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Is anthelmintic resistance a concern for heartworm control? What can we learn from the human filariasis control programs?

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Abstract

Heartworm prophylaxis is currently largely dependent on the ability of avermectins and milbemycins to arrest the development of third and fourth stages of *Dirofilaria immitis* for prolonged periods, without producing adulticidal effects. Major control programs, dependent on the activity of ivermectin, are being implemented for human onchocerciasis and lymphatic filariasis. The avermectins and milbemycins act on glutamate-gated and γ-aminobutyrate-gated chloride channel subunit proteins in nematodes. Ivermectin resistance has been widely described in trichostrongylid nematodes of ruminants. There is evidence that when ivermectin resistance occurs in nematodes, there may be selection on some, but not all of the genes that code for ligand-gated chloride channel subunit proteins as well as on some ABC-transporter genes, whose products may be involved in regulating macrocyclic lactone drug concentrations at receptors, and on some structural protein genes of amphidial neurones. Although ivermectin resistance has not been reported in filarial nematodes, there have recently been reports of suboptimal responses to ivermectin in *Onchocerca volvulus*. Evidence has been found of ivermectin selection on at least ABC-transporter genes and some neuronal structural protein genes in *O. volvulus*. To date, there is no evidence of avermectin/milbemycin resistance in *D. immitis*, also a filarial nematode. Chemotherapy against trichostrongylids of animals, human filariae, and *D. immitis*, relies on avermectins or milbemycins. However, control involves targeting different stages or processes in the nematode life cycles, different control strategies, different proportions of the nematode population in refugia, and different drug dosage rates. Consideration of the proportion of the *D. immitis* population normally in refugia, the life cycle stage targeted, and the anthelmintic dosages used suggest that it is unlikely that significant avermectin/milbemycin resistance will be selected in *D. immitis* with current treatment strategies.

Keywords: Heartworm; *Dirofilaria immitis*; Filariae; Ivermectin; Avermectin; Milbemycin; Drug resistance

1. Introduction

Chemotherapy with anthelmintics has played a major role in the control of nematode parasites of animals and humans. Avermectins, such as ivermectin (IVM), have played a key role in control of filarial nematodes, such as the heartworm *Dirofilaria immitis*; *Onchocerca volvulus,* which causes human onchocerciasis (river blindness); and *Wuchereria bancrofti*, which causes lymphatic filariasis or elephantiasis in humans. Other avermectins, such as selamectin, and milbemycins, such as moxidectin and milbemycin oxime, are also important in the prevention of heart-

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worm disease. Avermectins and milbemycins are also of major importance in the control of other nematode parasites in farm and companion animals. Avermectin, and to a lesser extent, milbemycin resistances have become widespread problems in the control of nematode parasites of ruminants (Kaplan, 2004).

Given that avermectin/milbemycin resistance has developed in many nematode parasites and that these anthelmintics are of key importance for the control of filarial nematodes in humans and animals, this review focuses on the situation in human filarial parasites where major regional and global control programs have been launched. These programs entirely depend on chemoprophylaxis with anthelmintics, how the avermectin/milbemycin anthelmintics work, our knowledge of the genetics and mechanisms of avermectin/milbemycin resistance, and selection factors that determine the rate of resistance development, in order to address the question of whether anthelmintic resistance is likely to develop from current heartworm control practices.

2. Anthelmintic resistance in nematode parasites

2.1. Geo-nematode parasites of animals

The most common anthelmintic resistance problems have occurred in geo-nematodes of ruminants and horses. Benzimidazole (BZ) resistance is widespread in trichostrongylid nematodes and small strongyles of small ruminants and horses, respectively. Resistance to the imidazothiazole/tetrahydropyrimidines is also common in these nematode parasites. Resistance to the avermectins is widespread in some trichostrongylid nematodes of ruminants, and there are increasing numbers of reports of developing resistance to the milbemycin anthelmintics in trichostrongylid nematodes of ruminants and in *Parascaris equorum* in horses. The anthelmintic resistance status in nematodes of animals has recently been reviewed (Kaplan, 2004).

2.2. Geo-nematode parasites of humans

There are currently only a few reports that suggest possible occurrence of anthelmintic resistance in human geo-nematode parasites (De Clercq et al., 1997; Reynoldson et al., 1997; Albonico et al., 2003). In the past, control of human geo-nematode parasites has focused on reducing morbidity in school-age children with periodic and often sporadic mass treatment of this cohort without substantial concurrent efforts to reduce transmission from other cohorts of human hosts (e.g. adults) or effective concurrent environmental prevention of transmission. Under these circumstances, selection pressure for the development of anthelmintic resistance is likely to be low in human geo-nematode parasites. However, the World Health Organization (WHO, 2001) is setting the following minimal targets aimed at reducing morbidity due to soil-transmitted nematode infections by 80%, which can be achieved by all endemic countries, as an integral part of the health system: (1) regular chemotherapy for at least 75% of all school-age children at risk of morbidity from geo-nematodes by 2010; (2) access to essential anthelminthic drugs by health services in endemic areas, down to the most peripheral level, for the treatment of symptomatic cases, as well as children, women, and other groups at risk of morbidity.

Furthermore, entire communities, involving large numbers of people (350 million or more) are to be treated annually, with combination albendazole (ABZ) plus diethylcarbamazine (DEC) or ABZ plus IVM as part of the programs of the Global Alliance for the Elimination of Lymphatic Filariasis (GAELF). ABZ and IVM treatment to prevent transmission of lymphatic filariae will also remove geo-nematodes. These various control measures will increase selection pressure for anthelmintic resistance to develop in human geo-helminth parasites. However, the free-living stages of these parasites often survive for long periods in soil, providing a very large refugium. Unless concurrent efforts are made to reduce environmental contamination and treatment frequencies increase from once per year, the large proportion of the nematode population in the unpressured free-living stages is likely to dilute out resistant worms that survive treatment, resulting in only a low level of selection for resistance in human geo-nematode parasites.

2.3. Filarial nematode parasites of humans

In 1987, WHO commenced using IVM to treat human onchocerciasis, following a generous donation from Merck & Co. (Molyneux, 1995). IVM, usually