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Towards control of schistosomiasis in sub-Saharan Africa

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Abstract

Approximately 80% of the 200 million people infected with schistosomiasis inhabit sub-Saharan Africa, and the annual mortality is estimated to be 280,000. Praziquantel is the drug of choice in the treatment of schistosomiasis and pregnant women may now be treated. It was agreed at the World Health Assembly in 2001 that at least 75% of school-aged children in high burden areas should be treated for schistosomiasis and soil-transmitted helminth infections by 2010 to reduce morbidity. A grant from the Bill and Melinda Gates Foundation to the Schistosomiasis Control Initiative, Imperial College of Science, Technology and Medicine, London has enabled control programmes to be initiated in Uganda, Tanzania, Zambia, Burkina Faso, Niger and Mali. Additional programmes have recently commenced in Zanzibar with a grant from the Health Foundation to The Natural History Museum, London and in Cameroon. Combination treatment for schistosomiasis, gastrointestinal helminths and filariasis reduces costs of control programmes. The EC Concerted Action Group on 'Praziquantel: its central role in the chemotherapy of schistosome infection' met in Yaoundé Cameroon in 2004 to discuss recent developments in laboratory and field studies. The use of standard operating procedures will enable data on drug action on schistosomes produced in different laboratories to be compared. With the ever increasing use of praziquantel there is a possibility of the development of resistance by schistosomes to the drug, hence the necessity to explore the activities of other compounds. Artemether, unlike praziquantel, is effective against immature schistosomes. The effectiveness of mirazid, an extract of myrrh, is controversial as data from different laboratories are equivocal. It is suggested that an independent body such as the World Health Organization should determine whether mirazid should be used in the treatment of schistosomiasis.

Introduction

Schistosomiasis (bilharzia) is one of the most prevalent parasitic diseases in the world: a water-borne disease, transmitted by freshwater snails, it is endemic in 76 countries of the tropics and sub-tropics, and it is

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estimated that there are in excess of 200 million people infected, with children being at particular risk. Of these, about 120 million have disease associated symptoms and a further 600 million are at risk of infection (WHO, 2002). Approximately 80% of the number of people infected occur in sub-Saharan Africa. Estimates of mortality are difficult to calculate, owing to the limited data available, but they may be as high as 150,000 per year as a result of non-functioning kidney (*Schistosoma haematobium* infection) and 130,000 from haematesis (*S. mansoni* infection) (van der Werf *et al.*, 2003). The global burden of the disease is 4.5 million disability adjusted life years, but recent studies suggest that this figure has been severely underestimated (WHO, 2002; King *et al.*, 2003, 2005). In the past, the vast majority of donor-funded vertical control programmes in Africa during the 1980s have been shown to be unsustainable (Engels *et al.*, 2002). The way forward for sustainable schistosomiasis control has been recently discussed (Utzinger *et al.*, 2003). Praziquantel (PZQ) is the drug of choice in the treatment of schistosomiasis: the marked reduction in price of praziquantel to less than 1 US$ per treatment, its effect on all species of schistosome, its lack of toxicity and ease of administration and the fact that it is now produced in a number of different countries contribute to it being the major chemotherapeutic weapon against schistosomiasis (Utzinger *et al.*, 2003). The evidence suggests that pregnant women who are infected with schistosomiasis may be treated with PZQ. In a retrospective study in Gezira, in Sudan it was shown that there was no significant difference in the rates of abortion and preterm deliveries between pregnant women who had received PZQ compared with those who had not received PZQ (Adam *et al.*, 2004). At the World Health Assembly (WHA) held in May 2001 Member States agreed on resolution WHA 54.19: that at least 75% of school-aged children in the high-burden regions should be regularly treated with PZQ by the year 2010 (WHO, 2001).

