SHORT REPORT: FAILURE OF STANDARD TREATMENT WITH PRAZIQUANTEL IN TWO RETURNED TRAVELERS WITH SCHISTOSOMA HAEMATOBIUM INFECTION

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Abstract. A single 40 mg/kg dose of praziquantel (PZQ) continues to be the standard treatment for schistosomiasis caused by S. mansoni and S. haematobium in all clinical settings. Experimental development of drug resistance and the recent isolation of S. mansoni strains with a natural tolerance to high doses of PZQ have raised concerns over the adequacy of such a dose. We describe two Spanish travelers with genitourinary schistosomiasis caused by S. haematobium in whom repeated standard treatment failed to clear the infection.

INTRODUCTION

Praziquantel (PZQ) is the current drug of choice for schistosomiasis. It has few and mild side effects, an affordable price, and a high activity against all five species of the parasite capable of producing disease in humans (Schistosoma mansoni, S. haematobium, S. japonicum, S. mekongi, and S. intercalatum).

When given at a single oral dose of 40 mg/kg, it has an overall cure rate (as defined by clearance of eggs from urine or stools) of 60–90% in individuals living in areas endemic for infection1–3 and nearly 100% in non-endemic situations (immigrants and travelers without re-infection).4 Its large-scale use in control programs of infected populations constitutes, along with health education, one of the most effective strategies for limiting morbidity and reducing parasite transmission.1

In populations living in disease-endemic areas, a significant proportion of cases in which PZQ given at a single oral dose of 40 mg/kg is apparently subcurative can be explained by pre-treatment parasite burdens, high re-infection rates, and the likely presence of immature stages of the parasite. In the case of returning travelers, only the latter should be considered.

Therapeutic failures to PZQ at a dose of 40 mg/kg have been reported in disease-endemic areas of Egypt4,8 and Senegal,5–7 raising the possibility of drug resistance, although collected evidence is far from being conclusive. Conversely, little has been reported on the therapeutic response to PZQ in patients in whom there is no chance of re-exposure to infection.4,8

We describe two Spanish travelers with genitourinary schistosomiasis caused by S. haematobium acquired during trips to Mali and Senegal who did not respond to two single oral doses (40 mg/kg) of PZQ.

CASE REPORT 1

A previously healthy 26-year-old Spanish man traveled to Mali for 16 days. He bathed in the Dogon country, where transmission of S. mansoni and S. haematobium occurs.9 Fifteen days after his return, he developed fever and chills, and consulted the casualty department of the Hospital Clinic in Barcelona, Spain. The results of a physical examination were normal. Hematologic testing showed an absolute eosinophilic count of 750 cells/mm³. Two blood cultures and a thick smear were negative. The fever and malaise subsided after a few days and the patient was subsequently discharged and referred to our Tropical Unit for follow-up. During the next six months, serial stool and urine sample examinations were conducted; results were negative for parasite ova. Serologic test results for schistosomiasis, fascioliasis, toxocariasis, trichinellosis, and cysticercosis were also negative. The patient did not return for additional tests and was lost to follow-up.

Two years later, he noticed terminal hematuria and was referred to us again. Samples of urine, stool, and semen were collected. Examination of semen specimens showed morphologically viable ova of S. haematobium, and the patient was treated with PZQ at a dose of 40 mg/kg. Transrectal ultrasonography showed no abnormal findings. Although the hematuria disappeared, semen samples continued to be positive throughout the follow-up, with some ova being morphologically viable. A second course of treatment with PZQ at a dose of 40 mg/kg was given. Three months later, semen samples showed the persistence of viable eggs, urine samples continued to be negative, and a prolonged course of treatment at a dose of 40 mg/kg/day for three consecutive days was prescribed. Follow-up throughout a 12-month period included three consecutive negative semen samples, after which he was considered cured.

CASE REPORT 2

A previously healthy 32-year-old Spanish man traveled to Senegal for one month. During the trip, he swam in the Gambia River (Kedougou region), where transmission of S. mansoni and S. haematobium is known to occur, and in the Casamance River (near Mlomp) in a section severely infested with S. haematobium.10 Two months after his return, he began complaining of intermittent lower abdominal pain with dysuria, perineal discomfort, and pain in the testes, especially during sexual intercourse. He also referred that his ejaculate had turned brownish in color and had a watery consistency. Under suspicion of chronic prostatitis, he received several courses of antibiotics, without improvement. Urinalysis yielded microhematuria. Transrectal ultrasonography showed prostatic calcifications and a thickened inferior vesical wall. An intravenous pyelogram showed a right hydroureter.

The patient was referred to us by a general practitioner with a presumptive diagnosis of schistosomiasis. Microbi-
logic analysis of urine and seminal fluid were positive for \textit{S. haematobium} ova. Serologic testing for \textit{Schistosoma} was weakly positive (titer = 1:80). The total eosinophilic count was 810 cells/mm$^3$. The patient received a single dose (40 mg/kg) of PZQ after which he became asymptomatic. Further urine and semen specimens were negative for parasite ova at follow-up four months later.

