Acta Tropica 176 (2017) 179–187

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Schistosomiasis: Drugs used and treatment strategies

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ARTICLE INFO

Keywords:
Neglected tropical diseases
Schistosomicides
Treatment

ABSTRACT

Neglected tropical diseases (NTDs) affect millions of people in different geographic regions, especially the poorest and most vulnerable. Currently NTDs are prevalent in 149 countries, seventeen of these neglected tropical parasitic diseases are classified as endemic. One of the most important of these diseases is schistosomiasis, also known as bilharzia, a disease caused by the genus Schistosoma. It presents several species, such as *Schistosoma haematobium*, *Schistosoma japonicum* and *Schistosoma mansoni*, the latter being responsible for parasitosis in Brazil. Contamination occurs through exposure to contaminated water in the endemic region. This parasitosis is characterized by being initially asymptomatic, but it is able to evolve into more severe clinical forms, potentially causing death. Globally, more than 200 million people are infected with one of three Schistosome species, including an estimated 40 million women of reproductive age. In Brazil, about 12 million children require preventive chemotherapy with anthelmintic. However, according to the World Health Organization (WHO), only about 15% of the at-risk children receive regular treatment. The lack of investment by the pharmaceutical industry for the development and/or improvement of new pharmaceutical forms, mainly aimed at the pediatric public, is a great challenge. Currently, the main forms of treatment used for schistosomiasis are praziquantel (PZQ) and oxaminiquine (OXA). PZQ is the drug of choice because it presents as a high-spectrum anthelmintic, used in the treatment of all known species of schistosomiasis and some species of cestodes and trematodes. OXA, however, is not active against the three Schistosome species. This work presents a literature review regarding schistosomiasis. It addresses points such as available treatments, the role of the pharmaceutical industry against neglected diseases, and perspectives for treatment.

1. Introduction

Neglected tropical diseases (NTDs) are diseases that primarily affect the world's poorest and most vulnerable populations. Currently they are prevalent in 149 countries, affecting 41.4 billion people, causing approximately 35,000 deaths per day worldwide (Cohen et al., 2016; Sah et al., 2015; Tlamçami and Er-Rami, 2014). These diseases are caused by infectious and parasitic agents that affect billions of people per year. NTDs are, in fact, “neglected” due to under-financing and low recognition by the pharmaceutical industries, although they represent a serious threat to health in poorly developed countries and are an obstacle to economic development (Brasil, 2010; Santos et al., 2012).

The World Health Organization (WHO) lists 17 neglected tropical infectious parasitic diseases that are endemic, among the ones that most affect the population: dengue, Chagas disease, schistosomiasis, leprosy, leishmaniosis, malaria, and tuberculosis (WHO, 2010). As the affected populations are mostly low-income people, the interest of the pharmaceutical industry in advancing therapies for these diseases is scarce, since it has a low potential for profitable return, even though there is investment for research related to these diseases (Santos et al., 2012).

Among the most important NTDs is schistosomiasis, also known as bilharzia. This disease is caused by the Schistosoma genus, which presents several species, such as *Schistosoma haematobium*, *Schistosoma japonicum* and *Schistosoma mansoni*, the latter being responsible for parasitosis in Brazil. In addition, the parasitosis is characterized as being asymptomatic, but may evolve into more severe clinical forms, and may even cause death (Sah et al., 2015; Steinmann et al., 2006; Weerakoon et al., 2015). This helminthiasis is highly prevalent in

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http://dx.doi.org/10.1016/j.actatropica.2017.08.002
Received 12 June 2017; Received in revised form 29 July 2017; Accepted 2 August 2017
Available online 10 August 2017
0001-706X/

subtropical regions of Africa, the Americas, and Asia (Cavalcanti et al., 2013.)

Neglected tropical diseases have become a public health problem due to the high morbidity rate worldwide. In many endemic areas, WHO recommends preventive chemotherapy or large-scale drug administration for the control of schistosomiasis, combined with access to safe drinking water, basic sanitation, hygiene education and control of snails, an intermediary host (WHO, 2012).

Praziquantel (PZQ), the first anthelmintic to meet WHO requirements, is the main drug used to treat schistosomiasis, being effective and well tolerated by the affected population and reducing parasitic load and severity of symptoms (Thetiot-Laurent et al., 2013; Gonnert and Andrews, 1977). Due to its importance in the fight against the disease, studies have focused on improving some of the specific properties, such as increasing solubility, or the search for new drug delivery systems (Arruá et al., 2015; Frezza et al., 2015; Frezza et al., 2013; Oliveira et al., 2016). In general, these actions aim to circumvent parasitic resistance, rapid uptake into the bloodstream after ingestion, and extensive first-pass metabolism (Arruá et al., 2015; Oliveira et al., 2016).

2. Neglected tropical diseases

NTDs are diseases found mainly, but not exclusively, in areas of poverty and are responsible for the morbidity and/or mortality of millions of people per year, comprising a set of 17 diseases (Cohen et al., 2014; Dias et al., 2013; Fenwick, 2012; Noden and Colf 2013; Rocha, 2012; Santos et al., 2012; Werneck et. al., 2011). One characteristic of NTDs is the chronicity and incapacitation of the affected individual; they may also lead to a deformation of the affected limb (Hortez and Brown, 2009).

