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CLINICAL TRIALS WITH OXAMNIQUINE, BY ORAL ROUTE, IN SCHISTOSOMIASIS MANSONI

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SUMMARY

Clinical trials with oxamniquine by oral route were carried out on 335 patients with active schistosomiasis, who were divided into 7 groups, as follows: *Group A*: 49 adults and 52 children (15 years or under 15 years of age) treated with a single dose of 10 mg/kg (capsules). *Group B*: 31 children treated with a single dose of 12.5 mg/kg (capsules). *Group C*: 40 adults and 33 children treated with a single dose of 15 mg/kg (capsules). *Group D*: 21 children treated with a single dose of 20 mg/kg (syrup), administered after a snack. *Group E*: 60 children treated with 10 mg/kg, twice a day (syrup). *Group F*: 24 children treated with 7.5 mg/kg, twice a day (capsules). *Group G*: 25 children treated, for 2 consecutive days, with 10 mg/kg/day, five children having received the drug in the form of syrup and the remainder, in the form of capsules. Dizziness, drowsiness, hallucination and excitability were the more important side-effects. They occurred 1 or 2 hours after drug administration and persisted, at most, for about 6 hours. Frequency and intensity of symptoms were seen to be correlated with dosage increase. Laboratory tests performed 3 days after the end of treatment revealed one patient with temporary leucopenia. Although statistical analysis revealed significant rise in the mean plasma transaminase levels, they were never found in individual cases, to be higher than 38 and 60 units for SGOT and SGPT, respectively. Parasitological control showed oxamniquine to be more active in adults than in children. In fact, in Groups A and B, the cure rates obtained were 78.78 and 93.81% for adults, and only 0.0 and 30.5% for children. When children were treated with 20 mg/kg, the cure rate was 66.66%, and, with 7.5 mg/kg and 10 mg/kg, twice a day, or 10 mg/kg/day x 2, the percentage of cure was about 85%. Actually, oxamniquine seems to be a promising schistosomicidal drug when orally administered.

INTRODUCTION

Oxamniquine (6-hydroximethyl-2-isopropylamino-methyl-7-nitro-1, 2, 3, 4–tetrahydroquinoline, U.K. 4271, Pfizer Limited, Sandwich, England) has shown to be highly effective in laboratory animals experimentally infected with *S. mansoni*, when administered by oral or parenteral route [3, 9].

Preliminary clinical trials carried out by KATZ et al. [6], in Brasil, demonstrated that oxamniquine, at the intramuscular dosage of 7.5 mg/kg, is also highly active against schistosomiasis mansoni, the only side-effect observed being tenderness at the site of injection. Further clinical trials on 104 patients

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confirmed these initial results [7]. In fact, from 71 followed-up patients, all but 5 were considered parasitologically cured, including 11 in the early phase of schistosomiasis (4 to 6 months after infection). All those patients but complained of pain at the site of injection. In most patients the pain was moderate or severe, lasting from 1 to 16 days [7].

In 1973, Pfizer Laboratories sponsored, in Rio de Janeiro, a meeting on oxamniquine whose scope was to evaluate clinical trials performed in Brasil and Africa. The working papers were published in a special issue of the "Revista do Instituto de Medicina Tropical de São Paulo" (Vol. *15*, Supplement 1, 1973).

The data presented by COUTINHO et al. [2], COURA et al. [1], PRATA et al. [10], SILVA et al. [11], and PEDRO et al. [8], were in accordance with those aforementioned, the researchers present having agreed that, although oxamniquine, per intramuscular route, produced few side and toxic effects as well as high percentage of cure in Brasil, the severe local pain would hardly indicate its use on a large scale for field treatment, and that its oral formulation could be an alternative.

SILVA et al. [12] administered oxamniquine in capsules, *per os*, to 109 *S. mansoni* patients divided into 3 groups of 29, 47 and 33 patients receiving, respectively, 10 mg/kg, 12-12.5 mg/kg and 15 mg/kg. The most frequent side effects were dizziness, nausea and drowsiness, their intensity and frequency increasing with the dosage employed. In 3 out of 81 patients, elevation of transaminase levels (more than 100 units) and leucopenia were observed. Hematuria and proteinuria were detected in 8 patients. The percentages of cure obtained were 70.0, 81.5 and 100.0, respectively.

