EFFICACY OF PRAZIQUANTEL DURING THE INCUBATION AND INVASIVE PHASE OF SCHISTOSOMA HAEMATOBIUM SCHISTOSOMIASIS IN 18 TRAVELERS

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Abstract. The efficacy of praziquantel started during the incubation period of schistosomiasis has not been studied. Eighteen tourists were infected by Schistosoma haematobium during summer 2003 after bathing once in the same cascade in Mali. We observed the efficacy of praziquantel given at different phases. They received praziquantel at the first consultation, from Days 10 to 15 after exposure to eight asymptomatic patients (Group 1), from Days 28 to 40 in 4 asymptomatic patients (Group 2), and from Days 20 to 39 in 6 patients with acute schistosomiasis (Group 3). All Group 1 patients developed acute schistosomiasis, compared with none of the Group 2 patients (P < 0.004). Among the 10 patients treated during the acute phase, clinical status deteriorated in four cases. Seventeen of the 18 patients developed chronic schistosomiasis. Early praziquantel treatment was thus less effective than later treatment in preventing acute schistosomiasis, while neither treatment effectively prevented chronic schistosomiasis.

INTRODUCTION

Acute schistosomiasis is increasingly reported in travelers returning from the tropics, especially from countries where schistosomiasis is endemic.1–6

Acute schistosomiasis can have life-threatening neurologic complications. Among 1,200 cases of Schistosoma japonicum schistosomiasis observed during the Leyte campaign (Philippines) in the Second World War, 27 (2.3%) were associated with neurologic complications, occurring during the acute phase in at least 12 cases, and 88% of these 27 patients had neurologic sequelae at 1 year.7 Only four case reports involving patients with acute Schistosoma mansoni or S. japonicum infection have since been reported.8–11

The efficacy of praziquantel, a schistosomicide, is controversial during the early phase of the Schistosoma life cycle. In humans, praziquantel has weak schistosomicidal efficacy. A 56% success rate was obtained in a study of 16 travelers treated an average of 5 weeks after exposure to Schistosoma haematobium.4 Some animal studies have suggested that praziquantel is more effective on schistosomula aged 7 to 20 days than on those aged 30 days.12,13 The efficacy of schistosomicidal treatment started 7–14 days postexposure (corresponding to the early phase of schistosomiasis incubation period) has not been studied in humans.

We treated a group of 18 travelers who had bathed once in the same contaminated Mali cascade at different times during a 1-month period. We evaluated the efficacy of praziquantel given at two different periods of the incubation phase and also during the acute phase of the disease.

MATERIALS AND METHODS

Eighteen tourists (7 men and 11 women, mean age 20 years) bathed once in Banani’s cascade in the Dogon region of Mali during summer 2003 (Table 1). Seventeen (94%) of the 18 bathers immediately experienced generalized pruritus lasting about 15 minutes, and 86% developed an erythematous macular punctiform nonpruritic exanthem (cercarial dermatitis) lasting 24 to 36 hours.

Two patients were hospitalized on August 18 with acute schistosomiasis. The other 16 patients, who were friends, consulted our unit at different times during the following weeks, seeking “preventive” treatment when asymptomatic and curative treatment when symptomatic. Eight asymptomatic patients received praziquantel (40 mg/kg) from Days 10 to 15 after exposure (Group 1), while another four asymptomatic patients (Group 2) received the same treatment from Days 28 to 40. The remaining six patients, who presented with acute schistosomiasis (Group 3), were also treated with praziquantel and were evaluated separately. Treated asymptomatic patients who developed acute schistosomiasis during follow-up received a second course of praziquantel. The clinical and biological features of acute schistosomiasis in Groups 1 and 2 (after failure of praziquantel prevention) were compared with those in Group 3.

