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PRELIMINARY CLINICAL TRIALS WITH OXAMNIQUINE, A NEW ANTISCHISTOSOMAL AGENT

Naftale KATZ [1, 2], J. PELLEGRINO [1, 3], Emílio GRINBAUM [2], Adelú CHAVES [1, 2] and Fábio ZICKER [1]

SUMMARY

Clinical trials with oxamniquine, an active metabolite of U.K. 3883, were performed in 24 patients with active schistosomiasis mansoni. The drug was administered in the form of capsules and by intramuscular injection. Tenderness at the site of injection was the only side effect observed. With the oral formulation, a decrease in white and red cell counts was observed in 2 out of 10 patients. Parasitological control performed one month after treatment revealed a decrease in the number of eggs excreted in the feces on 9 out of 10 patients. However, 4 to 6 months after treatment, only on 3 patients there has been detected a marked fall in egg excretion. The best schedule of treatment was a single intramuscular injection of oxamniquine (7.5 mg/kg). All patients so treated were parasitologically cured, including 4 in the early phase of schistosomiasis (5 to 9 months after infection). Further clinical trials with oxamniquine (U.K. 4271) should be encouraged.

INTRODUCTION

Recently, RICHARDS & FOSTER [10] demonstrated that a novel series of 2-aminomethyltetrahydroquinolines present schistosomicidal properties on laboratory animals.

U.K. 3883, one compound of this series (PELLEGRINO & KATZ [9]), has been extensively studied in mice, hamsters and several species of monkeys experimentally infected with *Schistosoma mansoni*. A highly therapeutic as well as prophylactic activity could be observed (CHEETHAM & MESMER [3]; FOSTER et al. [4, 5]; PELLEGRINO & KATZ [9]). This compound represents a promising lead, for it has been shown that it undergoes hydroxilation on the 6-methyl group in several animal species eventually forming an extremely active metabolite, the 6-hydroximethyl-2-isopropylaminomethyl - 7 - nitro - 1,2,3,4 - tetrahydroquinoline (oxamniquine, Pfizer Limited, Sandwich, England, Fig. 1).

This paper presents the data provided by preliminary clinical trials and laboratory follow-up of patients with active schistosomiasis mansoni treated with oxamniquine.

MATERIAL AND METHODS

Patients and treatment — Twenty-four adult (17 male and 7 female) patients with active schistosomiasis mansoni were treated in the "Hospital Evangelico", Belo Horizonte. In all cases viable *S. mansoni* eggs have been found by stool examination (Kato's technique [8]). The schedules of treatment using two different formulations of oxamniquine (capsules and injectable suspension) are shown in Table I.

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(1) "Instituto de Endemias Rurais, Centro de Pesquisas René Rachou", Belo Horizonte
(2) "Seção de Parasitoses, Prefeitura de Belo Horizonte"
(3) "Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais"
Contribution number 25 from the Schistosomiasis Research Unit
Address for reprints: Dr. Naftale Katz, Caixa Postal 1743 — 30000 Belo Horizonte, Brazil

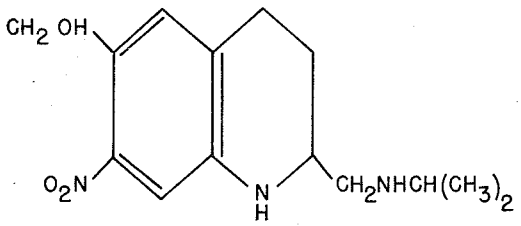

Fig. 1 — Chemical structure of oxamniquine.

In 20 patients, distributed in 4 groups, the following laboratory tests were performed once before and several times after treatment: haemogram, urinalysis, hepatic-function tests (bilirubin, thymol turbidity, serum transaminases, alkaline phosphatase), blood-urea nitrogen and electrocardiogram. The first post-treatment tests were performed on the following day after dosing and were repeated at 7 days, 6 to 8 weeks, 12 weeks or when as otherwise stated.

Twenty patients were of the chronic hepato-intestinal form of mansoni schistosomiasis and 4 were in the early phase (5 to 9 months infections) of the disease.

Assessment of drug activity — The evaluation of chemotherapeutic activity was based on the data provided by the examination of 6 or more stool samples collected within 4 to 6 months after treatment. The coprological examinations were performed according to the quantitative KATO's technique [8] and the hatching test as described by BLAIR et al. [2]. Patients were considered as cured when no viable eggs and/or miracidia could be found.

