

Running Title: Treatment of acute schistosomiasis

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A NEW APPROACH TO THE TREATMENT OF ACUTE SCHISTOSOMIASIS

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INTRODUCTION

Oxamniquine and praziquantel are potent schistosomicidal agents against mature *S. mansoni* infection in rodents, primates and man (Lambertucci et al, 1982). On the other hand, the reduced efficacy of these drugs against immature worms in experimental animals (Sabah et al, 1985) has implications for the treatment of acute toxæmic schistosomiasis. The best therapeutic approach to acute schistosomiasis is still unsettled. A low cure rate has been observed with all schistosomicidal agents used so far (Lambertucci et al, 1988; Katz et al, 1983) and certain authors even believe that the destruction of worms after treatment with schistosomicides liberates new antigens that may enhance the formation of immune complexes and consequently aggravate the clinical picture of acute schistosomiasis (Harris and Cook, 1987; Stuiver, 1984; Monson, 1987). There is also no good evidence that treatment of the acute syndrome with antischistosomal drugs alone alters the course of this serum sickness-like disease (Gazzinelli et al, 1985). In contrast, the use of steroids simultaneously with schistosomicides has given excellent results in a number of occasions (Gelfand et al, 1981; Farid et al, 1987).

In this paper, the experience of our group in treating 59 patients with acute schistosomiasis is reviewed and a synergistic effect between schistosomiasis and steroids in the treatment of experimental schistosomiasis mansoni is reported.

TREATMENT OF PATIENTS WITH ACUTE SCHISTOSOMIASIS

In the last 9 years, my colleagues and I have treated 59 patients with acute schistosomiasis (Lambertucci et al, 1980; Katz et al, 1983; Lambertucci et al, 1988; Gazzinelli et al, 1985). These patients were treated at different days after infection, varied in their age range and 30 out of 59 (51%) were asymptomatic when they received treatment (Table 1).

The diagnosis of the toxæmic form of schistosomiasis was based on epidemiological data (recent contact with stream water in a *S. mansoni* endemic area), on clinical data (acute enterocolitis, high fever, toxæmia, hepatosplenomegaly), and laboratory studies (eosinophilia above 1000/mm³ in differential count and viable *S. mansoni* eggs in the faeces). The finding of necrotic-exudative granulomata in liver biopsy established the diagnosis in doubtful cases (Neves, 1986).

Data in table 1 can be further extended, as follows: 1) the first 30 patients are soldiers of the Brazilian Army that were infected during military manoeuvres in a pond in Belo Horizonte (Minas Gerais State, Brazil). They were 18 to 19 years old on the occasion of the infection. 15 received oxamniquine and 15 praziquantel; the cure rate for both groups was 93%. They were asymptomatic when treatment was started. The absence of viable *S. mansoni* eggs in the stools in the following 6 months after

treatment, configured the criterium of cure;

2) 19 patients (6 to 14 years of age) with the toxaemic form of schistosomiasis were treated with oxamniquine, 55 to 77 days after infection. They were followed-up for 6 to 10 months after treatment. 9 out of 19 (47%) did not pass eggs in the stools from the first month after treatment onwards. On the other hand, 8 out of 9 (lately considered to be cured) continued to present signs and symptoms of acute schistosomiasis (diarrhoea, fever, abdominal colic pain, malaise) for a period of time post-treatment ranging from 8 to 15 days;

3) 10 patients in the age range of 5 to 27 years in the acute toxaemic phase of the disease were treated with oxamniquine plus prednisone and the cure rate was 90%. Signs and symptoms of acute schistosomiasis disappeared 24 to 48 hours after the beginning of treatment.

Based on the data summarized above, at least two conclusions can be drawn. Firstly, patients recently infected (90-day-old infection) that are asymptomatic behave - as far as treatment efficacy is concerned - like patients in the chronic phase of schistosomiasis. Secondly, patients in the acute toxaemic phase of the disease treated with oxamniquine plus prednisone, do much better than patients treated with oxamniquine alone (there is improvement in the cure rate and quick amelioration of the signs and symptoms of toxemia).

This leaves us with a question to be answered. Is there a synergistic effect between steroids and schistosomicides? So far, the anti-inflammatory effect of steroids (reducing the state of hypersensitivity) has been considered as the sole explanation for their dramatic effect in the treatment of acute schistosomiasis. Recent results, obtained in mice infected with *S. mansoni* suggest that steroids act synergistically with schistosomicides in the treatment of acute schistosomiasis (Lambertucci et al, 1989).