However, in view of the persistence of eosinophilia, another course of PZQ (40 mg/kg) was given. Seven months later, the patient was still asymptomatic, but urine and seminal fluid samples again contained parasite ova and the total eosinophilic count was 970 cells/mm$^3$. A third course of PZQ (40 mg/kg/day) for three consecutive days was prescribed. One year later, the results of blood and parasitologic tests were normal, and the patient was considered cured.

**DISCUSSION**

In comparison with microbial infections, it is not easy to establish a suitable definition of drug resistance that applies to parasitic infections. This holds especially true for schistosomiasis because of the variation in susceptibility of different maturation stages and sexes of the parasite, the different maturation rates in strains of diverse geographic origin, and the likely influence of host immunity in the efficacy of the drug. The high re-infection rates that occur in disease-endemic areas and the low drug bioavailability make it even more difficult to assess the actual efficacy of PZQ.

Reported laboratory induction of resistance to PZQ shows that emergence of PZQ resistance could actually occur if the necessary amount of drug pressure was exerted.\textsuperscript{11} In addition, the presence within a population of a gene or a group of genes that confer an inherent diminished susceptibility to the drug even before exposure to it cannot be excluded. This natural tolerance has been seen as the explanation for therapeutic failures of PZQ observed in Egypt,\textsuperscript{5} whereas the alarmingly low cure rates after PZQ treatment documented in a new highly endemic focus in northern Senegal can most likely be explained by the high intensity of transmission occurring among a non-immune population.\textsuperscript{6} In both epidemiologic settings \textit{S. mansoni} was the involved species.

In this rather obscure picture, the only hard fact is that true drug resistance to PZQ has not been confirmed in the field. Mathematical modeling seems to indicate that at the current treatment rates, PZQ resistance will likely take 10 or more years to emerge.\textsuperscript{12} The purpose of this report is not to bring new light on the picture of PZQ resistance, but to alert upon the probable inadequacy of the traditional and almost unanimously accepted dose of 40 mg/kg as the standard treatment of \textit{S. haematobium} infections.

From an epidemiologic point of view, the efficacy of PZQ at a single dose of 40 mg/kg is undisputable. However, there is increasing evidence supporting the notion that it may no longer seem justifiable to use it systematically at that standard treatment dose. This disparity of usefulness to clinicians and epidemiologists alike is highlighted in the above-mentioned cases, in which treatment with PZQ at a dose of 40 mg/kg was clearly subcurative. Although both patients were likely to have low parasitic loads and had no chance of getting re-infected, a third course of treatment at a dose of 40 mg/kg for three consecutive days was needed. The fact that in both cases treatment was begun after eight weeks reasonably rules out the potential presence of non-respondent schistosomulae.

Although there is a consensus on the use of higher doses of PZQ for the Asian parasite species that cause schistosomiasis,\textsuperscript{13} a review of 1,107 imported cases concluded that a change in the established dose for \textit{S. mansoni} and \textit{S. haematobium} was not yet justified.\textsuperscript{4} However, three years later a treatment failure with PZQ at a standard dose in a returning traveler with \textit{S. haematobium} infection was reported in whom a course of 40 mg/kg for three consecutive days was finally curative.\textsuperscript{8}

Another point to be considered is the poor bioavailability of PZQ. Its low hydrosolubility and fast metabolism after oral administration constitute a matter of concern for pharmacologists, who are still searching for more effective forms to improve drug activity. \textit{In vivo} studies show that liposomes improve the antischistosomal efficacy of PZQ because of prolonged drug levels.\textsuperscript{14} We can not rule out that our patients were particularly fast metabolizers of the drug and therefore had a worse clinical outcome. This is supported by evidence from a mouse model that suggests that some cases of PZQ resistance could be caused by host factors, whereas others could be attributable to the worms.\textsuperscript{15}

It has been speculated that when genital involvement occurs (as was the case of our two patients), higher doses or a longer course of treatment is desirable.\textsuperscript{16} It is not clear in these infections if PZQ effectively penetrates to the site of the worms. The possibility of ectopic adult worms in the prostate gland, an organ known to be pharmacologically hostile to many drugs, cannot be ruled out.

We believe that the present report helps raise doubts as to what a useful dose of PZQ for epidemiologic purposes should represent to the individual patient in clinical practice, with special emphasis on \textit{S. haematobium}. Moreover, we stress the need for more sensitive and more specific techniques to help detect treatment failure. The persistent absence of ova in different serial samples examined during follow-up still stands as the best evidence for parasitologic cure.

In those patients in whom eosinophilia was initially present, a reduction in the eosinophilic count is also a helpful tool to assess cure (patient 2). If eosinophilia persists, co-existing strongyloidiasis and filarial worm infection should be considered. Given the lack of sensitivity of the test procedures regularly used in the screening of this disease, we strongly recommend the routine inclusion of seminal fluid as a useful sample for diagnosis in males.\textsuperscript{17}

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