The patients had a physical examination in our unit and were prescribed laboratory tests (eosinophilia, schistosomiasis serology, Schistosoma ova detection in urine and feces) every 15 to 30 days until ova were detected, then every 3 months until 12 months after exposure. The routine techniques used for the diagnosis of Schistosoma ova in stool samples were Ritchie’s concentration and Kato smears. For the urine, the sample was centrifuged and the entire sediment was examined by microscopy.

The main end point was the occurrence of acute schistosomiasis in asymptomatic treated patients (Groups 1 and 2) and chronic schistosomiasis in symptomatic (Group 3) and initially asymptomatic patients.

Acute (invasive) schistosomiasis was defined by fever or urticaria associated with headaches, sweats, chills, myalgia, or cough and followed by hypereosinophilia and seropositivity for schistosomiasis. The clinical and biological signs of acute schistosomiasis are reported, together with the intervals between exposure and clinical onset, hypereosinophilia, and seropositivity. Serologic tests were based on hemaggulination (Cellognost-Schistosomiasis, Dade-Gehring, Marburg, Germany) and indirect immunofluorescence (Schistosoma mansoni homemade antigen, Laboratoire de Parasitologie-Mycologie, GH Pitié-Salpêtrière). The parasitologic failure rate is reported as the proportion of patients who developed successful treatment...
signs of chronic schistosomiasis, that is, excretion of *Schistosoma haematobium* ova, recurrent hematuria, eosinophilia persisting more than 100 days after its appearance, or rising anti-*Schistosoma* antibody titers. Patients were considered cured if they had normal physical findings, a normal eosinophil count, no urinary shedding of *Schistosoma haematobium* ova, and a stable or falling antibody titer 12 months after exposure.

Statistical analyses were performed with Statview software (Abacus Concepts, Berkeley, CA). The Mann-Whitney test was used to compare means, and Fisher’s exact test was used to compare proportions. *P* values < 0.05 were considered significant.

**RESULTS**

The mean interval between exposure and initial praziquantel treatment was 14 days (range 10–15 days) in Group 1, 33 days (28–40 days) in Group 2, and 26 days (20–39 days) in Group 3. All eight early-treated asymptomatic patients and none of the late-treated asymptomatic patients developed acute schistosomiasis (*P* < 0.004) (Table 2).

The manifestations of acute schistosomiasis (Table 3) did not differ significantly between Group 1 and Group 3 (data not shown). Overall, 14 patients developed acute schistosomiasis but only 10 of these patients were treated with praziquantel. Among these 10 patients (four in Group 1 and six in Group 3), four deteriorated during treatment. Two early-treated patients worsened within 24 hours after their second dose of praziquantel. The first patient developed more severe urticaria and bronchospasm that required supplemental oxygen and antihistamine therapy. The second patient developed signs of encephalopathy (confusion and dyscalculia) associated with subungual hemorrhages. MRI showed multiple bilateral cerebral infarcts in the border zone. Echocardiography and cardiac scanner were normal. Clinical signs of encephalopathy resolved after 48 hours of steroid therapy. Two patients in Group 3 had generalized urticaria that worsened 24 hours after their first dose of praziquantel.

Among the 13 febrile patients with acute schistosomiasis, hypereosinophilia and seropositivity appeared a mean of 30 and 26 days, respectively, after the onset of fever. All 18 exposed patients were infected, with hypereosinophilia and seroconversion (both assays) in every case. Hypereosinophilia and seropositivity occurred at mean intervals of 48 and 49 days after exposure, respectively. Seventeen of the 18 treated patients developed chronic schistosomiasis (Table 2). Morphologically, all the ova examined were characteristic of *Schistosoma haematobium* species; no other *Schistosoma* species were found in stool samples. The rates of parasitologic failure were 100%, 75% and 100% in Groups 1, 2 and 3, respectively. Patients with parasitologic failure received an-

