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OXAMNIQUINE (UK 4271) IN THE TREATMENT OF VESICAL SCHISTOSOMIASIS IN WESTERN NIGERIA

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SUMMARY

In this, the first reported trial from West Africa, the effectiveness of oral and parenteral oxamniquine against **S. haematobium** was investigated in two separate but related trials. The overall results were very disappointing. The parenteral preparation at a single dose of 7.5 mg/kg body weight was found to be ineffective in curing the infection, and although a maximal decrease of 46.4% was recorded after two months the severity and frequency of local side effects was such that it was considered undesirable to continue with the injectable formulation. The single dose of the oral preparation (range 9 — 25 mg/kg body weight) effected cure in only 17.2% of 29 patients with extremely light infections. Using three different schedules totalling 60 mg/kg over 2 — 3 days, there were no cures, though the most promising results in respect of reduction in egg counts and paucity of side effects were recorded, in patients treated with 10 mg/kg body weight twice daily for 3 days. It is suggested that by repeating this dose after two months, when the largest fall in egg counts was recorded (71.4%), a further reduction and possible cures might be obtained. The drug's relative freedom from serious side effects is confirmed.

INTRODUCTION

Oxamniquine (6-hydroxymethyl-2-isopropylaminomethyl-7-nitro-a, 1, 2, 3, 4 — tetrahydroquinoline) is a new schistosomicidal drug developed by Pfizer Limited in 1969. It is obtained by hydromethylation of 2-aminomethylhydroquinoline and has been shown in laboratory trials using mice, hamsters and monkeys to be effective in curing **Schistosoma mansoni** infection when given as a single dose, orally or by injection [8,9,13]. Cure rates in infections with the other two human species of schistosomes, **S. haematobium** and **S. japonicum** have however been very low [9]. Although clinical trials with oxamniquine in human infections have largely confirmed these laboratory observations [3,4,5,7,8,10,11,12,14,15,16,17,18] there still exist some conflicting reports about the drug's activity against **S. haematobium.**

The aims of this study were: 1) To determine the relative efficacy of the oral and parenteral preparations of the drug against **S. haematobium** in patients suffering from the infection in an endemic area of Western Nigeria, and 2) to assess its tolerance and toxicity at various doses. The study was undertaken in two phases.

Phase I

Patients and methods

51 Patients who were excreting viable **S. haematobium** ova in their urine were enrolled for this phase of the trial. 48 (94.1%) were school children aged between 6 and 15, the remaining 3 (5.9%) were aged 18, 21 and 25 years. 29 Were treated with a single dose of the oral preparation made up as capsules

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in a dose ranging between 9.0 mg/kg and 20 mg/kg body weight. The remaining 22 patients were treated with the parenteral preparation in a dose of approximately 7.5 mg/kg body weight, the single dose being divided into two equal parts, one half being injected deep into the gluteus maximus of each buttock. Patients who had received treatment for schistosomiasis within the preceeding six months were excluded from the trial.

All the 22 patients who received the parenteral form and the first 13 of those given the capsules were admitted to hospital for the first two weeks of the trial. Full physical examination of all the patients were carried out before and at the conclusion of the trial which included a period of follow-up lasting four months after the drug was administered.

Patients were questioned about systemic and local side effects on the day that treatment was administered and on the 3rd, 7th, 14th and 28th days thereafter. On these occasions venous blood and midstream urine specimens were obtained for haematological, biochemical and renal function tests. Urine albumin and sugar were tested for with "Albustix" and "Clinistix" respectively. The effectiveness of treatment was determined by counting the number and viability of eggs excreted in midday urine specimens before commencement of treatment (taking the mean egg count of two such specimens), and at monthly intervals for four months after treatment. Bell's filtration technique was used for egg-counting [1], while viability of eggs was determined by the hatching test and a high power microscopic examination for ciliary or embryonic movements, and flame cell's activity.

Patients who were still passing viable eggs at the end of the period of observation were treated with niridazole ("Ambilhar").

RESULTS

Excretion of Eggs

Oral preparation

Table I summarises the effect on egg excretion of treatment with oral oxamniquine. In 8 (27.6%) patients the urines were egg-free after 1 month, and 5 (17.2%) were still negative at the end of the fourth month. These five patients received 10 mg, 15 mg, 16 mg and 16.5 mg per kg body weight of the drug respectively. However the infections in all of these patients were extremely light, none being higher than 30 eggs per 10 ml of urine, and in 3 the counts were less than 10 eggs per 10 ml.