This paper presents the data on clinical and laboratory follow-ups of patients with active schistosomiasis mansoni treated with oxamniquine per oral route (capsules and syrup).

MATERIAL AND METHODS

Patients and treatment — Three hundred and thirty-five patients with active schistosomiasis mansoni were divided into 7 groups, as follows:

GROUP A: 49 adults and 52 children (15 years or under this age), treated with a single dose of 10 mg/kg (capsules).

GROUP B: 31 children treated with a single dose of 12.5 mg/kg (capsules).

GROUP C: 40 adults and 33 children treated with a single dose of 15 mg/kg (capsules).

GROUP D: 21 children treated with a single dose of 20 mg/kg (syrup) administered after a snack.

GROUP E: 60 children treated with 10 mg/kg, twice a day (bid) with 6-8 hour interval between doses (syrup).

GROUP F: 24 children treated with 7.5 mg/kg bid (syrup).

GROUP G: 25 children treated, for 2 consecutive days, with 10 mg/kg/day. Five children received the drug as syrup and the remaining twenty as capsules.

All of those individuals treated as outpatients in the Parasitosis Section of the Municipal Secretary of Health, Belo Horizonte, were eliminating viable *S. mansoni* eggs in their faeces, as demonstrated by a quantitative thick-smear technique (Kato's technique adapted by KATZ et al. [5]).

Patients from groups A and C were submitted to the following laboratory tests before, and 3 days after treatment: haemogram, urinalysis, hepatic-function tests (bilirubin, transaminases and alkaline phosphatase), blood-urea nitrogen and E.C.G.-E.E.G. was performed 2 to 6 hours after oxamniquine administration.

Three hundred and twenty-two patients were undergoing the chronic hepato-intestinal form; four of them, the hepato-splenic form, and the remaining nine were in the early phase of the disease.

Assessment of drug activity — The evaluation of chemotherapeutic activity was based on the data provided by 4 to 6 stool samples collected after the 4th month of therapy and examined after the coprological quantitative Kato-Katz technique [5].

Patients were considered as cured when no viable eggs could be found in their faeces.

Statistical analysis — All data were analysed by a computer, the value of t and its statistical significance being evaluated.

RESULTS

The percentage of side-effects observed in adults treated with 10 and 15 mg/kg (capsules) can be seen in Table I. Dizziness and drowsiness were the most frequent side-effects, their intensity being higher in those patients treated with 15 mg/kg. After administration of this dosage, one patient (2.5%) developed hallucination.

TABLE I

Percentage of side-effects observed in adults treated with oxamniquine (capsules)

Side effects	Schedule of treatment	
	Group A 10 mg/kg Single dose (%)	Group B 15 mg/kg Single dose (%)
Dizziness	16.67	62.50
Hallucination	0.00	2.50
Psychic excitement	0.00	2.50
Drowsiness	8.16	25.00
Headache	0.00	2.50
Nausea	4.08	5.00
Vomiting	0.00	2.50
Asthenia and/or muscle pain	8.16	12.50
No complaints	65.31	27.50
Number of patients	49	40

The side-effects observed in children treated with different schedules of oxamniquine (capsules and syrup) are shown in Table II. Again, dizziness and drowsiness were the commonest side-effects. In Group D, E and F, 9.52%, 1.67% and 4.17% of the patients, respectively, presented psychic excitation. Hallucination was observed in one patient treated with 10 mg/kg, bid.

The side-effects began to appear after one hour and persisted, at most, for about 6 hours.

As illustrated in Table II, patients treated with 7.5 mg/kg, bid (Group F) presented a higher percentage of side effects than did those treated with 10 mg/kg, bid. This fact could not be satisfactorily explained.

Table III and IV assemble the data from laboratory examinations performed before, and 3 days after treatment with oxamniquine at the dosages of 10 and 15 mg/kg (capsules), respectively. These examinations were not handicapped by any alterations requiring special care. Although statistical analysis revealed significant rise in the plasma transaminase mean levels, they were never seen, in individual cases, to be higher than 38 and 60 units for SGOT and SGPT, respectively. In one adult patient treated with a single dose of 10 mg/kg, the number of white cells fell from 5,200 to 3,000 three days after treatment, then rising to 16,600 after 15 days. ECG and EEG tracings did not show any alterations of clinical significance. Parasitological control revealed oxamniquine to be more active in adults than in children. In fact, in groups A and C, cure rates were 78.78% and 93.81% for adults and 0.0% and 30.5% for children. When children were treated with a single dose of 20 mg/kg, 10 mg/kg bid, 7.5 mg/kg bid and with 10 mg/kg/day x 2, the percentages of cure were respectively, 66.66, 86.37, 89.48 and 86.37 (Table V).

