

Companion Animal Parasite Council and American Heartworm Society
Heartworm Roundtable:
Reports of Lack of Efficacy of Macrocyclic Lactones
Atlanta, Georgia
August 25, 2010

This meeting was convened to discuss the implications of reports of lack of efficacy of macrocyclic lactones against *Dirofilaria immitis*, the canine heartworm. Participants concluded that while we do not have a comprehensive picture of the scope or severity of the problem, we agree that there is a problem. Discussions led to recommendations in four areas: resistance, prevention, testing, and treatment. The primary purpose of this summary of these discussions is to inform veterinary practitioners of our concerns and to provide guidance for appropriate intervention at this time.

RESISTANCE

There is evidence in some heartworm 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.

If an *in vivo* decrease in susceptibility is confirmed, future changes in preventive and therapeutic strategies may be required.

Most credible reports of lack of efficacy (LOE) that are not attributable to compliance failure are geographically limited at this time. The extent of this problem is obscured by demonstrated lack of owner and veterinary compliance, possible changes in environmental/vector factors, and newer, more effective antigen testing for heartworms, all of which contribute to what is interpreted to be a lack of efficacy.

The potential for resistance is *not* a reason to abandon use of approved preventive products. When properly used, macrocyclic lactones remain effective prophylactic agents in the vast majority of dogs.

Issues for Further Study

1. Develop, optimize, and subsequently validate tests for resistance using microfilariae, third-stage larvae, and potentially fourth-stage larvae.
2. Evaluate the effects of macrocyclic lactones on the *in vivo* suppression of circulating microfilariae in dogs by monitoring microfilarial counts at a specified time after the administration of a standard "microfilaricidal" dose of a macrocyclic lactone.
3. Identify potential genetic markers for resistance and better characterize these markers in field isolates.
4. Continue to identify and collect isolates of microfilariae refractory to treatment for use in the genetic marker analyses.
5. Determine the heritability of LOE of macrocyclic lactones using isolates of microfilariae identified from field cases where LOE is suspected to have occurred in dogs receiving optimal preventive therapy.
6. Examine LOE cases for potential explanations of product failure that may be separate from heritable resistance.

TESTING

It was generally agreed that current AHS and CAPC guidelines continue to be relevant even in the face of reports of LOE. A few recommendations were made for additions or for emphasis of the importance of testing:

1. Yearly antigen testing continues to be recommended. Microfilarial testing may be increasingly indicated. In addition, an increase in the number of instances of LOE may necessitate more frequent testing.
2. Prior to administration of preventives, a microfilarial test should be performed in dogs over 6 months of age.
3. At Day 0 prior to adulticide treatment, a microfilarial test should be performed.
4. At Day 30 of adulticide treatment, a microfilarial test should be performed in dogs that were previously microfilaremic. If microfilariae are still present, microfilaricidal therapy should be instituted and continued until the dog is cleared of circulating microfilariae.
 - a. There are no microfilaricidal drugs approved by the FDA but the use of macrocyclic lactones for this purpose is permissible under AMDUCA.
5. At 6 months post adulticide treatment, an antigen and microfilarial test should be performed. If positive, re-test in 3 to 6 months and in positive dogs, consider re-treating with melarsomine.

PREVENTION

Existing guidelines for the use of macrocyclic lactones should be followed. At this point, it is recommended that prevention be regularly continued and that testing be performed on a strict schedule and recorded accurately in medical records along with pre-prevention and on-going prevention administration records.

Client education should be emphasized via direct communication from veterinary staff and/or waiting room materials (e.g., videos), emphasizing the benefits of reduced exposure to mosquitoes:

1. If possible, keep animals indoors during times when mosquitoes are most active.
2. Maintain good mosquito control and consider the use of mosquito repellents to reduce exposure to mosquitoes.
3. Install screens where applicable.
4. Heartworm-positive dogs should not be relocated until they have been treated with melarsomine and rendered microfilariae free.

Perform microfilarial tests as part of the monitoring and treatment process.

It is recommended that veterinarians should **not**:

1. Vary from labeled directions for appropriate dose range or frequency of administration.
2. Concurrently administer multiple products

Pulse treatment with doxycycline deserves further evaluation.

