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# Artemether and Praziquantel a green light to treat the resistance schistosomiasis: A case Report

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**Abstract**

Schistosomiasis is a neglected tropical disease (NTD) that remains one of the most prevalent parasitic infections in Africa , *S. mansoni* and *S. haematobium* are the most common species that infect humans and the Praziquantel (PZQ) is the drug of choice for treatment despite the recent resistance to it .In this case report, we present an augmenting evidence to support the use of combination regimen of antimalarial drug, Artemether (ART) along with Praziquantel, as an efficient methodology in the treatment of resistant urinary schistosomiasis .

**Keywords:** Artemether, Praziquantel, Resistance Schistosomiasis, Sudan

**Introduction:**

Drug resistance associated with the treatment of human schistosomiasis appears to be an emerging

Problem requiring more attention from the scientific community and health provider [1].

Literature has presented a debate on the status of Praziquantel (PZQ) resistance; where a considerable number of studies in different endemic communities have investigated the mass PZQ use in schistosomiasis [2].

Treatment and morbidity control of schistosomiasis relies on a single drug, Praziquantel, there is one hypothesis that stands, if PZQ resistance was to emerge, current efforts to eliminate schistosomiasis would be severely challenged requiring alternative and/or complementary drugs.Therefore, there is a pressing need investigate alternative or synergistic drugs against schistosomiasis [3].

Artemisinin derivatives could provide an opportunity as these drugs are found active against surprisingly also against juvenile schistosomes [4].

Up to date, PZQ is the only freely available drug to treat Schistosomiasis. The hazard of induced Praziquantel resistance is hard to neglect, especially with the prolonged use of large-scale chemotherapy in infested populations. There for, an artemisinin/PZQ combination would be complimentary, and potentially additive [5].

In this case report, we present an augmenting evidence to support the use of combination regimen of antimalarial drug, Artemether Along with Praziquantel, as an efficient methodology in the treatment of resistant urinary schistosomiasis

**CASE REPORT:**

On this clinical encounter, a case of recurrent infections of urinary Schistosomiasis in a young Sudanese boy has shown remarkable results to a dual course of Artemether and Praziquantel.

A 16 year old school boy, originally from Kordufan - residing in Khartoum state was referred for consultation with non-resolving urinary schistosomiasis for the last two years. On the first three attacks, the patient was managed as a case of urinary schistosomiasis despite repeatedly negative urinary investigations (explained as improper sampling of urine and underdeveloped laboratory facilities in rural areas). He was given a single dose of 60 mg\kg of PZQ with substantial improvement. Clinical suspicion was correlated to patient's occasional visits to Tendelty, an endemic area for Bilharziasis where children usually take swims in infested swamps. High endemicity, typical presentations, and successful treatment were supportive of the diagnosis.

One year and a half later, the fourth attack also followed a rural visit with sever presentation at this time and positive urine analysis for schistosoma eggs.

The patient was admitted at Khartoum State Hospital, as a complicated case of schistosomiasis

with glomerulonephritis (acute kidney injury, hypertension and low C3 C4 levels). The patient was stabilized and given a single dose of PZQ (60 mg\kg). The outcome was full recovery of renal functions with persistence of terminal hematuria and positive urine test for eggs. The patient adhered to follow-up at the urology clinic for two years with repeated courses of treatment (PZQ 60mg\kg\day) and persistent with positive urine analysis of Schistosoma eggs. Finally referred to the Tropical Paediatric Unit, Tropical Diseases Teaching Hospital-Omdurman. Medical history was insignificant apart of the mentioned attacks. He was generally unwell with unremarkable examination. He was sent to the, Department of Clinical pathology & Immunology, Institute of Endemic Diseases, Division of Medical Laboratory of Khartoum University; for urine analysis, egg count and Hatching test. Schistosoma egg load reported at (5/10 ml) and hatching tests was positive. General blood tests are of normal hemoglobin levels and red blood cell indices and platelet count. Increased total leukocyte count (15.0 x $10^9$ /L) with eosinophils at (8.0 x $10^9$/L). Urinary was reddish, slightly turbid urine, with mild leukocytosis (8-10 pus cells) and RBCs count of over (100) Creatinine at (1.3 mg/dl), while urea and electrolytes were normal. Abdominal Ultrasonography indicated average normal liver and spleen, normal gallbladder, normal size and shape of kidneys with mild increase in echogenicity, no stones or obstructive changes. Urinary bladder showed thickened walls with a small lesion in the posterior wall of the bladder measuring (2.4 x 1.2) cm in size. Diagnosis was made of resistant schistosomiasis with chronic cystitis and bladder granuloma with heavy schistosoma eggs confirmed by Bladder cystoscopy and biopsy.

