NSAIDS & ANTICOAGULANTS

Use in Management of Heartworm Infection

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*The **Heartworm Hotline** column is cosponsored by **Today's Veterinary Practice** and **The American Heartworm Society** (**heartwormsociety.org**). This series presents questions and answers on topics related to heartworm infection, prevention, diagnostics, and/or treatment.*

This article is the last in a series of **Heartworm Hotline** articles that have addressed the use of **ancillary therapeutic drugs** in heartworm infection/disease.

A discussion of ancillary agents and heartworm infection (HWI) encompasses (**Table 1**, page 48):

- Anticoagulants
- Antithrombotics
- Corticosteroids
- Doxycycline
- Nonsteroidal anti-inflammatory drugs (NSAIDs).

This article will focus on the NSAID, aspirin, because of its role as an:

- Anticoagulant
- Anti-inflammatory
- Antithrombotic.

In addition, primary anticoagulants will be briefly discussed, to the degree that published data allows.

TVP Did you miss the previous articles on ancillary therapies? Don't worry—**Doxycycline in the Management of Heartworm Disease** (July/August 2012) and **Treating Heartworm Infection: Ancillary Corticosteroid Therapy in Dogs** (November/December 2012) are available at **todaysveterinarypractice.com**; select *Back Issues* or *Article Lists* on the homepage.

ASPIRIN

Antithrombotic agents, such as aspirin, have received a good deal of attention in the management of heartworm disease (HWD).[1-5] Potential benefits include:

- Reduction in severity of vascular lesions
- Reduction in thromboxane-induced pulmonary arterial vasoconstriction and pulmonary hypertension
- Minimization of postadulticidal pulmonary thromboembolism.[3]

Therapeutic Use

Aspirin has shown success in:

- Diminishing vascular damage caused by segments of dead worms[3]
- Reducing extent and severity of myointimal proliferation caused by implanted living worms
- Improving pulmonary parenchymal disease and intimal proliferation in dogs receiving thiacetarsamide (Sodium Carparsolate) after previous living heartworm implantation.[1]

Controversial Study Results

The studies mentioned in the previous paragraph, carried out in multiple laboratories, strongly support the use of aspirin in experimental canine HWD; however, none examined its utility in natural or clinical infections.

More recent studies have produced controversial results but, likewise, only utilized experimental models of heartworm infection and typically small numbers of subjects:

Leuthy & Colleagues. In 1989, 4 dogs with implanted heartworms received adulticide (thiacetarsamide) and aspirin.[2]

- The aspirin dose was 2.2 mg/kg Q 12 H for 3 weeks, beginning a week before adulticide administration in infections of 3 weeks' duration and continued for 3 additional weeks.
- None showed improvement in 4 categories of angiographic lesions at week 3 or 6 compared to the control or heparin-treated groups.
- Aspirin treated dogs had more severe tortuousity (determined by angiography) than the 4 control dogs and 4 dogs receiving heparin, but pulmonary size and luminal lesions were not significantly worse.
- Statistically, pulmonary vascular lesions were not significantly different between groups at necropsy.
- Considering the small number of dogs and inconsistent results, this study has most likely played too large a role in shaping recommendations for or against aspirin use in HWD.

- **Intimal:** Innermost membrane of an organ or part, especially the inner lining of a lymphatic vessel, an artery, or a vein
- **Myointimal:** Relating to, or being the smooth muscle cells of, the intima of a blood vessel

Boudreaux & Colleagues. In 1991, the aspirin dosage required to decrease canine platelet reactivity by at least 50% was evaluated.[5]

- This study used experimental models of HWI, which was induced with 7 live worms, followed by 7 dead worms. The latter were implanted after the 50% platelet function goal was reached, which took 5 to 9 days.
- Comparison of pulmonary vascular lesions was performed 3 weeks later at postmortem.

