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SPECIFIC TREATMENT OF ADVANCED SCHISTOSOMIASIS LIVER DISEASE IN MAN: FAVOURABLE RESULTS

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One hundred eighty-four patients with hepatosplenic schistosomiasis mansoni from the northeast of Brazil were studied. All were treated with a single dose of Oxamniquine or Praziquantel, and were observed over 6 to 12 months. Special attention was given to the evolution of severe hepatopathy. Favourable results were obtained, particularly with the compensated hepatosplenic form. Hepatic function showed great improvement. Hepatomegaly and splenomegaly were significantly reduced in size, to a greater or lesser extent, in the great majority of patients. The implications of the results obtained are considered below.

The specific treatment of schistosomiasis has been subject of many discussion and of a number of clinical and experimental trials. Only those aspects connected with the evolution, favourable or otherwise, of hepatic changes caused by *Schistosoma mansoni* will be treated here.

From the experimental point of view, pioneering works, mainly in mice, were carried out by Warren (1962), Cameron & Ganguly (1964), Cameron & Bhattacharyya (1965) and Cheever et al. (1965). More recently, the positive effects of treatment in animals have been shown by Schiller & Haese (1972), Andrade & Brito (1981), Melhorn et al. (1982), Morcos et al. (1985) and Andrade & Grimaud (1986). Hepatomegaly and splenomegaly, portal hypertension, granuloma lesions, hepatic fibrosis and vascular lesions of the liver caused by *Schistosoma mansoni* could be prevented or reversed at least in less advanced phases of the disease. On the other hand, other investigations, employing treatment at a later stage of infection, have shown only a partial regression of the lesions, whether due to *Schistosoma mansoni* in mice (Warren & Klein, 1969), or to *S. japonicum* in chimpanzees (Sadun et al., 1974).

In human pathology, specific treatment has been shown to give good results in some hepatosplenic cases, particularly over the long term. Both liver and spleen enlargement could be reduced through chemotherapy with different drugs: Antimonial (Sette, 1953; Kloetzel, 1963, 1967), Hycanthone (Bina, 1977), Oxamniquine (Coutinho et al., 1973; Coutinho & Domingues, 1980; Bina & Prata, 1983; Dietze & Prata, 1986), and Praziquantel (Coutinho et al., 1984; Domingues, 1986).

In this present contribution, we intend to show our current wide experience with the two new drugs Oxamniquine and Praziquantel in the treatment of severe forms of schistosomiasis mansoni, especially in hepatosplenic (HS) patients, living in a hyperendemic area, the northeast of Brazil. Analysis of liver function changes and of variations in size of liver and spleen over the long term, i. e. from six to twelve months after treatment, were the primary considerations.

MATERIAL AND METHODS

All patients were seen in the city of Recife, in the Outpatient clinics of Gastroenterology and of Schistosomiasis, and in the wards of Medicine of the "Hospital das Clínicas" of the "Universidade Federal de Pernambuco". Ages ranged from 10 to 71, with an average of 25. Three quarters of the patients were females. Single oral doses of 15 mg/kg of body weight of Oxamniquine (Ox) or of 40 mg/kg of Praziquantel (Pz) were administered.

Table I shows the number of patients treated related to the clinical forms and to the most important complications according to the classification used by Coutinho & Domingues (1981). It will be seen that the compensated hepatosplenic form, which is the most typical and less complicated of the severe forms of the illness, accounts for a majority of 62.5%. The other forms included the more advanced decompensated hepatic form, the cardiopulmonary, renal or tumoral forms of the disease and the hepatosplenic schistosomiasis complicated by other chronic infections, such as viral hepatitis or salmonellosis.

TABLE I

Treatment of hepatosplenic schistosomiasis – Distribution of cases according to the clinical forms

Clinical forms	Oxamniquine No.	Praziquantel No.	Total
HS compensated	40	75	115
HS transitional	12	3	15
HS decompensated	3	–	3
Cardiopulmonary hypertensive	6	8	14
Cardiopulmonary cyanotic	3	6	9
HS with nephropathy	8	–	8
HS with colonic polyposis	1	1	2
HS associated with chronic virus hepatitis	11	–	11
HS associated with chronic salmonellosis	6	1	7
Total	90	94	184

Table II shows the degree of infection, measured by the number of eggs per gram of faeces, according to the Kato-Katz technique in the group of patients using Praziquantel. It was found that there is a wide variation in degree of infection. About 50% of patients had a high parasitic load (> 1.000 eggs).

TABLE II

Distribution of patients according to number of eggs before use of Praziquantel

No. of eggs per gram of faeces	No. of cases	
< 100	4	48
100- 499	30	
500- 999	14	
1000-5000	36	46
> 5000	10	
Total	94	

Clinical examination of liver and spleen were always carried out with the patient in supine position. Special attention was given to the left lobe of the liver, palpable below the xyphoid appendix. The maximum diameter of the spleen was measured below the left costal margin.

