THE EVALUATION OF PRAZIQUANTEL EFFICACY IN THE TREATMENT OF SCHISTOSOMIASIS

Thesis

Submitted in Partial Fulfilment

for the Master Degree (M. Sc.)

(Parasitology)

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CAIRO 1986

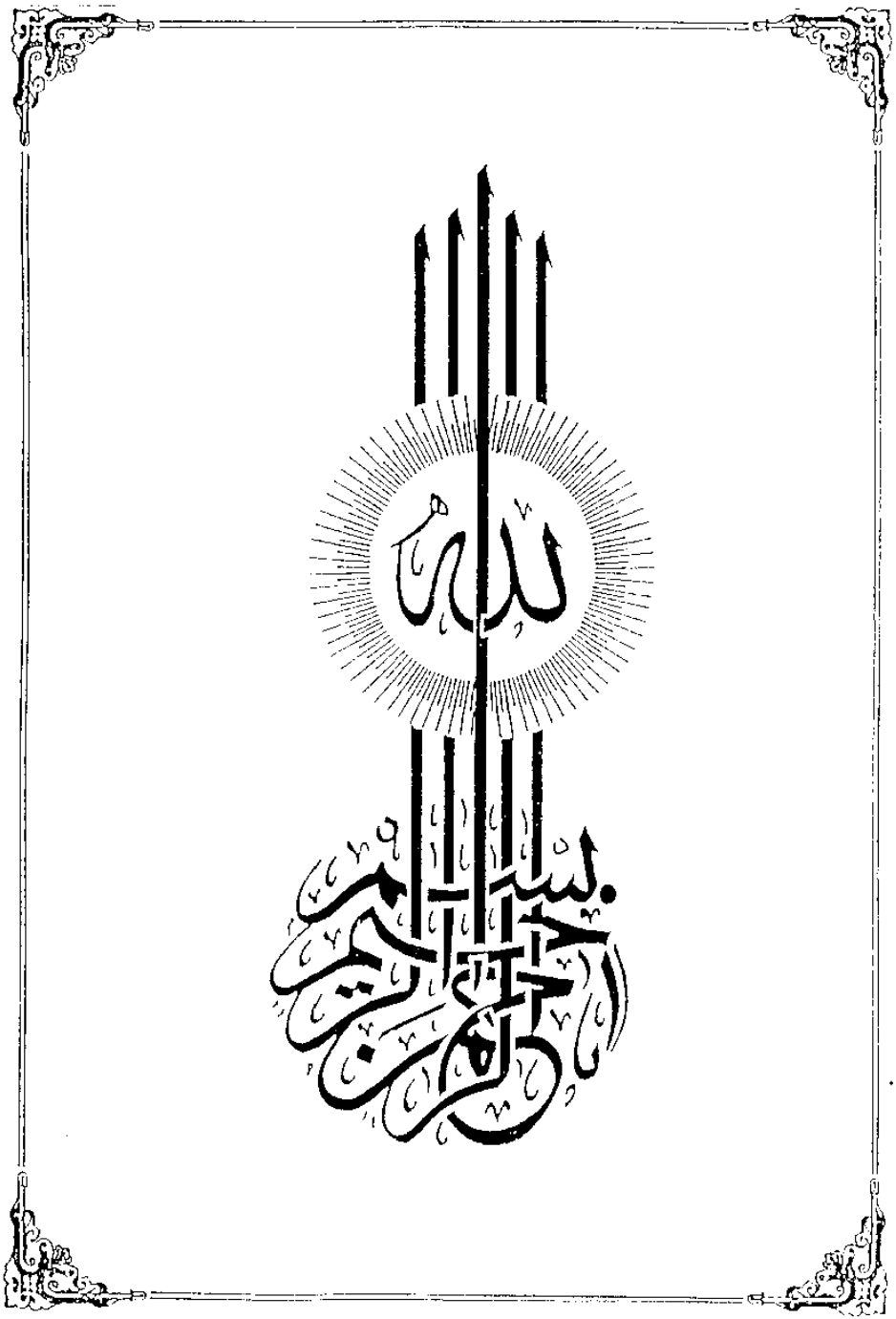
Acknowledgement

I would like to express my deepest gratitude to Professor Dr. Hamid M. Khalil, Professor of Parasitology and Head of the department who kindly suggested this interesting subject and supervised the work with constant encouragement and advice.

Thanks are also due to Dr. Mohamed H. Abdel Baki, Assistant Professor of Parasitology and to Dr. Hassan M.El Hady lecturer of Parasitogy who kindly helped in supervising this work.

My greatest apreciation to Professor Dr. Ahmed M.El Hawey, Professor of Tropical Medicine and Head of the department Faculty of Medicine El Azhar University for his valuable criticism and advices.

Also I owe very much to Professor Dr. Tosson A. Morsy, Professor of Parasitology who in the first place suggested to me the registration for this degree and guided me with valuable advices . In fact I would be glad to express my sincere thanks to the staff members of Department of Parasitology Faculty of Medecine, Ain Shams University where this work has been done.