TABLE 1. ANCILLARY THERAPIES FOR HEARTWORM DISEASE

Drug	Use in Heartworm Therapy	Limitations	AHS Recommendations
ASPIRIN *Anticoagulant* *Anti-inflammatory* *Antithrombotic*	• Severe canine HWD, with strict cage confinement and adulticidal therapy advocated • Asymptomatic feline HWI	• Do not use concurrently with corticosteroids • Discontinue if GI signs develop	Not endorsed for routine treatment of heartworm disease
CORTICOSTEROIDS *Anti-inflammatory*	• Pulmonary parenchymal complications (canine HWD) • Prevention/treatment of adverse reactions to microfilaricides and adulticides (canine HWD)	• Can cause side effects (PU/PD, muscle wasting, immunosuppression, hypercoagulability, psychological changes, endocrine and dermatologic abnormalities)	Glucocorticoids, such as prednisone, may be used in highly endemic areas, where animals are more likely to have significant worm burdens
DOXYCYCLINE *Antibiotic*	Potentially: • Reduces microfilarial burdens, ability of parasites to reproduce, infectivity, and lung reaction to worm death • Potentiates adulticidal therapy • Eliminates developing larva	• What is best concurrent therapy, exact dosage, initiation time-point, therapy duration, and risk/cost:benefit ratio? • In which disease stage is it useful?	If the slow-kill method is used (only out of necessity), it should be repeated in 60 days, so the dog receives ivermectin monthly and doxycycline 1 month on, 2 months off, etc, until antigen test is negative.
HEPARIN *Anticoagulant*	• Caval syndrome, prior to worm retrieval (canine HWI) • Disseminated intravascular coagulation (canine HWI) • Shown to reduce adverse reactions associated with thiacetarsemide therapy (canine HWD)	• Has not been studied with *melarsomine* adulticidal therapy	Not referred to in AHS guidelines
NSAIDS *Anti-inflammatory* (other than aspirin)	• Prevention/treatment of muscle inflammation associated with melarsomine injection	• Can cause side effects (GI hemorrhage, nephrotoxicity)	Not referred to in AHS guidelines

For more information on doxycycline and corticosteroid therapies, read **Doxycycline in the Management of Heartworm Disease** (July/August 2012) and **Treating Heartworm Infection: Ancillary Corticosteroid Therapy in Dogs** (November/December 2012), available at todaysveterinarypractice.com.

- The aspirin dosage required increased by nearly:
  - » 70% (from 6 to 10 mg/kg Q 24 H) with the experimental HWI model (live worm implantation)
  - » 200% (from 6 to 17 mg/kg Q 24 H) with the pulmonary thromboembolism model (dead worm implantation).
- There were no significant differences in severity of pulmonary vascular lesions in the 5 aspirin treated dogs compared to the 5 untreated control dogs.

Tarish & Colleagues. A 1993 study using experimental dead worm implantation (n = 3), compared flunixin meglumate (administered IV for 3 days) with necropsy and lung evaluation on day 5.[6]

- Flunixin did not provide pulmonary arterial benefit when compared to 2 untreated dogs and appeared to enhance vascular lesions

ASPIRIN: ITS ROLE IN CANINE HEARTWORM DISEASE

AHS Guidelines

The empirical use of aspirin for its antithrombotic effect or to reduce pulmonary arteritis is not recommended for dogs with HWI. Convincing evidence of clinical benefit is lacking and there is some research suggesting that aspirin may be contraindicated.

Recommendations If Used

Despite conflicting studies in the literature, Calvert and associates have successfully used a combination of aspirin and strict cage confinement with adulticidal therapy for severe HWD.[9]

- If used, aspirin, **2.2 mg/kg Q 12 H**, is administered daily beginning *1 to 3 weeks before* and *4 to 6 weeks after* adulticide administration.
- With protracted aspirin therapy, packed cell volume (PCV) and serum total protein should be monitored periodically.
- Aspirin is avoided or discontinued in the face of GI bleeding (melena or falling PCV), persistent emesis, thrombocytopenia (50,000/mm^3), and hemoptysis.[9]

Author Recommendations

While I do not employ aspirin in the management of canine HWI, an argument can certainly be made for its use, or at least justification for further, more definitive research in naturally occurring cases.

