

Resistance and Selection Issues

Contributing to the Emergence of Heartworm Disease



Emerging Heartworm Disease: Part 3

This publication will review the perceived resistance of heartworms to preventive drugs and genetic polymorphism of microfilaria. It will also review the importance of heartworm prevention, as well as treatment protocols used on heartworm-positive dogs.

Resistance

Resistance to current preventive medications is considered a very prominent topic. All major heartworm preventives are in the macrocyclic lactone class of antiparasitics. Those approved for use in dogs and cats include ivermectin, moxidectin, milbemycin, selamectin, and milbemycin. They demonstrate excellent lethality to the L₃ and L₄ stages of *Dirofilaria immitis*.

Based upon increased reports to the Food and Drug Administration, which monitors adverse events of approved animal products, questions related to resistance have been raised (Hampshire 2005). Perceived prevention failure reports occurred in most categories of heartworm prevention products. A majority of reported events stemmed from heartworm endemic states.

The process for reporting adverse events from heartworm preventives began in 1998. An increasing trend of adverse (lack of effectiveness) event reports related to heartworm prevention products demonstrated a rise from 2000 (n=405) to 2002 (n=951), a 57 percent increase. The event numbers rose again in 2003 (n=1503) and then fell in 2004 (n=393).

The information evaluated was found to be extremely deficient relative to quantity and quality of details related

to the patient and event. Information relative to previous heartworm prevention product administration, heartworm testing history, as well as breed, sex, or age distribution pattern was insufficient. In 2004, the FDA attempted to delineate the information to evaluate product events appropriately. The true incidence of product failure is difficult to evaluate based upon the data collected prior to 2004 (Hampshire 2005).

Previous reports indicated that no evidence of resistance was noted in the avermectin or milbemycin classes of parasiticide medications. In fact, the genetic selection was likely to be low for resistance based upon the number of genes involved, complexity of the resistance mechanism, treatment coverage, and extent of suitable habitat (Prichard 2005). It was felt that with the current heartworm control practices, overt resistance was extremely unlikely.

A factor that could offer better control may lie in the recommendations by the veterinary community regarding frequency of dosing. Dr. Byron Blagburn, a parasitologist from Auburn University, said in his report, "In reality, failure of any of the preventives to prevent heartworm infection in dogs is extremely rare (estimated to be less than 0.0001 percent)" (Blagburn, et al. 2007). However, genetic mapping has demonstrated that heartworms with different genetic makeup appear to exist, suggesting that a change has occurred in the heartworm parasite.

Blackburn evaluated strains of heartworms collected in the Mississippi Delta. LD₉₅ and LD₉₉ for macrocyclic lactones data was evaluated, and Blackburn



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determined that the LD₉₅ and LD₉₉ were different when compared to previous isolates of heartworms and other worldwide banked isolates. These studies involved microfilarial preventives labeled for L₃ and L₄ tissue stages of microfilaria.

These isolates were evaluated for genetic differences, and it was determined that the isolates collected in the Mississippi Delta have genetic differences from previous isolates (Lynn, Small animal endoparasites 2010). Is this resistance or selection? Widespread panic is not called for, because for this selection to take place, the heartworm type that demonstrates this selection must dominate the heartworm populous (T. Nelson, What's new in heartworm disease? 2010). It is felt that the efficacy of the heartworm preventives remains high when used according to the FDA-approved directions and that compliance is a major issue.

Medication compliance issues with the pet, the client, or the dispensing veterinary facility may explain many reports of lack of efficacy. Inadequate dosing intervals have been reported, which may allow a pet to develop heartworm disease. Many macrocyclic lactone preventives provide labeled instructions indicating monthly dosing. A client that gives heartworm preventive January 1 and again February 28 is technically following monthly instructions. To properly address the point in the life cycle in which the tissue stages are most sensitive, directions should indicate dosing the preventive every 30 days.

Many of the monthly heartworm preventives work on an "all in or all out" basis, and used as directed, they address the parasite load within 24 hours of absorbing the medication. During peak times of transmission, dogs may be infected with heartworm disease up to several times daily. Due to the life cycle and sensitivity of the L₃ and L₄ larval forms to heartworm pre-

