-32) | 29 (24-36) | 24 (16-38) |
| CREATININE | 0.7 (0.5-0.9) | 0.8 (0.7-1.0) | 0.9 (0.8-1.1) | 0.9 (0.8-1.2) |
| GLYCOSE | 89 (76-100) | 89 (64-100) | 72 (50-105) | 80 (60-98) |

() : range

T A B L E VII
Laboratory test performed in patients treated with oxamniquine (15 mg/kg single oral dose)

| LABORATORY TEST | Before treatment Mean (range) | After treatment Mean (range) | |
|----------------------|-------------------------------------|------------------------------|---------------------------|
| | | 24 hs | 4 months |
| HEMATOLOGY | | | |
| HEMOGLOBIN | 15.4 (13.2-16.8) | 15.2 (13.8-16.5) | 14.7 (13.3-15.6) |
| HEMATOCRIT | 48 (42-51) | 48 (43-49) | 46 (40-51) |
| ERYTHROCYTE COUNT | 5300000 (4600000-5600000) | 5270000 (4700000-5700000) | 5042000 (4400000-5600000) |
| LEUCOCYTE | 7271 (6200-8500) | 6857 (6200-7800) | 7528 (6000-12400) |
| NEUTROPHILE | 56 (48-67) | 51 (37-62) | 47 (36-64) |
| EOSINOPHILE | 6 (2-9) | 7 (6-9) | 17 (10-28) |
| LYMPHOCYTE | 30 (20-40) | 34 (26-48) | 30 (18-39) |
| MONOCYTE | 6 (3-9) | 6 (5-8) | 4 (2-7) |
| BIOCHEMISTRY | | | |
| SGPT | 14 (8-20) | 12 (8-16) | 36 (8-66) |
| SGOT | 13 (10-16) | 14 (12-16) | 30 (12-58) |
| BILIRUBIN TOTAL | 0.9 (0.6-1.5) | 0.7 (0.6-0.9) | 0.7 (0.5-0.9) |
| ALKALINE PHOSPHATASE | 3.8 (2.8-4.9) | 3.2 (2.3-4.9) | 3.8 (1.0-6.0) |
| BUN | 21 (16-30) | 22 (15-35) | 21 (13-30) |
| CREATININE | 0.7 (0.6-0.9) | 0.7 (0.6-0.8) | 0.7 (0.5-1.0) |
| GLYCOSE | 75 (63-88) | 67 (60-77) | 79 (72-98) |

() : range

T A B L E VIII

Parasitological results of patients treated with single oral dose of oltipraz or oxamniquine

| Drug | Schedule (mg/kg) | Number of patients | | | % of eggs reduction |
|-------------|------------------|--------------------|-------------|-----------|---------------------|
| | | Treated | Followed-up | Cured (%) | |
| Oltipraz | 10 | 6 | 6 | 1 (16.7) | 85.6 |
| | 20 | 6 | 5 | 2 (40.0) | 99.6 |
| | 25 | 6 | 5 | 4 (80.0) | 98.3 |
| Oxamniquine | 30 | 6 | 5 | 5 (100.0) | 100.0 |
| | 15 | 7 | 6 | 4 (66.7) | 98.6 |

antischistosomal activity is considered, to oxamniquine at 15 mg/kg for adult treatment.

This first clinical trial with oltipraz shows that the best schedule to be chosen for next assays is a single oral dose of 25 to 30 mg/kg.

Further clinical trials with this new promising drug are strongly encouraged.

RESUMO

Ensaio clínico com oltipraz na esquistossomose mansoni

Ensaio clínico com oltipraz foi realizado em pacientes adultos, portadores de *S. mansoni*, visando-se encontrar a dose efetiva. Quatro grupos com 6 pacientes cada, foram tratados com 10, 20, 25 e 30 mg/kg em dose única oral de oltipraz e um grupo de 7, tratados com oxamniquine na dose única oral de 15 mg/kg. Os efeitos colaterais com o oltipraz foram raros e de intensidade leve. Os exames complementares (hemograma, função hepática, creatinina, ureia, sumário de urina, glicemia, ECG e EEG) não revelaram alterações significativas, a não ser eosinofilia encontrada 1 mês após o tratamento. O controle parasitológico (repetidos exames de fezes quantitativos — método de Kato-Katz) realizado após o 1.º e 4.º mês do tratamento, mostrou um percentual de cura de 16,7, 40,0, 80,0 e 100,0%, respectivamente com as doses de 10, 20, 25 e 30 mg/kg de oltipraz, enquanto a oxamniquine curou 66,7%.

Em todos os esquemas realizados, o percentual de redução do número de ovos das fezes, nos pacientes não curados, foi em torno de 90%. Os Autores concluem ser o oltipraz uma droga esquistossomicida promissora, e sugere

rem que novos ensaios clínicos sejam realizados.

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