Field trials of praziquantel and oxamniquine for the treatment of schistosomiasis mansoni in Burundi

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Abstract

Praziquantel and oxamniquine were evaluated under operational conditions for use in mass-treatment campaigns in the Rusizi Plain, Burundi. After 6 weeks, the cure rates for oxamniquine at 20, 30 and 40 mg/kg in children (<20 years) were respectively 47%, 67% and 86%; in adults they were 86%, 97% and 97%. The egg reduction rates were over 98% in all groups. For praziquantel at 20, 30 and 40 mg/kg the cure rates in children were respectively 58%, 63% and 78%; in adults, 55%, 87% and 91%. The egg reduction rates were respectively 92%, 96%, 98% and 91%, 98%, 98%. These results were largely confirmed by a follow-up 3 months after treatment. Oxamniquine frequently caused important dizziness and drowsiness, and in 2 cases epileptiform seizures. The side effects of praziquantel were mainly mild transient colics and diarrhoea. The cost of oxamniquine (in Burundi) was twice to three times the cost of praziquantel. Because of its better acceptability and its lower cost, with only slightly less good parasitological results, praziquantel, at 40 mg/kg in a single dose, has been selected as the drug of choice for mass-treatment campaigns in Burundi.

Introduction

In Burundi, a series of epidemiological and operational studies has been performed in order to establish a national control programme of *Schistosoma mansoni*. In one study, we tried to select the optimal drug and treatment schedule for mass treatment in local operational conditions. Praziquantel and oxamniquine were assessed. In this paper we compare their intrinsic therapeutic and operational value: therapeutic efficiency, side effects, acceptability, ease of administration, preferably in a single dose, and cost.

Population, Material and Methods

Originally, one trial took place for each drug in two adjacent localities, Maramvya and Bulinga, situated in the Rusizi Plain, where schistosomiasis mansoni is widespread (GRYSEELS, 1984, 1985). In Maramvya (population about 800), oxamniquine was tried out, and in Bulinga (population about 1400) praziquantel was used, each at 20, 30 and 40 mg/kg body weight in a single dose. However, oxamniquine at 40 mg/kg quickly proved to cause such important side effects that it was subsequently given in 2 doses with a 4 h interval. An additional trial was held afterwards in the nearby village of Bulamata (population about 1000), where praziquantel at 30 and 40 mg/kg (to which the choice by then had narrowed) was further evaluated. In each village, all inhabitants were invited to a convenient central spot, fully identified, and asked to produce a fresh stool sample. Double 25 mg Kato slides were prepared and examined by two different microscopists 24 to 36 h later, and the egg load per gram (epg) calculated. A random 15% sample of the slides and duplicate slides with grossly different results were re-examined and checked by the investigator, with satisfactory results. People showing eggs of *S.mansoni* in the stools were then invited for treatment; the different schedules were randomly allotted (single-blind). The available commercial forms of the drugs, delivered directly by the manufacturer, were used: 250 mg capsules and 5 g/100 ml syrup, or both, for oxamniquine, divisible 600 mg tablets for praziquantel. Pregnant women were excluded from treatment (and treated after delivery). The patients were kept under observation for at least an hour after treatment, and interviewed the day after treatment about side-effects.

The treated subjects were re-examined with the same parasitological method 6 weeks and 3 months after treatment.

Results

In Maramvya, 707 people were examined, 465 of whom showed eggs of *S. mansoni* in the stools; 430 were treated. In Bulinga 1309 subjects were examined and 457 of 504 positive cases were treated. In Bulamata 818 subjects were examined and 333 of 343 positive patients treated.

The cure rate (percentage of subjects treated who became parasitologically negative) 6 weeks after treatment, the percentage of moderate and heavy infections before and after treatment, and the egg load reduction rates (calculated as the percentage reduction of the geometric means of epg+1) are summarized in Table 1. The cure rates and egg reduction rates after 3 months are shown in Table 2. Although this period is long enough to allow for reinfection to take place, they confirm in general the 6 weeks results on which further discussion will be based.

The results from Bulamata and Bulinga for praziquantel 30 and 40 mg/kg have been pooled. Some people in Maramvya receiving oxamniquine 40 mg/kg did not re-attend for their second dose, and have been included in the 20 mg/kg group.

In adults, oxamniquine gave excellent results at both 30 and 40 mg/kg, with very high cure rates and egg reduction rates, and elimination of all moderate and heavy infections. Though the cure rate was significantly lower at 20 mg/kg ($\chi^2=5{\cdot}14$, $P<0{\cdot}05$), the results were still quite satisfying. In children, oxamniquine gave good results at 40 mg/kg. At 30 mg/kg, and certainly at 20 mg/kg, the cure rates were much lower ($\chi^2=15{\cdot}41$, $P<0{\cdot}005$), though the egg reduction rates were still high.