A helpful step in the right direction towards achieving this target has been a 5-year programme, first set up in October 2002. Thirty million US $ from the Bill and Melinda Gates Foundation has been made available to the Schistosomiasis Control Initiative (SCI) based at Imperial College of Science, Technology and Medicine since October 2002. The SCI is a partnership between Imperial College, London, UK, the Seattle-based Bill and Melinda Gates Foundation, the World Health Organization, Geneva and the Danish Bilharzizasis Laboratory, Copenhagen. As recently as 8 January 2005 a new Helminth Control Laboratory on Zanzibar was opened. The building, funded by a partnership between The Health Foundation and SCI, is a major milestone in the 'Kick out Kichocho' (*kichocho* is Kiswahili for bilharzia) campaign which is being run by The Natural History Museum, London and the Ministry of Health, Zanzibar. On Zanzibar Island (Unguja) treatment concentrates on children and 132,000 school-aged children have been treated to date. A different strategy is being adopted on Pemba Island and mass chemotherapy has been offered to the whole population. Official launches of national helminth control programmes took place in Uganda in March 2003, Unguja Island (Zanzibar) on 18 October 2003, Pemba Island (Zanzibar) on 5 January 2004, Burkina Faso on 6 May 2004, Niger on 6 October 2004 and Mali on 23 November 2004.

Control programme in Cameroon: the EC Concerted Action Group and the Schistosomiasis Control Initiative

Programmes have also been initiated in other countries, for example, 25 March 2004 heralded the official opening of the schistosomiasis and soil-transmitted helminths control programme in Cameroon where at least 2 million people are infected with schistosmiasis, 5 million are at risk and more than 10 million are infected with gastrointestinal helminths (Tchuem Tchuenté *et al.*, 2003). There is a strong political commitment for this initiative from the Ministries of Public Health and National Education. At the time of the opening of the control programme in Cameroon there was a meeting in Yaoundé of the EC Concerted Action Group on 'Praziquantel: its central role in the chemotherapy of schistosome infection', where delegates discussed the latest initiatives regarding the control of schistosomiasis and gastrointestinal helminths in Africa. The substantial increase in the use of PZQ to control schistosomiasis raises concerns about the possibility of the evolution of resistance by schistosomes to the drug (Cioli & Pica-Mattoccia, 2003). One of the reasons for concern is the dearth of new compounds to be tested against schistosomes and the general lack of interest in developing such compounds by the pharmaceutical industry. Furthermore, it is known that single-dose treatments of benzimidazoles in humans reduce the intensity of infection of *Trichuris trichiura* and hookworms, but have low cure rates. The widespread use of such programmes may lead to the selection of drug-resistant strains of gastrointestinal nematodes. Indeed, reduced sensitivity of hookworms to mebendazole compared with pre-treatment campaign values has been observed on Pemba Island (Zanzibar) (Albonico *et al.*, 2004). The EC Concerted Action Group recently met again, this time in Luxor, Egypt in March 2005 to discuss further developments linked to the control of schistosomiasis and gastrointestinal helminths.

The Schistosomiasis Control Initiative is based upon the premise that if children are treated with PZQ annually or at least every two years, they are much less likely to suffer the extreme morbidity caused by the disease. Furthermore, regular treatment with benzimidazoles (albendazole/mebendazole) for the removal of gastrointestinal worms will improve nutritional status, growth, school attendance and the cognitive ability of schoolchildren (Crompton & Neisheim, 2002). The combination of treatment for various parasitic diseases such as schistosomiasis, gastrointestinal helminths and filariasis, where relevant and practicable, reduces the cost of control programmes. Nevertheless, there are many imponderables, not solely associated with the potential development of resistance by the parasites to the drugs, relating to the control programmes in all of the chosen countries: for example, will governments embark upon national control programmes? If so, will the national control programme

be sustainable? Does school-based delivery of drugs actually reach 75% of school-aged children? Is it possible for community-based treatment to reach those children who do not attend school, and high risk groups (fishermen, irrigation workers) who need treatment? Does treatment lead to a demand for further treatment? No doubt the answers to such questions will become apparent with time as the control programme in each country develops. The SCI board is concentrating efforts on six countries, namely Uganda, Zambia, Tanzania (including Zanzibar) in East Africa, and Mali, Niger and Burkina Faso in West Africa with the overall aim of treating 15 million individuals by 2007 with PZQ and benzimidazoles. The SCI has additional links with, for example, The Wellcome Trust (advocacy), Danish Bilharziasis Laboratory (research component of the programme, training, monitoring and evaluation), World Food Programme (deworming), DFID (donations to countries selected by SCI for support), the London School of Hygiene and Tropical Medicine (Geographical Information System mapping) and The Natural History Museum, London (control programme on Zanzibar) and to be more effective in the long term it will be beneficial if additional partners/donors are brought into the relevant control programmes. It is essential that the chosen countries make their national control programmes sustainable for the future, and it is vital that additional measures such as the provision of clean water, adequate sanitation and health education are included in the control programmes if they are to be extended beyond morbidity control.