DISCUSSION

According to our clinical trials, oral formulations of oxamniquine showed high therapeutic activity and low toxicity. However, two facts must be recalled: its lower activity against the infection in children and the appearance of such side-effects as hallucination and psychic excitation.

Actually, in adults, the schedule of a single oxamniquine dose of 15 mg/kg produces more than 90% of cure against only 30.5%,

TABLE II

Percentage of side-effects observed in children treated with oxamniquine (capsules and syrup)

Side effects	Schedule of treatment						
	Group A 10 mg/kg Single dose	Group B 12.5 mg/kg Single dose	Group C 15 mg/kg Single dose	Group D 20 mg/kg Single dose	Group E 10 mg/kg bid	Group F 7.5 mg/kg bid	Group G 10 mg/kg/ day × 2
Dizziness	3.85	3.26	6.06	23.81	13.33	54.17	40.00
Hallucination	0.00	0.00	0.00	0.00	1.67	0.00	0.00
Psychic excitement	0.00	0.00	0.00	9.52	1.67	4.17	0.00
Drowsiness	15.38	9.68	6.06	28.57	8.33	25.00	0.00
Headache	0.00	6.45	3.03	4.76	6.67	12.50	12.00
Nausea	1.92	0.00	3.03	4.76	1.67	0.00	12.00
Vomiting	3.85	0.00	3.03	0.00	1.67	4.17	8.00
Asthenia and/or muscle pain	0.00	0.00	0.00	0.00	1.67	4.17	4.00
No complaints	69.23	80.65	78.79	47.62	69.33	33.33	48.00
Number of patients	52	31	33	21	60	24	25

TABLE III

Paired-comparison analysis of laboratory examinations performed before and 3 days after treatment with oxamniquine (10 mg/kg, single dose, capsules)

Tests	No. of patients	Mean	Difference	T value	Significance
Haemoglobin	49	15.39	0.19	0.903	N.S.
Haematocrit	49	46.00	0.00	0.000	N.S.
Red cells	49	4.850000	0.10	1.247	N.S.
White cells (total)	49	6.500	0.05	0.238	N.S.
Neutrophils	49	55.16	0.27	0.142	N.S.
Eosinophils	49	14.57	0.84	0.660	N.S.
Lymphocytes	49	30.27	0.59	0.407	N.S.
Direct bilirubin	49	0.22	0.02	1.673	N.S.
Indirect bilirubin	49	0.29	0.00	0.264	N.S.
SGOT	49	19.20	4.14	3.959	**
SGPT	49	17.57	3.82	2.853	*
Alkaline phosphatase	46	3.84	0.33	1.815	N.S.
Blood-urea nitrogen	49	25.06	0.33	1.387	N.S.

N.S. = not significant * = $p \leq 0.01$ level ** = ≤ 0.001 level

TABLE IV

Paired-comparison analysis of laboratory examinations performed before and 3 days after treatment with oxamniquine (15 mg/kg, single dose, capsules)

Tests	No. of patients	Mean	Difference	T value	Significance
Haemoglobin	48	14.12	0.11	0.644	N.S.
Haematocrit	48	44.88	1.60	1.663	N.S.
Red cells	48	4.700000	0.09	1.189	N.S.
White cells (total)	48	6.550	0.15	0.577	N.S.
Neutrophils	48	51.02	0.27	0.138	N.S.
Eosinophils	48	15.31	1.29	1.389	N.S.
Lymphocytes	48	33.04	1.19	0.673	N.S.
Direct bilirubin	48	0.19	0.03	1.923	N.S.
Indirect bilirubin	48	0.26	0.05	2.696	*
SGOT	47	23.91	0.85	0.570	N.S.
SGPT	47	19.03	0.53	0.391	N.S.
Alkaline phosphatase	46	5.22	0.32	1.563	N.S.
Blood-urea nitrogen	48	24.83	3.04	1.959	N.S.

