



HHS Public Access

Author manuscript

Future Med Chem. Author manuscript; available in PMC 2016 March 17.

Published in final edited form as:

Future Med Chem. 2015 ; 7(6): 681–684. doi:10.4155/fmc.15.9.

Something old, something new: is praziquantel enough for schistosomiasis control?

W Evan Secor and

Parasitic Diseases Branch, Division of Parasitic Diseases & Malaria, Center for Global Health, Centers for Disease Control & Prevention, 1600 Clifton Road NE, Atlanta, GA 30329, USA

Susan P Montgomery

Parasitic Diseases Branch, Division of Parasitic Diseases & Malaria, Center for Global Health, Centers for Disease Control & Prevention, 1600 Clifton Road NE, Atlanta, GA 30329, USA

Keywords

mass drug administration; praziquantel; schistosomiasis

In recent years, more people living in schistosomiasis endemic areas are receiving treatment with praziquantel. The combination of the World Health Assembly's resolution 54.19, the WHO preventive chemotherapy strategy for neglected tropical diseases, and the recognition of the considerable health impact of schistosomiasis even in persons who do not have severe fibrotic disease led financial donors and drug companies to provide the resources that have allowed availability of a much higher number of treatments for at risk individuals [1]. However, the available resources to provide treatment still are insufficient for the vast number of people who need it. The WHO treatment guidelines for schistosomiasis were drafted before sufficient quantities of praziquantel were available to make mass drug administration (MDA) a realistic possibility and were therefore primarily focused on treatment strategies to reduce morbidity. Now that praziquantel MDA has been implemented more widely, there is also a push for elimination of schistosomiasis [2]. Efforts to evaluate the efficacy of a single intervention, praziquantel MDA, are underway; however, there is growing evidence that once yearly MDA, the highest frequency of treatment in the current guidelines, will not by itself be sufficient to lower prevalence in high risk communities to rates where elimination of transmission is feasible [3–5]. There are many critical questions concerning the current and future treatment of schistosomiasis that need to be addressed.

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Author for correspondence: W Evan Secor, Tel: +1 404 718 4141, Fax: +1 404 718 4193, was4@cdc.gov.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Current schistosomiasis control programs rely on one drug, praziquantel. Praziquantel has clear advantages over the schistosomiasis treatment drugs that preceded it and no widespread resistance has developed despite its use for over 30 years. Paradoxically, the general success of praziquantel may have reduced the impetus for drug companies to pursue development of new drugs to treat schistosomiasis. But praziquantel does have a number of limitations. First, it is only effective against adult parasites and a single treatment may not kill all worms, especially in individuals with high-intensity infections. Similarly, for persons with heavy worm burdens, the side effects of treatment can be very unpleasant, even if somewhat short lived [6]. The side effects and bitter taste that some people experience have contributed to reduced compliance, leading to decreased coverage of treatment in the population targeted by the MDA [7]. Young children, who are increasingly recognized as at high risk of infection, are excluded from most control program because of these factors as well as the large size of the tablets. Fortunately, efforts are underway to develop pediatric formulations of praziquantel. Control programs should consider including pharmacovigilance in the monitoring and evaluation of praziquantel MDA, a critical need that has mostly been ignored to date. Including pharmacovigilance in routine MDA evaluations would mean that factors affecting coverage, such as reasons for poor participant compliance, as well as data to evaluate potential drug efficacy problems are systematically collected. Targeting the specific issues behind poor coverage levels and identifying the possible development of schistosome resistance to praziquantel promptly are critically important to efficiently manage schistosomiasis control programs.

Despite its key role in schistosomiasis treatment, how praziquantel works as well as putative resistance mechanisms in drug tolerant parasites remain essential areas of investigation. By better understanding how praziquantel affects schistosomes, it may be possible to refine the molecular structure to be more effective or less unpleasant in terms of taste or side effects. For example, the R-enantiomer of praziquantel is the active form of the drug while the S-enantiomer may contribute to the bitter taste and side effects of treatment [8,9]. If these observations are true and it is possible to produce the R-enantiomer in a cost-effective manner, several of the current concerns about praziquantel, such as the size of the tablets, could be moderated. Similarly, it may be possible to make small alterations in drug structure to overcome resistance. Real progress in this area has not been possible as evidence for development of praziquantel resistance is still mostly indirect and no field-derived clinically resistant isolates are available for detailed study. However, if and when they become available, the elegant approach that has recently been described for identification of the oxamniquine resistance mechanism could similarly be applied for praziquantel and praziquantel structural modifications explored [10,11].

