Review: Policy change for praziquantel

Generic praziquantel in South Africa: the necessity for policy change to provide cheap, safe and efficacious schistosomiasis drugs for the poor, rural population

ST Berge, N Kabaterine, SG Gundersen, M Taylor, JD Kvalsvig, Z Mkhize-Kwitshana, C Jinabhai, EF Kjetland

An estimated 4.5 million South Africans, mainly in settings of rural poverty, are in need of treatment for urogenital schistosomiasis. In spite of severe morbidity and mortality, schistosomiasis remains a neglected disease with an important gender impact. The World Health Organization recommends regular mass treatment of all school-aged children. In areas endemic for schistosomiasis children are treated with a single dose of praziquantel, used for almost 30 years as the drug of choice. If administered in childhood, praziquantel has been proven to effectively prevent schistosomiasis-related morbidity, as well as reduce the socio-economic impact of the disease. Moreover, preventing urogenital schistosomiasis may also reduce HIV transmission in sexually active females. In this paper we examine the impact of the disease, the use of generic praziquantel and the need for a change in health and drug policy in order to make generic praziquantel available for mass treatment campaigns in South Africa. Generic praziquantel has been on the market for almost 30 years. Although elsewhere available free of charge, or at low cost, affordable generic versions of praziquantel are not obtainable in South Africa.

Peer reviewed. (Submitted: 2009-00-00, Accepted: 2010-00-00). © SAJEI South Afr J Epidemiol Infect 2011;26(1):22-25

Introduction

Epidemiology

Urogenital and intestinal schistosomiasis, caused by Schistosoma haematobium and Schistosoma mansoni, respectively, is highly prevalent in sub-Saharan Africa. Over 800 million people are currently at risk of infection in 76 endemic countries, 46 of which are in Africa, which is also home to 85% of the population at risk and 97% of all such infections. There are an estimated 112 million cases of S. haematobium infection in sub-Saharan Africa. Both S. haematobium and S. mansoni are frequently associated with human disease. Together they represent a major parasitic burden in tropical areas, ranking second only to malaria in public health impact. The peak age of acquisition is in school-aged children because of the amount of time spent playing in infested waters. Women doing household chores and men swimming or fishing are also at high risk of infection. South Africa harbours over 25.7 million people at risk of schistosomiasis, with an estimated 4.5 million infections. Both S. haematobium and S. mansoni are endemic in five of the nine provinces in the country, with 10.8% of the population infected.

Morbidity due to schistosomiasis

When infections are left untreated or treated too late, the repercussions of ova deposition may adversely affect population health over many years. Children are especially vulnerable and may become physically and intellectually compromised. The symptoms may be severe but diffuse and non-specific, leading to anaemia, attention deficit disorder, learning disabilities, school absenteeism and high school dropout rates. In Kenya, a school-based deworming programme reduced school absenteeism by a quarter, with the largest reduction among the youngest children. The disease causes an annual loss of between 1.7 and 4.5 million disability-adjusted life years. It is also estimated that annual global mortality could be as high as 300,000 cases, half of which are caused by urogenital schistosomiasis. Haematuria is the first sign of established disease, appearing 10-12 weeks after infection. Later manifestations include dysuria, major bladder wall pathology such as calcification, and major hydropneprosis, caused by occlusion of the renal ducts due to a fibrotic reaction to the schistosome eggs, leading to severe kidney damage. Annual mortality from S. haematobium related to non-functioning kidneys may be 150,000 deaths. The extrapolated figures with respect to morbidity in South Africa are listed in Table 1. There are approximately 54 million cases of S. mansoni in sub-Saharan Africa, half that of S. haematobium. The infection is associated with diarrhoea, blood in the stools, hepatosplenomegaly, haematemesis and ascites.