Then patient was discussed with the Department of Clinical Pathology & Immunology, Institute of Endemic Diseases, and University of Khartoum, Sudan. The management plan determined a course of Artemether injections (intramuscular route, twice a day for the period of two weeks) with two doses of PZQ, (60mg\kg\day) before and after the Artemether course. As Oxamniquine is not considered effective against S.haematobium, and Metrifonate was not available. The patient and his guardian were vigorously counselled on the treatment and were requested to adhere to follow up of the bladder mass with regular Abdominal Ultrasound (US).In two weeks appointment, abdominal Ultrasound showed a regression in the size of the trigonal granuloma to (1,5x 0.5 cm). Full urine analysis and eggs count was clear for the first time during the last two years. Abdominal Ultrasound (US) and urine for schistosoma eggs was done again at two occasions – one month apart- showing absence of eggs and persistent

regression of the trigonal granuloma as confirmed by cyctoscopy and biopsy, last Urinary Ultrasound showed normal bladder wall with complete disappearance of the mass.

**DISCUSSION:**

In our clinical presentation, we have reported a case of resistant *S. haematobium* infection to PZQ, where the patient has been consistently visiting his hometown at least one month before each of first three attacks. In these rural areas, bathing and swimming among children in swamps infested with S. Haematobium eggs is very common. This primary finding may support the hypothesis of repeated infections over a presentation of resistance to PZQ in our patient. It is true that variation in patterns of Schistosoma infection depend on exposure time as well as age and gender, but it is mainly affected by water contact through occupational or recreational activities conducted in infested open water [6]. Our patient responded well to treatment with Praziquantel in his first three attacks of infection. We have not been able to secure if he has stopped excreting eggs and thus was completely cured in each of the attacks. Although a spontaneous cure unrelated to PZQ therapy may have occurred, we note important information raising the possibility of persistent case sub-clinical infection. One of the factors being the estimated mean life expectancy of adult S. haematobium worms, which is 2.9-3.3 years [7]. Also, there was no animal-model data for us to indicate that the strain that infected our patient was susceptible to PZQ.

This case report allows clinicians to consider different aspects regarding Schistosoma treatment. Firstly, the poor efficacy of PZQ in the early phase of infection, where the development of schistosomules is not synchronous and different stages of the parasitic lifecycle may overlap [8]. As a consequence, adult worms start egg excretion when circulating schistosomules are still around. In the last attack of our patient, the infection was not cleared out by repetitive doses of Praziquantel. Overall, there are many hidden factors that could have affected the response to PZQ, although not reported in the medical history of our patient. A point to consider is the poor bioavailability of PZQ. We did not analyze the pharmacokinetics of PZQ in our patient. Yet Praziquantel is known be more hydrophobic with fast metabolism in oral administration [9]. The possibility of a gastrointestinal pathology or a gastric co-infection could have reduced the efficacy of PZQ. Other factors like the incomplete adherence to treatment affect the outcome in such patients. Thus, this does not exclude the prospect of resistant type of infection. Long-term hyper exposure and high level of infection without adequate treatment

could conceive tolerance to the drug. Considering various host and parasite factors that can cause suboptimal response to PZQ therapy and the implications of persistent infection for post treatment monitoring of patient, we believe that the present report raises doubts about the optimum useful dose of PZQ for epidemiologic purposes.