Liver function analysis was carried out according to standard tests: aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), gamma glutamiltransferase (Gamma-GT), alkaline phosphatase (AP), leucine aminopeptidase (LAP), bilirubin, bromosulphalein (BSP) and electrophoresis of serum proteins.

RESULTS

The long-term study, i. e., from 6 to 12 months after specific treatment with either Oxamniquine or Praziquantel, shows, apart from a marked improvement in symptoms, great recovery of hepatic function in the great majority of cases. This was particularly seen in cases of the compensated hepatosplenic form.

These successful results can be accurately checked by the mean value analysis of SGOT, SGPT, Gamma-GT and LAP, before treatment and one year after Praziquantel (Table III, Fig. 1). The same good results are shown with serum albumin and gamma globulin (Table IV, Fig. 2). Levels of bilirubins, both total and direct, and of BSP, which were near normal in the majority of patients before treatment, show no change. Alkaline phosphatase, which in some cases had been high before treatment, showed a significant fall to normal level after treatment. In relation to Oxamniquine, the results of the liver function were equivalent to these demonstrated with Praziquantel.

TABLE III

Mean values of aminotransferases and gammaglutamiltransferase, before and one year after Praziquantel

Enzyme	Before		After	
	No.	Mean	No.	Mean
SGOT	92	24.0	30	18.5
SGPT	92	22.7	30	17.2
GAMMA-GT	69	39.2	20	24.3

TABLE IV

Mean values of serum proteins, before and one year after Praziquantel

Protein	Before		After	
	No.	Mean	No.	Mean
Albumin	90	3.18	30	3.47
Gammaglobulin	90	2.75	30	1.69

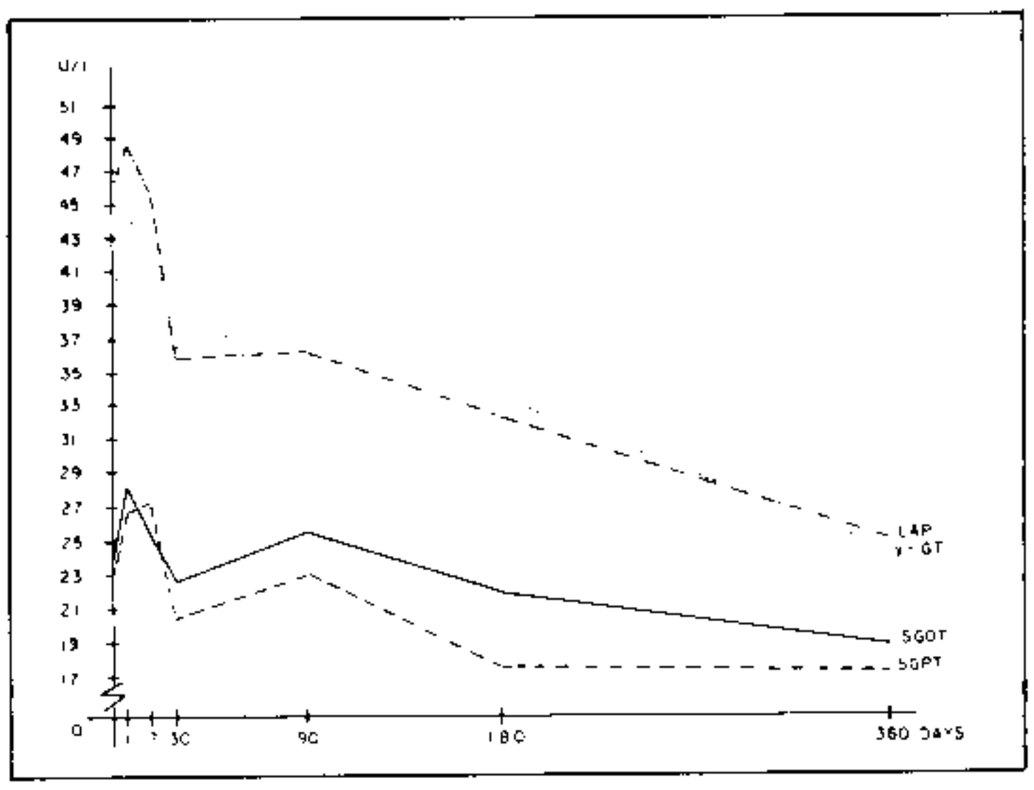

Fig. 1: evolution of serum enzymes in schistosomal hepatosplenic patients after Praziquantel therapy.