Schistosomiasis is also important because of the significant negative consequences it has both on the economy and on public health. The effects on child development may result in a generation of adults disadvantaged by the irreversible repercussions of this infection, with significant deleterious consequences for public health and the economy.
Table 1: Estimated number of individuals with morbidity or pathology due to *S. haematobium* in sub-Saharan Africa and South Africa, respectively

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Sub-Saharan Africa (million)</th>
<th>South Africa (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk of infection</td>
<td>436</td>
<td>25.7</td>
</tr>
<tr>
<td>Infected</td>
<td>112</td>
<td>4.5</td>
</tr>
<tr>
<td>Haematuria in last 2 weeks</td>
<td>70 (51-87)</td>
<td>2.8</td>
</tr>
<tr>
<td>Female genital schistosomiasis</td>
<td>18-42</td>
<td>1-2</td>
</tr>
<tr>
<td>Dysuria in last 2 weeks</td>
<td>88 (67-102)</td>
<td>3.5</td>
</tr>
<tr>
<td>Minor bladder wall pathology</td>
<td>18 (5.1-27)</td>
<td>0.7</td>
</tr>
<tr>
<td>Major bladder wall pathology</td>
<td>9.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Moderate hydronephrosis</td>
<td>9.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Estimated number of individuals with morbidity or pathology due to *S. haematobium* by age group in sub-Saharan Africa in millions (90% confidence interval), adapted from van der Werf, 2003.19 Figures from South Africa are calculated using van der Werf’s table and Chitsulo’s (2000) estimates for South Africa.1 Figures for female genital schistosomiasis are from Kjetland, et al. (2008).

Schistosomiasis and HIV

HIV/AIDS is one of the biggest health problems in South Africa today, with over 5.7 million people and 27.4% of men and women between 30-34 years of age infected.27-29 Women comprise 57% of the HIV-infected population in Africa, and studies from areas endemic with *S. haematobium* report that 33%-75% of infected women also suffer from female genital schistosomiasis involving the lower genital tract.3,10-12

In 2009, WHO stated that it is biologically plausible that female genital schistosomiasis poses a risk for secondary HIV acquisition.30 In cross-sectional studies in Zimbabwe and Tanzania research has identified an association between female genital schistosomiasis and the acquisition of HIV, although this needs to be confirmed in other studies.31-32 The study done in Zimbabwe by Kjetland et al indicates that women with genital schistosomiasis may have an almost threefold risk of having HIV. It has been suggested that the cervical lesions of genital schistosomiasis may increase susceptibility to the virus in women because of frailty and inflammation of the epithelium of the genital mucosal membranes.31,34

Mass treatment for schistosomiasis has been successfully implemented in many countries, and with over half of South Africa’s population at risk, regular treatment in transmission areas is required in order to prevent morbidity and secondary infections.18-20 However, in South Africa the cost of praziquantel is 50 times higher than the WHO standard treatment used in the rest of Africa and hence mass treatment cannot be implemented. This paper seeks to explore the reasons behind the lack of affordable schistosomiasis treatment in South Africa.

Methods

Information in this paper is exclusively from peer-reviewed articles or from published WHO reports, one WHO statement, one statement by the health minister and one letter from South African HIV clinicians to the health minister. Authors spoke to and corresponded with members of the Preventive Chemotherapy and Transmission Control Unit in the WHO, members of the former Parasite Control Programme in South Africa and the South African Medical Research Council for studies and information. All provided published references. PubMed online (1980 to 2010) was searched, using the following search strategy: ("Schistosomiasis haematobia"[Mesh]) OR ("Schistosomiasis"[Mesh]) AND ("Schistosomicides"[Mesh]) OR ("Praziquantel"[Mesh]) AND ("South Africa"[Mesh]) OR ("Africa South of the Sahara"[Mesh]). Three hundred and forty-three articles were identified, 287 of which were excluded based on their low relevance to this paper, mainly because of their focus on immunology, travel medicine or intestinal schistosomiasis. Reference lists of all the studies that were included in the pool of retrieved studies were examined in order to identify further original peer reviewed studies. In total, 126 studies were reviewed; however the information was often reported in several sources and the key references are quoted here.

