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CLINICAL TRIALS WITH ORAL OXAMNIQUINE (UK 4271) FOR THE TREATMENT OF MANSONIAN SCHISTOSOMIASIS

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SUMMARY

Oral oxamniquine (UK 4271) was given to 109 schistosomotic patients according to the following schedules: Group I, 10 mg/kg of body weight (29 patients); Group II, 12-12.5 mg/kg (47 patients); Group III, 15 mg/kg (33 patients). Parasitological cure was observed in 14 out of 20 patients from Group I (70.0%), in 22 out of 27 patients from Group II (81.5%) and in all 23 patients from Group III (100.0%). Oral oxamniquine in a single dosis of 12 to 15 mg/kg is a very promising drug for the treatment of Schistosomiasis mansoni.

INTRODUCTION

According to our experience [8] and to the other [2, 3, 7] hycanthone showed to be the best available drug for the treatment of mansonian schistosomiasis with a cure rate of 85% after a single intramuscular injection of 2.5 mg/kg of body weight.

However, some toxic effects on the liver cell, and more rarely, on the miocardium has been observed [1, 3]. A few cases of death due to toxic hepatitis have been published [3].

Oxamniquine (UK 4271), a new schistosomicide obtained by hydroxymethylation of 2-aminomethyltetrahydroquinoline (UK 3883) seems to be a very efficient drug with low toxicity for man, when given by intramuscular route in a single dosis of 7.5 mg/kg of weight.

Besides a cure rate of 92.7%, oxamniquine produced only slight increases of serum glutamic piruvic transaminases in 20% of 53 patients [9]. Only one of them showed an increase of 490 U. of S-GPT. Local pain, however, was very severe in 40 out of 53 patients.

As such symptom precludes the use of intramuscular oxamniquine in large scale we started a trial with the oral form in order to stablish its tolerance and efficacy.

MATERIAL AND METHODS

MATERIAL

A total of 109 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: 10 mg/kg of weight: 29 patients;

Group II: 12-12.5 mg/kg of weight: 47 patients;

Group III: 15 mg/kg of weight: 33 patients.

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.

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METHODS

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

Side effects were obtained by expontaneous descriptions from each patient (Table II).

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.

Stool examinations were performed according to the quantitative Kato's method as modified by KATZ et al. [5] and to the sedimentation technique of HOFFMANN, PONS & JANNER [4].

Each stool specimen was submitted to two counts and two sedimentation tests.

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

In 4 patients urine analysis was performed daily or every other day for a period of 15 to 20 days.

Biochemical data — Transaminases, bilirubin and blood urea nitrogen (BUN) determinations were performed as previously described [9].

RESULTS

1) *Side effects* — Oral oxamniquine was very well tolerated at the dosis of 10 and 12-12.5 mg/kg (Groups I and II). Many patients from Group III (42.4%), however, complained of moderate to severe dizziness. Such symptoms were of short duration (1 to 2 hours) and disappeared expontaneously. No symptomatic medication was given to the patients (Table II).

2) *Biochemical data* — As shown in Table III, IV and V there was a slight increase of transaminases in some patients. Significant increases of GPT, higher than 100 K.U. were observed in only 4 patients, but the highest level was 179 K.U. (Table VI). Furthermore, no change in bilirubin levels was observed.

Blood cell counts did not show any significant change except a slight decrease of leu-

TABLE I

Sex, age and clinical forms of 109 patients with mansonian schistosomiasis on different schedules of oral oxamniquine

Clinical data	Number of cases (%)		
	10 mg/kg	12 mg/kg	15 mg/kg
Sex			
Males	17 (58.5)	22 (46.8)	13 (39.4)
Females	12 (41.4)	25 (53.2)	20 (60.6)
Age			
8 — 12 ys.	1 (3.4)	10 (21.3)	2 (6.1)
13 — 20 ys.	5 (17.2)	7 (14.9)	8 (24.2)
21 — 30 ys.	15 (51.7)	17 (36.1)	10 (30.3)
31 — 40 ys.	5 (17.2)	3 (6.4)	10 (30.3)
more than 40 ys.	3 (10.3)	10 (21.3)	3 (9.1)
Clinical forms			
Hepatointestinal	26 (89.6)	38 (80.8)	28 (84.8)
Hepatosplenic	3 (10.4)	9 (19.2)	5 (15.2)
Total (109)	29	47	33