THE ASSOCIATION OF STEROIDS AND SCHISTOSOMICIDES IN THE TREATMENT OF EXPERIMENTAL SCHISTOSOMIASIS

CBA mice were infected with 150 cercariae and divided into 4 groups, as follows: a) treated with oxamniquine or praziquantel; b) treated with oxamniquine or praziquantel plus dexamethasone; c) treated with dexamethasone, and d) untreated (control). At least 7 mice were used in each of the treated and untreated groups.

Oxamniquine was given orally (60 mg/kg body weight, single dose) on the 28th day after infection and praziquantel was administered orally (250 mg/kg, body weight) on day 21 and day 23 after infection. The drugs were ultrasonicated briefly in 2.5% Cremophor EL (Sigma) in water to give the appropriate concentration of drug for oral administration. Dexamethasone, at a concentration of 0.7 microgram/ml, was added to the drinking water of the infected mice (Groups B and C) starting at 3 or 4 weeks after infection until the day of perfusion.

The number of *S. mansoni* eggs in mouse faeces was established by a ninhydrin method (Doenhoff et al, 1978a).

Following perfusion of mice (43 days after infection), the intestine from duodenum to rectum and the liver (minus the 2 ventral median lobes, kept for histology) were stored at - 20°C. The 2 tissues were separately digested in 5% potassium hydroxide for 16 h at 37°C (Cheever, 1968) and *S. mansoni* eggs counted as described by Doenhoff et al (1978b).

RESULTS

The livers of mice in Groups A, C and D were larger than the livers of mice in Group B. This difference was probably caused by the presence of granulomas and fibrosis. Histological examination of liver sections obtained from Group B mice revealed fewer and smaller granulomas.

There was no significant difference in the number of worms recovered from mice in the 4 groups studied. There was, however, a remarkable reduction (96% in the gut; 81% in the liver) in the number of eggs in the tissues of mice treated with oxamniquine plus dexamethasone.

Oxamniquine alone or dexamethasone alone reduced the number of eggs excreted in faeces. However, the association of both drugs (Group B) caused an even greater reduction in the number of faecal eggs. The differences were statistically significant (Group A vs Group B, $p = 0.01$; B vs C, $p = 0.01$; B vs D, $p = 0.01$). Similar results were obtained when oxamniquine was replaced by praziquantel.

COMMENTS

The reduction in the number of eggs produced per worm pair in mice treated with both drugs suggests that the steroids affected, in some way, the fecundity of *S. mansoni* worms.

We have no clear explanation for the synergistic effect of schistosomicides and steroids on oviposition. Although we do not know the mechanism of action, steroids seem to block or delay the recovery and development of worms affected by praziquantel as well as those exposed to oxamniquine. These findings suggest a non-specific effect. Knowledge of the rate of incorporation of tritiated thymidine by the worms treated with these drugs in association with steroids would certainly throw some light on the subject.

SUMMARY AND CONCLUSIONS

Clinical and experimental evidence indicates that steroids act synergistically with schistosomicides in the treatment of Katayama syndrome.

Due to the low efficacy of schistosomicides in the acute

toxaemic phase of schistosomiasis, some authors have suggested that specific treatment for schistosomiasis should be delayed, in these patients, until the disease has entered its chronic stage (Stuiver, 1984; Harries and Cook, 1987). A dramatic improvement (quick amelioration of symptoms and higher cure rates) was observed when patients with acute schistosomiasis were treated with steroids and schistosomicides.

We do not know the explanation for the synergistic effect between steroids and schistosomicides but it has been demonstrated that the association of drugs affected, in some way, the fecundity of *S. mansoni* worms.

The data and arguments presented here reinforce the need to use steroids in conjunction with schistosomicides for the treatment of patients with Katayama syndrome. This approach will give better cure rates, speed the recovery time (reducing the demand for hospital treatment) and improve the quality of medical care.

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Table 1 - Number of patients with acute schistosomiasis treated with oxamniquine, praziquantel and oxamniquine plus prednisone. Percentage of cure at different days after infection.

Number of patients	Age range Years	Days after infection	Symptoms	Chemo-therapy	Cure %
15	18-19	90	No	OXA	93
15	18-19	90	No	PZQ	93
19	6-14	55-77	Toxaemic	OXA	47
10	5-27	49-55	Toxaemic	OXA + PREDN	90

OXA= Oxamniquine (15-20 mg/kg, body weight, single dose)
 PZQ= Praziquantel (50 mg/kg, body weight, divided in two equal doses)
 PREDN= Prednisone (1 mg/kg, body weight for one week beginning one day before oxamniquine; 0.5 mg/kg, body weight during the second week and 0.25 mg/kg in the third week).

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