TREATMENT

Based upon recent findings, veterinary medical knowledge and acceptable stewardship of our available medications and patients, slow kill or soft kill is **NOT** recommended and should not be used.

Existing AHS and CAPC treatment guidelines remain intact and should continue to be followed. The reader is referred to the CAPC (www.capcvet.org) and AHS (www.heartwormsociety.org) websites for greater detail.

Severity of heartworm disease varies. The following classes of heartworm disease require stage-specific medical management:

- **Class 1. Asymptomatic or mild:** No clinical signs or radiographic changes, no lab abnormalities. May see a loss of body condition, decreased exercise tolerance, and an occasional cough.
- **Class 2. Moderate:** Occasional cough and mild to moderate exercise intolerance, slight loss of body condition, increased lungs sounds (crackles and pops), and mild to moderate radiographic changes such as an enlarged right ventricle. Lab results may demonstrate anemia and proteinuria.
- **Class 3. Severe:** Anemia, weight loss, exercise intolerance, tachypnea at rest, severe and persistent cough, difficulty breathing, fainting episodes, sneezing of blood or bloody mucus, pleural effusion and/or ascites. Radiographs show an enlarged right ventricle and pulmonary artery and changes in the lungs. Lab work may show anemia, thrombocytopenia, and proteinuria.
- **Class 4. “Caval syndrome”:** Not amendable to medical management. Sudden onset with collapse, hemoglobinuria, and dyspnea. This class is often fatal without prompt surgical intervention.

Consensus Treatment Recommendations

Day 1 following a positive heartworm antigen test:

1. Begin restriction of heavy activity
 - a. For all cases, perform a microfilarial test (modified Knott's test) and identify microfilariae. Initiate macrocyclic lactone of choice and continue as needed (PRN).
 - b. Initiate doxycycline at 10 mg/kg twice daily (BID) for 30 days
 - i. *Note:* Few studies have been done in heartworm-infected dogs to determine the best timing, dosage, or treatment schedule for doxycycline. This dosage/treatment schedule has been used successfully in several laboratory studies and veterinary hospitals, but may need to be refined in the future.
 - ii. *Note:* When administering doxycycline, caution owners that doxycycline hyclate can injure the esophagus. Animals should be given water or food after administration to ensure that tablets pass to the stomach.

Day 30 to Day 60:

1. Strict restriction of activity (for one month, minimum).
2. Administer the initial dose of melarsomine at 2.5 mg/kg intramuscularly (IM).
3. Initiate dosing of prednisone or prednisolone at 1 mg/kg every 24 hours, with decreasing dosage over a 2- to 4-week period.
4. Repeat microfilaria test at 30 days (see Testing).

Day 60 to Day 90:

Note: If the dog has waited longer than 90 days for the second injection of adulticide, then a second course of doxycycline therapy may be indicated.

1. Continue strict restriction of activity.
2. Administer second dose of melarsomine followed by third dose 24 hours later, both at 2.5 mg/kg IM.
3. Resume prednisone or prednisolone at 1 mg/kg every 24 hours, with decreasing dosage over a 2- to 4-week period.

Six months after the last treatment with melarsomine:

1. Retest for antigen and microfilariae (modified Knott's test).
 - a. If antigen and microfilaria negative:
 - i. Continue macrocyclic lactone of choice PRN all year round.
 - ii. Repeat antigen test at 12-month intervals.
 - iii. Emphasize and monitor strict compliance with year-round preventive administration.
 - b. If microfilaria positive but antigen negative:
 - i. Treat with macrocyclic lactone.
 - ii. Repeat microfilarial test (modified Knott's test) in 7 days; if positive, continue macrocyclic lactone treatment and testing until cleared of microfilariae.
 - iii. Doxycycline may be useful in reducing numbers of microfilariae and for potentiating macrocyclic lactone destruction of remaining adults.
 - c. If positive for antigen test but negative for Knott's test:
 - i. Continue macrocyclic lactone of choice all year round
 - ii. Retest in 3 to 6 months.
 - iii. If positive at that time, consider re-treating with melarsomine.