TABLE II

Side-effects in 109 patients on different schedules of oral oxamniquine

Symptoms	29 patients 10 mg/kg	47 patients 12-12.5 mg/kg	33 patients 15 mg/kg
No symptoms	19 (65.5%)	29 (61.8%)	9 (27.3%)
Dizziness	4 (13.8%)	6 (12.8%)	17 (51.5%)
Mild	1 (3.5%)	2 (4.3%)	3 (9.1%)
Moderate	1 (3.5%)	0 (0.0%)	7 (21.2%)
Severe	2 (6.8%)	4 (8.5%)	7 (21.2%)
Nausea	1 (3.5%)	3 (6.4%)	4 (12.1%)
Sleepiness	0 (0.0%)	2 (4.2%)	2 (6.1%)
Diarrhea	5 (1.7%)	0 (0.0%)	0 (0.0%)
Headache	1 (3.5%)	2 (4.2%)	0 (0.0%)
Vomiting	0 (0.0%)	0 (0.0%)	2 (6.1%)
Others	1 (3.5%)	3 (6.4%)	9 (27.3%)

TABLE III

Serum transaminases before and after oral oxamniquine in a single dosis of 10 mg/kg

Serum transaminases	Before treatment	After treatment	
		2nd day	10th day
S-GOT			
Normal: 8-40 K.U.	25 (92.5%)	24 (88.8%)	16 (72.7%)
41-100 K.U.	1 (3.7%)	3 (11.1%)	6 (27.3%)
more than 100 K.U.	1 (3.7%)	0 (0.0%)	0 (0.0%)
Average	23.4	22.3	33.0
No. of patients	27	27	22
S-GPT			
Normal: 5-35 K.U.	25 (92.5%)	25 (92.5%)	19 (86.4%)
36-100 K.U.	2 (7.4%)	2 (7.4%)	2 (9.1%)
more than 100 K.U.	0 (0.0%)	0 (0.0%)	1 (4.5%)
Average	18.8	30.3	26.6

TABLE IV

Serum transaminases before and after oral oxamniquine in a single dosis of 12-12.5 mg/kg

Serum transaminases	Before treatment	After treatment	
		2nd day	10th day
S-GOT			
Normal: 8-40 K.U.	29 (100.0%)	28 (100.0%)	27 (93.1%)
41-100 K.U.	0 (0.0%)	0 (0.0%)	2 (6.9%)
more than 100 K.U.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Average	16.0	18.5	21.2
No. of patients	29	28	29
S-GPT			
Normal: 5-35 K.U.	27 (93.1%)	27 (96.4%)	25 (86.2%)
36-100 K.U.	2 (6.9%)	1 (3.6%)	4 (13.7%)
more than 100 K.U.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Average	13.4	14.2	19.7

TABLE V

Serum transaminases before and after oral oxamniquine in a single dosis of 15.0 mg/kg

Serum transaminases	Before treatment	After treatment	
		2nd day	10th day
S-GOT			
Normal: 8-40 K.U.	25 (96.1%)	17 (94.4%)	21 (84.0%)
41-100 K.U.	1 (3.8%)	0 (0.0%)	4 (16.0%)
more than 100 K.U.	0 (0.0%)	1 (0.0%)	0 (0.0%)
Average	18.4	23.7	25.5
No. of patients	26	18	25
S-GPT			
Normal: 5-35 K.U.	23 (88.5%)	16 (88.9%)	21 (84.0%)
36-100 K.U.	3 (11.5%)	1 (5.5%)	1 (4.0%)
more than 100 K.U.	0 (0.0%)	1 (5.5%)	3 (12.0%)
Average	17.5	22.8	31.6

TABLE VI

Serum transaminases higher than 100 U.K. after different schedules of oral oxamniquine (A = 10 mg/kg; C = 15 mg/kg)

Patient no.		No. of eggs/g	Clin. form(*)	S-GOT			S-GPT		
				Pre	2nd	10th	Pre	2nd	10th
27	A	261	HS	101	55	92	99	50	115
28	C	5,102	HS	52	135	36	46	179	122
83	C	462	HI	40	26	93	42	39	170
85	C	1,295	HI	11	27	48	28	34	134

(*) HS = Hepatosplenic; HI = Hepatointestinal

kocyte in three patients. Post-treatment eosinophila was frequently observed.

Significant urinary sediment changes, detected in 8 male patient (Table VII) were characterized by hematuria and, more rarely, by proteinuria.

3) *Efficacy* — Parasitological cure was observed in 14 out of 20 patients from Group I (70.0%) in 22 out of 27 patients from Group II (81.5%) and in all 23 patients from Group III (100.0%).

