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HEARTWORM DISEASE IN DOGS: AN UPDATE – 2011

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Prophylaxis

Prevention of HWI is an obvious and attainable goal for the veterinary profession. Prevention failure results from ignorance on the part of owners as to the presence or potential severity of HWI, lack of owner compliance, or from inadequate instruction on preventative measures by the attending veterinarian.

Studies of owner compliance have revealed that approximately 55% of dog owners that use veterinary care purchase heartworm preventative, and enough medication is dispensed only to meet the needs of approximately 56% of those dogs. Hence the proportion of “cared for” dogs in the population that receive adequate heartworm prophylaxis is less than one third. If one takes into consideration doses purchased but not administered and dogs that are never taken to a veterinarian, the percentage of protected dogs falls drastically. This was emphasized in North Carolina in 1999, when Hurricane Floyd caused extensive flooding and disruption in the poorest part of the state. Of dogs rescued from the floodwaters, 67% were infected with heartworms.

Macrocyclic Lactone (Macrolide) Antibiotics

The introduction of the macrocyclic lactone endectocides (macrolides), ivermectin (Heartgard®, Iverhart®, TriHeart®), ivermectin with pyrantel pamoate (Heartgard® Plus, Iverhart Plus®, TriHeart® Plus), ivermectin with pyranel pamoate and praziquantel (Iverhart Max®), milbemycin oxime (Interceptor®), milbemycin with lufenuron (Sentinal®) and with spinosad (Trifexis®), selamectin (Revolution™), and moxidectin (ProHeart®, ProHeart® 6), and moxidectin with imidicoprid (Advantage/MultiTM) has provided the veterinary profession with highly effective, incredibly safe heartworm preventatives in a variety of formulations and with a variety of spectra. These agents, because they interrupt larval development (L3 and L4) during the first 2 months after infection, have a large temporal window of efficacy and are administered monthly. These products have enjoyed great efficacy, virtually 100%, when used as directed. Recently, a single isolate (MP3) from north-eastern Georgia has shown restistance/tolerance to some macrocyclic lactones, when administered once 30 days after heavy experimental challenge.

All are safe in collies when used as directed at preventive dosages. They each have microfilaricidal efficacy and render female heartworms sterile. Hence microfilarial tests for HWI cannot be reliably used in dogs...
receiving these products. Prophylaxis should be commenced no later than 6 to 8 weeks of age in endemic areas or as soon thereafter as climatic conditions dictate.

Macrolides should be administered precisely as indicated by the manufacturer. If accidental lapses of more than 6 weeks occur, the preventative should be reinstituted at recommended doses and maintained for at least 12 consecutive months. In the event of a lapse in preventative administration during a time of known exposure risk, an antigen heartworm test should be performed 7-8 months after the last possible exposure to determine if infection has occurred. Year-around use is recommended by the AHS and by CAPC in all areas of the U.S.

**Macrocyclic Lactone “Resistance/Tolerance”**

In 2005, the FDA-CVM reported an increase in the reports of LOEs (Lack of Effectiveness) for macrocyclic lactones and required that such agents no longer be labelled as “perfect” in terms of efficacy. This failure of complete rapid microfilarial clearing, coupled with concern in the Mississippi River delta region (areas of LA, AR, MS, TN), has caused concern that resistance to this class of drugs may be developing. The proof of this is small, but taken together, the data argue that a small percentage of microfilariae, isolated from dogs in this region have characteristics suggesting tolerance to the drug group. A joint consensus of the AHS and CAPC stated the following. “There is evidence in some HW populations for genetic variations that are associated with decreased in vitro susceptibility to the macrocyclic lactones. Whether the observed genetic variations constitute heritable resistance is being investigated. Most credible reports of LOE that are not attributable to compliance failure are geographically limited at this time. The extent of the problem is obscured by demonstrated lack of owner and DVM compliance, possible changes in environmental and vector factors, and more effective antigen testing. The potential for resistance is not a reason to abandon use of approved preventive products.”

The concern relative to the presence of circulating microfilariae in dogs that are started and maintained on monthly preventives is that they could be a source of propagation of microfilariae that are preselected for resistance to macrocyclic lactones. In 2005, Prichard wrote “Consideration of the proportion of the D. immitis population in refugia, the life cycle stage targeted, and the anthelmintic dosages used suggest that it is unlikely that significant avermectin/milbemycin [macrolides] resistance will be selected in D. immitis with current treatment strategies.” However, this belief was based upon the assumption that people were using the preventives as per label instructions, not using them as adulticides and microfilarial suppressants. The prudent approach is simply to administer the products as approved by the FDA: as preventives that should be given to microfilaria-negative dogs. This means that the “soft” or “slow” kill approach to adulticidal therapy should be avoided. Likewise, one could argue against the use of macrocyclic lactones in microfilaria-positive dogs prior to beginning them on adulticidal therapy (ie, a method advocated by this author; see below) as 10% to 20% of these dogs will have circulating microfilariae for months after they start this regimen – microfilariae that have seen a macrocyclic lactone. If this approach is utilized, the clinician must ensure that microfilaria are eradicated in the first months of macrolide therapy. All current heartworm preventives belong to the same class of molecule, the macrocyclic lactones, and thus, we need to be very prudent in our long-term stewardship of these drugs.