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Introduction and Aim of the work.

Introduction

Schistosomiasis is one of the major debilitating infections (Warren, 1978 and Manson Bahr et al, 1982). It is estimated that more than 200 million people are infected world wide (Jordan and Webbe, 1969).

Prevalence in Egypt

The two species causing human schistosomiasis in Egypt are Schistosoma haematobium and S.mansoni, recent estimates of infected persons were about 20 million in 1974 (Ayad, 1974) and 16 million in, 1976 (Agamieh 1976) Schistosomiasis was suggested to affect 6.9 million Egyptians out of about 20 million living in the rural areas (Miller et al, 1978).

In the Nile Delta where mixed infection is prevalent it was reported that S.mansoni prevalence rate varies from 40.5% to 55% or even to 74% of the infected persons (El Alamy and cline 1977, and Mahmoud, 1979).

It has also been reported that 80% of primary school children in some areas in Luxor (Upper. Egypt) are

infected with the predominant species S.haematobium (Higashi 1979). Increased prevalence was found to be closely associated with water development projects and irrigation systems, schistosoma by its 2 types were detected in Tahrir province a newly reclamed area from the desert as result to introducing canal irrigation system which were invaded with the intermediate snail hosts (El. Guindy et al, 1985). However during the earlier years of this land reclamation project no Schistosomiasis was found in Tahrir province (Khalil, 1964).

In a study conducted at Siwa Oasis which is separated from the Nile Valley by a stretch of desert 320 Km. wide and where cultivation areas are irrigated by Roman wells cut off completely from the Nile, It was found that Schistosomiasis was absent among the inhabitants (Khalil et al, 1976). Snails were existant in wells but none was known to harbour infection (Rifaat et al, 1965). In Quena and Aswan governorates prevalence of schistosomiasis nearly doubled and reached respectively 14% and 15.6% after the construction of the High Dam which resulted in the change from basin to perenial irrigation system favouring for the prevalence of the suitable intermediate host (Khalil et al, 1976). A similar increase for Schistosomiasis was noted at Sudan in the near by localities around Sennar Dam (Khalil, 1967).

Morbidity

In urinary Schistosomiasis caused by S.haematobium, the early stages are characterized by haematuria and dysuria. Large masses of eggs, inflammatory cells, and connective tissue may be seen in the bladder and elsewhere. Obstructive uropathy is the lesion of greatest consequence and frequently results from lesions of the ureter or ureterovesical function (Mc Cully et al 1976).

The Schistosome eggs rather than the host tissues calcify in the submucosa of the bladder and ureters appearing grossly as sandy patches and radiologically as diagnostic linear calcifications. The inflammation and scarring of the urinary bladder have been associated with an increased incidence of carcinoma of the bladder in Egypt (Lehman et al, 1973). Urinary Schistosomiasis predisposes to urinary tract infection in 22% of adults suffering from uncomplicated urinary bilharziasis (Abdallah 1946) . Laughlin et al, (1978) found bacteruria in 6.5% of active Schistosomal egg passer. Abdel-Wahab et al, (1977) reported higher rates of Salmonella bacteruria in Schistosomal patients in Egypt.

Schistosomiasis caused by S.mansoni may result in hepatosplenic disease which is associated with Symmer's

clay pipestem fibrosis (Cheever and Andrade, 1967 and Mc Cully et al, 1976). The parenchyma between fibrotic areas is typically well preserved maintaning nearly normal hepatic function which is one of the clinical hallmarks of hepatosplenic Schistosomiasis (Rodriguez, et al,1955 and Von Lichtenberg, 1970).

Patients with bilharzial hepatic fibrosis are susceptible to bacterial infection propably due to depressed immune responses. (El Hawey et al, 1981).Severe portal hypertension is anatomically presinusoidal (Andrade and Cheever 1971) and is haemodynamical caused by occlusion of portal venules (Coutinho,1968). Patients may have repeated bouts of bleeding due to oesophageal varices (Arap et al, 1976) and exsanguination is the major cause of death, which most commonly occurs after three or four decades (Rodriguez et al, 1955 and Cheever and Andrade, 1967).

Intestinal lesions are first colonic polyposis which may be marked by extensive loss of fluid, blood, and protein (Lehman et al, 1970). The second intestinal lesion of clinical importance is intense focal fibrosis and inflammation usually in the form of mass lesions termed bilharziomas (Mc Cully,et al, 1976).

Diagnosis of Schistosomiasis

A positive diagnosis must precede contemplation of chemotherapy before treatment is undertaken, it must be established that the infection is active. Not only should eggs be found in excreta but the eggs must be viable. The translucent eggs with the presence of a well formed miracidium (Perhaps with flame-cell movement) clearly indicates an active infection. The distinctive structure of the eggs will allow species identification(Cook, 1982).

If infection is not accompanied by regular appearance of eggs in excreta, then active infection can be discovered by means of serological tests as the Circumoval precipitin (COP) test, the Enzyme linked immunosorbent assay (ELISA)....etc (Kagan, 1968).