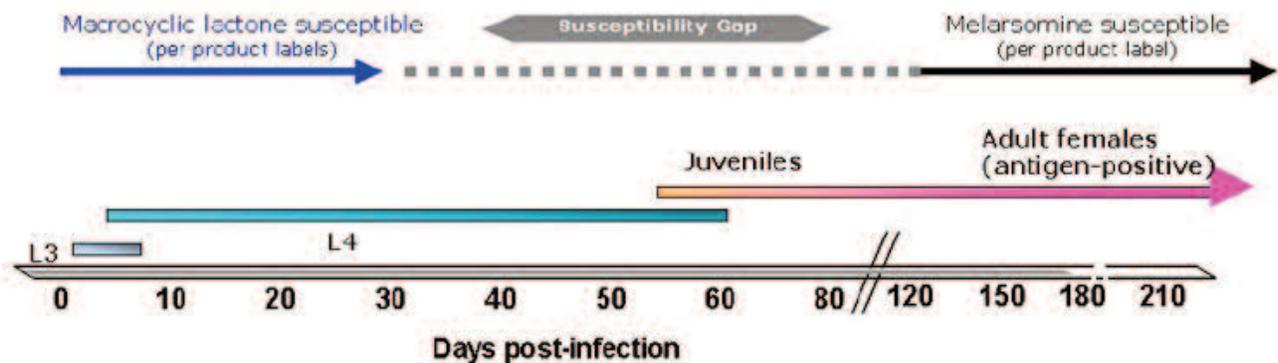
ventives, delivery of preventive every 30 days is recommended. After 30 days, the opportunity for L₄ larva to mature to a juvenile heartworm is present, and heartworm preventives have demonstrated little efficacy on juvenile heartworms. Medications such as moxidectin with a sustained-release method of delivery may be more effective in endemic areas (Lynn, Pharmacology of veterinary parasiticides 2010).

Compliance Issues

Heartworm preventives provide protection against heartworms and other zoonotic endoparasites such as roundworms and hookworms (Merial Ltd. 2010). It is possible that veterinarians are not emphasizing the importance of following the recommended administration of these products. In a recent article measuring records for heartworm, flea, and tick preventive use, 13–23 percent of pet owners bringing their pets to a veterinary teaching hospital were questioned about these products. Only 50 percent of the patients seen for a wellness exam were reported as being given these products year-round.

This study strongly suggests that the veterinary profession must be more proactive in educating their clientele about the importance of these products (Gates and Nolan 2010). The American Heartworm Society estimates that only 50 percent of dogs in areas where heartworm disease occurs are actually on heartworm preventives. Of those prescribed heartworm prevention products, only about 75 percent receive all of the doses (American Heartworm Society 2007).

Adulticide therapy with melarsamine is reported to have treatment success rates ranging from 92–98 percent. These 2–8 percent "treatment failures" can lead to heartworm-positive dogs available for hosting infection in the community. These failures may not be detected until the post-adulticide test is performed 6



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Figure 1. Susceptibility gap of heartworm treatment.

months later. Many treatment protocols are available; however, the American Heartworm Society recommends the split-dosed method to achieve the highest (98 percent) success rate.

Based on what we know of the heartworm life cycle and the effective stages of macrocyclic lactones and adulticides, patients testing antigen positive for *D. immitis* should be placed on heartworm preventives for 3–4 months prior to adulticidal treatment to allow juvenile heartworms to develop into adults. Patients not currently on or placed on heartworm preventives for this period have demonstrated incomplete removal of adults. This may account for disappointing results seen in the post-adulticide therapy testing (Merial Ltd. 2010).

The American Heartworm Society (AHS) continues to support research to determine apparent resistance of populations of heartworms to medications. The following recommendations are offered:

- Continue to use approved heartworm preventives as labeled, and report potential resistance to the manufacturer.
- Reduce exposure of pets to mosquitoes by using mosquito control methods, keeping pets inside at night, and using insect repellents.
- Treat all known heartworm-positive pets with an approved adulticide according to the manufacturer's and AHS guidelines.

Veterinarians are encouraged to use doxycycline with the adulticide protocol, and discontinue heartworm preventives used for "slow kill" for heartworm infections (American Heartworm Society 2010). Slow kill involves placing the patient on monthly heartworm prevention without addressing the adult heartworms.

Conclusion

Canine heartworm disease continues to cause significant morbidity and mortality to animals in the United States. Despite excellent preventive products, sensitive diagnostic testing, and effective adulticide therapies, the case numbers continue to escalate.

Documentation of heartworm disease has been demonstrated to show increased incidence and geographic expansion. These increases may be related to changes in vectors, reservoir host movements, and climate condition changes. Guidelines established by the American Heartworm Society are available to assist the veterinarian with current preventive recommendations such as year-round every-30-day medications, staging and therapy recommendations, and client education materials.

Please talk to your veterinarian for the best prevention and treatment recommendations for your particular situation.

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