Praziquantel in adults gave comparably good results at 30 and 40 mg/kg, though not as excellent as oxamniquine. The 20 mg/kg schedule gave much poorer cure rates ($\chi^2=19{\cdot}11$, $P<0{\cdot}005$) and unsatis-

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Table 1—Cure rates and egg output reduction rates 6 weeks after treatment with oxamniquine or praziquantel

Dosage	N	M.E.L.	Percentage of subjects with >100	Percentage of subjects with >350epg	C.R.	E.R.R.	Percentage of subjects with >100	Percentage of subjects with >350 epg
Oxamniquine								
Children (<20 years)								
20 mg	57	466	84	60	47	98·1	16	4
30 mg	42	271	76	48	67	98·7	2	0
40 mg	49	307	71	45	86	99·4	4	0
Adults (≥20 years)								
20 mg	95	105	49	19	86	98·5	1	0
30 mg	76	105	45	18	97	99·0	0	0
40 mg	67	124	47	21	97	99·1	0	0
Praziquantel								
Children								
20 mg	109	79	35	11	58	91·8	16	5
30 mg	197	110	50	16	63	96·1	8	2
40 mg	176	120	56	20	78	98·1	4	1
Adults								
20 mg	61	60	23	5	55	91·2	8	2
30 mg	113	79	39	12	87	98·0	1	0
40 mg	96	81	33	10	91	98·2	2	0

N = number of subjects examined at the 6 week follow-up.
M.E.L. =mean egg load (geometric)
C.R. = cure rate (percentage of subjects becoming parasitologically negative)
E.R.R. = egg output reduction rate (percentage reduction of geometric means of individual epg+1]
epg = eggs per gram of stool

Table 2—Cure rates and egg output reduction rates 3 months after treatment with oxamniquine and praziquantel

Dosage	N	Cure rate (%)	Egg reduction rate (%)
Oxamniquine			
Children (<20 years)			
20 mg	52	46	98·1
30 mg	41	71	99·0
40 mg	45	82	99·4
Adults (≥20 years)			
20 mg	91	81	98·2
30 mg	71	94	98·8
40 mg	58	97	99·0
Praziquantel			
Children			
20 mg	100	53	91·7
30 mg	187	60	95·2
40 mg	165	71	97·3
Adults			
20 mg	53	72	95·8
30 mg	102	75	96·9
40 mg	84	85	97·7

N = number of subjects examined at both 6 weeks and 3 months follow-up

Table 3—Frequency (percentage) of side effects after treatment with oxamniquine and praziquantel

	Oxamniquine			Praziquantel		
Dose	20 mg	30 mg	40 mg	20 mg	30 mg	40 mg
N	170	129	131	173	318	280
Diarrhoea	0·5	1·6	0·8	24·9	30·5	28·9
Abdominal pain	0·6	0	1·5	16·8	27·0	30·7
Nausea	4·7	8·5	16·7	1·2	1·9	1·4
Dizziness	32·0	46·5	53·4	5·8	7·2	10·0
Somnolence	20·0	27·9	34·4	0	1·9	2·1

N = Number of subjects treated and interviewed

factory egg reduction rates, and failed to eliminate some heavy infections. Remarkably, however, these results had improved somewhat at the 3-month follow-up.

In children, praziquantel gave acceptable results only at 40 mg/kg. When the drugs were compared at equal dosages, significantly different cure rates (higher for oxamniquine) were observed only in adults at the 20 and 30 mg/kg regimens (χ^2 respectively 16·65 and 5·05; $P<0·005$ and $<0·05$). Egg reduction rates were in general better with oxamniquine, certainly at the lowest dosage; this result may be partly biased by the higher initial egg loads in Maramvya, the oxamniquine trial village.

The frequency of side effects is summarized in Table 3. For oxamniquine, dizziness, often pronounced, and sleepiness were frequent and were dose-related. In general, they appeared within one hour after administration; many of the people complained first of pronounced dizziness which forced them to lie down, and then fell asleep not unlike epileptics after a seizure. In fact, two people showed convulsions of arms and legs, lasting about 15 sec, during this process; both were adults, one treated with 20 and the other with 30 mg/kg. Neither had a previous history of epilepsy. Nausea was another relatively frequent and dose-related complaint. In all cases, however, these side effects had subsided 24 h after treatment.

For praziquantel, diarrhoea and abdominal pain were most frequently reported (and observed): in

most cases, a colicky pain developed 30 min to one hour after treatment, followed by the production of 2 or 3 loose stools. These side effects subsided in general within 6 h after treatment. They were not of much concern to the population, which regarded them rather as proof of the efficiency of the drug. Dizziness was also relatively frequently reported, though never with the intensity observed after oxamniquine treatment. Urticaria appeared in 7 people treated with praziquantel, 5 at 30 mg/kg and 2 at 20 mg/kg. The need to adjust the correct doses of oxamniquine in children receiving the syrup complicated and slowed down the mass treatment process. Administration of broken praziquantel tablets was easier and quicker.