TABLE I

Variation in egg counts/10 ml urine in 29 patients treated with oral Oxamniquine

Count	Pre-treatment	1st Month	2nd Month	3rd Month	4th Month
0	0	8	5	5	5
1 —	10	3	4	5	3
10 —	10	9	13	5	10
100 —	5	2	0	2	2
200 +	4	6	4	2	4
Absent	0	1	3	10	5
Mean Egg Count	118	108	87	63	99
% of Pre-treatment Mean Count		91.5%	73.7%	53.4%	83.9%

16 Of the 24 patients who reported for examination at the end of the fourth month were excreting fewer eggs, and the overall mean percentage reduction in egg count for each of the four months after treatment was 8.5%, 26.3%, 46.6% and 16.1% respectively.

Parenteral preparation

Table II summarises the effect on egg counts of treatment with the intramuscular preparation. All 22 patients so treated continued to excrete viable eggs throughout the four months of the trial.

The percentage changes in the mean egg count relative to the pre-treatment values for the four months after treatment were an increase of 2.6% in the first month, a reduction of 46.4% and 6.2% for the second and third months respectively, followed by an increase of 15.1% at the end of the fourth month. Only 9 (40.9%) of the patients were excreting fewer eggs at the end of the trial than at the beginning.

TABLE II

Variations in egg counts/10 ml urine in 22 patients treated with injectable Oxamniquine

Count	Pre-treatment	1st Month	2nd Month	3rd Month	4th Month
0	0	0	0	0	0
1 —	2	2	2	1	1
10 —	8	7	11	8	6
100 —	3	7	2	2	5
200 +	9	5	3	6	7
Absent	0	1	4	5	3
Mean Egg Count	192	197	103	180	221
% of Pre-treatment Mean Count		102.6%	53.6%	93.8%	115.1%

Table III summarises the changes in egg excretion in all 51 patients. All patients subsequently treated with niridazole ("Ambilhar") were cured within three months.

TABLE III

Variation in egg counts/10 ml in 51 patients (pooled oral and injection)

Count	Pre-treatment	Post-treatment			
		1st Month	2nd Month	3rd Month	4th Month
0 —	0	8	5	5	5
1 —	12	5	6	6	4
10 —	18	16	24	13	16
100 —	8	9	2	4	7
200+	13	11	7	8	11
Absent	0	2	7	15	8
Mean Egg Count	150	146	103	118	153
% of pre-treatment Mean count		97.3%	68.7%	78.7%	102.0%

The only patient who was infected with both **S. mansoni** and **S. haematobium** ceased to excrete **S. mansoni** eggs in the stool at the end of 2 weeks, although he was still excreting viable **S. haematobium** eggs in his urine at the end of three months, after which he defaulted.

TOXICITY

Haematological Tests

No significant changes in haemoglobin, packed cell volume, total and differential white cell counts were recorded with either formulation. The minor transient alterations that were noted had returned to pre-treatment levels within a month.

Biochemical Tests

In only 4 patients, all of whom were given oral oxamniquine, were there significant elevations in serum transaminases. These occurred in tests conducted between the third and fourteenth days after treatment, but had returned to normal at the end of 4 weeks. A similar observation was made by KATZ et al. in their study in Brazil [10]. Estimations of blood urea, bilirubin and total protein values remained normal in all patients throughout the period of the trial.

Creatinine phosphokinase (C.P.K.) estimations were done on all patients treated with the parenteral preparation, and in 18 (81.8%) of these, there was a sharp elevation in value two days after treatment was administered, with a return to normal at the end of the same week. This represents, in the absence of other functional disturbances, evidence of transient local muscle damage and not hepatoxicity. In the other three patients, the C.P.K. values remained normal throughout (see Fig. 1).

Urine Tests

These remained essentially unchanged in all patients. Indeed there was no glycosuria in any of the 51 patients. Microscopic examination of centrifuged deposit was unremarkable. There was no significant or consistent pattern in the slight changes in the frequency or concentration of erythrocytes of leucocytes. In 4 cases urinary casts were observed only after treatment was commenced, but this did not persist beyond a solitary occasion in three patients. In one child on the oral preparation it was detected on two consecutive occasions. These observations did not appear to be significant or dose related.