Aspirin Should:

- NOT be prescribed with concurrent corticosteroid therapy
- NOT be used in symptomatic patients (on corticosteroids)
- BE stopped if an asymptomatic patient decompensates, developing respiratory signs and requiring corticosteroid therapy.

- Once again, this study should not be overinterpreted, as it:
  - » Involved an antiprostaglandin other than aspirin
  - » Was brief in duration
  - » Had only 2 dogs in the control group.

Despite the limitations of these studies, the American Heartworm Society does not endorse antithrombotic therapy for routine treatment of heartworm disease.

HEPARIN

Therapeutic Use

Low-dose *calcium* heparin has been studied in canine HWD and was shown to reduce adverse reactions associated with thiacetarsemide administration in dogs with severe clinical signs, including heart failure.[8]

- In this study, calcium heparin was administered at 50 to 100 IU/kg SC Q 8 to 12 H *for 1 to 2 weeks before* and *3 to 6 weeks after* adulticidal therapy.
- Compared to antiprostaglandins (aspirin or ibuprofen), calcium heparin:

ASPIRIN: ITS ROLE IN FELINE HEARTWORM DISEASE

Although not a well-accepted practice, this author does use aspirin in ***asymptomatic* feline HWI**.

Study Results

The use of aspirin in cats has been questioned as the associated vascular changes consume platelets, increasing their turnover rate and effectively diminishing the antithrombotic effects of the drug.[10] In addition:

- Conventional doses of aspirin did not prevent angiographically detected vascular lesions.
- Dosages of aspirin necessary to produce even limited histologic benefit approached the toxic range.

Author Recommendations

However, I continue to advocate aspirin administration in cats with asymptomatic HWI because:

- Proliferative, inflammatory, and thrombotic vascular lesions are severe (see **Figure**)
- Therapeutic options are limited
- At conventional doses (**40–80 mg PO Q 72 H**), aspirin is generally harmless, inexpensive, and convenient
- Quoted negative studies were based on relatively insensitive estimates of platelet function and pulmonary arterial disease (thereby possibly missing subtle benefits).

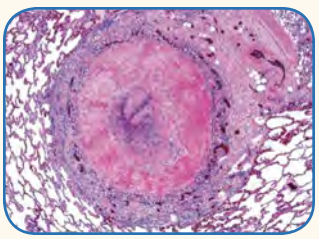

Figure. *This photomicrograph of a large feline pulmonary artery demonstrates perivascular inflammation, severe myointimal proliferation, and thrombosis, resulting in vascular occlusion. This emphasizes the impact heartworms have on pulmonary vasculature in cats and suggests the possible beneficial effect of antithrombotics, such as aspirin, in slowing progression of such lesions.*

» Reduced thromboembolic complications
» Improved survival.

- Dogs in both groups received prednisone at 1 mg Q 24 H.

Note: Calcium heparin can be used interchangeably with sodium heparin; this study[8] chose the former, the following study chooses the latter.[9]

Additional Recommendations

Calvert advocates *sodium* heparin:[9]

- For heartworm induced thrombocytopenia, 75 IU/kg SC Q 8 H for at least 7 days to weeks and until platelet counts are greater than 150,000/mm^3
- For disseminated intravascular coagulation, 75 to 150 IU/kg SC Q 8 H until resolved
- For pulmonary thromboembolism, 75 to 150 IU/kg SC Q 8 H until platelet count is normal
- Prior to adulticidal therapy, 75 IU/kg SC Q 8 H during melarsomine therapy, continuing for 3 weeks afterwards, plus cage rest in high-risk patients.

Author Recommendations

I do not routinely embrace heparin therapy for dogs with HWI except in cases of:

- Caval syndrome, prior to worm retrieval; 100 IU/kg IV sodium heparin, administered immediately preoperatively
- Disseminated intravascular coagulation; 75 to 150 IU/kg SC Q 8 H until resolved for HWD with evidence of coagulopathy:
  » Bleeding, ecchymoses, sometimes petechia
  » Abnormal clotting tests
  » Thrombocytopenia, increased fibrin split products, D-dimers, etc.

