The Use of Reduction of Splenomegaly as a Parameter for Therapeutic Response in Hepatic Schistosomiasis

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DOI: http://dx.doi.org/10.5915/23-2-15068

Abstract

The effectiveness of praziquantel in the treatment of hepatic schistosomiasis was studied in 30 patients with bilharzial splenomegaly. Reduction in splenomegaly was used as a parameter of therapeutic success. Twenty one out of 30 patients improved when treated by repeated doses of praziquantel. The number of administered doses necessary to achieve clinical improvement was directly related to the pretreatment size of the spleen. The patients were divided into three groups according to the size of the spleen; up to 5 cm below the costal margin in the mid-clavicular line (Group 1), between 5-10 cm in Group 2, and more than 10 cm in Group 3. The rate of improvement was 100% in Group 1, 75% in Group 2, and 25% in Group 3.

Key words: *Schistosomiasis, splenomegaly, praziquantel*

The most common cause of enlargement of the spleen in Egypt is bilharziasis. Early in the disease the spleen is moderately enlarged as a result of toxemia. Later, the enlargement is partly due to toxemia and partly due to portal hypertension.[1]

Bilharzial ova are the main pathogenic agent leading to fibrosis and are the primary elements in provoking overt disease.[2] Enlargement of the liver and spleen is related to the intensity of infection with schistosoma mansoni.[3,4] The spleen enlarges progressively. Splenic size bears little relationship to the portal pressure. It is larger in young people and in macronodular cirrhosis. An enlarged spleen is the single most important diagnostic sign of portal hypertension.[5]

Hepatosplenic schistosomiasis caused by S. mansoni is more difficult to treat and is associated with greater morbidity and mortality than urinary schistosomiasis caused by S. hematobium.[6] In the last few years, the treatment of schistosomiasis has been simplified by using newer schistosomicidal drugs (i.e. praziquantel) in a single dose.[7] In Egypt, the total dose is higher than that found effective elsewhere, which may be due to differences in the worm strain.[8]

The serum concentration of the drug in hepatosplenic patients may be three times higher than that in the intestinal group.[7] A continuously changing drug concentration can give rise to a varying response. If a prolonged response is required, it is preferable to wait until the effect of the first dose begins to diminish and then to repeat the dose.[9]

The aim of this study was to measure the effectiveness of praziquantel in the elimination of S. mansoni in human patients. A reduction in the size of the spleen was used as a parameter of the therapeutic effect.

Materials and methods

Subjects for this study were recruited from a pool of patients attending the tropical clinic at El-Manzalah District Hospital in the period between August 1988 and July 1989. They were investigated for bilharzial infestation by urine and stool examination. Of those who were positive, 30 patients who were found to have splenomegaly during clinical examination agreed to participate in this study.

All patients were given a thorough clinical examination. The following laboratory investigations were performed: liver function tests; glutamic ox-

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Table 1. The size of the spleen and the number of praziquantel doses required to achieve response and improvement.

	Group 1 n = 10	Group 2 n = 12	Group 3 n = 8
Size of spleen	4.0 ± 1.3* (2–5)	8.4 ± 1.4 (6–10)	12.5 ± 2.0 (11–16)
Number of doses to achieve a reponse	1.9 ± 0.9 (1–3)	3.6 ± 1.6 (1–7)	12.5 ± 2.0 (2–10)
Number of doses to achieve improvement	8.9 ± 4.8 (4–18)	12.7 ± 2.4† (8–17)	15 ± 1.0† (14–16)

* Mean ± standard deviation and range.

† There were three patients in group 2, and 6 patients in group 3 who did not achieve improvement. The number of doses administered to these patients is not included in these numbers.

Table 2. Results in relation to sex of the patient.

	Males n = 22	Females n = 8	
Age (years)	35.5 ± 10.7	27.0 ± 11.8	NS*
Size of spleen (cm/MCL)	8.5 ± 3.7	6.6 ± 3.8	NS
Number of doses at which a response was achieved	3.4 ± 2.2	2.6 ± 1.0	NS
Number of patients improved	14 (64%)	7 (88%)	
Number of doses at which improvement was achieved	11.2 ± 3.9	11.0 ± 4.6	NS

*Statistically nonsignificant difference.

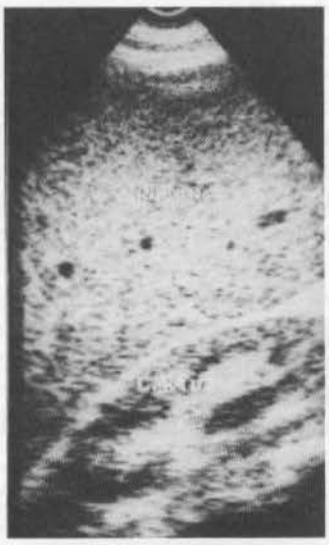

Figure 1. Sonogram of the spleen before treatment.

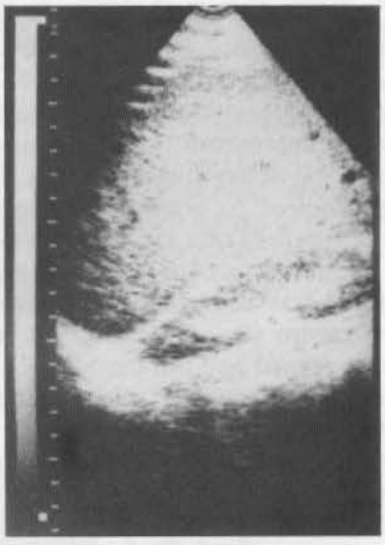

Figure 2. Sonogram of the spleen (sample patient) after treatment.

alacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), albumin and bilirubin, hemoglobin and creatinine measurements. Electrocardiography (ECG) and abdominal ultrasonography were also performed. The patients were divided into three groups according to the size of the spleen. The spleen size was measured in the supine position and was recorded in centimeters below the left costal margin at mid-clavicular line (MCL). The size of the spleen was confirmed by percussion. The first group (G1) was those having a spleen enlarged to 5 cm/MCL. The second group (G2) was those having a spleen size of 6-10 cm/MCL. The third group (G3) was those with splenomegaly greater than 10 cm/MCL.