The first control programme initiated by SCI commenced in Uganda in March 2003, where schistosomiasis is concentrated in the vicinity of lakes and rivers and is found in 38 out of 56 districts, with a total of 3.5 million people infected, with a further 5 million at risk of infection. A larger percentage of the total population suffer from soil-transmitted helminths (Kabatereine *et al.*, in press). The distribution and delivery of drugs, and the consequent monitoring and evaluation of the control programme is complex. Clear communication of the aims of the programme to the target population must take place (community sensitization) followed by the selection and training of drug distributors, and the registration and treatment of the target population. The monitoring and evaluation will record the effect of treatment on the prevalence and intensity of infection, the improvement of anaemia levels, changes in morbidity and eventually the improvement of cognitive ability. The use of school teachers in such programmes is desirable, especially in the programme where children are being treated, yet such an approach is not without problems. Some teachers demand incentives, others require close supervision, and some children may exhibit side effects, especially if treated before eating, thereby requiring additional support.

To simplify the allocation of tablets in rural areas where a balance may be unobtainable, a height measuring pole is routinely used to assess the required number of praziquantel tablets. Early experience in the Uganda programme showed that it was necessary to modify the WHO dose pole, extending the length of both the bottom and the top of the pole, to accommodate children under 128 cm who receive one tablet and also a band at the top of the pole for children to receive five tablets of PZQ. The pole is not designed for adults: where it is used it does speed up drug delivery because it negates the necessity of weighing individuals and relating weight to dose of drug.

The initial data from Uganda are encouraging: for example, in the pilot phase over 200,000 children and 300,000 people from one sub-county of each district in Uganda have been treated, and in 2004 an additional 900,000 were treated and the original 500,000 re-treated. For example, at Runga, Hoima District there has been a mean egg reduction of 846 to 150 epg, approximately a 5-fold reduction in average egg counts. So, 1.4 million people had received treatment in Uganda by the end of 2004 (SCI, 2004). At the meeting in Yaoundé numerous aspects of the control of schistosomiasis were discussed. Generally, the problems, i.e. regarding prevalence and intensity of infection, associated with schistosomiasis are fewer in those countries which are situated on the perimeter of the distribution of schistosomiasis, compared with those nearer the 'epicentre' of the disease, for example, sub-Saharan countries. The national control programme in Morocco has been very successful in reducing prevalence and intensity of infection, nevertheless, difficulties are being encountered in eliminating the disease primarily owing to insufficient compliance of the population and the presence of infected immigrants. There are now relatively few cases of active transmission (e.g. only six cases in Tala province). It is anticipated that there will be a door-to-door census and mass treatment with PZQ in the remaining affected villages, and elsewhere systematic treatment of suspected patients and immigrants (Laamrani *et al.*, 2000). An additional problem in some sub-Saharan countries, apart from cost of control programmes, is that many of these countries over the years have been ravaged by internal/external conflict (e.g. southern Sudan, north-west Uganda, Ruanda/Burundi, Democratic Republic of the Congo) leading to political instability with obvious detrimental consequences for health programmes. Furthermore, there have been man-made environmental impacts which have markedly exacerbated problems regarding schistosomiasis; the construction of the Diama barrage on the Senegal River, northern Senegal and the Manantali dam on the Bafang River, Mali (tributary of the Senegal River), has resulted in the establishment and spread of intestinal schistosomiasis as well as the spread of urinary schistosomiasis. The changes in water quality (decrease of salinity) and increase of irrigation associated with rice culture have been key factors leading to a massive increase in schistosomiasis in the Senegal river basin (Southgate, 1997). In some countries, such as Kenya, there is no national control programme, whereas in Zimbabwe schistosomiasis is apparently on the increase because control programmes are less active than in previous years and PZQ is not available in the rural areas where the disease is most prevalent.

Praziquantel, arthemether and mirazid

Praziquantel has an efficacy of 80–90%, and PZQ resistance can be selected for in the laboratory.