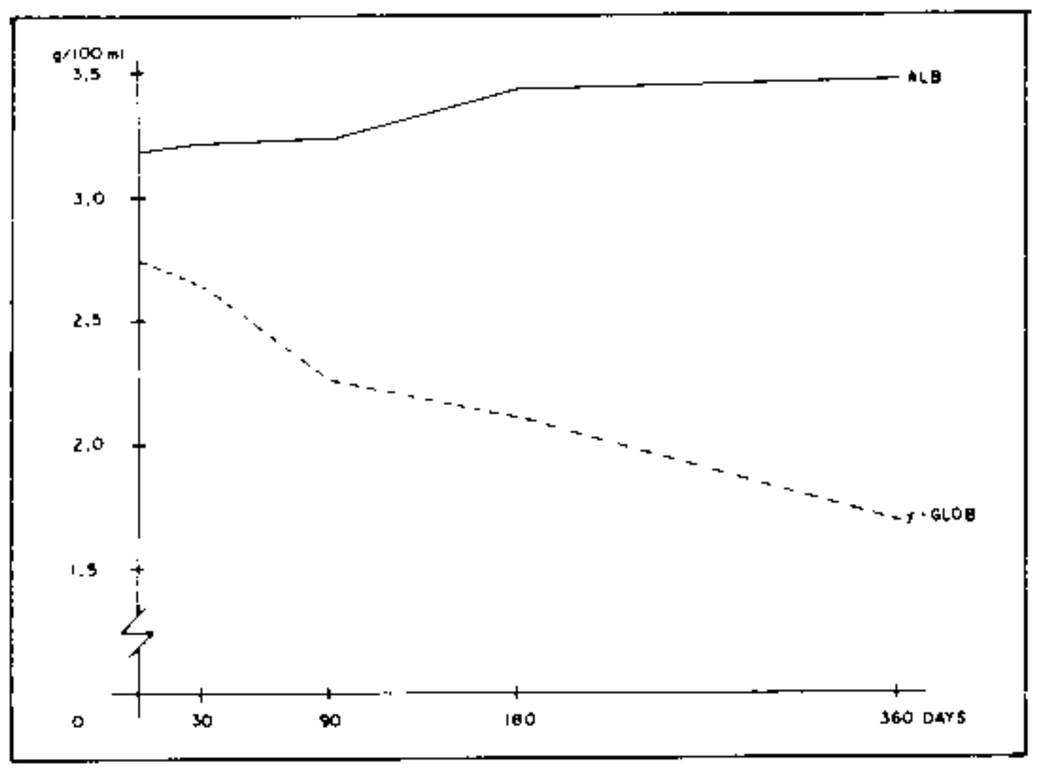

Fig. 2: evolution of plasma proteins in schistosomal hepatosplenic patients after Praziquantel therapy.

Table V shows that, six months after Oxamniquine, a reduction in size of the liver was evidenced in 54.3% of patients, and of the spleen in 53.5%. Table VI shows, six months after Praziquantel, a size reduction of the liver was present in 62.1% of patients, and of the spleen in 57.4%. Table VII shows that, one year after Praziquantel, size reduction of the liver was evidenced in 80.9$ of patients, and of the spleen in 78.7$.

TABLE V

Size variations of liver and spleen, six months after Oxamniquine

Size variations	Liver		Spleen	
	No.	%	No.	%
None	12	34.2	12	42.8
Increased	4	11.4	1	3.5
Reduced	19	54.3	15	53.5
Total	35	100.0	28*	100.0

* Not included 7 patients splenectomised.

TABLE VI

Size variations of liver and spleen, six months after Praziquantel

Size variations	Liver		Spleen	
	No.	%	No.	%
None	22	33.3	20	37.0
Increased	3	4.5	3	5.5
Reduced	41	62.1	31	57.4
Total	66	100.0	54*	100.0

* Not included 12 patients splenectomised.

TABLE VII

Size variations of liver and spleen, one year after Praziquantel

Size variations	Liver		Spleen	
	No.	%	No.	%
None	8	19.05	7	21.21
Increased	0	0	0	0
Reduced	34	80.95	26	78.79
Total	42	100.00	33*	100.00

* Not included 9 patients splenectomized.
Note: in 15.5% the reversal of spleen was complete.

It is also worthy of note that, six months after Praziquantel, in no case the spleen become impalpable, while after 12 months 15.15$ of patients showed a total regression. This indicates a reversion from the HS form to the less severe hepatointestinal form.

DISCUSSION

The satisfactory results shown by liver function analysis, and the reduction in size of

liver and spleen over the long term, following treatment with the new drugs, Oxaminiquine and Praziquantel, bear out and extend the findings of other researchers, and those anticipated by the present authors. They are also in accord with data from experiments on animals.

