EDITORIAL

NITAZOXANIDE: AN IMPORTANT ADVANCE IN ANTI-PARASITIC THERAPY

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The field of anti-parasitic drugs has had a shaky history. The major pharmaceutical companies have increasingly focused their drug development efforts on the major markets, with potential annual sales of at least $100 million. This has not worked well for development of anti-parasitic drugs. Most patients develop parasitic infections due to poverty. Thus, while there may be millions of cases in developing countries, the number able to support the high prices of branded drugs is small. A few new drugs have come into the market. For example, mefloquine, albendazole, ivermectin, and atovaquone-proguanil have all come to the U.S. market since 1990. However, even this limited number of new drugs is somewhat deceiving. Mefloquine and atovaquone-proguanil are largely supported by their use in malaria prophylaxis. In this case, the millions of wealthy Western tourists provide a substantial market for these high-price drugs. In addition, the U.S. military initiated the development of mefloquine, and safety data for atovaquone was supported by its development for treatment of Pneumocystis pneumonia, for which there was a substantial market in the U.S. Ivermectin has never had a large market for human diseases. However, its development and manufacture were supported by the lucrative market as a prophylaxis for canine heartworms.

Between 1990 and 2000, the number of anti-parasitic drugs available for human use in the United States actually shrank. Diethylcarbamazine (DEC), quinacrine, and niclosamide were withdrawn from the U.S. market. Eflornithine was heralded as the “resurrection” drug for its dramatic effects in West African trypanosomiasis, yet its sole manufacturer stopped production. Finally, praziquantel was withdrawn from the U.S. market. It appeared that there was actually a “disappearing arsenal” of anti-parasitic drugs.

Some of these problems have been reversed in response to political pressure. Eflornithine itself was resurrected. The drug proved an effective topical depilatory, thus ensuring that the base compound was being manufactured. In response to pressure led by World Health Organization, and Médicins Sans Frontière, the manufacturer agreed to formulate some drug for intravenous use and make it available for treatment of trypanosomiasis.5 Praziquantel was re-instated when the marketing company realized that the public relations losses from withdrawing the drug out-weighed the cost savings from ending production.

In this context, the development of nitazoxanide is quite remarkable. Nitazoxanide was originally discovered in the 1980s by Jean François Rossignol at the Pasteur Institute. Initial studies demonstrated activity versus tapeworms.3 In vitro studies demonstrated much broader activity. Dr. Rossignol subsequently led the preclinical and clinical development of albendazole and halofantrine. He co-founded Romark Laboratories, with the goal of bringing nitazoxanide to market as an anti-parasitic drug. Initial studies in the United States were conducted in collaboration with Unimed Pharmaceuticals, Inc. (Marietta, GA) and focused on development of the drug for treatment of cryptosporidiosis in acquired immunodeficiency syndrome. Controlled trials began shortly after the advent of effective anti-retroviral therapies. The trials were abandoned due to poor enrollment and the Food and Drug Administration rejected an application based on uncontrolled studies.

Rather than abandon their efforts, Romark launched an impressive series of controlled trials. No other agent has proven efficacy in the treatment of cryptosporidiosis. However, a placebo-controlled study of nitazoxanide in cryptosporidiosis demonstrated significant clinical improvement in adults and children with mild illness.4 Among malnourished children in Zambia with chronic cryptosporidiosis, a three-day course of therapy not only led to clinical and parasitologic improvement, but also improved survival.5 In Zambia5 and in a study conducted in Mexico,6 nitazoxanide was not successful in the treatment of cryptosporidiosis in advanced infection with human immunodeficiency virus at the doses used. However, it was effective in patients with higher CD4 counts.6,7 Also, higher doses seem to have some effect in uncontrolled and unpublished studies. In treatment of giardiasis, nitazoxanide was superior to placebo and comparable to metronidazole. Nitazoxanide was successful in the treatment of metronidazole-resistant giardiasis.8 Studies have suggested efficacy in the treatment of cyclosporiasis, isosporiasis, and amebiasis.

There have also been several controlled trials of nitazoxanide for treatment of infection with intestinal helminths.9 As shown in the study by Diaz and others in this issue of the journal, nitazoxanide is effective against Ascaris, Trichuris, and Hymenolepis.10 However, some patients require repeated dosing. Other controlled trials have demonstrated some activity against chronic fascioliasis, for which there is no currently licensed therapy available.11 However, the response rates are lower than those described with triclabendazole. In all studies, nitazoxanide has been extremely well tolerated with adverse effects similar to placebo.

Studies have suggested a number of possible indications for treatment of specific parasites. Given its broad anti-parasitic spectrum, it is tempting to use nitazoxanide empirically. Can nitazoxanide be used as an alternative to albendazole or mebendazole in mass chemotherapy of intestinal helminths? Before this could be done, it will be important to confirm its activity against hookworm species. It will also be important to know whether it can be safely used in a variety of patient groups (e.g., Are there adverse effects in onchocerciasis and Loa loa infections seen with DEC in Africa?).

In both developing and developed countries, intestinal protozoans are important causes of persistent and chronic diarrhea. It is difficult to identify specific causes with currently available tests. Multiple stool examinations may be needed to identify Giardia. Cryptosporidium requires specialized tests (modified acid fast or fluorescent stains), which are not uni-
formally performed by all laboratories unless requested. Antigen-detection assays may improve the diagnostic yield, but can be expensive and are underused. Currently, cryptosporidiosis is underdiagnosed. The cost and inconveniences of multiple stool examinations will usually be greater than the cost of treatment. Can nitazoxanide be used empirically instead of aggressively pursuing a parasitologic diagnosis? A comparison of empirical therapy versus pursuing diagnosis and specific treatment should be compared in post-travel diarrhoea.

Finally, pre-clinical studies have suggested significant activity of nitazoxanide against some bacterial pathogens, including Campylobacter, Clostridium difficile, and Helicobacter pylori. Will these observations translate into clinical efficacy? Controlled trials are clearly indicated. If nitazoxanide proves effective for these indications, the potential market associated with these common infections may provide a major source of revenue that will help insure drug availability. For now, we should celebrate the arrival of an important new addition to the anti-parasitic arsenal.

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