Oxamniquine Cures *Schistosoma mansoni* Infection in a Focus in Which Cure Rates with Praziquantel Are Unusually Low

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An outbreak of *Schistosoma mansoni* in northern Senegal was observed in 1988, and chemotherapy with praziquantel in this recently established focus resulted in very low parasitologic cure rates. Among other explanations, the emergence of a praziquantel-tolerant parasite strain was feared. To study this hypothesis further, 138 persons with endemic *S. mansoni* infection were randomly allocated to treatment with either 20 mg/kg oxamniquine or 40 mg/kg praziquantel. Parasitologic cure rates at 6 weeks were significantly higher in the oxamniquine group (79%) compared with those in the praziquantel group (36%; $P = .0043$). The reduction in egg counts was generally good, but 12% less reduced in the praziquantel group. These results confirm that cure rates with praziquantel were abnormally low, whereas oxamniquine performed satisfactorily, as in other areas in which *S. mansoni* is endemic. The possibility of a praziquantel-tolerant *S. mansoni* strain must therefore be studied carefully.

During the last decade, praziquantel has been the drug of choice for the treatment of intestinal schistosomiasis in Africa [1]. This drug is considered to be safe and efficacious. However, in a *Schistosoma mansoni* focus in northern Senegal, cure rates after praziquantel treatment were low compared with those in other areas in which *S. mansoni* is endemic [1, 2]. This focus has only recently emerged and is characterized by extremely high intensities of infection [3]. Lack of immunity may also play a role, considering the synergistic action of praziquantel with host immune responses [4]. However, the spread of a genetically homogeneous schistosome strain with low susceptibility to praziquantel cannot be excluded [2, 5]. The aim of the present study was to compare the efficacy of praziquantel in this focus with that of another schistosomicidal drug, oxamniquine, in a controlled field trial.

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Samples have been collected in consultation and full cooperation with both the local authorities and the persons concerned. Persons showing schistosome eggs in their stools were treated according to protocols recommended by WHO and local authorities current at the time of study.

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Population and Methods

The study village, Ndombo, consists of 3000–4000 inhabitants and is situated along a main irrigation canal, not far from the town of Richard-Toll in northern Senegal. The area has been described in detail elsewhere [3]. All study subjects ($n = 138$) were residents from this village, and after extensive information about the research and its aims, they volunteered to participate. Each person submitted to a parasitologic examination: 2 stool samples were collected at 2 different days before treatment, and duplicate 25-mg Kato slides were prepared from each sample [6]. The slides were examined 24–72 h after preparation by two microscopists unaware of the given treatment. Participants were prestratified by age, intensity of infection, and history of previous praziquantel treatment and then randomly allocated to treatment with either 40 mg/kg praziquantel (Distocide; Shin Poong, Seoul, Korea) or 20 mg/kg oxamniquine (Vansil; Pfizer, Groton, CT) by lottery. Pregnant women and children <5 years old were excluded from the study. Parasitologic examination was repeated at 3 and 6 weeks after treatment.

Egg counts per gram of feces (epg) were calculated as the arithmetic mean of individual egg counts multiplied by 40. As egg counts approximate a log-normal distribution, geometric means were derived from $\log^{10}$-transformed epg from positive egg counts (epg >0) only. χ^2 test and t test statistics and 95% confidence intervals of means were used to compare groups. Parasitologic cure was defined as not excreting eggs in stools at 6 weeks after treatment. Egg count reduction was calculated as [1 − (geometric mean epg after treatment/geometric mean epg before treatment)] × 100.

Results

The study population is described in detail in table 1. No significant differences were found between treatment groups

Table 1. Characteristics of treatment groups; no significant differences were found regarding age, sex, history of previous treatment, and intensity of infection.

	Praziquantel	Oxamniquine	Significance
5–19 years	34 (51%)	39 (54%)	$\chi^2 = 0.020$
⩾20 years	32 (49%)	33 (46%)	$P = .888$
Age range (years)	5–75	5–71	
Sex ratio (no. male/no. female)	22/44	30/42	$\chi^2 = 0.694$
			$P = .405$
Previous praziquantel treatment	27 (41%)	34 (47%)	$P = .1530$
Geometric mean egg count (eggs/g of stool)	260	393	$P = .167$
95% confidence interval	174–389	258–598	
n	66	72	

with respect to age, sex, intensity of infection, and history of previous treatment. According to the parasitologic data, subjects treated with oxamniquine showed significantly better cure rates at 6 weeks after treatment than did those who received praziquantel: 79% versus 36% ($P = .0043$; figure 1). The reduction in egg counts 6 weeks after treatment was higher in the oxamniquine group than in the praziquantel group: 94% versus 82% (figure 2).