TABLE 2. RISK FACTORS FOR RENAL DAMAGE WITH NSAID THERAPY

- **Congestive heart failure**
- **Dehydration**
- **Dietary sodium restriction**
- **Diuretic use**
- **Pre-existing renal disease**
- **Use of ACE inhibitor**
- Blood loss
- Hepatic cirrhosis

The **bolded phrases**—risk factors associated with cardiac disease (and, therefore, HWD)—indicate that concern/caution is warranted when using NSAIDs in patients with HWI, especially those with heart failure and/or proteinuric renal disease.

Nevertheless, based on the above-mentioned study by Vezzoni, et al, this drug class may also have benefits when used with adulticidal therapy in high-risk patients.[8] *Note:* This therapy has not been studied with *melarsomine adulticidal* therapy.

NSAIDS OTHER THAN ASPIRIN

The advent of an effective group of NSAIDS (ie, carprofen, deracoxib, firocoxib, meloxicam, tepoxalin) has opened the door for chronic management of pain and inflammation in veterinary patients.

Adverse Effects

Although this development represented a major breakthrough, these agents can cause adverse side effects, most prominently in the form of gastrointestinal (GI) upset or hemorrhage and/or nephrotoxicity. Although uncommon, nephrotoxicity due to NSAID use is precipitated by multiple factors, some of which are present in patients with HWD (**Table 2**).

Author Recommendations

Due to these concerns, I see little utility for NSAID use in management of HWI, except to treat or prevent muscle inflammation associated with melarsomine injection. For this purpose, I advocate administration of a veterinary-approved NSAID at approved dosages for *2 to 3 days before* and *3 to 4 days after* melarsomine injections. ■

ACE = angiotensin-converting enzyme; HWD = heartworm disease; HWI = heartworm infection; NSAID = nonsteroidal anti-inflammatory drug; GI = gastrointestinal; PCV = packed cell volume

References

1. Rawlings CA, Keith JC, Schaub RG, et al. Post adulticide treatment pulmonary disease and its modification with prednisolone and aspirin. In Otto GF (ed): *1983 American Heartworm Society Symposium Proceedings*, p 122.
2. Leuthy MW, Sisson DD, Kneller SK, et al. Angiographic assessment of aspirin for the prevention of pulmonary thromboembolism following adulticide therapy. In Otto GF (ed): *1989 American Heartworm Society Symposium Proceedings*, p 53.
3. Atwell RB, Sutton RH, Carlisle CH. The reduction of pulmonary thromboembolic disease (*D immitis*) in the dog associated with aspirin therapy. In Otto GF (ed): *1983 American Heartworm Society Symposium Proceedings*, p 115.
4. Keith JC, Rawlings CA, Schaub RG. Effect of aspirin on canine pulmonary artery disease caused by *Dirofilaria immitis*. In Otto GF (ed): *1983 American Heartworm Society Symposium Proceedings*, p 119.
5. Boudreaux MK, Dillon AR, Ravis WR, et al. Effects of treatment with aspirin or aspirin/dipyridamole combination in heartworm-negative, heartworm-infected, and embolized heartworm-infected dogs. *Amer J Vet Res* 1991; 52:1992-1999.
6. Tarish JH, Atwell RB. The effect of prostaglandin inhibition on the development of pulmonary pathology associated with dead *Dirofilaria immitis*. *Vet Parasitol* 1993; 49:207-217.
7. Lunsford KV, Mackin JV. Thromboembolic therapies in dogs and cats: An evidence-based approach. *Vet Clin North Amer Small Anim Pract* 2007; 37:579-609.
8. Vezzoni A, Genchi C. Reduction in post-adulticide thromboembolic complications with low dose heparin therapy. In Otto GF (ed): *1989 American Heartworm Society Symposium Proceedings*, pp 73-83.
9. Calvert CA, Rawlings CA, McCall JW. Heartworm disease. In Fox PR, Sisson D, Moise SN (eds): *Textbook of Canine and Feline Cardiology*. Philadelphia: WB Saunders, 1999, pp 702-726.
10. Rawlings CA. Pulmonary arterography and hemodynamics during feline heartworm disease. *J Vet Intern Med* 1990; 4:285-289.

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