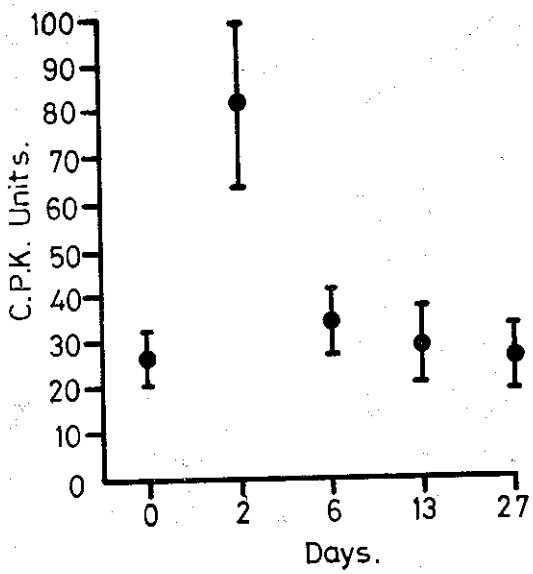

Fig. 1 — Fluctuations in C.P.K. values after treatment with intramuscular oxamniquine

Clinical Symptoms

The effect of treatment on four symptoms were studied viz: haematuria, dysuria, abdominal pains and the presence of blood in stools. The results are summarised in Table IV.

TABLE IV

Clinical symptoms in all 51 patients (Oral and injection)

	Percentage number with symptoms				
	Pre-treatment	1st Month	2nd Month	3rd Month	4th Month
Haematuria	68.6%	50%	51.1%	53.8%	61.4%
Dysuria	31.4%	14%	22.2%	17.9%	15.9%
Abdominal pain	47.1%	32%	26.5%	17.9%	11.4%
Blood in stool	9.8%	0%	2.2%	2.2%	0%

Approximately 50% and 75% of patients with dysuria and abdominal pains respectively were free of these symptoms at the end of four months. All 5 patients who claimed to pass blood in their stools, occasionally, before treatment was commenced reported that they no longer did so at the end of the trial, although examinations of their stools before treatment and throughout the trial were negative for blood. There was however, no significant improvement in the occurrence of haematuria.

Side Effects

Systemic side effects — 24 Patients experienced various types of systemic side effects (47.1%), the frequency and distribution of these side effects are summarised in Table V. All were transient and mild.

TABLE V

Distribution and frequency of systemic side effects in 51 patients given oral and parenteral Oxamniquine

Side Effect	Capsules	Injection
Abdominal pain	7	—
Drowsiness	3	—
Nausea	2	2
Dizziness	2	—
Rash	2	—
Headache	2	—
Fatigue	1	—
Pyrexia (*)	—	7

(*) range 99.6°F — 104.2°F

Local side effects

Local side effects in patients treated with injection were recorded in respect of pain, tenderness and induration of the side of the injection. None of these side effects persisted beyond the first ten days. The findings are summarised in Table VI.

Phase II

Patients and Methods

57 Pupils of St. Paul's School Odoona in Ibadan, aged 7 — 14 years who were excreting viable **S. haematobium** ova were enrolled and allocated at random into three treatment regimens of the oral preparation each totalling 60 mg/kg body weight.

Group A (19 patients) 15 mg/kg twice daily x 2 days

Group B (19 patients) 10 mg/kg twice daily x 3 days

TABLE VI

Frequency and severity of local side effects in 22 patients treated with intramuscular Oxamniquine

Grade	PAIN					TENDERNESS					INDURATION				
	Day					Day					Day				
	0	2	6	13	27	0	2	6	13	27	0	2	6	13	27
0	8	1	12	22	19	4	0	7	22	19	20	4	10	22	19
1	7	2	6	0	0	10	1	8	0	0	1	13	8	0	0
2	6	8	2	0	0	7	6	5	0	0	1	3	3	0	0
3	1	5	2	0	0	1	10	1	0	0	0	2	1	0	0
4	0	6	0	0	0	0	5	1	0	0	0	0	0	0	0
Absent	0	0	0	0	3	0	0	0	0	3	0	0	0	0	3

Grading
0 = Absent
1 = Mild/Slight
2 = Moderate
3 = Severe, but mobile
4 = Unbearable, compelled to stay in bed.

Group C (19 patients) 10 mg/kg 8 hourly x 6 doses.

Three pre-treatment midday urine specimens were collected from each patient, and the mean egg count of the three as evaluated by Bell's filtration method was taken to represent the intensity of infection. Full physical examination and haematological, biochemical and renal function tests were carried out on all patients as in the first phase of the trial. Evaluation of the results of treatment over four months was similarly carried out.

Results

Egg Excretion

The effect of treatment on the excretion of eggs in all three treatment groups is summarised in Tables VII and VIII.

