complex arthritis. Circulating immune complex (CIC) assays reacted to S. mansoni adult worm and egg antigens. Clinical symptoms and CIC levels decreased and gradually disappeared after two courses of praziquantel.

4. EFFECTS OF TREATMENT ON DISEASE

4.1 Egg excretion

Oxamniquine and praziquantel are the drugs of choice for treatment of S. mansoni infection. The use of hycanthone and niridazole has decreased because of their recognized toxicity and side-effects. Metrifonate was found to be effective against S. mansoni only when the worms parasitize the perivesical plexus and S. mansoni eggs have been found in the urine before treatment (117).

Oxamniquine is well known to affect adult male worms more than adult female worms. Surface damage is greater in adult male than female S. mansoni following either oxamniquine or praziquantel administration in animal experiments (31, 251).

Treatment of infected individuals with oxamniquine or praziquantel causes diminution or cessation of S. mansoni egg excretion, reducing contamination of the environment. There are only a few mild side-effects. The cure rates of oxamniquine and praziquantel are more or less the same when optional or standard dosages are used. Most of the reports showed that cure rates with the two drugs 3-12 months after treatment varied between 60% and 90% while mean egg reduction rates were between 80% and 95% in persons not cured (9, 16, 31, 51, 103, 111, 178, 220, 223, 224, 226, 296, 343). When the same dosage of drugs according to body weight is used, children usually have lower cure rates as well as milder side-effects compared with the adults (220, 226, 312). Praziquantel appears to have the same therapeutic effect on different geographical strains of S. mansoni, whereas therapeutic effects of oxamniquine on different S. mansoni strains from Brazil, Egypt and elsewhere were different. In Brazil and the New World, a single dose of 15 mg/kg may cure a person with the infection (220, 344), however, in Egypt, 3-4 times this dosage is needed if the same cure rate is to be achieved (9, 111, 223, 226).

A remarkable difference in assessment of the therapeutic efficacy using a quantitative oogram and the Kato-Katz techniques was reported by da Cunha & Pedrosa (104). The cure rates in terms of tissue egg count assessed by the oogram and stool egg count by Kato-Katz techniques were 29.2% and 91.7% respectively for praziquantel and 22.7% and 86.3% respectively for oxamniquine at 6-month follow-ups. However, 6 months after treatment, the oogram showed a sharp fall (83%) in the mean number of living eggs per gram of tissue in the non-cured cases.

Dias et al. (115) isolated strains of S. mansoni from persons who had been repeatedly treated with oxamniquine or oxamniquine and hycanthone. Progenies were resistant to oxamniquine and hycanthone but sensitive to praziquantel and niridazole. No resistance of S. mansoni to praziquantel has so far been reported (51).

Three persons with acute schistosomiasis experienced temporary high fever after praziquantel treatment (185, 266). In 1 child, high fever lasted for 6 days with significant gastrointestinal disturbances (266). In heavy infection with S. mansoni, the passage of blood in the stools shortly after praziquantel treatment was reported (299). After oxamniquine treatment, a fever may develop in some patients 24-48 h after completing treatment and last for 2-6 days. This timing coincides with an increase in schistosomal antigen excretion in the urine (54, 152). This type of reaction was only reported in Egypt. Hallucination and epileptiform convulsions in patients following oxamniquine have been reported (111, 178, 219). No permanent sequelae to adverse side-effects have been recorded (51, 54, 152, 223, 224, 305, 341).

4.2 Decrease in morbidity

Infection with S. mansoni causes intestinal and hepatic disease, growth retardation in children and a series of laboratory changes. These can be corrected, in part, by specific treatment.

(1) Intestinal disease: Remarkable effects have been recorded on colonic polyposis with chemotherapy (2, 52, 54, 140, 153, 201, 226). Niridazole was found to be the most effective among antischistosomal drugs for S. mansoni in resolving polyposis and the associated symptoms: bloody diarrhoea, tenesmus, abdominal cramps, anaemia and hypoalbuminaemia, because of its immunosuppressive, anti-inflammatory as well as its schistosomicidal effects (153). Of the 29 patients with extensive polyposis (as evidenced by air-contrast barium enema and sigmoidoscopy or fibreoptic colonoscopy) treated with niridazole, clinical improvement occurred in nearly all, with rapid cessation of bloody diarrhoea and complete disappearance or marked decrease in the size and number of the colonic polyps (153). However, the recognized toxicity of niridazole and the long course of treatment needed have limited its use, especially in patients with impaired liver function and in debilitated patients (226). Oxamniquine was also effective, with mild side-effects, but the symptoms decreased more slowly and less completely than with niridazole in diffuse colonic polyposis (140, 226). Kilpatrick et al. (226) and El-Masry et al. (140) have suggested that patients with severe colonic polyposis be first treated with oxamniquine to relieve the symptoms; then, once serum albumin and other liver function tests are normal and if polyps and their associated symptoms are still not fully resolved, niridazole treatment should follow.