Another critical consideration for schistosomiasis control programs is decision making about treatment approaches in the context of more sensitive diagnostic tools. Egg detection has long been the mainstay of schistosomiasis diagnosis and provides most of the basis for treatment strategies in the current WHO guidelines. However, these methods have known sensitivity limitations as well as challenges with respect to sample collection and handling, especially for detection of *Schistosoma mansoni* or *S. japonicum* eggs in stool. Many groups are working to identify new methods that are cost effective and technologically appropriate;

these efforts are challenging given the lack of a gold standard for active infection to determine a new test's sensitivity and specificity. Coupled with a shift in goals from morbidity control to elimination, changing the guidelines from parasitological detection of infection to DNA-, antigen- or antibody-based tests will require a commitment to extensive operational research that is well coordinated among program managers, researchers and donors. Fortunately, recent funding initiatives promote increased collaboration among these groups and while much work remains, the schistosomiasis community is beginning to better align research priorities with program needs. Additional field studies using standardized methods and reporting should provide the evidence base for development of new guidelines.

Annual treatment with praziquantel will continue as the backbone of most control programs for the foreseeable future but new interventions will likely be needed to achieve control or elimination of schistosomiasis in many areas. For persons with *S. japonicum* infection, annual MDA may not even be sufficient for morbidity control [5]. Improved interventions could include development and implementation of new treatment drugs or protective vaccines, more frequent treatment with praziquantel, or coupling treatment with interventions that interrupt the role cercaria-contaminated fresh water plays in transmission [12]. A great deal of effort has gone into identifying new compounds and vaccines for schistosomiasis and these efforts should continue. However, as there are no ongoing clinical trials, these new tools are still many years away from incorporation into control or elimination programs. Derivatives and rational drug design for modified praziquantel and oxamniquine may be useful in the event of clinical resistance and may require less time for approval due to experience with the parent compounds. The antimalarial drugs artesunate and mefloquine have some activity against schistosomes, but their use alone or in combination with praziquantel does not seem to improve efficacy compared with praziquantel alone [13].

New strategies for praziquantel MDA may improve the drug's impact. Double treatments of praziquantel within a short time period yield an incremental improvement on cure rate and reduction in infection intensity but at a relatively high cost for the amount of health benefit realized and with no apparent benefit for reduced transmission the following year [14–16]. Studies on MDA at 6 month intervals are needed to evaluate any greater impact than once annual MDA for reducing force of transmission and could be performed immediately as no preclinical testing is required. Other operational research needs for praziquantel include evaluation of the efficiency and safety when used in conjunction with drugs for other neglected tropical diseases in integrated MDAs. In addition, with the recognition that schistosomiasis may increase risk of infection with malaria or HIV [17,18], the benefits of treating schistosomiasis on reducing the transmission or manifestations of these and other coinfecting agents should be considered.

Combining praziquantel treatment with environmental improvements such as access to clean water, sanitation or control of the intermediate snail host are critical needs that are only beginning to be addressed [19]. Improved water and sanitation typically requires behavioral change as well as significant infrastructure investment and broad political and community commitment. Community-led total sanitation efforts have expanded in some schistosomiasis

endemic areas, with encouraging reports of progress [20]. The continued expansion and adoption of these programs hopefully will supplement drug-based control efforts.

The momentum for control and elimination of schistosomiasis is greater than it has ever been and is growing. More resources and stronger commitments make this an exciting time for schistosomiasis research but also reveal the magnitude of the current knowledge gaps and the need for new tools. Additional work toward finding new drugs and interventions as well as better utilization of the existing tools are both needed and should be viewed as partners for accomplishing the same goals rather than competitors. Furthermore, collaboration across disparate fields ranging from basic chemistry and immunology to operational and behavioral research, all with an eye toward program needs, will be necessary to achieve control and elimination of schistosomiasis.

Biographies



W Evan Secor



Susan P Montgomery

References

1. World Health Organization. Schistosomiasis: number of people treated in 2011. *Wkly Epidemiol Rec.* 2013; 88(8):81–88. [PubMed: 23540050]
2. Rollinson D, Knopp S, Levitz S, et al. Time to set the agenda for schistosomiasis elimination. *Acta Trop.* 2013; 128(2):423–440. [PubMed: 22580511]
3. Njenga SM, Mutungi FM, Wamae CN, Mwanje MT, Njiru KK, Bockarie MJ. Once a year school-based deworming with praziquantel and albendazole combination may not be adequate for control of urogenital schistosomiasis and hookworm infection in Matuga District, Kwale County, Kenya. *Parasit Vectors.* 2014; 7:74. [PubMed: 24552246]
4. Lelo AE, Mburu DN, Magoma GN, et al. No apparent reduction in schistosome burden or genetic diversity following four years of school-based mass drug administration in Mwea, central Kenya, a heavy transmission area. *PLoS Negl Trop Dis.* 2014; 8(10):e3221. [PubMed: 25299057]

