

Preventive Anthelmintic Chemotherapy — Expanding the Armamentarium

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In 2012, more than 260 million tablets of albendazole (at a dose of 400 mg) and mebendazole (at a dose of 500 mg) were distributed to school-age children as preventive chemotherapy against soil-transmitted helminthiases; altogether, more than 700 million people received such treatment.^{1,2} Preventive chemotherapy means large-scale preventive treatment against human helminthiasis and trachoma with the use of safe, single-dose, quality-assured medicines.¹ Regular treatment of at-risk populations is used as a public health tool to prevent illness and, for certain infections, to reduce transmission.^{1,3} The strategy relies on large-scale donations of medicines every year by the pharmaceutical industry, distributed through the World Health Organization (WHO) or other partners. Its purpose with regard to soil-transmitted helminths is not to cure infected persons but to decrease the intensity of infection and reduce associated illness with the use of subsequent rounds of single-dose treatment implemented at regular intervals. In fact, a single administration of anthelmintic agents is rarely associated with a 100% cure rate, especially when affected persons have large numbers of worms, but it is consistently associated with significant egg-reduction rates — the proxy indicator for intensity of infection and therefore illness.

The development of drug resistance through selective pressure is an inherent risk in the large-scale use of existing anthelmintic agents. Such risk — even if anthelmintic resistance is not yet a public health problem in helminthiasis in humans — will inevitably increase with the expansion of disease-control activities. The WHO therefore recommends that egg-reduction rates in sentinel sites be regularly assessed to monitor the efficacy of anthelmintic agents in large-scale interventions with preventive chemotherapy.⁴

In this issue of the *Journal*, Speich et al.⁵ report the results of a randomized trial designed to compare the combination of albendazole plus oxantel pamoate with albendazole, oxantel pamoate, and mebendazole monotherapies as pre-

ventive chemotherapy. The combination therapy was associated with an overall higher cure rate and egg-reduction rate, as compared with the anthelmintic agents administered alone.

In the study area of Pemba Island, human densities are high and sanitation levels are low: less than 40% of households have a latrine.⁶ During the past 25 years, preventive chemotherapy has been implemented regularly through schools and communities or during large-scale distribution of various combinations of albendazole, mebendazole, ivermectin, and praziquan- tel, to control schistosomiasis and soil-transmitted helminthiases and to eliminate lymphatic filariasis. The cure and egg-reduction rates associated with albendazole or mebendazole as measured by the authors, albeit remarkably low, comply with the reference values^{7,8} and previous results from the same island.⁹ Furthermore, the finding of very high levels of prevalence and intensity of infection are indicative of intense transmission of soil-transmitted helminths, despite previous treatment efforts. This calls for a comprehensive strategy of disease control that cannot rely on preventive chemotherapy alone but that demands the provision of safe drinking water, basic sanitation, health promotion, and education, as recommended by the 2013 World Health Assembly resolution on neglected tropical diseases.³

A key message is that other anthelmintic combinations beyond the one reported by Speich et al. should be tested and assessed in large population-based studies. For example, pyrantel plus oxantel pamoate had been assessed previously, with overall results that were similar to those observed here with albendazole plus oxantel pamoate.¹⁰ However, the pyrantel–oxantel pamoate combination is not readily available on the international market. In addition, at the same research study site, the combination of mebendazole plus levamisole has proven more effective than any single anthelmintic agent against hookworm infection.¹¹ Levamisole — another forgotten anthelmintic agent — is still included in the WHO Model List of Essential

Medicines and could be effectively used in combination with benzimidazoles. These combinations have the possible advantage of associating benzimidazoles with medicines belonging to other anthelmintic families, providing the potential to counter selective drug pressure and delay the onset of resistance.

It is essential that such combinations are also assessed for their safety and made available to expand preventive chemotherapy not only for soil-transmitted helminthiases but also for infections caused by other nematodes, trematodes, and cestodes. Preventive chemotherapy should eventually extend to alternative or combined uses of medicines with different target sites on the parasites. For soil-transmitted helminthiases, this process should entail broadening target sites beyond the β -tubulin, the microtubule protein against which the action of the benzimidazoles is directed, in order to increase efficacy and delay the development of resistance.

Collaboration among WHO and neglected tropical disease constituents with the pharmaceutical industry has addressed problems of access to medicines against neglected tropical diseases. Quality-assured diethylcarbamazine — an antifilarial agent that had been scarcely available on the market — is again accessible through the WHO, thanks to an innovative approach by a nonproprietary company donating the medicines and ensuring their high quality by means of a prequalification process.¹² The availability of other medicines that have been considered obsolete should be addressed with the same pragmatic and constructive mindset. Research and development of new anthelmintic agents are urgently needed, such as that occurring with the anti-wolbachia consortium¹³ and the reformulation of flubendazole¹⁴ as macrofilaricides for onchocerciasis and lymphatic filariasis. The work initiated by Speich et al., Albonico et al.,⁹⁻¹¹ and other researchers should be encouraged and expanded to include all helminthic infections that are neglected tropical diseases, and research-based companies, including those working on animal and human health, could help bridge knowledge gaps and facilitate the development of new treatments.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1312403

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