| Table 1 | Characteristics of 18 travelers infected by *S. haematobium* and treated with praziquantel |
|-----------------|----------------------------------|------------------|
| Group 1: Early-treated asymptomatic patients | Group 2: Late-treated asymptomatic patients | Group 3: Patients treated when symptomatic |
| Number of patients (exposed = infected) | 8 | 4 | 6 |
| Sex (M/F) | 2/6 | 1/3 | 21/38 |
| Age (y): mean (range) | 21 (20–21) | 19 (18–19) | 20 (19–28) |
| Date of exposure | 15/08/2003 | 1/08/2003 | 20/07/2003 (n = 1) |
| | | | 01/08/2003 (n = 4) |
| | | | 15/08/2003 (n = 1) |
| Swimmer’s itch | 100% | 100% | 83% |
| Mean interval (days) from exposure to praziquantel treatment (range) | 14 (10–15) | 33 (28–40) | 26 (20–39) |

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
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<tr>
<td>Chronic schistosomiasis†</td>
<td>8 patients:</td>
</tr>
<tr>
<td></td>
<td>• 5 with ova in urine</td>
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<tr>
<td></td>
<td>• 1 persistent hematuria</td>
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<tr>
<td></td>
<td>• 1 persistent eosinophilia at 190 days</td>
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<tr>
<td></td>
<td>• 1 ascending antibody titer (one IFI dilution) at 12 months</td>
</tr>
<tr>
<td>Patients without signs of chronic schistosomiasis†</td>
<td>0</td>
</tr>
<tr>
<td>Cured</td>
<td>8 patients</td>
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</tbody>
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*NA, not applicable.
*Day of the first consultation and first treatment with praziquantel.
†After one or two praziquantel doses.
other one to two courses of praziquantel. After 12 months of follow-up, all the patients are asymptomatic and none has urinary Schistosoma ova excretion.

**DISCUSSION**

Early praziquantel treatment, from Days 10 to 15 after exposure (during the schistosomiasis incubation period), had no apparent benefit in these asymptomatic travelers infected by Schistosoma haematobium. When given later (from Days 28 to 40), praziquantel prevented acute schistosomiasis but failed to prevent chronic schistosomiasis in 75% of cases.

All early-treated asymptomatic patients (Group 1) developed acute schistosomiasis after initial treatment. The manifestations of acute schistosomiasis were similar to those in untreated patients (Group 3), suggesting that praziquantel has no noteworthy effect on Schistosoma haematobium schistosomula when given from Day 10 to Day 15 after exposure. This conflicts with the results of some experimental studies showing greater praziquantel efficacy on schistosomula aged from 8 to 20 days compared with those aged 30 days. But this concords with the results of another experimental study showing that praziquantel efficacy increased with parasite age of schistosomula from 3 to 42 days. It should be noted, however, that Schistosoma mansoni is used routinely in experimental studies.

Praziquantel appeared to be more beneficial in the four asymptomatic patients who presented, and were treated, later, as none of them developed acute schistosomiasis. It is conceivable, however, that these four patients were naturally more resistant to the infection or less heavily infected. In that regard, they had bathed in the cascade on August 1, whereas the early-treated patients had bathed on August 15. None of those in the four asymptomatic patients who were treated later developed chronic schistosomiasis.

With 14 cases of acute schistosomiasis, this is the fifth largest series involving travelers, after a series of 30 cases in Brazil, 16 cases in Malawi and Mozambique, 15 cases in Mali, and 14 cases in Burkina Faso. It is also the second largest series involving S. haematobium. The reported attack rate is between 92% and 100% (100% in our study). Pruritus just after exposure is reported by 12–100% of patients, depending on the study. Cercarial dermatitis due to human schistosomiasis has occasionally been described as a urticular pruritic rash lasting more than 24 hours. Ninety-four percent of our patients reported diffuse pruritus lasting approximately 15 minutes, and 86% developed exanthem composed of punctiform erythematous macular nonpruritic lesions lasting less than 36 hours. The frequency of clinical signs in our patients is in keeping with that observed in other large series (> 10 patients) (Table 4).