Treatment worldwide

Efficacy and recommendations

Praziquantel is highly effective in killing adult worms and cure rates are 75-85% for *S. haematobium* and 63-85% for *S. mansoni*.36 Given as mass treatment in the low transmission season, efficacy is even higher. Mass treatment with praziquantel in endemic areas has been shown to reduce the burden of urogenital schistosomiasis in North, West and East Africa, South America and Asia, and in 1997-2000 also in rural KwaZulu-Natal province of South Africa.7,17,24 The pilot programme established by the Department of Health of KwaZulu-Natal found a significant reduction (95.3%) in egg excretion three weeks after treatment and a 94.1% cure rate for heavy infections. More recently, Sissooko et al (2009) found an egg reduction rate of 95.6% using praziquantel.39 Furthermore, for all years of observation in the period from 1984-1992, King et al (2000) found that treatment with praziquantel consistently reduced the mean *S. haematobium* egg counts by more than 83.0%. In another study, three treatments with praziquantel during primary school years reduced bladder pathology at a later age to almost zero and even a single treatment given in childhood seems to prevent half the cases of genital schistosomiasis in women.11,12 Thus, early intervention through mass treatment of the endemic communities is vital to avert the serious impact of the disease, and has proven to efficiently reduce the burden of disease from schistosomiasis. This highlights the effective capacity of praziquantel chemotherapy as one of the major preventive interventions to control the disease.

The recommended dose for praziquantel is 40 mg/kg body weight for *S. haematobium*. Table 2 shows that a child weighing 45 kg needs three tablets of praziquantel to treat a schistosomiasis infection. However, unless the total burden of parasites in the bodies of water is lowered through mass intervention, reinfections are and will continue to be common in endemic areas. Furthermore, praziquantel only has an effect on the adult worm.14 Hence, in order to increase the effect of treatment, mass treatment should be given during the low transmission season when worms have matured; in South Africa this would be in winter.17,27

WHO and donors have donated or provided praziquantel at very low cost.35 An increasing number of countries in the region, such as Uganda, Zambia, Niger, Cameroon, Burkina Faso and Mali, have met the WHO target of regularly deworming at least 75% of their school-age children by 2010.31 However, although South Africa implemented a mass treatment pilot programme in KwaZulu-Natal Province in 1997-2000, there have been no mass treatment interventions since.42

The history of praziquantel

Praziquantel was developed in the laboratories of Bayer, Germany, at the beginning of the 1970s. In 1977 the drug company E. Merck, now Merck KGaA, discovered praziquantel’s anti-cestode and anti-trematode effects. Thereafter, Bayer and WHO carried out the first clinical trials in endemic areas together. They identified praziquantel as the drug of choice
Table 2: Praziquantel prices in USD

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Manufacturer</th>
<th>Country</th>
<th>Package</th>
<th>Current price per 600 mg tablet</th>
<th>Price to treat a child, 45 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biltricide® in SA</td>
<td>Bayer Pharmaceuticals</td>
<td>Germany</td>
<td>10 tablets in blister packages</td>
<td>4.49</td>
<td>13.47</td>
</tr>
<tr>
<td>Generic praziquantel</td>
<td>IDA foundation</td>
<td>Netherlands</td>
<td>500 tablets</td>
<td>0.0751</td>
<td>0.2253</td>
</tr>
<tr>
<td>Generic praziquantel</td>
<td>Missionpharma</td>
<td>Denmark</td>
<td>1,000 tablets</td>
<td>0.0863</td>
<td>0.2589</td>
</tr>
<tr>
<td>Generic praziquantel</td>
<td>IMRES</td>
<td>Netherlands</td>
<td>100 tablets</td>
<td>0.0982</td>
<td>0.2946</td>
</tr>
<tr>
<td>Generic praziquantel</td>
<td>Action Medeo</td>
<td>Germany</td>
<td>250 tablets</td>
<td>0.1729</td>
<td>0.5187</td>
</tr>
</tbody>
</table>

*Prices from International Drug Price Indicator Guide.41 From 2009 no longer sold in batches of 1,000 tablets.

for the treatment of schistosomiasis.43-46 Although the collaboration between Bayer and WHO was a success with regard to the trials, there was apparently no written agreement on subsequent pricing and distribution.