Discussion

Treatment with praziquantel normally results in cure rates between 60% and 95% [2]. However, in this focus in northern Senegal, treatment with the standard drug regimen of 40 mg/kg resulted in a parasitologic cure of only 18%–36%, depending on the follow-up period after treatment [2, 7]. Various explanations could be forwarded, such as the very high intensities of infection and the recent nature of this focus; however, after several in-depth studies, these possibilities could be rejected (unpublished data). The most important component of the chemotherapeutic field trials was a comparison between praziquantel and oxamniquine. Normally, both drugs are equally effective against *S. mansoni;* however, if important differences in cure between the two drugs were to be found, they might be caused by regional parasite strain characteristics.

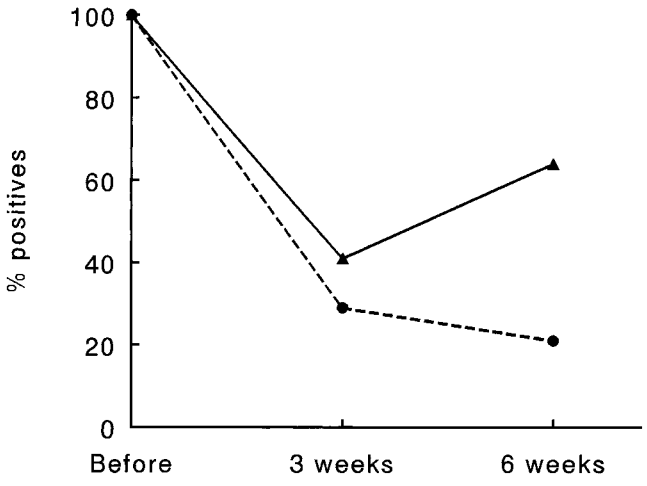

Figure 1. Parasitologic cure (% positive) after treatment with praziquantel (▲, 40 mg/kg) and oxamniquine (●, 20 mg/kg). $\chi^2 = 18.92$; $P = .0043$.

The potential emergence of a parasite strain less susceptible to praziquantel treatment has been extensively debated [8]. Although praziquantel resistance has never been reported in other areas in which schistosomiasis is endemic, the epidemic nature of this focus may have caused a homogeneous and praziquantel-tolerant strain to become apparent. The existence of strain-related variations in tolerance was described for different antimonial drugs [9]; however, this phenomenon was only recently reported for praziquantel by Fallon and Doenhoff [10]. In a laboratory setting, they were able to select a schistosome strain not susceptible to praziquantel, but this characteristic did not remain constant when the drug pressure was removed. Additionally, in the same setting, 1 isolate from the Senegal focus appeared to be more tolerant to praziquantel treatment [5]. We therefore compared praziquantel with oxamniquine in a field study, as oxamniquine is considered as effective as praziquantel for community treatment [11].

The best follow-up period for monitoring parasitologic cure has been a topic of discussion [8]. Six weeks is considered the optimal follow-up period for the evaluation of schistosomiasis treatment, as this is the ''parasitologic window'' in which most eggs from previous infections would be excreted and eggs from prepatent infections would not yet have appeared. At the 6-week follow-up in this focus, the parasitologic cure rate obtained by oxamniquine treatment was significantly better than that of praziquantel and, in contrast to praziquantel, highly comparable with what has been observed in other areas [1, 12].