However, schistosomal polyposis has been successfully treated solely with oxamniquine by Bassily et al. (54) and Abaza et al. (2). In the latter study, 20 patients were treated with oxamniquine at a total dose of 40 mg/kg given in 2 divided doses over 2 days. Clinical improvement was significant. Bloody diarrhoea stopped by the end of the second week. Three months after treatment, mean levels of haemoglobin and serum iron increased from 8.9 g/dl and 85 mg/dl before treatment, to 12.5 g/dl and 149.5 mg/dl respectively. The mean serum albumin level was 3.1 g/dl before and 3.9 g/dl 3 months after treatment. All these increases were statistically significant. The polyps completely resolved in 5 patients, and in 15 the size of the polyps was markedly reduced. Chemotherapy may not resolve big or pedunculate polyps and the associated symptoms (59, 60). In these cases multiple endoscopic polypectomy may be the treatment of choice (201).

(2) Hepatic disease: Hepatic schistosomiasis with splenomegaly and with or without ascites can be safely treated with either oxamniquine or praziquantel.

The therapeutic effects of the two current antischistosomal drugs on hepatic disease with S. mansoni infection are encouraging. Farid et al. (152) reported that 11 cases of advanced hepatic schistosomiasis with ascites and poor liver functions were safely treated with oxamniquine in a dose of 20 mg/kg for 3 consecutive days after diuretics had reduced ascites and their general condition had improved with other supplementary treatment. Six to 15 months after treatment, none had a recurrence of ascites. In 5 of 8 patients who were followed-up, the enlarged liver had become smaller, although the size of the spleen did not change. Sleigh et al. (341) carried out a cohort study in Brazil involving 191 individuals who were treated with oxamniquine in 1977 and who were followed up until 1985. During the 8 years no new cases of persistent splenic enlargement occurred and 90% of the splenomegaly that was present before treatment regressed; hepatomegaly also regressed. Prevalence of hepatomegaly decreased from 90% in 1977 to 31% in 1985 and splenomegaly from 18% in 1977 to 3% in 1985. Other reports also recorded the regression of hepatosplenomegaly (239, 272) as well as regression of liver nodules (305). Progressive decrease in hepatomegaly and splenomegaly in S. mansoni infections was also reported after praziquantel (51, 103, 223, 224, 272, 357) or hycanthone (248) treatment.

The effects of chemotherapy with oxamniquine and praziquantel on liver function, intrasplenic pressure and portal-vein diameter measured by ultrasonography were studied

in hepatic schistosomiasis by Massoud et al. (252). They found that oxamniquine caused a slight increase in serum GPT but that praziquantel did not. An increase in portal-vein diameter associated with a significant transient increase in portal pressure was observed only after praziquantel, but not oxamniquine, treatment. The authors suggested that a greater hepatic shift of S. mansoni worms after praziquantel treatment might be the cause. In animal experiments, Morcos et al. (269) found that in praziquantel-treated mice, liver fibrosis was arrested or diminished, and liver collagen content had decreased to the normal levels compared with control mice by 20 weeks after treatment. Andrade & Brito (25) showed that one month after curative treatment with oxamniquine, the extensive destruction, obstruction and distortion of the intrahepatic portal vein system caused by S. mansoni infection had significantly regressed and had become normal in mice 6 months after chemotherapy. Shrinkage of egg granulomas and formation of new vascular channels have also been observed. Reduction in size of egg granulomas has been observed after praziquantel treatment (31, 68). A rapid, although incomplete, resorption of fibrosis was also shown in infected mice after curative chemotherapy with oxamniquine or hycanthone (26).

4.3 Epidemiological impact

Longitudinal community-based observations of the effect of treatment on the prevalence of schistosomiasis due to S. mansoni and the intensity of infection have been reported by Ouma et al. (287) in Kenya, Sleigh et al. (344) and Santos & Coura (330) in Brazil, Jordan et al. (211, 212) in St Lucia, Sukwa et al. (357) in Zambia and Polderman & Manshande (300) in Zaire. In Kenya, all those initially found to be heavily infected (more than 300 S. mansoni epg of stool) and all those at re-survey in the two subsequent years with more than 200 and 100 epg of stool, respectively, were treated with hycanthone. Reduction in the intensity of infection in the total population was observed. However, after an initial considerable drop in prevalence, subsequent decreases were smaller. In Brazil, after a single dose of oxamniquine, 191 individuals were followed at different intervals up to 33 months. Cure rates declined from 80% at 3 months to 46% at 33 months. Those not cured showed a decrease in egg counts that were still 66% lower than pretreatment levels at 33-month follow-up. The authors concluded that single-dose oxamniquine treatment reduced the potential contamination factor and protected the community from high worm burdens for almost 3 years, although by the end of observation the prevalence began to rise (344). In another report from Brazil, after a single dose of oxamniquine, both improvement in the clinical conditions and reduction in stool-egg counts were significant in the treated group after 1 year compared with the untreated controls. However, 6 years later, eggs in the stool returned to the same levels as before treatment in the treated group although they were still lower than in the controls. Clinical conditions were deteriorated in both groups. The authors recommended that the chemotherapy interval should not be longer than 3 years, and other preventive measures should be added (330). In St Lucia, after two selective population chemotherapy campaigns (treatment of all infected persons) using hycanthone in 1975 and oxamniquine in 1976, in high transmission areas prevalence dropped from 24.5% to 6.1% and in low transmission areas from 7.4% to 3.3%, at follow-ups in 1977. The potential contamination in the high and low transmission areas was reduced by 85% and 66% respectively (211). In Zambia, repeated treatment with praziquantel was given to all those with S. mansoni eggs in the stool at different follow-up examinations in a community cohort of 523 subjects during a 16-month period of observation. By the end of the study, prevalence had fallen from 64.8% before intervention to 11.5%, and intensity of infection had dropped from 28.2 to 0.5 epg (geometric mean) of stool (357). In Zaire, treatment of all subjects who excreted more than 100 epg of faeces with hycanthone without other control measures was reported to have only a temporary effect. The faecal egg counts among the treated persons returned to about two-thirds of the original level at 1-year follow-up (300). Chemotherapy with oxamniquine or praziquantel combined with frequent molluscicidings of all possible transmission sites was carried outin one village with high prevalence in Zaire. Although reduction of transmission was achieved in a short-term follow-up, this type of approach was not considered to be cost-effective by the author (298).