A- Diagnosis of Active infection :

1. Urine examination (S.haematobium)

   The urine is precipitated first, then centrifuged and examined microscopically for viable schistosome eggs.

2. Stool examination (S. mansoni)

   a- In heavy infection, a simple fecal smear will be sufficient to detect infection (Cook, 1982).

b- In lighter infection, concentration techniques such as formol-ether technique may be used (Knight et al, 1976).

3. (COP) test

If infection is not accompanied by regular appearance of Schistosome eggs in excreta (Kagan, 1968).

B- Diagnosis of severity or intensity of infection:

(Patient evaluation)

It has been stressed, that quantifying the intensity of infection by counts of eggs per gram of feces, the Kato technique is propably the most widely used quantitative technique (Peters et al, 1980)or per 10 ml aliquot of urine (Peters et al, 1976), is important for patient evaluation as it will give some indication to the intensity of the infection and the need for treatment.

That was due to the fact that 10 years ago because of the toxicity of available medication it have been more important to do an egg count, because some thought might have been given to witholding treatment of lesser infections.

A large level of egg excretion would weight heavily in favour of use of toxic compounds.

With the increasing safety of the currently available drugs however, antischistosomal therapy should be offered to any patient with active infection regardless of the intensity of the infection, as effective therapy will halt the disease process if treatment is instituted early (Cook et al, 1974).

C- Diagnosis for evaluating efficacy of treatment :-

(Cure assessment)

Occasionally, pathological evidence of recent or chronic Schistosomiasis may not be accompanied by regular appearance of Schistosome eggs in excreta.

Serological or indirect methods of diagnosis may then be helpful (Kagan 1968).

Hillyer et al, (1980) compared results from 3 serologic tests, the Circumoval precipitin (COP) test, the Ouchterlony immunodiffusion and the Enzyme-linked immunosorbent assay (ELISA),with results from reference parasitological tests in 32 Egyptian male patients infected

with Schistosoma mansoni, Schistosoma haematobium and with both species of schistosomes, from these tests only the (COP) test, correctly identified all of those with Schistosome infection, although differentiation as to Schistosome species was impossible.Circumoval precipitates around S. haematobium eggs derived from human urine were more numerous and larger than those around S.mansoni eggs obtained from mouse livers.

Ouchterlony immunodiffusion done with schistosome worm antigens failed to diagnose correctly approximately 20% of infected individuals.

The (ELISA) correctly identified 94% of the infected individuals, although two individuals with moderate to high egg excretion levels were negative. This study demonstrated that (COP) test with either S.mansoni or S.haematobium eggs can be used for the serodiagnosis of Schistosome infections in Egypt. The (COP) test offers great advantages in permitting an assessment of cure of individuals following specific therapy (Shoeb et al 1967) and also in evaluating the efficacy of treatment in recent cases (Weltman 1982).

Treatment of Schistosomiasis

Trivalent antimony compounds (Plorde 1980) including Tartar emetic (antimony potassium tartrate), Stibophen (Fouadin), and Stibocaptate (Astiban), have been the traditional agents for this disease, and are administred in several doses either intravenously or intramuscularly.

Antimonials cause toxic side effects, arrhythmias collapse, and sudden death have been reported (Halawani, 1964). Also they may cause hepatitis, acute nephritis (Lippincott et al, 1947), haemolytic anaemia and thrombocytopenic purpura (Halawani et al, 1955) .Heart, renal or liver disease therefore constitutes a contraindication to therapy with this group of agents (Plorde 1980).

Non-antimonial compounds as Ambilhar (niridazole) (Goble, 1969), that can be taken orally in several doses is less toxic than the antimonials and probably highly effective, although there has been a high incidence of neurological abnormalities in the form of psychotic episodes, or convulsions, especially with patients with hepatosplenic form of the disease (Basmy et al, 1968 and Coutinho and Barreto, 1978) Hycanthone (Cook et al., 1976;

and Warren et al, 1978) another non-antimonial preparation that can be administred in a single intramuscular injection, proved to posess hepatotoxic and mutagenic properties that limits its usefulness.

Currently Schistosomiasis is treated by :

1- Oxamniquine, which is only effective against S.mansoni probably because S.haematobium when under the influence of the drug does not migrate to the liver (Beaver et al, 1984).

2- Metrifonate (Bilarcil), while not effective against S.mansoni - nor S. japonicum it is the leading drug for the treatment of vesical Schistosomiasis because of its low cost, efficacy and ready tolerability by the patients.

Unfortunately the prolonged duration of the course of treatment requiring 4 weeks (5 to 15 mg/Kg.b.w - given at 2 weeks interval for 3 doses) renders the regiment unsatisfactory for mass treatment (Davis and Bailey 1969).

3- Praziquantel (Biltricide), the newest and perhaps most important drug, is effective against all three major human Shistosome species in single dose of 40 mg/Kg.b.w., exellent cure rates have been evaluated with both