In 1983, the Korean Shin Poong company developed a new method for the synthesis of the drug. They were the first alternative pharmaceutical company to produce praziquantel.46 As Bayer priced Biltricide at 38.65 USD/packet (8 x 600 mg tablets); the Korean-based company recognised the need for a cheaper alternative, facilitating a decrease in price. By 1985, approximately one million people had been treated with the Korean low-cost praziquantel.47

In the ensuing decade the inflation-adjusted prices of praziquantel decreased. The Egyptian government recognised schistosomiasis as the biggest health problem in the country, and initiated a comprehensive control programme. EIPICO, the Egyptian International Pharmaceutical Company, obtained the active ingredient of praziquantel from the Shin Poong company and later started to produce it themselves.46,48 In 1987-1988 EIPICO’s entry further reduced prices and gave the company a majority share of the private and public markets. As Bayer’s patent expired, several other pharmaceutical companies also started to manufacture praziquantel, reducing the cost of the drug to current price.

Generic drugs and cost

Generic preparations of praziquantel have been tested extensively and are of high quality.49,50 The International Drug Price Indicator Guide reports an average price of USD 0.1209/tablet for different praziquantel generics, with the lowest being USD 0.0751/tablet (supplied by IDA foundation). Outside South Africa several brands have been shown to be available under various names in different countries, some of which are also used in the Southern African Development Community (SADC): Distocide (Shin Poong, EIPICO), Bilharzid (Pharco, Egypt), and Prazitel (Cosmos, Kenya), see Table 2. In South Africa, however, currently the Medicines Control Council and the National Department of Health only have Bayer’s Biltricide for the treatment of schistosomiasis, making treatment unaffordable in afflicted districts (personal communication). This poses several challenges that this paper seeks to address.

Today, outside South Africa, praziquantel is available as low-cost generic brands. Furthermore, outside South Africa, mass drug distribution can be done by trained non-medical staff such as school staff and community workers. However, even though the patent for praziquantel has expired, no South African company has introduced generic praziquantel into their development pipeline. Countries like Zambia, Nigeria, Mozambique and Uganda have all implemented mass treatment campaigns in this manner since the 1980s, some attaining countrywide coverage in the last few years.51 Contrary to the current practice in South Africa, other countries accept WHO-accredited generic praziquantel. Furthermore, none of the companies producing this in other countries have attempted to register their generic praziquantel for the use against schistosomiasis in South Africa. This is due to a time-consuming, expensive, scientifically unnecessary, elaborate registration process.52 Furthermore there is a lack of planned mass treatment implementation programmes.

In his 2010-11 health budget speech, the South African Minister of Health emphasised that prevention must be the mainstay of the country’s approach against the declining life expectancy in South Africa, referring particularly to HIV.53 The minister further stressed the need to purchase antiretroviral drugs at the lowest possible cost from whatever source. A similar argument can be brought forward for generic praziquantel: urogenital schistosomiasis is extremely common and a possible risk factor for HIV in women; it must be prevented and the generic, cheaper drugs should be made available to South Africans.

Generic companies producing a wide range of drugs have overcome concerns about the quality of drugs that are sold in significant quantities in sub-Saharan Africa.54 A sub-Saharan African observational study of antiretroviral (ARV) drugs found that 63% of these are generics and cost on average one-third of the prices charged by brand companies.54 Eighty-five per cent of the ARV generic drugs are manufactured in India.55,56 The remaining 15% are manufactured in South Africa, mostly under voluntary licences provided by brand companies. Hence, there is a precedent for large-scale use of generics in South Africa.

