Molecular & Biochemical Parasitology 195 (2014) 23–29

Contents lists available at ScienceDirect

Molecular & Biochemical Parasitology

Review

Schistosomiasis control: praziquantel forever?

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ARTICLE INFO

Article history:
Received 8 April 2014
Received in revised form 7 June 2014
Accepted 13 June 2014
Available online 21 June 2014

Keywords:
Schistosomiasis
Praziquantel
Oxamniquine
Drugs
Resistance
Mechanism of action

ABSTRACT

Since no vaccine exists against schistosomiasis and the molluscs acting as intermediate hosts are not easy to attack, chemotherapy is the main approach for schistosomiasis control. Praziquantel is currently the only available antischistosomal drug and it is distributed mainly through mass administration programs to millions of people every year. A number of positive features make praziquantel an excellent drug, especially with regard to safety, efficacy, cost and ease of distribution. A major flaw is its lack of efficacy against the immature stages of the parasite. In view of its massive and repeated use on large numbers of individuals, the development of drug resistance is a much feared possibility. The mechanism of action of praziquantel is still unclear, a fact that does not favor the development of derivatives or alternatives. A large number of compounds have been tested as potential antischistosomal agents. Some of them are promising, but none so far represents a suitable substitute or adjunct to praziquantel. The research of new antischistosomal compounds is an imperative and urgent matter.

Contents

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http://dx.doi.org/10.1016/j.molbiopara.2014.06.002
0166-6851/

1. Introduction

For countless centuries, schistosomiasis has been, and still is, a serious scourge for people living in tropical and sub-tropical areas of the world [1]. Estimates of the total number of currently infected people are usually around 200 million, ranging from 193 [2] to 207 [3] million, while the number of people at risk of infection has been calculated to be between 600 and 779 million [2,3]. The development of water resources in several tropical countries has probably contributed to maintain these figures at relatively constant – if not increasing – levels in recent years [3]. Mortality has been estimated at 280,000 deaths/year in Sub-Saharan Africa [4], while the overall level of disability caused by schistosomiasis has been recently re-evaluated and extended to include previously neglected effects of chronic infection like anemia, growth stunting and diminished physical and mental fitness [5]. It is customary to summarize the situation by saying that, among parasitic diseases, schistosomiasis ranks second after malaria for the number of people infected and for its health impact.

Such being the general picture of the disease, the immediate connection that comes to mind of anyone considering possible tools for its control, is undoubtedly the word "praziquantel" (PZQ). Indeed, this drug is used today so extensively and so exclusively that alternative options appear as something to which lip service, rather than real investment, is usually paid. Yet, we must avoid the trap of an excessive 'medicalization' of the problem and we must first of all remind ourselves that schistosomiasis is a disease of poverty, so that its full control could be achieved, in principle, just by removing the socio-economic causes that lay at its basis [6]. We should not forget that the eradication of schistosomiasis from Japan was hardly dependent on drugs for its success [7]. The often-recommended 'integrated approach' to control schistosomiasis should comprise, among other measures, sanitation, water supply, ecological interventions and health education. In the transmission of schistosomiasis, snails are the intermediate hosts, but the real vector is man: it is a baffling truism that if people avoided urinating or defecating in or near water bodies, transmission would be automatically interrupted, at least in places where non-human hosts are absent. However, the rapid spread – even in the most deprived settings – of electronic communication tools seems to remain a largely underused opportunity to raise awareness of health problems.

When the costs of interventions are taken into account, there is no doubt that PZQ chemotherapy is today a very good buy, especially when combined with the distribution of drugs against other parasites. PZQ is unquestionably providing enormous benefits to endemic populations, since, among other things, it helps break the vicious circle whereby poverty is a cause of disease and disease is a cause of poverty. However, a more farsighted approach should contemplate a substantial redressing of the balance from the present overwhelming preponderance of mass drug distribution in favor of other non-medical measures that may turn out to be more rewarding in the long run.

2. Vaccines

The major shortcoming of chemotherapy is that it does not prevent re-infection, thus requiring repeated treatments of people living in endemic areas. Preventive vaccination would clearly overcome this problem and the quest for a schistosomiasis vaccine actually represents a sizeable portion in the records of schistosomiasis research. Toward the end of the 1970s, optimism about the feasibility of a vaccine was encouraged by the finding that mice exposed to irradiated cercariae exhibited over 80% resistance to a subsequent challenge with normal cercariae [8]. A number of natural and recombinant antigens in various formulations were tested in an effort to identify the immunogen(s) active in irradiated cercariae, but none gave the expected high protection when tested in the mouse. WHO sponsored an independent trial to test six antigens proposed by various research groups, but the results were flatly negative, since none of them reached the minimum goal of 40% protection in the mouse [9]. This may be construed as a turning point, since in subsequent years vaccine research maintained a rather soft profile. Recent progress in the analysis of the schistosome genome, transcriptome and proteome, especially with regard to tegument proteins, has revived the hopes for a vaccine [10]. Undeniably though, the road to a safe, effective, long-lasting and cheap vaccine is still very long and frightfully crowded with uncertainties.

3. Molluscicides

Until the 1970s, molluscicides were at the forefront of schistosomiasis control, to be later displaced by the newly available drugs for human use [11]. In spite of the adoption of a reasonably good chemical, niclosamide, the practice of molluscicide has always faced serious problems. Local communities are understandably reluctant to accept that their water bodies turn yellowish while fish and other aquatic organisms undergo death and putrefaction [12]. The molluscicidal effects are short-lived and a few surviving snails are sufficient to subsequently re-populate treated sites. In addition, the cost of chemicals is far from negligible, especially for large water bodies. Today, the consensus seems to be that only under special circumstances focal molluscicide may be recommended as an adjunct to chemotherapy and other measures.

In spite of a substantial standstill in the practice of chemical snail control, a flourishing of reports has appeared over the years in the literature, regarding plant-derived molluscicides that could be potentially developed at the local level [13]. None of the proposed products, however, has been able, so far, to overcome the challenges of high efficacy and mass production.

On a related topic, snail control has been attempted using predatory or competing organisms like fish, prawns or different snail species [14], but practical applications of this interesting approach are as yet unavailable.

4. Enter praziquantel

The early events in the development of PZQ have been repeatedly reviewed [15–17]. A series of compounds synthesized at Merck, Germany, in a project designed to find new tranquillizers, were passed on to Bayer to be screened for anthelmintic activity. The astonishing fact is that the screening for antischistosomal activity of the initial compounds and of over 400 subsequently tested derivatives was carried out using mice infected with *S. mansoni*, complemented with *in vitro* observation of whole parasites [18]. Yet, the selected product, PZQ, is such a highly optimized compound that it is still unsurpassed for safety and antiparasitic efficacy among countless chemicals (analogs and otherwise) that have been tested up to this day.

The reasons for PZQ success can be classified under four main headings: efficacy, safety, operational convenience, price.

4.1. Efficacy

When measured by parasite egg excretion about four weeks after treatment with 40 mg/kg, the effects of PZQ can be very broadly summarized as 60–90% cure (no eggs in feces) and 80–95% average reduction in the number of excreted eggs in noncured patients. This can be regarded as a very good result, but it was