Case Report: Treatment of Schistosomiasis in a Patient Allergic to Praziquantel: A Desensitization and Treatment Protocol

Trupti A. Patel, Joanna Lukawska, Jennifer Rowe, and Robin L. Bailey

Abstract. Praziquantel is the mainstay of treatment of Schistosomiasis, which affects at least 262 million people worldwide. It is also used in the treatment of other trematode as well as cestode infections, with few safe and effective alternatives. It is generally well tolerated and allergic reactions are rare. In this report, we present a case of schistosomiasis with a history of a hypersensitivity reaction to praziquantel. Skin-prick and intradermal testing were performed, followed by treatment through rapid desensitization. This protocol may be of value to those patients requiring praziquantel treatment with a history of IgE-mediated allergy to the drug.

INTRODUCTION

Schistosomiasis, also known as bilharzia, is an infectious disease caused by trematode parasites of the genus Schistosoma. Three species account for the majority of human infection—Schistosoma mansoni, Schistosoma haematobium, and Schistosoma japonicum. Infection occurs through contact with freshwater containing cercariae, the larval form released from snails, the intermediate host. Cercariae penetrate human skin, become schistosomulae in tissue and migrate through several tissues and stages to become adult worms, which take their final residence in the mesenteric veins (S. mansoni) or in the pelvic venous plexus and veins around the bladder (S. haematobium). Disease caused by this parasite results from the immunologic reactions to egg-derived antigens produced by adult worms in addition to the mechanical effects of eggs trapped in blood vessel walls. The chronic effects, which can be severe and debilitating, include hepatosplenomegaly, periportal fibrosis and portal hypertension, and urogenital inflammation and fibrosis. According to the World Health Organization (WHO), at least 262 million people worldwide required preventive therapy for schistosomiasis in 2013 (WHO 2015), and more than 700 million people live in endemic areas (WHO 2014).

Praziquantel, a pyrazino-isoquinoline derivative, is currently the treatment of choice for schistosomiasis. It was developed in 1975 after the discovery of its anthelmintic properties by Merck and Bayer in 1972. It acts against the adult worms (poor activity against immature schistosome larvae) and is given in a standard dose of 40 mg/kg for S. haematobium and S. mansoni and 60 mg/kg for S. japonicum.

There are currently few alternatives to praziquantel. Antimicrobial compounds and metronidazole were previously used but are now obsolete due to their excessive toxicity. Oxamniquine is the only other drug available for treating schistosomiasis. It is effective against S. mansoni, but has no effect on S. haematobium. Widespread resistance has occurred, and it is now only used on a large scale in Brazil. More recently, research has demonstrated the potential use of artemisinin derivatives, which only act on the immature larval forms of developing schistosomes. Its use would therefore be limited to combination therapy with praziquantel in areas of continuous exposure. Further research is needed on dosing, formulation, and drug interactions as well as, more importantly, the impact in malaria-endemic regions on the development of resistance before it is adopted for widespread use.

Praziquantel also successfully treats other trematode, including Fasciola hepatica, Clonorchis sinensis, and Paragonimus westermani, and cestode, including Hymenolepis nana, Diphyllobothrium latum, Echinococcus granulosus, and Taenia species, infections. It is generally well tolerated (common transient side effects include headache, dizziness, sleepiness, abdominal pain, and diarrhea), highly effective, and safe. Allergic reactions including hypersensitivity reactions and anaphylaxis are exceedingly rare and there have only been five published reports describing hypersensitivity reactions. In a Cochrane review of drug treatment of urinary schistosomiasis, 30 randomized-controlled trials enrolling 8,165 participants were included in the analysis. There were no reported hypersensitivity or anaphylactic reactions to praziquantel in those studies where data on adverse effects were available.

In this report, we present a case of allergy to praziquantel with subsequent successful desensitization and treatment of schistosomiasis. This case demonstrates the potential utility of our desensitization protocol for patients who develop an allergic response to this drug.

CASE REPORT

In August 2012, a 31-year-old white female, normally resident in the United Kingdom (UK), was referred to the Hospital for Tropical Diseases, London, for post-tropical screening having recently returned from Malawi. She had a history of frequent travel to Africa since her partner was from a village on the shores of Lake Malawi and had significant freshwater exposure. She was asymptomatic and had no significant past medical history. Schistosomiasis enzyme-linked immunosorbent assay, microscopy of terminal urine, and stool microscopy for ova, cysts, and parasites were negative. A full blood count and differential were normal.

Of note was that she had self-treated with praziquantel acquired in Malawi in October 2011. She developed pruritic hands and feet with the first dose, lasting an hour, although tolerated the second dose taken several hours later. She repeated the treatment in January 2012. She took a single dose on this occasion. Within 1 hour, she developed a generalized migratory urticaria lasting approximately 1 hour with no other associated symptoms and no syncopal symptoms or angioedema.
She had further screening tests in February 2014 having returned to Lake Malawi in the intervening years. At this stage, her schistosomiasis serology was positive at level two (0.494, cutoff 0.260) with all other tests remaining negative. Since she was due to return again to Lake Malawi, treatment was deferred until 3 months after her return in November 2014. On return, her serology had risen to positivity at level 4 (0.714), consistent with further freshwater exposure.

