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FURTHER CLINICAL TRIALS WITH OXAMNIQUINE (UK 4271), A NEW ANTI-SCHISTOSOMAL AGENT

Luiz Caetano da SILVA [1], Hoel SETTE Jr. [1], Dalton A. F. CHAMONE [1], Amadeo SÁEZ-ALQUEZAR [2], Jane Alba PUNSKAS [3] and Silvano RAIA [3]

SUMMARY

Oxamniquine (UK 4271) showed to be an efficient drug for the treatment of schistosomiasis mansoni in adults. Similar cure rates were obtained with single oral dosis of 12.5 and 15.0 mg/kg of body weight (81.8% and 82.7%, respectively). Tolerance and toxicity do not seem to preclude its use in large scale, but further studies are needed.

INTRODUCTION

Our first results on Oxamniquine (UK 4271) [1, 2] showed that this drug is very efficient for the treatment of schistosomiasis mansoni. As previously mentioned, pain at the injection site precludes the use of intramuscular Oxamniquine in large scale [1]. As to the oral drug, the small number of patients and the shorth time of follow-up in some of them did not allow us to draw definite conclusions at the time of our first report [2].

This paper represents a continuing study of a larger number of patients, treated by oral Oxamniquine, with a reasonable follow-up.

MATERIALS AND METHODS

Material

A total of 227 patients with viable eggs of *S. mansoni* in their stools was grouped according to the following schedules of oral Oxamniquine in a single dosis:

Group I — 12.5 mg/kg body weight: 112 patients.

Group II — 15.0 mg/kg body weight: 115 patients.

Group II includes 95 patients who were treated with capsules (IIa) and 20 who used syrup (IIb).

Clinical data, side-effects and preliminary parasitological studies of 47 patients from Group I and 33 from Group II were presented in our first report [2].

Sex, age and clinical forms are shown in Table I. These patients came from different states and are now living in a non-endemic area.

Methods

Oral ingestion of the capsules was directly supervised by one of us (H.S.J.).

Side-effects were obtained by spontaneous descriptions from each patient. In order to study the influence of food and wakefulness condition on the incidence of side-effects, 61 adult patients from Group IIa were randomly allocated to the following schedules: Group A, 21 fasting patients; Group B, 20 patients who received the drug after lunch; Group C, 18 patients who took the drug at night, after a light meal.

(1) Instituto de Medicina Tropical de São Paulo, Liver Unit, Hospital das Clínicas, Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia (IBEPEGE), São Paulo, Brasil
(2) Liver Unit, Hospital das Clínicas, São Paulo, Brasil
(3) Liver Unit, Hospital das Clínicas and IBEPEGE, São Paulo, Brasil
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The influence of food and of wakefulness condition was studied by comparing respectively Groups A and B, and Groups B and C.

Criteria of cure was based on negative monthly stool examinations for 6 months and on the absence of viable eggs in rectal biopsies performed at the sixth month. As far as efficacy is concerned, only adult patients have a complete follow-up study.

Stool examinations were performed as previously described [2].

Blood and urine collections were done just before and on the 3rd and 10th day after treatment.

Biochemical data — Transaminases, bilirubin and blood urea nitrogen (BUN) determinations were performed as previously described [1]. Only data from patients treated with capsules (all patients from Groups I and 56 from Group IIa) will be presented.

RESULTS

1) *Side-effects* — As a whole, Oxamniquine was well tolerated, mainly at the dosis of 12.5 mg/kg (Table II). As to Group II, the incidence of side effects seems to be similar but, as previously mentioned, 18 patients from this group were treated before sleeping (Group C) and 20 patients soon after lunch (Group B). Table III shows that administration of Oxamniquine to fasting patients (Group A) produces a higher incidence of symptoms when compared to patients treated after lunch. No difference was seen when we compared side-effects in Group B and C.

2) *Biochemical data* — There was a slight increase of transaminases in a few patients. Levels higher than 100 K.U. were observed in only 4 of them (Table IV). No change in bilirubin levels was observed.

Significant urinary changes were detected in 6 out of 52 male patients (11.5%) and were characterized by hematuria and/or proteinuria, as seen in Table V.

3) *Efficacy* — Parasitological cure was observed in 54 out of 66 patients from Group I (81.8%) and in 43 out of 52 patients from Group IIa (82.7%) (Table VI). Patients from Group IIb were recently treated.

TABLE I

Sex, age and clinical forms of 227 patients with mansonian schistosomiasis on different schedules of oral oxamniquine

Clinical data	Schedules (No. of cases and %)		
	12.5 mg/kg	15 mg/kg	
		Capsules	Syrup
Sex			
Males	66 (58.9)	44 (46.3)	11 (55.0)
Females	46 (41.1)	51 (53.7)	9 (45.0)
Age			
5-12 ys	15 (13.4)	4 (4.2)	17 (85.0)
13-20 ys	23 (20.5)	28 (29.5)	3 (15.0)
21-30 ys	52 (46.4)	33 (34.7)	
31-40 ys	12 (10.7)	21 (22.1)	
more than 40 ys	10 (8.9)	9 (9.5)	
Clinical forms			
Hepatointestinal	97 (86.6)	80 (84.2)	12 (60.0)
Hepatosplenic	15 (13.4)	15 (15.8)	8 (40.0)
Total (227)	112	95	20