RESULTS

No side effects were observed in 9 patients treated with the oral formulation. Only one patient presented a mild anorexia for 2 days.

With the intramuscular injection, 12 patients complained tenderness at the site of injection, which constituted the only side effect observed. In 11 patients, pain was severe and in one moderate, lasting from 3 to 12 days after the injection.

The data provided by laboratory tests performed in 10 patients treated with the intramuscular formulation showed in 2 cases an increase of eosinophilia (from 11 to 21% and from 10 to 36%) one week after dosing. In one case (5 mg/kg), one week after treatment, a definite increase of serum glutamic oxalacetic transaminase (SGOT) level (from 25 to 110 Roitman-Frankel units) and serum glutamic pyruvic transaminase (SGPT), from 30 to 100 units was observed. After 3 weeks, transaminase levels (SGOT and SGPT) returned to normal.

In 2 patients dosed with the oral formulation (total dose: 200 mg/kg) a decrease in white blood cells could be detected. Actually, one patient, with 8,950 white cells per mm^3 before treatment presented 5,700 white cells 20 days later. In the same patient red-cell counts fell from 4,5 million to 3,0 million per mm^3, one month after treatment. In the second patient the white cell count fell from 6,000 to 4,050 per mm^3, 3 days after dosing and, 5 months later (last control), to 3,200. In other 2 patients an increased eosinophilia, within the second week (from 10 and 9% to 42 and 24%, respectively) was observed. In 3 patients treated orally with a total of 400 mg an increase was detected in the eosinophils from 14 to 25%, 2 to 10%, and 21 to 53% on days 3,3 and 36 days, respectively. No alterations in other laboratory tests could be detected.

Electrocardiographic tracings after oxamniquine therapy revealed that in 5 cases, dosed with the oral formulation, no ECG alterations were found. In the remaining 5 cases, 3 showed a discreet increase of T wave and, one a slight diminution, and in another, the T wave changed from plus-minus to positive in V_1 and V_3.

In 8 cases, dosed with the intramuscular formulation no modifications of the ECG were found. In one patient the T wave changed from negative to positive in V_1 and in another patient an increase of T wave voltage and a slight elevation of ST segments were observed.

Interruption of egg laying by schistosomes could be observed in all patients treated intramuscularly (Table II). The parasitological control revealed that with 5 mg/kg, 2 patients were cured and 2 relapsed. However, it must be pointed out that a transitory relapse was observed in 2 patients (A - 3 and A - 5) in the second month after therapy, as judged by

the presence of mature eggs in the feces. Nevertheless, repeated stool examinations and hatching tests from 3 months on were always negative (Table II). With the schedule of 7.5 mg/kg, i.m., 8 patients that have been followed-up did not present viable eggs and/or miracidia after repeated stool examinations. Four of these patients (B - 6 to B - 9) were treated within 5 to 9 months after exposure to infested waters. Patients treated with 50 mg bid x 2 days (capsules) were not cured. Patient C-4 had negative stool examinations for viable eggs, but the hatching test revealed swimming miracidia (Table III). In the other group of patients treated orally (100 mg bid x 2 days) there was, again, no parasitological cure. However, in 3 cases it was observed a definite decrease in the numbers of schistosome eggs eliminated with the feces (Table III).

TABLE I

Schedule of treatment performed in 24 patients with two different formulations of oxamniquine

Formulations of oxamniquine	Schedules of treatment × days	Number of patients
Capsules	50 mg/bid. × 2	5
	100 mg/bid × 2	5
Suspension for intramuscular injection	5 mg/kg/day × 1	5
	7.5 mg/kg/day × 1	9

TABLE II

Assessment of therapeutic activity of oxamniquine by intramuscular administration (*A*: 5 mg/kg; *B*: 7.5 mg/kg)

Patients	Number of *S. mansoni* eggs per gram of feces (*)					Hatching test (**)
	Before treatment	After treatment (months)				
		1	2	3	4 to 6	
A — 1	448	45	150	125	32	+
A — 2	1134	ND	ND	0	20	ND
A — 3	65	0	24	0	0	–
A — 4	909	0	15	ND	ND	ND
A — 5	1150	0	100	0	0	–
B — 1	217	0	0	0	0	–
B — 2	195	144	0	0	0	–
B — 3	638	750	ND	ND	ND	ND
B — 4	1300	0	0	0	0	–
B — 5	91	0	0	0	0	–
B — 6	1428	0	0	0	0	–
B — 7	3872	0	0	0	0	–
B — 8	1206	0	0	0	0	–
B — 9	1373	0	0	0	0	–