Few studies have concerned themselves with analysing liver function in man long after treatment, especially with Oxamniquine and Praziquantel. The levels of the enzymes SGOT, SGPT, Gamma GT, and FA in some cases first rises in the 1st and 2nd weeks after therapy, then gradually falls to normal values. Albumin also, which is slightly below normal before treatment, tends to normalise at from 6 to 12 months. Yet, as Table IV and Fig. 2 show, it is above all gamma globulin, which is usually high in the HS forms, that indicates the most meaningful improvement after specific therapy.

These improvements in liver function are probably connected with the striking reduction of schistosomiasis-related inflammatory activity in the liver; i. e., granuloma and portal infiltration. This reduction has been observed after treatment of mice infected with *Schistosoma mansoni* and in the treatment of chimpanzees infected with *Schistosoma japonicum*. Furthermore, liver function improvements are probably related also to the regression of intra-hepatic vascular lesions as seen in mice after specific medication (Andrade & Brito, 1981).

Both hepatomegaly and splenomegaly were reduced within six months to a similar extent with either Oxamniquine or Praziquantel (see Tables V and VI). Twelve months after treatment with Praziquantel, however, the reduction is more striking: 80.9% of hepatomegaly, and 78.7% of splenomegaly. As for splenomegaly, it is worth stressing that, six months after Praziquantel, spleen regression was not complete in any of the patients; while at 12 months it was complete in 15.15% of the patients as a whole, and in 18.52% of those with compensated HS form.

This complete regression of the spleen i. e., a change from the hepatosplenic to the hepato-intestinal form after treatment, was observed by Kloetzel several years ago (1967) and, more recently, by Bina & Prata (1983) and by Dietze & Prata (1986). These 1983 and 1986 studies refer to patients who are, generally, younger and who have been infected relatively recently, or who have less developed spleens. This is not the case in the present study.

There is reason for endorsing the advice of Dietze & Prata that specific treatment should be administered to almost all hepatosplenic patients who have no history of digestive hemorrhage. Twelve to 18 months should be allowed to see the effects of such treatment before surgical intervention is considered. This advice, obviously, will be in need of modification should there occur a massive digestive hemorrhage. After this has been arrested, consideration should be given to choosing between selective surgical treatment and other indicated therapies, such as sclerotherapy of the esophageal varices, and administration of propanolol.

Although hepatomegaly was reduced in 60% to 80%, i. e., in the vast majority of cases, reduction was complete in none of them. The liver, while showing slight to moderate reduction of hardness and of the typical nodules, as mentioned by Dietze & Prata, remained palpable. This reduction of hardness, together with the regression of the liver size itself, would seem to indicate, apart from the reduction in inflammatory activity referred to above, a regression of the hepatic fibrosis. This has shown to be the case in mice, but remains to be demonstrated in human pathology.

On the other hand, partial or total regression of the spleen in the present study and in the work of authors quoted would seem to suggest a reduction, to a greater or lesser extent, of portal hypertension. This has been shown experimentally, but remains to be demonstrated in clinical and hemodynamical studies in man.

Success in treating some cases of advanced forms of schistosomotic liver disease has been mentioned also by authors from Egypt, who have administered either Oxamniquine (Farid et al., 1980) or Praziquantel (Bassily et al., 1985).

All of these successful results of specific treatment are particularly seen in the pure compensated HS form; i. e., without other associations or complications. When complications are present, good results have only been found in those cases where the evolutive process has not reached a more advanced stage, or become irreversible. Both Oxamniquine and

Praziquantel therapy have yielded good results in all cases under study where chronic salmonellosis is linked to HS schistosomiasis, as well as in the few patients with the tumor form i. e., with multiple intestinal polyps. With the hypertensive cardiopulmonary form, benefit depends on the stage of the disease: while there have been cases of clinical and hemodynamic improvement, other more advanced cases have shown little or no regression. The same could be said of patients with schistosomotic nephropathy; the experience of the authors, together with that of the Nephrology Group of the "Hospital das Clínicas" of Recife, is in line with that recently presented by Martinelli et al. (1987) in Bahia.

Finally, cases of chronic viral hepatitis associated with schistosomotic liver disease would not appear to benefit directly from specific treatment for it. This is because the cases that have made the best progress, in the authors' experience, have been, as expected, those that show persistent chronic hepatitis. Whereas cases of active chronic hepatitis, with or without cirrhosis, follow their own course. They do not, furthermore, undergo modification of the persistent presence of HBsAg in blood after anti-schistosomiasis therapy.

By all mean, unless there is any precise contraindication, it is recommended that specific treatment with the new oral drugs, which are well tolerated, should be started as early as possible, even in severe forms of the disease. The aim will be to arrest its progress, and minimize as much as possible its clinical and pathological signs.

Apart from some observed instances of abnormal reactions that appeared soon after treatment, probably due to a state of hypersensitivity to antigen products from dead worms (Coutinho, 1975), it has not been possible to find evidence that specific therapy has in any way contributed to later worsening of the clinical, histological or physiopathological expressions of the disease.

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