Prepatent infections may explain in part the difference in cure, as such infections become susceptible to praziquantel treatment 1 week later than they become susceptible to oxamniquine treatment [13]. However, after the randomization procedure, the oxamniquine group still possessed higher intensities of infection and therefore probably maintained even more prepatent infections than the praziquantel group. One would therefore expect that the former group would exhibit lower cure

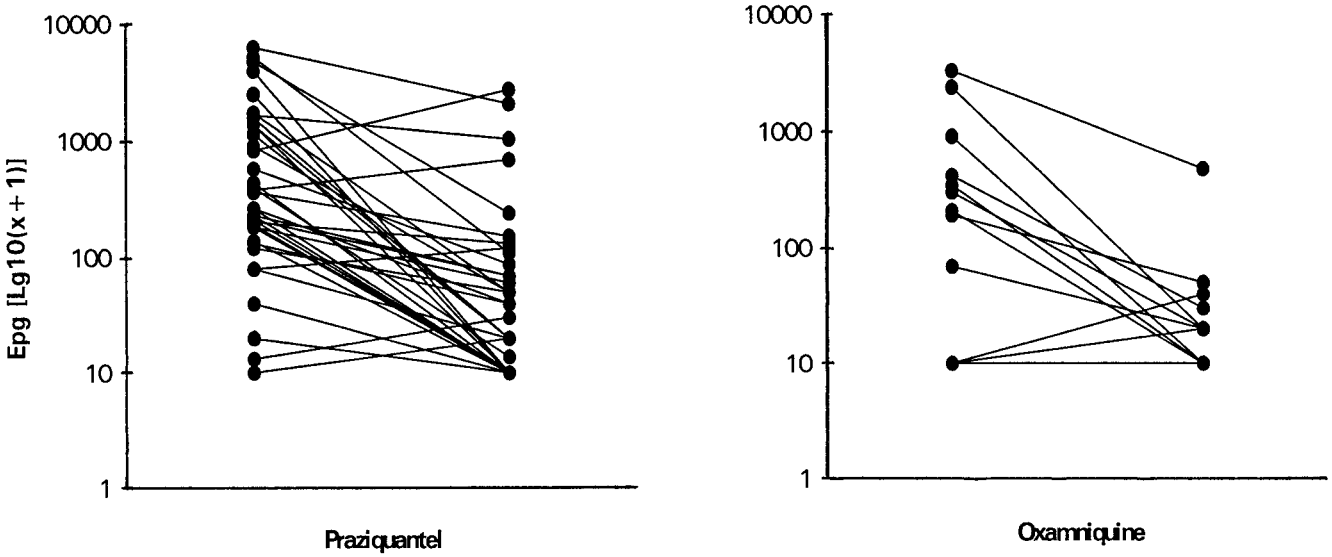

Figure 2. Egg count reduction in subjects who did not achieve cure after treatment with either praziquantel (n = 42) or oxamniquine (n = 15), before and 6 weeks after treatment.

rates or at least cure rates similar to those of the praziquantel group. Furthermore, in the focus of Maniema, Zaire, intensities of infection equally high as those in this Senegalese focus were encountered [12]. However, in the Zairian focus, cure rates after oxamniquine treatment were inferior to those obtained by praziquantel treatment [12]. An abundance of prepatent infections alone can thus not sufficiently explain the low parasitologic cure rates observed after praziquantel treatment in this Senegalese schistosomiasis focus.

The different working mechanisms of praziquantel and oxamniquine may justify the divergence in cure rate observed; oxamniquine is thought to bind with the parasite DNA, which then leads to cellular damage and death over a prolonged period [9]. Our observations correspond with this theory, as the curve of cure in the oxamniquine group continued to decline after 3 weeks (figure 1). Praziquantel, however, binds to the adult worm tegument, causing acute damage, tetanoid immobilization, and lysis of the worm tegument through host-dependent immunologic responses [4]. During in vitro experiments, it has been shown that worms can recover from these damages when challenged with a subcurative dose [14], and we probably observed this phenomenon, as cure rates appeared to decline after 3 weeks in the praziquantel group.

Immune responses are necessary for an optimal result of praziquantel treatment, as they act synergistically with this drug [4]. It is possible that these responses still were immature in this recently emerged focus. However, if insufficient immune responses were to explain the low cure rate after praziquantel treatment, cure rates would improve in subjects receiving subsequent treatments, and this was not the case (unpublished data).

In conclusion, we have demonstrated that parasitologic cure rates after treatment with 20 mg/kg oxamniquine were significantly better than after 40 mg/kg praziquantel. This observation supports the hypothesis about a Senegalese schistosome strain with an increased tolerance to the latter drug. To still be able to design adequate control strategies in the future, further studies should be undertaken to verify this hypothesis, and efforts should be made to understand the underlying mechanisms of this phenomenon.

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