**Therapy**

**Adulticidal therapy** With 2 doses, the efficacy of melarsomine is over 90% (FDA pivotal study) with the useful flexibility of a 50% worm kill with 1 dose. This then allows “split-dose” protocol to be utilized in
severely afflicted individuals or in those in which pulmonary thromboembolism (PTE) is a concern. This method allows destruction of only one-half the worms initially (1 IM injection of 2.5 mg/kg), thereby lessening the chance for embolic complications. This single dosage is followed by a 2 dose regimen in 1-3 months, if clinical conditions permit. While the manufacturer recommends this protocol (Figure 1) for severely affected dogs, the author employs it in all cases unless there is financial constraint or underlying concern for arsenical toxicity (for example, preexistent severe renal or hepatic disease). One disadvantage to the “split-dose” method, in addition to the expense, is the need for 2 months’ exercise restriction.

In 55 dogs, with severe heartworm disease (HWD) and treated in this 3-dose manner, 96% had a good or very good outcome with >98% negative for antigenemia 90 days post-therapy. Although symptomatic and even fatal PTE can result from treatment with melarsomine, no case of severe PTE was seen in the 382 dogs of this series. Of the 55 severely affected dogs, 31% had “mild or moderate PTE”; no fatalities resulted. The most common sign was fever, cough, and anorexia 5-7 days post-treatment. This was associated with mild perivascular caudal lobar pulmonary radiographic densities and subsided spontaneously or after corticosteroid therapy.

The most common complication to melarsomine therapy is the local inflammatory reaction at the injection site. This can be minimized by following the manufacturer’s directions explicitly (change needles before injecting, choose deep IM site with care, put pressure on site after injection, and alternate sites). In addition, corticosteroids (e.g. dexamethasone) or NSAIDs can be given at the time melarsomine is administered to lessen the reaction.

“Soft” or “Slow” Kill It is now known that certain macrolides have adulticidal properties. Ivermectin, when administered for 31 months continuously has nearly 100% efficacy in young heartworm infections. It has been shown, however, that lung and pulmonary vascular manifestations of HWD still result when ivermectin “prophylaxis” is begun 5.5 and 6.5 months post-infection and continued for 1 year. Selamectin, when administered continuously for 18 months killed approximately 40% of transplanted worms. Sustained release moxidectin also appears to have some adulticidal efficacy. Recent data suggests that an aggressive macrolide protocol (ivermectin, given at 6 ug/kg weekly instead of monthly), coupled with a complex regimen of doxycycline (10 mg/kg/day) will hasten worm destruction, with worm eradication with approximately 9 months’ therapy. Furthermore, microfilariae are eradicated more quickly in this manner. This has caused many to invoke the use of doxycycline routinely in the management of heartworm infection in dogs. While there may be a role for this therapeutic strategy (Slow Kill) in cases in which patient age, financial constraints or concurrent medical problems prohibit melarsomine therapy, the current recommendations are that macrolides not be adapted as the primary adulticidal approach.

As mentioned above, aggressive macrolide therapy (ivermectin, given at 6 ug/kg weekly instead of monthly), coupled with a complex regimen of doxycycline (10 mg/kg/day) hastens worm destruction and quickly eradicates microfilariae. This has resulted in increasing use of doxycycline in the management of HWI in dogs.

Cage rest is an important aspect of the management of HWD after adulticidal therapy, after PTE, or during therapy of heart failure. This can often be best, or only, accomplished in the veterinary clinic. If financial constraints preclude this, crating at home and/or tranquilization are useful alternatives.

Microfilaricidal therapy A 90% microfilaricidal success rate can be expected with preventive dosages of ivermectin25, while milbemycin at 500 mcg/kg cleared 6/8 (75%) dogs which had received adulticide therapy.
and did not harbor male and female adults; microfilarial numbers were reduced by 99% on the day after after treatment. A slower microfilarial kill rate can also be achieved with ivermectin, moxidectin, moxidectin-imidacloriprid, and selamectin at preventative doses.

The time-honored approach to ridding the patient of microfilariae involves macrolide therapy (50 mcg/kg for ivermectin or 500 mcg/kg milbemycin) instituted 3-6 weeks after adulticide. In 2-3 weeks, a second microfilaria concentration test is performed and, if negative, preventative started. If still positive, the treatment is repeated or alternatively, chemoprophylaxis begun (assuming that no adverse reaction occurred on the initial treatment). Persistent antigenemia (after 6-7 months) indicates continued patent infection.

This author chooses an alternative approach, beginning the administration of a macrolide preventative at the time of diagnosis, often days to weeks prior to adulticidal therapy. With the “slow microfilaricides” (ivermectin, moxidectin, or selamectin), there is little chance of an adverse reaction, but the owner is warned and advised to administer the medication on a day when he/she will be at home. If Milbemycin (a superior microfilarial agent) is used, it is administered in the hospital and/or preceded by administration of dexamethasone and benadryl, as described above. If this approach is used, the dog must be rendered microfilariae-free by 1-3 months post-diagnosis. Recent evidence demonstrates that concurrent usage of a macrolide and doxycycline reduces microfilarial numbers more rapidly, rendering dogs negative in less than 3 months. It is imperative that dogs on macrocyclic lactones be rendered microfilaria-free.