TABLE II

Side-effects in 225 patients on different schedules of oxamniquine

Symptoms	12.5 mg/kg Group I	15 mg/kg	
		Group IIa	Group IIb
No symptoms	64 (58.2%)	48 (50.5%)	11 (55.0%)
Dizziness	34 (30.9%)	38 (40.0%)	2 (10.0%)
Mild	8 (7.3%)	7 (7.4%)	1 (5.0%)
Moderate	13 (11.8%)	21 (22.1%)	1 (5.0%)
Severe	13 (11.8%)	10 (10.5%)	0 (0.0%)
Nausea	4 (3.6%)	8 (8.4%)	1 (5.0%)
Sleepiness	5 (4.5%)	9 (9.5%)	4 (20.0%)
Headache	6 (5.5%)	5 (5.3%)	1 (5.0%)
Diarrhea	2 (1.8%)	3 (3.2%)	0 (0.0%)
Vomiting	0 (0.0%)	3 (3.2%)	1 (5.0%)
Others	3 (2.7%)	8 (8.4%)	0 (0.0%)

TABLE III

Incidence of side-effects in adult patients who received oral oxamniquine before breakfast (Group A) after lunch (Group B) and at night (Group C)

Symptoms	Groups (No. and %)		
	A	B	C
No side-effects	7 (30.4)	15 (75.0)	14 (77.8)
With side-effects	16 (69.6)	5 (25.0)	4 (22.2)
Total of patients	23 (100.0)	20 (100.0)	18 (100.0)

Influence of food (Group A × Group B): $x^2 = 8.5$ ($p < 0.01$)
Influence of wakefulness condition (Group B × Group C): $x^2 = 0.04$ ($p > 0.05$)

TABLE IV

Serum transaminases higher than 100 U.K. after different schedules of oral oxamniquine (I = 12 mg/kg; IIa = 15 mg/kg)

Patients and schedules	No. of eggs/g	Clinical form (*)	S — GOT (**)			S — GPT (**)		
			Pre	2nd	10th	Pre	2nd	10th
I — M.C.N.	6600	HI	34	79	71	35	104	34
IIa — T.V.S.	5102	HS	52	135	36	46	179	122
IIa — G.P.S.	462	HI	40	26	93	42	39	170
IIa — E.D.C.	1295	HI	11	27	48	28	34	134

(*) HS = Hepatosplenic; HI = Hepatointestinal (**) Pre — and post-treatment

TABLE V

Urinary sediment changes in six male patients after oral oxamniquine

Patients	Dosis mg/kg	Clinical form	Pre-treatment			3rd day			10th day		
			Alb.	RBC	WBC	Alb.	RBC	WBC	Alb.	RBC	WBC
E.P.F.	12.5	HI	Neg.	1,500	5,500	Pos.	83,250	2,200	Pos.	183,000	555
J.A.P.	12.5	HS	Pos.	14,400	8,900	0,35 g	227,000	1,600	12,0 g	16,600	5,550
J.B.L.S.	12.5	HI	Neg.	3,300	16,100	Neg.	2,200	14,900	Neg.	67,000	15,700
A.F.A.	12.5	HI	0.2 g	3,800	4,200	0.2	6,000	5,600	0.9	30,000	20,000
L.F.C.	15	HS	0.1 g	5,550	6,100	Neg.	19,900	22,200	—	—	—
V.J.S.	15	HI	Neg.	1,100	Neg.	Neg.	29,400	3,900	Neg.	10,000	5,500

Neg. = Negative Pos. = Positive

TABLE VI

Efficacy in 118 patients treated with oral oxamniquine in a single dosis of 12.5 mg/kg and 15 mg/kg

Group	Dosis mg/kg	No. of patients controlled	No. of patients cured	% of cure
I	12.5	66	54	81.8
II	15.0	52	43	82.7
Total	12.5/15	118	97	82.2

DISCUSSION

A rigid adherance to the criteria of cure in 118 patients showed that cure rate after oral Oxamniquine in adult patients is very satisfactory (82.2%). Such cure rate is comparable to that found in patients treated with Hycanthone [3].

It is worth mentioning that our experience with children is limited and a longer time is needed to establish the cure-rate in this group of patients. However, our first results strongly suggest that a single dosis of about 20 mg/kg or of 10 mg twice a day — should be used for treatment of patients under 40 kg of body weight. Tolerance and efficacy after such dosis must be urgently established.

The only significant side-effect in adults was dizziness, mainly in fasting conditions. As previously pointed out, such symptom disappears spontaneously in a matter of one to two hours. The main complaint in children was drowsiness.

The incidence of side-effects was significantly lower after lunch and a night. Cure rate with Oxamniquine given after meals should be compared with that found after treatment with empty stomach.

Biochemical changes were characterized by slight increase of transaminases in some patients. An increase of transaminases over 100 K.U. was observed in only 1% of patients of Group I and in 6% from Group II.

As 15 patients from Group I and 15 from Group II (Table I) presented the hepatosplenic form, the hepatotoxicity of the drug does not seem to be high. A comparative study of liver and renal changes after Oxamniquine and Hycanthone is urgently needed. There is a strong possibility that the urinary changes are due to the antigen-antibody complexes formed after treatment [2].

RESUMO

Estudos clínicos com oxamniquine (UK 4271), nova droga esquistossomicida

Oxamniquine (UK 4271) mostrou ser uma droga eficiente para o tratamento da esquistossomose mansoni, em adultos. Foram obtidos índices de cura semelhantes com dose única de 12,5 e 15,0 mg/kg de peso corporal (81,8% e 82,7%, respectivamente). A tolerância e toxicidade não parecem impedir seu uso em larga escala, mas há necessidade de novos estudos.

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