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Review

Schistosomiasis mass drug administration in the Philippines: lessons learnt and the global implications

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Abstract

Schistosomiasis was first reported in the Philippines in 1906. A variety of treatments have been deployed to cure infection and to control the disease in the long-term. We discuss the journey to combat the disease in the Philippines and the lessons learnt which have implications for schistosomiasis control globally.

Keywords: Schistosomiasis; Treatment; Mass drug administration; Control

1. Introduction

Schistosomiasis is an intravascular disease caused by trematode worms of the genus *Schistosoma*. As of 2011, the disease was endemic in 78 countries [1]. The World Health Organization (WHO) estimated in 2012 that 249 million people are at risk of infection and in need of preventive chemotherapy [2]. The burden of schistosomiasis caused by *Schistosoma haematobium*, *Schistosoma japonicum* and *Schistosoma mansoni* was estimated at 24–29 million disability adjusted life years [3].

Considerable optimism surrounds Mass Drug Administration (MDA) for the control of schistosomiasis globally, for which praziquantel (PZQ) has served as the cornerstone since its inception in 1979. Numerous studies have claimed that preventive chemotherapy (i.e. 40 mg/kg of praziquantel), given annually or biannually, can significantly reduce the prevalence and intensity of infection, and control morbidity in the long-term [4–13]. In the last decade, close to one billion US dollars has been raised for MDA campaigns for neglected tropical diseases largely from international donors and delivered vertically to local endemic communities through national health care services largely using unpaid volunteers [5,14].

Praziquantel (PZQ), a pyrazinoisoquinoline derivative (Fig. 1), is a safe and highly effective oral drug that is active against all schistosome species. PZQ is the mainstay of treatment and a critical part of community-based schistosomiasis control programs globally, including those in the Philippines [15–17]. Since its discovery in the mid-1970s, its

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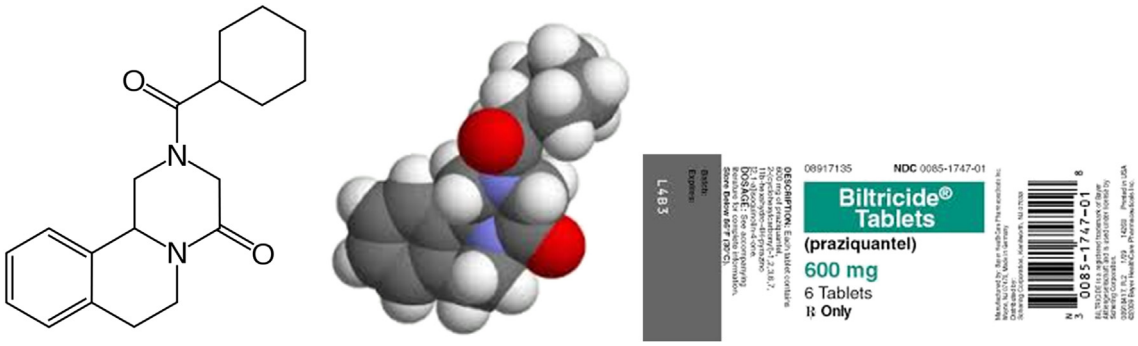

Fig. 1. The chemical structure of the drug praziquantel (Biltricide) used for the mass drug administration of schistosomiasis globally.

safety and efficacy have ensured its widespread use. It is absorbed well but undergoes extensive first-pass hepatic clearance [15]. PZQ is secreted in breast milk and is metabolized by the liver, and its (inactive) metabolites are excreted in the urine [15]. Side effects of PZQ treatment are minimal, and PZQ can be used to treat young children and pregnant women [16]. PZQ acts within one hour of ingestion, although its precise action on adult worms is unknown. It appears to cause tetanic contractions and tegumental vacuoles, causing worms to detach from the wall of the vein and die [15]. Schistosome calcium ion channels have been suggested as the molecular target of PZQ, but the evidence remains indirect and a recent study implicated myosin light chain as an alternative target of PZQ [17].

Standard treatment of chronic schistosomiasis is 60 mg/kg of PZQ in divided doses; for mass chemotherapy a single dose of 40 mg/kg is used [16]. There is also some evidence, albeit very controversial, that resistance to PZQ may be emerging in Africa, where there has been heavy exposure to PZQ and there are reports of *S. mansoni* and *S. haematobium* infections that are not responsive [17]. There have been no reports of the development of resistance of *S. japonicum* to PZQ in the clinical treatment of patients in the Philippines [17].

Periodic treatment of bovines (water buffalos [called Carabao in the Philippines], cattle) with PZQ, managed by local veterinarians, is now being considered for control programs for *S. japonicum* in the Philippines. This is because they are large animals (water buffaloes often exceed 300 kg in weight), they deposit considerable amounts of excreta near or in surface water, live for 10–12 years, and can carry large parasite burdens and develop hepato-intestinal disease. In China bovines have been successfully treated and in some localities have been removed to halt transmission. In agricultural areas in the Philippines, where *S. japonicum* is endemic, 10–80% of bovines are infected [18]. PZQ is curative, but the animals become reinfected. In most areas of endemicity, a large proportion (70%) of the environmental contamination may be traced back to bovine defecation and a high proportion of schistosome eggs [17]. The treatment doses (25 mg/kg for water buffaloes and 30 mg/kg for cattle) are lower than that used for humans because the collateral effects may be fatal, which is thought to result from portal occlusion by dead worms in heavily infected animals, as noted in other forms of cattle schistosomiasis [17]. Older buffaloes tend to excrete fewer viable eggs than those less than 18 months old; this could reflect self-cure, decreased egg viability, or decreased egg production by female worms, and all have been described for other forms of bovine schistosomiasis [17].

2. History of MDA for schistosomiasis control in the Philippines

Schistosomiasis (*Schistosoma japonicum*) was first reported in the Philippines in 1906. Approximately 12 million people living in 28 endemic provinces located in 12 different regions of the country are at risk of infection (Fig. 2) [19,20]. Overall, a total of 190 municipalities and 20 cities are affected by the infection. Villages in Gonzaga, Cagayan province and municipality of Calatrava in Negros Occidental (northern and central parts of the Philippines, respectively) were the most recently identified endemic foci, confirmed in 2004 and 2006, respectively [21].

Control of schistosomiasis in the Philippines was initially focused on snail control due to the lack of an effective, nontoxic and economical drug that could be used for mass treatment [19,22]. Use of antimonials, Fuadin and tartar emeric, for treatment of schistosomiasis was introduced in the country during the outbreak of the disease among United States (US) and allied forces in 1944 in the island of Leyte. The efficacy of the drugs was low as 31% of the cases remained stool-positive when the soldiers were tested back in US hospitals [23].

After the liberation of the Philippines, Stibophen, a trivalent antimonial preparation, was introduced in a trial with a course of nine intramuscular injections that resulted to a cure rate of 78.2% [24]. Following the trial, the Schistosomiasis Control Pilot Project (SCPP) used it as part of the support strategy for agro-engineering methods of snail control together with environmental sanitation and health education. SCPP was implemented in Palo, Leyte in collaboration with WHO starting in 1953 [19]. After three years of implementation, the snail population was almost eradicated and the human prevalence of infection was reduced from 38.9% to 32.0% [25]. These strategies were tried in the towns of Mayorga, La Paz and Burauen in Leyte before being formally implemented nationwide under the National Schistosomiasis Control Program in 1961 [19]. Further trials were conducted with an