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Schistosomes evolve and co-evolve in response to changes in the host or environment. Thus knowledge of how the phenotype and genotype of the parasite population changes in response to PZQ pressure may raise important theoretical and applied implications for the success of the control programmes. Studying life-history traits and cost benefit trade-offs in PZQ tolerant and susceptible schistosome isolates will be important for understanding their epidemiology and possible maintenance and/or spread throughout the natural host population. One of the disadvantages of PZQ is that it is ineffective against immature parasites (schistosomula) of *S. mansoni* (24 h post-infection to maturity) in the definitive host. However, artemether is known to be effective against immature schistosomes in the definitive host, and Elkoby (Egyptian Organization for Biological and Vaccine Production) reported an evaluation of the prophylactic effect of artemether on human schistosomiasis in a randomized double blind controlled trial in primary schools in Egypt by comparing the performance of PZQ with PZQ and artemether. The data revealed significant differences between the PZQ and combined drug regimen, and there is little doubt that in areas of high transmission the combined drug will be more effective. These data support earlier studies on the combined treatment with praziquantel and artemether on *S. mansoni* in experimentally infected animals (Utzinger *et al.*, 2001). Nevertheless, as artemether is a prophylactic and curative drug for malaria, it is advisable that it should not be used for treatment of schistosomiasis in areas where malaria transmission is also occurring, minimizing the possibility of resistance developing.

With the extensive use of PZQ in control programmes, and for treatment of schistosomiasis by clinicians, and the consequence of the possible development of resistance by the parasite, it is important to explore the potential of other drugs as tools for treatment. Mirazid is an extract of myrrh, an aromatic gum resin derived from the plant *Commiphora molmol* and has been attracting support as an alternative to PZQ in Egypt. Sheir *et al.* (2001) claimed initial cure rates against *Schistosoma mansoni* of 91.7% (3 daily does of 10 mg kg^{-1}), and 2 months post initial treatment of a cure rate of 98.1% (6 daily doses of 10 mg kg^{-1}). These claims, coupled with the natural origins of the drug, appeal to the population at large. However, Botros *et al.* (2005) examined the potential of mirazid as a chemotherapeutic weapon against schistosomiasis. A trial was carried out on 144 schoolchildren and 235 adults who were all positive for *S. mansoni* infection using mirazid and praziquantel. All of the positive subjects were randomly assigned into two groups: the first received mirazid at a dose of 300 mg day^{-1} for three consecutive days and the second group received PZQ at a single dose of 40 mg kg^{-1}. All treated subjects were examined 4–6 weeks post-treatment using the Kato-Katz technique. Mirazid showed low cure rates of 9.1% and 8. 9% in *S. mansoni*-infected schoolchildren and household members, respectively compared with cure rates of 62.5% and 79.7%, respectively, in those treated with PZQ. In a randomized trial, Botros *et al.* (2005) reported a cure rate of only 15.6% compared with 73.7% for PZQ after initial treatment, and 8.9% (less than the spontaneous cure rate) and 76.3% for PZQ after the second treatment. The reduction of geometric mean egg counts was 17.2% and 28% after the second treatment, compared with figures of 84% and 88.2% for PZQ. Such insignificant cure rates strongly suggest that mirazid is unlikely to play a role in control programmes, and indeed there is a strong argument that it should be withdrawn from the market. It is not used by the Ministry of Health and Population, but successful advertising campaigns still encourage its use by physicians and private clinicians. The data in the literature relating to the effectiveness of this drug are highly variable, and it is suggested that tests under the supervision of an independent body, such as the World Health Organization, should resolve once and for all its potency, or lack of, as a chemotherapeutic weapon in the battle against schistosomiasis.

Standard operating procedures

Looking ahead and monitoring for resistance of schistosomes to PZQ, especially in those countries where it has been widely used in the past and where there is planned increase use in the future, the EC Concerted Action Group is in the process of adopting standard operating procedures so that data from different laboratories are comparable.

Concluding remarks

The plight of Africa in its fight against disease and poverty was recently highlighted by the British Prime Minister in his address to the G8 countries and at the launch of the Report of the Commission of Africa (2005). With regard to schistosomiasis and gastrointestinal helminths, the tools (PZQ and benzimidazoles, respectively) exist for control and reducing morbidity, and it is hoped that the clear benefits to the population receiving regular treatment, particularly schoolchildren, in improving their health and cognitive ability will become apparent and be a source of encouragement to other countries to initiate national control programmes where none currently exists, especially in those countries in sub-Saharan Africa.

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