Discussion

Both oxamniquine and praziquantel have been the subject of several clinical and operational therapeutic trials. Both are regarded as safe, efficient and generally well tolerated drugs, suitable for mass treatment. However, the efficiency, tolerance and acceptability seem to vary considerably (NOZAIS & DEVELOUX, 1983) from one area to another and therefore it is useful to try to select the optimal drug regimen for each control programme. It was thus our aim to evaluate the drugs in the actual, local operational conditions which would apply in a mass treatment campaign. Therefore we preferred to evaluate each drug in a different village; our study qualifies thus as two separate trials rather than a randomized blind comparison (which is not possible in the field, given the different forms under which the drugs are presented). This method does not permit unbiased comparison. For one thing, heavy infections were more frequent in Maramvya than in Bulinga, which is one of the reasons why we conducted an additional study of praziquantel 30 and 40 mg/kg in Bulamata, where heavy infections were also more frequent. However, this seems not to have influenced the parasitological cure rates, which were rather better in Maramvya than elsewhere. Concerning side effects, interrogation of the subjects 24 h after treatment without including, e.g., a placebo control group, is certainly liable to produce bias. However, direct observation of the treated subjects for an hour after treatment objectively confirmed the most salient conclusions. Further, it was in fact the aim of the study to evaluate how the population "experiences" the drug, rather than objectively to demonstrate clinical side-effects.

Oxamniquine has been shown to be efficient at doses ranging from 15 to 60 mg/kg (BOUDIN *et al.*, 1982; BRANCHINI *et al.*, 1982; CLARKE *et al.*, 1978; DA SILVA *et al.*, 1974; GENTILINI *et al.*, 1981; IBRAHIM, 1980; KAPEND'A *et al.*, 1982; KATZ *et al.*, 1977; KATZ *et al.*, 1981; LAMBERTUCCI *et al.*, 1982; NOZAIS & GUENIER, 1979; OMER, 1978). It has been observed in different regions that higher dosages may be needed in children than in adults (BOUDIN *et al.*, 1982; CLARKE *et al.*, 1978; NOZAIS & GUENIER, 1979). In our study, it gave acceptable results in adults at 20 mg/kg and excellent results at 30 mg/kg; whereas for children the cure rate became acceptable only at 40 mg/kg, though the egg reduction rates were good at lower dosages. For large scale use this clearly efficient drug has, however, severe drawbacks. Dizziness and sleepiness have been described by other authors (DA SILVA *et al.*, 1974; GENTILINI *et al.*, 1981; KAPENDA'A *et al.*, 1982; NOZAIS & GUENIER, 1979; OMER, 1978), generally as mild and transient. In our study population, however, they were so pronounced and frequent that the drug would certainly frighten away at least part of the population in a mass treatment campaign. The occurrence of epileptiform seizures in people with no previous history of epilepsy makes its large scale use in operational, relatively little controlled, conditions ethically questionable. The importance of these side effects may be related to the fact that, in this area, most people take no substantial breakfast. Overcoming this problem in operational conditions would seem no easy task. The need to split the 40 mg/kg, and perhaps even the 30 mg/kg, dose into 2 parts is another serious operational disadvantage, as well as the impractical presentation of the drug in indivisible large capsules.

Praziquantel has been shown to be efficient at dosages ranging from 30 to 65 mg/kg (BRANCHINI *et al.*, 1982; COUTINHO *et al.*, 1981; KATZ *et al.*, 1979; KATZ & ROCHA, 1982; MACMAHON, 1981; OMER, 1981; RANQUE *et al.*, 1981; SAIF & ABDEL-MEGUID, 1981; SCHUTTE *et al.*, 1983; SMITH *et al.*, 1981). In our study, praziquantel gave somewhat less good results than oxamniquine. In children, 40 mg/kg was required to obtain more or less satisfactory cure rates and egg reduction rates. In adults, satisfactory results were achieved with 30 and 40 mg/kg.

The main side effects of praziquantel, colicky pain and diarrhoea starting shortly after intake and lasting a few hours, have been described elsewhere (COUTINHO *et al.*, 1981; EL ALAMY *et al.*, 1981; KATZ *et al.*, 1981; MACMAHON *et al.*, 1981; OMER, 1981; POLDERMAN *et al.*, 1984; RANQUE *et al.*, 1981). In our study population these symptoms were of little importance, always transient and accepted by the population. The ease of administration of the divisible praziquantel tablets and the absence of problems in giving a single dose, allow for quick and easy mass treatment procedures.

The price of the drugs in 1985, as quoted by the manufacturer after clear explanation of the scope of the campaigns to be undertaken, was US $ 0·81 per capsule (250 mg) for oxamniquine and US $ 0·47 per tablet (600 mg) for praziquantel. The cost of an average dose (body weight 35kg, 40 mg/kg) would thus be $4·5 for oxamniquine and $1·1 for praziquantel. Even if the dose for oxamniquine were reduced to 20 mg/kg, its cost would be more than double that of praziquantel. It appears, however, that oxamniquine is made available at considerably lower prices in other countries, so this conclusion may not be valid elsewhere.

Oxamniquine is thus not selected for use in the mass-treatment campaigns of the schistosomiasis control programme in Burundi, because of its important side effects and its high cost. Praziquantel, though perhaps slightly less efficient parasitologically, is a better tolerated, cheaper, well-accepted and convenient drug for large-scale use, at least in the Burundese operational conditions. Praziquantel, at a uniform single dose of 40 mg/kg, has thus become the drug of choice in our control programme.

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