The last infection in our patient was sever with features of glomerulonephritis and acute kidney injury could be due to immune complex formed in response to the repetitive Schistosoma infection deposited on glomerular renal basement membrane leading to glomerulonephritis and renal failure. However, Schistosomiasis may produce a broad spectrum of glomerular pathology; as in obstructive nephropathy, chronic pyelonephritis or parasite-specific immune-mediated tubular injury [10]. Although the last attack was finally cleared according to the urine investigations which were nil for parasite eggs, no biopsy specimens were obtained to confirm that he did not still have viable eggs in his bladder tissues. The incidence of these pathologies in our population is unknown since many cases are subclinical or resolve spontaneously. Our patient typically presented with feature of nephritis and acute kidney injury that resolved with anti-Schistosoma treatment. There for, we find the monitoring and follow-up of renal function an essential protocol in our population, to any case which reports a yield of re-infections. We also note that the last infection persisted for two years with failure to respond to repeated courses of PZQ which resulted in complications namely chronic cystitis and bladder granuloma (a known long term genito-urinary squeal of repeated or non-resolving *S. heamatobium* infection [11]. These were seen on the radiological findings of our patient. Although early Cyctoscopy examination is usually unnecessary in an endemic area [10], duration of infection of intensity at the time of diagnosis are vital factor for structural abnormalities. Our patient was requested to undergo a biopsy as bladder neoplasia has reported incidence in patients as high as 4.5% of those with urinary bilharziasis in some endemic areas [10]. The choice of Artemether for treatment of our patient was based on many reports on it is use successfully on the treatment of cases of treatment failure with PZQ [4,12,13,14].

There are several host and parasite factors as possible causes of the suboptimal response to therapy, and the documented benefit of using ART/PZQ combinational therapy [15,16,17].

Artemisinin derivatives drugs metabolized in the blood into dihydro-artemisinin and sequentially generate free radicals, the heme iron first attacks and breaks the end peroxide linkage to Artemisinin, producing an oxygen-free radical, which is then rearranged to produce a carbon-free

radical that causes lethal damage through the alkylation of parasite proteins indicates that the same pathway is followed with respect to *Schistosoma*. To be effective, the drug needs to be ingested by the parasite, enabling the interaction with hemin or heme causing damage to the worm gut by generating one or many substances toxic to these worms in amounts overwhelming the pathway leading to the hemozoin, the fact that the gut suffers particularly severe damage after ART treatment supports this chain of events [18] .

Single-celled malaria plasmodia and schistosome worms are phylogenetically very distant from each other, and one might think that the damage caused by the Artemisinin to both these organisms would be due to different principles. A derivative of antimalarial Artemisinin is found chemo prophylactic to PZQ affecting refractory young developmental stages of schistosome parasites [19].

Therefore, Artemisinin derivates are true transmission-blocking drugs as they target stages before egg production starts contributing to disease elimination.

The mechanism is yet not determined, but hemoglobin digestion by both parasites in host erythrocytes and interference with the formation of hemozoin is considered [20].

The use of this regimen came with a surprising response within two weeks in our patient. To consolidate on our results, we recommend that our experience should be replicated on a large-scale clinical trial in endemic areas of Sudan, taking to note the arguments raised by our review, among which most importantly; is the co-endemicity of Malaria and the developed resistance to anti-malarial drugs.

**Conclusion:**

The distinction between worm burden reduction and failure to eradicate infection in these reports is not always clear. The success of our treatment trial may help pediatrician, physician and urologists in Sudan helping many patients with the same story which, if not treated early may end up with devastating complications. This may also support better preventive measures and effective early treatment of schistosomiasis at large.

**Declaration of Interests**

The authors state they have no conflicts of interest to declare.

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