TABLE VII

Effect of treatment on mean egg count per 10 ml (% change)

Interval	Groups			All groups
	A	B	C	
Pretreatment	318	427	269	338
1st month	242 (—23.9)	137 (—67.9)	157 (—41.6)	179 (—47.0)
2nd month	184 (—42.1)	122 (—71.4)	265 (—1.5)	190 (—43.8)
3rd month	394 (+23.9)	187 (—56.2)	170 (—36.8)	250 (—26.0)
4th month	328 (+3.1)	426 (—0.2)	186 (—30.9)	313 (—7.4)

The pattern of fluctuations in groups A and B were identical. There was a sustained fall in the first two months with a return to pre-treatment levels and higher in groups B and A respectively after four months. The sharpest fall in egg counts (71.4%) occurred after two months in group B, whilst in group C an irregular swing was recorded over the four month period (see Fig. 2). None of the 57 patients was cured.

TABLE VIII

Effect of treatment on egg excretion in three groups treated with oral oxamniquine

Group (*)	A					B					C				
Egg Count/ 10 mls urine	Pre- (**) treat- ment	Post treatment				Pre- (**) treat- ment	Post treatment				Pre- (**) treat- ment	Post treatment			
		1st month	2nd month	3rd month	4th month		1st month	2nd month	3rd month	4th month		1st month	2nd month	3rd month	4th month
0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
1 —	5	4	12	5	7	5	6	10	11	5	3	10	7	5	6
100 —	9	5	3	4	7	8	3	2	3	4	9	3	4	9	8
250 —	1	4	2	5	2	4	3	1	1	3	5	4	5	5	1
500 —	3	0	1	0	1	1	0	1	3	3	2	1	1	0	2
1000 —	1	1	1	1	2	1	0	0	0	2	0	0	1	0	0
Abs.	0	5	0	4	0	0	6	5	1	2	0	0	1	0	2
Total	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19

(*) Group A 15 mg/kg b.d. x 2 days
Group B 10 mg/kg b.d. x 3 days
Group C 10 mg/kg 8 hourly x 6 doses
(**) Mean counts from 3 consecutive daily specimens

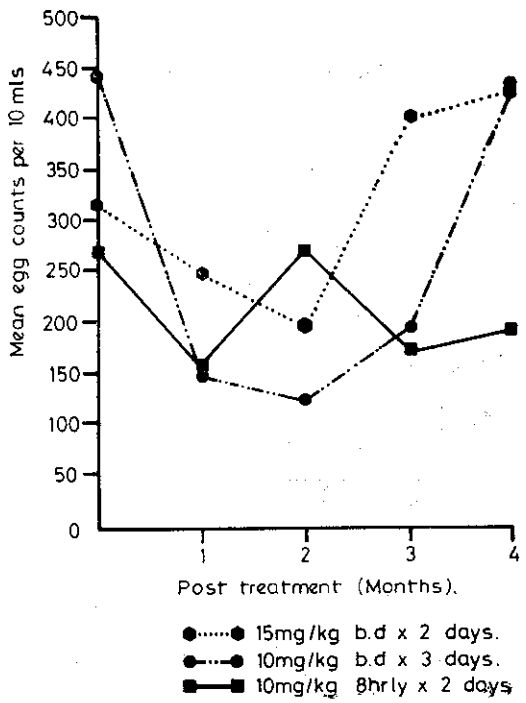

Fig. 2 — Mean monthly fluctuations in egg excretion in three groups of patients treated with oral oxamniquine

Toxicity

No clinically significant alterations in haematological, biochemical and renal function tests were noticed.

Side effects

The frequency of side effects recorded is summarised in Table IX. The highest number of side effects occurred in group A. 11 Patients had 19 separate episodes of side-effects in group A, 4 patients had 4 episodes in group B and 10 patients had 12 episodes in group C.

TABLE IX

Frequency of systemic side effects in three groups of patients treated with oral Oxamniquine

Side Effects	Groups		
	A	B	C
Abdominal pain	0	0	4
Nausea & vomiting	1	0	2
Drowsiness	8	2	1
Dizziness	9	1	5
Rash	1	0	0
Headache	0	1	0
Total	19	4	12

Clinical signs and Symptoms

No significant alteration in clinical signs of symptoms was noticed in any of the groups of patients after treatment.

DISCUSSION

The ideal schistosomicidal drug should be effective, cheap, safe and simple to administer. The results of the first phase of this trial indicate that oxamniquine was ineffective against **S. haematobium** when given either as a single oral dose of up to 20 mg/kg body weight or by injection at a dose of 7.5 mg body weight. Cure rates were low, 17.2% (5/29) and nil (0/22) for the oral and injectable preparations respectively, while reduction in egg excretion for both were equally disappointing over the four months period of follow up after treatment.