This patient was reviewed in the Drug Allergy Unit at University College London Hospital. She underwent standard allergy assessment involving skin prick (50 mg/mL) and intradermal (1:1,000, 0.05 mg/mL) testing with praziquantel. She tested negative to both. Despite the negative skin test results, there was a clear IgE-mediated history of praziquantel allergy and so the patient was considered suitable for rapid desensitization.

She was premedicated with 200 mg of intravenous hydrocortisone 1 hour prior to the procedure. She then underwent a 12-step rapid desensitization protocol, reaching a cumulative dose of 2,800 mg in 330 minutes. Emergency medication including adrenaline, antihistamines, hydrocortisone, bronchodilators, and oxygen was available. At step 10, a cumulative dose of 1,000 mg, she complained of pruritic earlobes. No treatment was administered and she recovered within 30 minutes. At step 11, a cumulative dose of 1,800 mg, she complained of pruritic arms. There was no evidence of a skin rash or angioedema and again no rescue treatment was administered. Following complete resolution of the pruritus 30 minutes later, she received her final dose of 1,000 mg praziquantel. This was well tolerated, except for mild erythema of the toes and mild urticaria of the toes, dorsum of the feet, anterior thighs, and knees. She was then treated with oral cetirizine 20 mg. Her urticaria resolved within 30 minutes and the patient was discharged home 1 hour following the completion of the protocol.

**DISCUSSION**

This report describes the desensitization protocol to praziquantel in a patient who required treatment of schistosomiasis. The diagnosis of drug allergy is based on the patient’s medical history and, if possible, the results of diagnostic (skin or challenge) tests.14

Although her initial immediate hypersensitivity reaction was to praziquantel sourced in Malawi, the symptoms were reproduced with praziquantel sourced in the United Kingdom, albeit at a diminished level, during the desensitization procedure. A challenge test to confirm the diagnosis was not performed in this case due to the strong history of two previous reactions.

Treatment with praziquantel is recognized to increase specific IgE and Th2 responses as a result of the release of antigenic proteins from dying eggs and worms.15 However, the timing of this response, which may in itself result in a hypersensitivity reaction in the setting of a heavy burden of infection, would be much later than immediate post-ingestion of the drug as in this case.

Skin testing to praziquantel is neither standardized nor validated. The predictive value of the test is therefore variable. Lower dilutions of the drug were not used in this case for further intradermal testing as the large drug particles would likely give an irritant reaction indistinguishable from a true positive reaction.

In this case, it was deemed necessary to treat the patient for her current infection with praziquantel, which involved a desensitization process as no suitable alternative drug treatment is available. Desensitization aims at altering the immune response to the drug and results in temporary tolerance, allowing the patient to receive the medication. Praziquantel, whose exact mechanism of action against trematodes and cestodes remains unclear, is rapidly absorbed through the gastrointestinal tract (up to 80% of the orally administered dose) and reaches its maximum plasma concentration within 1–2 hours.16 In view of the short half-life of the drug and its rapid elimination, we designed a rapid drug desensitization protocol (Table 1). Premedication for desensitization can be achieved with steroids, antihistamines, H2-receptor antagonists, and leukotriene receptor antagonists such as montelukast. They are used to ameliorate minor IgE-mediated symptoms some patients experience during the course of desensitization. In this case, hydrocortisone was the steroid used. It is worth noting that in sensitized patients, administration of premedication followed by full therapeutic dose of a drug may not prevent anaphylaxis.19

Desensitization involves the reintroduction of small, but incrementally increasing, amounts of the drug at fixed time intervals. Rapid drug desensitization (RDD) protocols are remarkably safe and allow for administration of the full dose of first-line therapy in as many as 99.9% of patients.18 The mechanism of RDD is not fully understood. However, the biochemical mechanism by which RDD induces specific mast cell tolerance is likely to be associated with the molecular stabilization of membrane-bound IgE receptors.19

There are only two previous published methods of praziquantel desensitization. In one report, the procedure involved increasing doses in a total of seven increments at 90-minute intervals.8 In this case, 30 minutes after the sixth dose, half of the total maximum dose, the patient developed an urticarial rash that was subsequently managed with 250 mg intravenous hydrocortisone and an anti-histamine. Three further days of praziquantel treatment were given, for _P. westermani_ infection, with no adverse effects. The second report involved premedication with hydroxyzine (10 mg every 6 hours), dexamethasone (4 mg IV every 6 hours), and prednisone (15 mg every 8 hours) 6 hours before administering praziquantel in 13 divided doses at 15-minute intervals.11 Hydroxyzine and praziquantel were continued for a total of 24 days and prednisone for an additional 2 weeks. The regimen used in this case was for the treatment of neurocysticercosis, hence the high corticosteroid use and lengthy treatment course. It would be

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difficult to justify using these doses in the case of preventive therapy for schistosomiasis and it was unclear in this report whether true desensitization was achieved. In comparison to these two methods, ours minimized the development of a Type I hypersensitivity reaction without the excessive use of corticosteroids. To date, the patient has not required re-treatment with praziquantel, but is likely to require further desensitization should the need arise.

Allergic reactions to praziquantel seem to be an emerging problem. It is a highly efficacious drug in the treatment of trematode and cestode infections where alternatives are lacking. Our protocol for desensitization is a method that could be used for those patients who report hypersensitivity.

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