Most of the neglected diseases are transmitted to humans through animals, which act as reservoirs for the pathogens and contribute to the spread of the diseases (Hortez and Fujiwara, 2014; Noden et al., 2013; Rocha, 2012; Werneck et al., 2011). Prevention and control of parasitic diseases require knowledge of the ecological phenomena involving man, the parasite, and the intermediary hosts or vectors of these parasites (Santos, 2011).

Over 200 million people are infected with one of the three Schistosoma species globally, including an estimated 40 million women at reproductive age (Olveda et al., 2016; Sah et al., 2015). These diseases cause great debilitation in infected people, especially children, as is the case of schistosomiasis and hookworm, which cause malnutrition, suppression of growth and cognitive deficits. In pregnant women, these infections can cause premature delivery, low birth weight, and increased maternal morbidity and mortality. In adults, it may cause disfigurement of limbs, such as lymphatic filariasis or blindness, due to trachoma and onchocerciasis (Hortez and Brown, 2009).

Among the NTDs, malaria affects approximately 17 million people, intestinal helminthiasis is present in 8 million children, dengue fever in 4–5 million people and more than 800 thousand people contract Chagas' disease (Caplan and Zink, 2014; Hortez et al., 2014; Kyelem et al., 2015).

In Latin America and the Caribbean there are approximately 48 million people living below the poverty line, that is, under $1.25 a day, while 99 million people live on less than $2 a day (Caplan et al., 2014; Hortez and Fujiwara, 2014). In this region, there are seven countries with a human development index (HDI) below 100 and with poverty levels equivalent to many African countries: four are in Central America (Guatemala, Nicaragua, Honduras and El Salvador). In Brazil, poverty is mainly concentrated in the northeastern part of the country, including the states of Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Rio Grande do Norte and Sergipe (Hortez et al., 2014).

NTDs, such as ascariasis, hookworm infection and the trichuris infection, together with schistosomiasis (caused by Schistosoma mansoni) are among the most prevalent in Brazil. About 12 million Brazilian children require preventive chemotherapy with albendazole or mebendazole. However, according to WHO, in Brazil, only approximately 15% of children at risk receive regular deworming. Although a national schistosomiasis control program has been in place since 1975, which includes drug administration, WHO estimates that less than 3% of the almost 1.5 million Brazilians infected with *S. mansoni* are receiving adequate treatment with Praziquantel or Oxamniquine (Hortez et al., 2014).

Brazil is considered the largest and most populous country in Latin America and has the highest burden of neglected tropical diseases, in terms of individuals requiring pharmacotherapy (Gabrielli et al., 2013). In Brazil, the populations most affected by NTD are located in the suburbs of large cities and in rural areas, where there is a greater index of underdevelopment. The lack of broad coverage of health services and the small control over natural resources serve as a dissemination factor for NTDs (Rocha, 2012).

A monitoring system through a specific surveillance should not only present as the purpose of its program the discovery, investigation and interruption of continuous transmission, but it should also include the prevention of infection. An effective surveillance system enables program managers to identify areas of risk, affected population groups, as well as trends for infections in humans and animals requiring intervention and control measures when necessary. As an example, strict monitoring of Schistosoma in Japan has not been discontinued, since infected intermediary hosts remained long after the disease in humans was declared eliminated in the country in 1996 (Bergquist et al., 2015).

The application of molluscicides could be a strategy for the chemical control of slugs and snails. This is based on the use of metaldehyde and methiocarb in tablet, granular, and liquid formulations. Metaldehyde baits are toxic after ingestion, leading to dehydration and subsequent death of organisms. Similar to carbamate, methiocarb acts on the central nervous system, inhibiting acetylcholinesterase, causing the death of the animal (Cardoso et al., 2015).

2.1. Schistosomosis

Schistosomiasis, also known as a bilharzia, is a disease caused by Schistosoma trematode, and S. mansoni is responsible for the parasitosis in Brazil (Malhado et al., 2016; Santos, 2011; Webster et al., 2013). This pathology occupies the third position among the main tropical diseases after malaria and intestinal helminthiases, caused mainly by three main species of Shistosomas that are capable of infecting man. These are: *S. mansoni* and *S. japonicum*, which reside in the portal system of the liver and mesenteric arteries, and *S. haematobium*, which inhabits vessels of the bladder and/or genital tract (Lee et al., 2014; Sah et al., 2015).

Current estimates from the Global Burden of Disease Study 2010 suggest that 252 million people are infected with schistosomes, 90% of whom live in sub-Saharan Africa. WHO reports that by 2014, at least 258 million people worldwide required regular and frequent preventive treatment for schistosomiasis. Recently, however, the disease has appeared in Europe on the French island of Corsica (Merrifield et al., 2016).

This parasite originated in the basins of two important rivers: the Nile and Yangtze (Novaes et al., 1999; Webster et al., 2013). Eggs of the genus Schistosoma, the etiological agent of schistosomiasis, have been found in the viscera of Egyptian mummies. This helminth spread through the African continent and it was brought to the Americas through the slave trade. However, only S. mansoni was thrived here, probably due to the meeting of compatible intermediary hosts and environmental conditions similar to those of the region of its origin (Novaes et al., 1999). The groups most vulnerable to this infection are children and pregnant women, due to the forms of contagion and also because these are risk groups more prone to reinfection (Othman and Soliman, 2015; Webster et al., 2013).

Schistosomiasis arrived in Brazil in the middle of the 16th century,