Although some improvement in the symptoms of dysuria, abdominal pains and the passage of blood in stools was recorded there was no similar improvement in the occurrence of haematuria. All 5 patients who claimed to pass blood in the stools, before treatment was administered, reported freedom from this symptom at the end of the period of observation, though at no time before or during treatment was there a laboratory confirmation made of this symptom. The only patient with concomitant **S. mansoni** infection was cured of that infection but continued to excrete viable **S. haematobium** ova throughout the period of trial.

There was no evidence of toxicity with either preparation, and though tolerance was good in respect of oral oxamniquine, the limit of tolerance in respect of local side effects of the intramuscular preparation would appear to have been reached. In studying the local side-effects of a single intramuscular injection of oxamniquine, REES et al.[15] using 4 mg/kg, and DONAHUE [6] who used doses up to 13.3 mg/kg have suggested that by dividing the dose between two or more sites, the pain and induration provoked by the injection might be better tolerated. This suggestion has not been borne out by this trial, where approximately 7.5 mg/kg was divided between two sites. COUTINHO et al. [4] came to a conclusion similar to ours in their trial in Brazil. The average duration of the local side-effects of 5-10 days is similar to that reported by SILVA et al. [17] and most other workers.

The decision to undertake phase II of the trial was prompted partly by reports communicated to us by the manufacturers that some other workers have indicated that more satisfactory results were obtained when oral oxamniquine was administered in divided daily doses for 2 - 3 days, and partly from the experience we gained in the first phase. In the second trial the best result in respect of reduction in egg counts occurred in the group of patients (B) treated with 10 mg/kg twice daily for 3 days, but even this result was far from satisfactory. The most marked reduction (71.4%) was recorded at the end of the second month of treatment, but the egg counts were back to pre-treatment levels by the fourth month. This group also had the fewest number of side-effects.

We feel that the administration of a second and similar course of oxamniquine at the end of the second month might result in further reduction in egg excretion, and possibly higher cure rates, although there is a possibility that such multiple and repeated dose regimens may have a cummulative effect that could result in an increase in the frequency of undesirable clinical side effects and toxicity.

The impression that **S. haematobium** is less sensitive to oxamniquine than **S. mansoni** is confirmed by this study. So is the findings of other workers that African schistosomiasis appears to be less responsive to treatment than the South American form of the disease. Furthermore this study agrees in practically all respects with the results of the Rhodesian trials conduced by CLARKE et al. [3] and lends support to the view that infections in children, the majority of whom (105/108) comprised these trials, are more difficult to cure [2], irrespective of the chemotherapeutic agent used, though we are still to determine oxamniquine's effectiveness in adults.

The relative absence of serious toxic side effects that have been widely reported from other centres is confirmed by this study which also showed that there were fewer side effects when the same total dose is spread over 3 days than 2 days. Further trials with differ-

ent dose regimens of the oral preparation as we have suggested should be encouraged.

RESUMO

Oxamniquine (UK 4271) no tratamento da esquistossomose vesical na Nigéria Ocidental

Empreendeu-se na África Ocidental uma investigação pioneira sobre a eficácia da oxamniquine administrada pelas vias oral e parenteral contra o **S. hematobium,** em dois planos de pesquisa diversos, porém inter-relacionados. Os resultados gerais não revelaram o sucesso desejado. A preparação parenteral em uma dose única de 7,5 mg/kg de peso corpóreo mostrou-se ineficaz na cura da doença e, apesar de haver sido observada uma redução máxima de 46,4% ao fim de dois meses, a severidade e freqüência dos efeitos colaterais locais foram de intensidade tal que se considerou indesejável continuar com a formulação injetável. A dose única da preparação oral (de 9 - 25 mg/kg peso corpóreo) curou apenas 17,2% de 29 pacientes que apresentavam infestações extremamente ligeiras. Utilizando três esquemas de tratamento diferentes, cuja dose total era de 60 mg/kg durante 2-3 dias, não se obtiveram curas, embora se registrassem resultados os mais promissores com relação à redução no número de ovos e paucidade de efeitos colaterais, em pacientes tratados com 2 x 10 mg/kg peso corpóreo durante 3 dias. Sugere-se que a repetição deste último esquema após dois meses, prazo em que se registrou a queda mais pronunciada nas contagens de ovos (71,4%), poder-se-iam obter nova redução no número de ovos e possível cura. Confirmou-se a relativa isenção de efeitos colaterais na oxamniquine administrada por via oral.

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