(*): Mean of two counts
(**): 4 to 6 months after treatment
ND: Not done

TABLE III

Assessment of therapeutic activity of oxamniquine by oral administration
(*C*: 50 mg/bid. × 2 days; *D*: 100 mg/bid. × 2 days)

Patients	Number of *S. mansoni* eggs per gram of feces (*)					Hatching test (**)
	Before treatment	After treatment (months)				
		1	2	3	4 to 6	
C — 1	78	44	0	21	20	+
C — 2	97	0	0	ND	39	+
C — 3	623	146	170	620	222	+
C — 4	178	0	0	ND	0	+
C — 5	550	95	382	ND	229	+
D — 1	5500	204	74	78	65	+
D — 2	1377	350	368	ND	800	+
D — 3	2745	279	780	ND	143	+
D — 4	415	171	210	ND	309	+
D — 5	592	130	156	ND	ND	ND

(*): Mean of two counts
(**): 4 to 6 months after treatment
ND: Not done

DISCUSSION

U.K. 3883, one of the most active compounds of the 2-amino-methyl 1,2,3,4-tetrahydroquinoline series [10], is metabolized in mouse and monkeys to the corresponding 6-hydroximethyl derivative which has been shown to be curative in single i.m. doses of 5 to 7.5 mg/kg [1]. This active metabolite — oxamniquine — was shown to be very effective in curing mice, hamsters and monkeys experimentally infected with *S. mansoni* [9]. It is interesting to remark that similarly to what occurs with the metabolism of Miracil D — transformed by the action of *Aspergillus sclerotiorum* to hycanthone — U.K. 3883 is converted by hydroximetilation to U.K. 4271 (oxamniquine) [10, 11]. In mice it has been shown that *per os*, the schistosomicidal activity of U.K. 4271 is similar to the parent compound U.K. 3883, but by the intramuscular route its activity is very much superior [10].

In clinical trials, oxamniquine, administered orally up to a total dose of 400 mg was only slightly active, reducing the numbers of excreted eggs in 3 out of 9 patients. Oxamniquine, at the schedule used did not present side effects. However, a definite reduction in the white and red cell counts were observed in 2 and 1 patient, respectively. ECG tracings from patients presented modifications but without clinical significance.

When oxamniquine was administered by the intramuscular route (7.5 mg/kg, single dose) parasitological cure could be achieved in all treated patients, including 4 acute-stage patients. This finding is very important since in early *S. mansoni* infections other antischistosomal agents, like hycanthone, present in general poor activity [6]. The only drawback is the severe tenderness occurring at the site of injection and lasting for several days. In one patient a definite increase of SGOT and SGPT levels were observed after treatment but returning to normal after 3 weeks. Alterations of the ECG, in most patients, were of no clinical significance. Transitory relapse was observed in two patients dosed with 5 mg/kg i.m. in the second month after therapy as judged by the presence of mature eggs in the feces. A similar finding has been reported in patients treated with hycanthone [7].

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The results presented in this paper emphasize the necessity of conducting further clinical trials with the intramuscular formulation of oxamniquine.

RESUMO

Ensaios clínicos preliminares com a oxamniquine, um novo agente esquistossomicida

Ensaios clínicos com a oxamniquine, metabólito ativo do U.K. 3883, foram realizados em 24 pacientes com esquistossomose mansoni ativa. A droga foi administrada por via oral e intramuscular. Dor no local da injeção foi o único efeito colateral observado. Com a formulação oral foi detectada baixa no número de glóbulos brancos e vermelhos em 2 dos 10 pacientes tratados. O controle parasitológico, realizado 1 mes após o tratamento, revelou diminuição do número de ovos de *S. mansoni* eliminados com as fezes em 9 pacientes. Todavia, 4 a 6 meses após o tratamento, somente em 3 pacientes havia uma baixa significativa do número de ovos. O melhor esquema foi o de uma única injeção, intra-muscular, na dose de 7,5 mg/kg. Houve cura parasitológica em todos os pacientes deste grupo, inclusive 4 que haviam se infestado 5 a 9 meses antes do tratamento clínico. Os dados laboratoriais e clínicos sobre a atividade terapêutica da oxamniquine até agora obtidos indicam a necessidade de novos ensaios com este promissor medicamento.

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