Only two studies have described the acute phase of S. haematobium infection. The clinical manifestations are similar to those due to S. mansoni infection, with fever, headache and signs of immediate hypersensitivity (urticaria, bronchospasm, cough, rhinitis). However, diarrhea and abdominal pain, which are common with S. mansoni, are rare with S. haematobium, being observed in none of 16 patients in one study and in only 2 of our 14 patients. Seventy-one percent of our patients developed sometimes severe neck pain, a symptom reported in only one other study. As the usual biological signs (hypereosinophilia and seropositivity) only appear 2 to 4 weeks after the onset of fever (the mean intervals were 30 and 26 days, respectively, in our patients), a history of potential exposure and dermatitis are the main diagnostic elements of schistosomiasis in febrile travelers.

The success rate of praziquantel therapy started during acute schistosomiasis varies with the time since exposure. Overall, the failure rate was 92% among our 12 asymptomatic patients treated within 40 days after exposure and 100% in the 10 patients treated during acute schistosomiasis. Doherty and others reported a 44% failure rate after a single dose of praziquantel given to 16 patients with the Katayama syndrome, whereas Visser and others reported a failure rate of only 29% in 28 patients. However, chronic schistosomiasis was more frequent than acute schistosomiasis in this latter study (19 patients shed Schistosoma ova at the onset of treatment).

The optimal management of patients with acute schistosomiasis is controversial. Some authors combine praziquantel with steroids, although this roughly halves praziquantel plasma levels. Other authors treat first with corticosteroids then with praziquantel, and yet others withhold treatment during the acute phase. Artemether seems to be a promising preventive treatment because it is active in vivo against juvenile forms of schistosomiasis.
human beings, the efficacy against *S. haematobium* seems to be moderate.\textsuperscript{23} Our results clearly suggest that praziquantel can be detrimental when given during the acute phase. Indeed, 4 of our 10 patients who received praziquantel during acute schistosomiasis deteriorated, three with allergic manifestations (urticaria, bronchospasm) and one with encephalopathy associated with cerebral microinfarcts. Steroid therapy was beneficial in our patient with cerebral microinfarcts. Such a clinical deterioration after praziquantel treatment in patients with acute schistosomiasis has only been mentioned in seven patients in four instances.\textsuperscript{1,3,18,24} It was not life-threatening but required a corticosteroid treatment in one patient. As praziquantel administration during acute schistosomiasis can be associated with a clinical deterioration, it should be avoided at this stage.

This reaction looks like an Herxheimer reaction. In an experimental model of acute schistosomiasis, praziquantel provoked pulmonary bleeding in a dose-dependent manner.\textsuperscript{25} One possible explanation for this initial deterioration is that parasite lysis by praziquantel increases antigen exposure and potentiates the immune response. The immune response is complex in this setting, and includes allergic-like manifestations and circulating immune complexes.\textsuperscript{26} It is difficult to know whether clinical signs during the migration phase are directly due to schistosomula or rather to the immune response to schistosomula antigens. Eosinophils, with their potential cardiac, vascular, and pulmonary toxicity, also seem to play a major pathophysiologic role. Indeed, whether triggered by a parasite during invasive helminthiasis or due to a pure inflammatory disease such as the hypereosinophilic syndrome, hypereosinophilia is associated with strikingly similar cerebral complications.\textsuperscript{9} In this setting, corticosteroids seem more appropriate than praziquantel. Interestingly, one case report describes a favorable outcome of encephalopathy complicating the migration phase of *S. japonicum* infection after treatment with steroids alone.\textsuperscript{8} In a mouse model, schistosomicide-steroid combination therapy was more effective than either drug used alone but only on the fecundity of *S. mansoni* worms.\textsuperscript{19}

In conclusion, late praziquantel treatment, given after the 28th day postexposure, may prevent acute schistosomiasis, but neither early nor late treatment effectively prevented chronic schistosomiasis. Praziquantel should not be given during the acute phase of the disease because of toxicity and lack of efficacy.

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