N.S. = not significant * = $p \leq 0.01$ level

TABLE V

Assessment of oxamniquine therapeutic activity (capsules and syrup)

Schedules of treatment	Age	No. of patients treated	No. of patients followed	Patients considered cured	
				(No.)	(%)
Group A: 10 mg/kg, single dose	Adults	49	33	26	78.78
	Children	52	38	0	0.00
Group B: 12.5 mg/kg, single dose	Children	31	30	1	3.33
Group C: 15 mg/kg, single dose	Adults	40	16	15	93.81
	Children	33	23	9	39.13
Group D: 20 mg/kg, single dose	Children	21	18	12	66.66
Group E: 10 mg/kg, bid	Children	60	52	10	86.37
Group F: 7.5 mg/kg, bid	Children	24	19	17	89.48
Group G: 10 mg/kg/day × 2	Children	25	22	19	86.37

in children. This difference can probably be accounted for by the differences in the metabolism of the drug in these age groups. The best schedules for children seem to be 7.5 to 10 mg/kg, twice a day, since the percentages of cure obtained were about 85% and the drug tolerability good.

It must be pointed out that oxamniquine is better tolerated when administered after a meal than on an empty stomach (Eyakuze, V.M., personal communication). This finding has been confirmed by us, when comparing the side-effects observed in Group D (single dose of 20 mg/kg, after a snack) with another trial, in which no food was previously given [4]. In the latter schedule, 2 out of 7 treated children developed visual or auditive hallucinatory pictures.

In 600 field patients treated with oxamniquine (15 mg/kg), 3 adults developed hallucinations (COURA, J.R., personal communication). We can thus conclude that oxamniquine, per oral route, may indeed induce, in a few patients (adults and children), psyco-neurological side-effects.

Other toxic effects of oxamniquine requiring further investigation are leucopenia and hematuria.

So far, about 2,000 patients have been treated, in Brasil, with oxamniquine per oral route. This limited number does not allow a final conclusion about the drug tolerability, although preliminary trials have shown oxamniquine to be a promising schistosomicidal drug. Pilot projects for mass treatment as well as comparative studies with hycanthone in the field of toxicity, mutagenicity and carcinogenicity, as recommended by the WHO consultant group [13], are highly desirable.

RESUMO

Ensaios clínicos com oxamniquine, por via oral, na esquistossomose mansônica

Ensaios clínicos com oxamniquine, por via oral, foram realizados em 335 pacientes com esquistossomose mansônica ativa, os quais foram divididos em 7 grupos: *Grupo A*: 49 adultos e 52 crianças (15 anos ou menos) tratados com dose única de 10 mg/kg (cápsulas). *Grupo B*: 31 crianças tratadas com dose única de 12,5 mg/kg (cápsulas). *Grupo C*: 40 adultos e 33 crianças tratados com dose única de 15 mg/kg (cápsulas). *Grupo D*: 21 crianças tratadas com dose única de 20 mg/kg (xarope), administrada após um lanche. *Grupo E*: 60 crianças tratadas com 10 mg/kg, duas vezes ao dia (xarope). *Grupo F*: 24 crianças tratadas com 7,5 mg/kg, duas vezes ao dia (cápsulas). *Grupo G*: 25 crianças tratadas com 10 mg/kg/dia, durante 2 dias seguidos, 5 delas tendo recebido oxamniquine em forma de xarope e o restante, em cápsulas.

Tonturas, sonolência, alucinação e excitação psíquica foram os principais efeitos colaterais observados. Estes apareceram 1 a 2 horas após administração da oxamniquine e persistiram no máximo por 6 horas. A freqüência e intensidade da sintomatologia foi diretamente proporcional à dose empregada. Exames complementares realizados 3 dias após o tratamento revelaram que em um paciente houve leucopenia transitória e que apesar de haver uma diferença estatisticamente significativa nas médias das transaminases séricas, tais níveis individualmente, nunca foram além de 38 e 60 unidades, respectivamente, para TGO e TGP. O controle parasitológico demonstrou que a oxamniquine foi mais ativa em adultos que em crianças. De fato, nos Grupos A e B, os percentuais de cura foram respectivamente de 78,78% e 93,81% para adultos e de 0,0 e 30,5% para crianças. Quando as crianças foram tratadas com 20 mg/kg, o percentual de cura foi de 66,66% e com 7,5 mg/kg e 10 mg/kg, duas vezes ao dia, ou 10 mg/kg/dia x 2, em torno de 85%. A oxamniquine administrada por via oral pode ser considerada como uma promissora droga esquistossomicida.

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