No alternatives to praziquantel

Praziquantel is the drug of choice for the treatment of all forms of schistosomiasis. There are two other antischistosomal drugs - oxamnique and metrifonate - effective against S. mansoni and S. haematobium, respectively.46 Oxamnique has more side-effects and is more expensive than praziquantel, but has been used in other countries.46,57 South Africa has a substantially higher prevalence of S. haematobium than S. mansoni, and oxamnique is also no longer commercially available.58 S. haematobium (urogenital schistosomiasis) may be treated with metrifonate, which was cheaper than praziquantel until recently. However, today there is little difference in price between the two drugs, and other factors need to be considered. Mefronate treatment must be given in three doses, two weeks apart.59,60 A mass chemotherapy cost study comparing praziquantel and metrifonate in the Congo and Mali found that the operational cost was significantly higher with a three-dose, compared to the one-dose, regimen with praziquantel.61 Once the prevalence was reduced, the operational cost outweighed the drug expenses. Other alternatives to praziquantel include artesmin derivatives which are primarily used against malaria and exhibit antischistosomal activity, and Miraizid® is sold only in Egypt due to its disputed efficacy.62

Conclusion

Urogenital schistosomiasis represents a major health problem in South Africa.41 The country has the highest HIV prevalence in the world and the role of female genital schistosomiasis in driving the HIV epidemic
is yet to be explored. Furthermore, the disease itself causes severe morbidity. Simple, effective, cheap and commercially available generics have been on the market for over 20 years, have been used widely, and are widely recommended, including by the WHO. Several countries have successfully established schistosomiasis national control programmes with generic praziquantel at a price of less than USD 0.10 per tablet, and there has been no evidence of development of any resistance. These generics have proven to be of the same excellent quality at a current 1/50th of the price in South Africa. Generic drugs were used extensively and successfully in national control programmes in both China and Egypt, and later on in Burkina Faso, Mali and Niger, with aid from the international community.16,46,62,63 Currently schistosomiasis is extensively and successfully in national control programmes in both Africa can control schistosomiasis and its debilitating implications. HIV, following Minister Motsoaledi’s speech in April 2010, so that South schistosomiasis at a cost of USD 4.49 per tablet. We urge that donated and the Department of Health must now purchase praziquantel for 23. Kjetland EF, Kurewa EN, Ndhlovu PD, 4. King CH, Dangerfield-Cha M. The unacknowledged impact of chronic schistosomiasis. 12. Kjetland EF, Ndhlovu PD, Kurewa EN, 11. Silva IM, Thiengo R, Conceicao MJ, 8. Moodley I, Kleinschmidt I, Sharp B, Craig M, Appleton C. Temperature-suitability maps for schistosomia- 7. Saathoff E, Olsen A, Magnussen P, Kvalsvig JD, Becker W, Appleton CC. Patterns of 6. Fenwick A. Waterborne infectious diseases - could they be consigned to history? 5. Murray PR, Pfaller MA, Rosenthal KL. Medical Microbiology. 42-43 42-43 36. Wegner DHG. The profile of the trematocidal compound praziquantel. 35. Savioli L, Gabrielli AF, Montresor L, Chitsulo L, Engels D. Schistosomiasis control in Africa: 8 years after World Health Assembly Resolution 54.19. Parasitology 2009; 36: 1077-1081 34. Downs J, Mguta C, Kaatano G, 33. Downs J, Mguta C, Kaatano G,. An estimate of the global needs for praziquantel within 32. Utroska JA, Chen MG, Dixon H, 31. Chien CV, Fenwick A, West LLP. HIV/AIDS Drugs for Sub-Saharan Africa: How do Brand and Generic, 30. Chitsulo L, Loverde P, Engels D. Schistosomiasis. 29. Korte R, Schmidt-Ehry B, Kielmann AA, Brinkmann UK. Cost and effectiveness of different approaches to 28. HSRCSA. South African national HIV prevalence, incidence, behaviour and communication survey. 27. Chitsulo L, Loverde P, Engels D. Schistosomiasis control programmes in West Africa. 26. Kikoski R, Tennant K, Haskel L, et al. Double blind studies of tolerance to praziquantel in Japanese patients with Schistosoma japonicum infections. Bull World Health Organ 1981; 59: 721-727 25. 1/50 th of the price in South Africa.Generic drugs were used and there has been no evidence of development of any resistance. with generic praziquantel at a price of less than USD 0.10 per tablet, successfully established schistosomiasis national control programmes are widely recommended, including by the WHO. Several countries have...