5. Ross AG, Olveda RM, Chy D, et al. Can mass drug administration lead to the sustainable control of schistosomiasis? *J Infect Dis.* 2015; 211(2):283–289. [PubMed: 25070942]
6. Won KY, Abudho B, Blackstock AJ, et al. Assessment of quality of life as a tool for measuring morbidity due to *Schistosoma mansoni* infection and the impact of treatment. *Am J Trop Med Hyg.* 2014; 90(2):322–328. [PubMed: 24323511]
7. Omedo MO, Matey EJ, Awiti A, et al. Community health workers' experiences and perspectives on mass drug administration for schistosomiasis control in western Kenya: the SCORE Project. *Am J Trop Med Hyg.* 2012; 87(6):1065–1072. [PubMed: 23091190]
8. Oliario P, Delgado-Romero P, Keiser J. The little we know about the pharmacokinetics and pharmacodynamics of praziquantel (racemate and R-enantiomer). *J Antimicrob Chemother.* 2014; 69(4):863–870. [PubMed: 24390933]
9. Meister I, Ingram-Sieber K, Cowan N, et al. Activity of praziquantel enantiomers and main metabolites against *Schistosoma mansoni*. *Antimicrob Agents Chemother.* 2014; 58(9):5466–5472. [PubMed: 24982093]
10. Valentim CL, Cioli D, Chevalier FD, et al. Genetic and molecular basis of drug resistance and species-specific drug action in schistosome parasites. *Science.* 2013; 342(6164):1385–1389. [PubMed: 24263136]
11. Guglielmo S, Cortese D, Vottero F, et al. New praziquantel derivatives containing NO-donor furoxans and related furazans as active agents against *Schistosoma mansoni*. *Eur J Med Chem.* 2014; 84:135–145. [PubMed: 25016371]
12. Secor WE. Water-based interventions for schistosomiasis control. *Pathog Glob Health.* 2014; 108(5):246–254. [PubMed: 25175875]
13. Keiser J, Silué KD, Adiossan LK, et al. Praziquantel, mefloquine-praziquantel, and mefloquine-artesunate-praziquantel against *Schistosoma haematobium*: a randomized, exploratory, open-label trial. *PLoS Negl Trop Dis.* 2014; 8(7):e2975. [PubMed: 25033291]
14. King CH, Olbrych SK, Soon M, Singer ME, Carter J, Colley DG. Utility of repeated praziquantel dosing in the treatment of schistosomiasis in high-risk communities in Africa: a systematic review. *PLoS Negl Trop Dis.* 2011; 5(9):e1321. [PubMed: 21949893]
15. Tukahebwa EM, Vennervald BJ, Nuwaha F, Kabatereine NB, Magnussen P. Comparative efficacy of one versus two doses of praziquantel on cure rate of *Schistosoma mansoni* infection and re-infection in Mayuge District, Uganda. *Trans R Soc Trop Med Hyg.* 2013; 107(6):397–404. [PubMed: 23596262]
16. Garba A, Lamine MS, Barkiré N, et al. Efficacy and safety of two closely spaced doses of praziquantel against *Schistosoma haematobium* and *S. mansoni* and re-infection patterns in school-aged children in Niger. *Acta Trop.* 2013; 128(2):334–344. [PubMed: 22940014]
17. Ndeffo Mbah ML, Gilbert JA, Galvani AP. Evaluating the potential impact of mass praziquantel administration for HIV prevention in *Schistosoma haematobium* high-risk communities. *Epidemics.* 2014; 7:22–27. [PubMed: 24928666]
18. Ndeffo Mbah ML, Skrip L, Greenhalgh S, Hotez P, Galvani AP. Impact of *Schistosoma mansoni* on malaria transmission in Sub-Saharan Africa. *PLoS Negl Trop Dis.* 2014; 8(10):e3234. [PubMed: 25329403]
19. Knopp S, Mohammed KA, Ali SM, et al. Study and implementation of urogenital schistosomiasis elimination in Zanzibar (Unguja and Pemba islands) using an integrated multidisciplinary approach. *BMC Public Health.* 2012; 12:930. [PubMed: 23110494]
20. What influences open defecation and latrine ownership in rural households: findings from a global review. www.wsp.org