Jordan (209) has reported a comparative study on cost-effectiveness of the 3 main intervention measures, namely, chemotherapy, snail control and provision of water supplies, for the transmission control of S. mansoni in 3 isolated valleys in St Lucia. After 2 years, chemotherapy reduced the incidence from 18.8% to 4.1%, snail control, from 22% to 9.8% and water supplies, from 22.7% to 11.3%. Annual costs per capita for the first 2 years were $ 1.1, $ 3.7 and $ 4.0, respectively. Chemotherapy seemed to be the cheapest and most effective measure for transmission control, affording the additional benefit of morbidity control. On the other hand, a longitudinal study in Brazil showed that chemotherapy alone was not sufficient for the control programme, and that sanitation and snail control were equally important for transmission control (227).

Andrade & Bina (24) noted pronounced changes in the frequency of severe schistosomiasis due to S. mansoni in the northeast of Brazil in a survey of autopsy data before and after new antischistosomal drugs were available for large-scale use. Although the histopathological findings were the same for the two periods, the overall number of autopsies in which death was due to schistosomiasis progressively decreased, and hepatic schistosomiasis in younger persons was less frequent compared with the past. The authors suggested that curative treatment for schistosomiasis could prevent the development of hepatic disease and that, following curative therapy, patients with schistosomiasis seemed to maintain a residual immunity to re-infection, the latter being confirmed by an experimental study by the same authors (24).

5. CONCLUSIONS

The basic pathological change in S. mansoni infection is the egg granuloma with inflammatory and fibrotic reactions. The formation and modulation of the egg granuloma are suggested to be mainly T-lymphocyte-mediated. Intensity of the infection is a major factor which influences clinical manifestations and severity of the disease but other factors, such as superimposed infections, malnutrition and genetic background, may also play a role. Most persons in endemic areas with light infections are asymptomatic. Intestinal disease is mainly seen in the large intestine. In Egypt, colonic polyposis is an outstanding feature in S. mansoni infection. The infection finally causes liver fibrosis and portal hypertension. Its sequela, upper gastrointestinal bleeding from oesophagogastric varices, is the major problem for mortality from the disease. Hepatic coma may ensue. In patients with concomitant HBV infection, deterioration of liver function and chronic hepatic failure can be expected. Egg deposits in the pulmonary vessels causing pulmonary hypertension and cor pulmonale, and deposits of S. mansoni immune complexes in the glomeruli inducing glomerulonephritis, are usually found in fibrotic liver disease and are more frequently seen in S. mansoni than other schistosome infections. Assessment of morbidity is mainly based on clinical features, stool egg count and other laboratory findings. In recent years, ultrasound examination has revealed characteristic appearances of periportal fibrosis of the liver which can be differentiated from other hepatic diseases and this technique has its value in estimating the extent and degree of hepatic lesions. Chemotherapy with effective drugs against S. mansoni promotes reduction in transmission and reduces the incidence of serious disease without eradicating the infection. In endemic areas where chemotherapy is properly used, prevalence, intensity of the infection and the disease pattern have been changing considerably. Although progress has been made in assessment of morbidity of the infection during the past decade, investigations to elucidate further the disease mechanisms, to clarify controversies on morbidity associations and to improve control measures are necessary.

ACKNOWLEDGEMENTS

The authors wish to express their sincere thanks to Dr A.W. Cheever, Laboratory of Parasitic Diseases, National Institute of Health, Bethesda, USA, Dr P. Jordan, Ware, UK, Professor John H. Cross, Department of Preventive Medicine/Biometrics, Uniformed Service University of the Health Sciences, Bethesda, USA, Dr E. Doehring, Department of Paediatric Nephrology and Metabolic Disorders, Kinderklinik, Medizinische Hochschule, Hanover, Federal Republic of Germany, Professor S.P. Mao, Emeritus Director, Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine, Shanghai, China and Dr A. Davis, Director, Parasitic Diseases Programme, World Health Organization, Geneva, Switzerland, for their critical reviews of this manuscript.

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