All patients were given praziquantel 40 mg/kg weekly. The doses were given on a full stomach. Each dose was divided in two equal parts given four hours apart. The patients were followed weekly for response, improvement, and for any adverse reactions.

Response was defined as: a) Reduction in the size of the spleen as measured in the MCL, i.e., shortening of the distance between the tip of the spleen and the lower border of the costal margin, b) Change in the consistency of the spleen from firm to soft, c) Flattening: the reduction of the bulging of the spleen into the abdomen in the antero-posterior diameter, with or without reduction in size, d) Mobility: an adherent spleen became mobile after treatment, and e) Tenderness in the left hypochondrium.

Improvement was considered to have occurred if the spleen completely regressed behind the costal margin.

Patients who did not improve (non-responders) were later followed by sigmoidoscopy to exclude the presence of active bilharziasis.

Results

Our sample included 30 patients; 22 males and 8 females. There were 10 G1, 12 G2 and 8 G3 patients.

The results are considered in regards to both response and improvement.

Response was achieved in all patients. The number of doses required to achieve a response differed among the groups (Table 1). The difference between the first and second groups was highly significant ($P < 0.001$) and was also significant between the first and third groups ($P < 0.05$), but was insignificant between the second and third groups.

All G1 patients (100%) achieved improvement. The improvement rate in G2 was 75% (9 out of 12). Only two out of eight (25%) patients in the third group improved. The difference in the improvement rate among the three groups was statistically significant, $x^2 = 12.13$, ($P < 0.005$).

The number of doses required to achieve improvement varied among the different groups (Table 1). There were three G2 patients who did not show improvement after receiving 12, 14, and 19 doses each. There were six G3 patients who did not show improvement after receiving 11, 15, 18, 20, 21, and 23 doses each.

There was a positive correlation between the pretreatment size of the spleen and the number of doses at which a reponse was achieved ($r = 0.49$, $P < 0.01$)(Figure 1). There was also a positive correlation between the pretreatment size of the spleen and the number of doses at which improvement was achieved; ($r = 0.59$, $P < 0.01$)(Figure 2).

There were no statistical differences between males and females in regard to age, size of the spleen, number of doses at which a response occurred, or number of doses at which improvement was achieved (Table 2).

During the course of the study, no abnormalities in laboratory investigations were detected. There was improvement in the hemoglobin concentration after treatment. The difference between hemoglobin concentration before (8.5 ± 2.3 g/dl) and after treatment (11.0 ± 0.8 g/dl) was statistically significant ($t = 4.33$, P .0005).

For those nine patients who did not improve, sigmoidoscopy was offered. Two of the nine refused sigmoidoscopy. In two, there was no evidence of schistosoma ova. One patient had only dead ova, but four out of the seven patients still had living ova.

Ultrasound pictures of the spleen before and after treatment are presented in Figures 3 and 4 respectively, showing a typical treatment response.

Discussion

The liver pathology in schistosomiasis is attributable to lodgement of the schistosoma mansoni ova in the small intrahepatic portal radicals.[10] The eggs impact in the presinusoidal branches of the portal vein and granulomas form there obstructing portal blood flow and causing portal hypertension with varices and congestive splenomegaly.[11] Hypertrophy of the hepatic artery and a relative increase in blood flow, help to maintain sinusoidal perfusion. In the early stages of active hepatic schistosomiasis, the progressive enlargement of the spleen is due to congestion. Ova or worms are rarely found in the splenic pulp. The role of increased splenic blood flow in the genesis of portal hypertension is controversial.[5] In the later stages, there is diffuse fibrosis associated with marked destruction of musculoelastic tissue of the trabeculae and capsule.[11] The capacity of the liver sinusoids as a main drainage route of blood from the spleen is reduced as a result of this fibrosis. It is assumed that when fibrosis is halted under the effect of treatment by praziquantel, some capacity of the sinusoids and drainage of blood from the spleen is restored. This is why the size of the spleen was reduced.

Praziquantel has a serum half life of about 0.8-1.5 hours in adults with normal renal and hapatic functions; however, the serum half life of the drug metabolites is 4-5 hours.[12] The therapeutic threshold of a particular drug is the amount of that drug necessary to produce a desired response.[13] In some cases, it may be necessary to use the maximum tolerated dose to achieve a therapeutic effect.[14] The absence of a therapeutic effect was seen in four out of seven patients who were found by sigmoidoscopy to still have active bilharziasis even after multiple repeated doses (21 ± 3). This reveals that the treatment of schistosoma mansoni can be very difficult, but that repetition of treatment is essential to minimize the burden of infestation and prevent complications. Previously only two doses were recommended in heavy infestation.[15]

The safety of praziquantel was proved in regard to the effect on renal function, liver function, and ECG.[16] Monitoring of our patients by weekly clinical examination and laboratory investigation revealed no toxicity or side effects of praziquantel therapy.

In conclusion, this study shows that a single dose of praziquantel is insufficient to achieve an acceptable cure rate of schistosoma mansoni and that multiple doses are mandatory. This finding needs further confirmation on larger samples of cases of schistosoma mansoni infestation to help to redesign the best therapeutic strategy.

Acknowledgement

We gratefully acknowledge the support of this study by professors Salah El-Din Mostafa, A.M. Mandour, Dr. Sabry Elzahary, and Dr. Mohamed Saber.

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