It is worth mentioning that three non-cured patients from Group II weighted less than 40 kg.

DISCUSSION

According to KATZ et al.[6] oxamniquine produced no side-effects in schistosomotic patients when administered orally up to a total dosis of 400 mg. Such dosis, however, was only slightly active, reducing the numbers of excreted eggs in 3 out of 9 patients.

We performed our trial with three differen schedules 10.0 mg/kg (Group I), 12.0-12.5 mg/kg (Group II) and 15.0 mg/kg (Group III).

Cure-rates show that oxamniquine is highly active, even in dosis of 10 mg/kg of body weight. Thus, parasitological cure was obtained in 14 out of 20 patients from Group I (70.0%), in 22 out of 27 patients from Group II (81.5%) and in all 23 patients from Group III (100.0%).

The only significant side-effect was dizziness which appeared with the same frequency in Groups I and II but increased steadily in Group III. Such symptom, however, disappeared expontaneously in a matter of one to two hours.

No prophylatic medication was used.

As far as side-effects are concerned, the oral formulation compares favorably with intramuscular oxamniquine, which produces a severe pain on the local of injection[9].

Biochemical changes seemed to be less frequent with the oral drug. Thus, an increase of transaminases over 100 K.U. was observed in 3 out of 81 patients (3.7%) with the oral drug and in 3 out of 44 patients (6.8%) after IM oxamniquine.

Slight leukopenia was observed in only three patients and does not seem to be an important complication.

Urinary changes characterized by hematuria and proteinuria were observed in 8 male patients (Table VII). Three of them (J. R. V. V., J. A. P. and A. F. A.) had already showed abnormal results before treatment. In patient J. A. P. a nephrotic syndrome was observed and took eight weeks to disappear.

Some studies are in progress in order to differentiate renal changes due to a direct

TABLE VII

Urinary sediment changes in some male patients after oral oxamniquine

Patients no.	Dosis (mg/kg)	Clin.(*) form	Pre-treatment			3rd day			10th day		
			Alb.	RBC	WBC	Alb.	RBC	WBC	Alb.	RBC	WBC
7. M.P.	10	HI	Neg.	4,440	Neg.	Neg.	10,000	555	Neg.	17,500	1,100
8. A.C.O.	10	HI	Neg.	550	1,650	Pos.	2,800	2,800	Neg.	1,100	550
10. J.R.V.V.	10	HI	Neg.	19,250	7,700	Neg.	101,000	1,600	Neg.	1,100	2,800
15. J.F.F.	10	HI	Neg.	550	550	Neg.	Neg.	Neg.	Pos.	1,670	1,100
20. E.P.F.	12	HI	Neg.	1,500	5,500	Pos.	83,250	2,200	Pos.	183,000	555
32. J.A.P.	12	HS	Pos.	14,400	8,900	0,36 g	227,000	1,600	12,0 g	16,600	5,550
40. V.J.F.	15	HI	Neg.	1,100	Neg.	Neg.	29,400	3,900	Neg.	10,000	5,500
94. A.F.A.	12,5	HI	0,2	3,800	4,200	0,2	6,000	5,600	0,9	30,000	20,000

(*) HI = Hepatointestinal
HS = Hepatosplenic

action of the drug from those consequent to the formation of antigen-antibody complexes. Such complexes seem to be an important cause for the glomerular changes observed in Schistosomiasis mansoni [10].

Summing up, oral oxamniquine is a very promising drug for the treatment of schistosomiasis mansoni. Our preliminary results on tolerance and efficacy suggest that the ideal dosis for human cases should be between 12 and 15 mg/kg of body weight. It is our feeling that 12 to 12.5 mg/kg should be given to patients over 40 kg of weight and 15 mg to the other patients. New trials on this problem are in progress.

RESUMO

Estudos clínicos com a oxamniquine (UK 4271) administrada oralmente para o tratamento da esquistossomose mansônica

Administramos a oxamniquine (UK 4271) por via oral a 109 pacientes esquistossomóticos, de acordo com os seguintes esquemas: Grupo I, 10 mg/kg de peso (29 pacientes); Grupo II, 12 a 12,5 mg/kg (47 pacientes); Grupo III, 15 mg/kg (33 pacientes). Cura parasitológica foi observada entre 14 de 20 pacientes do Grupo I (70,0%), em 22 de 27 pacientes do Grupo II (81,5%) e em todos os 23 pacientes do Grupo III (100,0%).

A oxamniquine oral, em doses únicas de 12 a 15 mg/kg de peso mostrou-se altamente esquistossomicida.

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