

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.



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 postadulthood pulmonary thromboembolism.³

Therapeutic Use

Aspirin has shown success in:

- Diminishing vascular damage caused by segments of dead worms³
- Reducing extent and severity of myointimal proliferation caused by implanted living worms
- Improving pulmonary parenchymal disease and intimal proliferation in dogs receiving thiacetarsamide (Sodium Carparosolate) 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 tortuosity (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

- **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

results, this study has most likely played too large a role in shaping recommendations for or against aspirin use in HWD.

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 <i>Anticoagulant</i> <i>Anti-inflammatory</i> <i>Antithrombotic</i>	<ul style="list-style-type: none"> • Severe canine HWD, with strict cage confinement and adulticidal therapy advocated • Asymptomatic feline HWI 	<ul style="list-style-type: none"> • Do not use concurrently with corticosteroids • Discontinue if GI signs develop 	Not endorsed for routine treatment of heartworm disease
CORTICOSTEROIDS <i>Anti-inflammatory</i>	<ul style="list-style-type: none"> • Pulmonary parenchymal complications (canine HWD) • Prevention/treatment of adverse reactions to microfilaricides and adulticides (canine HWD) 	<ul style="list-style-type: none"> • 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 <i>Antibiotic</i>	Potentially: <ul style="list-style-type: none"> • Reduces microfilarial burdens, ability of parasites to reproduce, infectivity, and lung reaction to worm death • Potentiates adulticidal therapy • Eliminates developing larva 	<ul style="list-style-type: none"> • 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 <i>Anticoagulant</i>	<ul style="list-style-type: none"> • Caval syndrome, prior to worm retrieval (canine HWI) • Disseminated intravascular coagulation (canine HWI) • Shown to reduce adverse reactions associated with thiacetarsamide therapy (canine HWD) 	<ul style="list-style-type: none"> • Has not been studied with <i>melarsomine</i> adulticidal therapy 	Not referred to in AHS guidelines
NSAIDS <i>Anti-inflammatory</i> (other than aspirin)	<ul style="list-style-type: none"> • Prevention/treatment of muscle inflammation associated with <i>melarsomine</i> injection 	<ul style="list-style-type: none"> • 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 ($50,000/\text{mm}^3$), 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.

HEPARIN Therapeutic Use

Low-dose *calcium* heparin has been studied in canine HWD and was shown to reduce adverse reactions associated with thiacetarsamide 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).

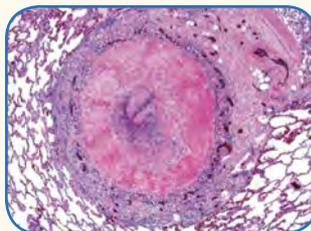


Figure. This photomicrograph of a large feline pulmonary artery demonstrates perivascular inflammation, severe myointimal proliferation, and thrombosis, resulting in vascular occlusion. This emphasizes the impact

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 study⁸ 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/mm³
- 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 adjuvant 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

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.

IV sodium heparin, administered immediately pre-operatively

- 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.

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

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COMFORTIS®-Cats (spinosad)

Chevable Tablets
Before using COMFORTIS chewable tablets, please consult the product insert, a summary of which follows:
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Indications:
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), for one month, on cats and kittens 14 weeks of age and older and two pounds of body weight or greater.
Dosage and Administration:
COMFORTIS is given orally once a month, at the minimum dosage of 22.5 mg/lb (50 mg/kg). Administer COMFORTIS with food for maximum effectiveness. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
Contraindications:
There are no known contraindications for the use of COMFORTIS.
Warnings:
Not for human use. Keep this and all drugs out of the reach of children.
Precautions:
Use with caution with concomitant extra-label use of ivermectin. The safe use of COMFORTIS in breeding, pregnant, or lactating cats has not been evaluated.
Adverse Reactions:
In a well-controlled US field study, which included a total of 211 cats (139 treated with COMFORTIS and 72 treated with an active topical control once a month for 3 treatments), no serious adverse reactions were attributed to the administration of COMFORTIS. The most frequently reported adverse reaction in cats was vomiting.
Percentage of Cats (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS (n=139)	Active Topical Control (n=72)	COMFORTIS (n=135)	Active Topical Control (n=69)	COMFORTIS (n=132)	Active Topical Control (n=67)
Vomiting	14.4	1.4	14.8	1.4	13.6	4.5
Lethargy	3.6	0	0.7	0	1.5	1.5
Anorexia	2.2	0	0.7	0	2.3	1.5
Weight Loss	1.4	0	0	0	3	0
Diarrhea	1.4	1.4	0.7	2.9	2.3	1.5

Over the 3-month (3-dose) study, vomiting occurred on the day of or the day after at least one dose in 28.1% (39/139) of the cats treated with COMFORTIS and in 2.8% (2/72) of the cats treated with the active topical control. Three of the 139 cats treated with COMFORTIS vomited on the day of or the day after all three doses. Two cats that received extra-label topical ivermectin on Day -1 of the field study developed lethargy on Day 1 after COMFORTIS administration on Day 0.
For technical assistance or to report an adverse drug experience, call Elanco at 1-888-545-5973. Additional information can be found at www.comfortis.com. For a complete listing of adverse reactions for spinosad reported to the Center for Veterinary Medicine, see Adverse Drug Experience Reports under <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation>

Effectiveness:
In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 98% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. In a separate well-controlled laboratory study, COMFORTIS demonstrated 100% effectiveness on the first day following treatment and >90% effectiveness on Day 30. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In a field study conducted in households with existing flea infestations, flea count reductions of 97.5% were observed one month after the first treatment and 99.3% after three monthly treatments with COMFORTIS. Cats with pre-existing signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis, and pruritus as a direct result of eliminating the fleas.

Storage Information:
Store at 20 to 25°C (68 to 77°F), excursions permitted between 15 to 30°C (59 to 86°F).
How Supplied:
COMFORTIS is available in four tablet sizes for use in cats: 90, 140, 270 or 560 mg. Each tablet size is available in color-coded packages of 6 tablets.
NADA #141-277, Approved by the FDA
Manufactured by Elanco Animal Health, A Division of Eli Lilly and Company, Indianapolis, IN 46285

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Chevable Tablets
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Indications:
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on dogs and puppies 14 weeks of age and older and 3.3 pounds of body weight or greater.
Dosage and Administration:
COMFORTIS is given orally once a month, at the recommended minimum dosage of 13.5 mg/lb (30 mg/kg). Administer COMFORTIS with food for maximum effectiveness. If vomiting occurs within an hour of administration, redose with another full dose. If a dose is missed, administer COMFORTIS with food and resume a monthly dosing schedule.
Contraindications:
There are no known contraindications for the use of COMFORTIS.
Warnings:
Not for human use. Keep this and all drugs out of the reach of children.
Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with COMFORTIS (see POST APPROVAL EXPERIENCE).
Precautions:
COMFORTIS is for use in dogs and puppies 14 weeks of age and older.
Use with caution in breeding females and in dogs with pre-existing epilepsy. The safe use of COMFORTIS in breeding males has not been evaluated.
Adverse Reactions:
In a well-controlled US field study, which included a total of 470 dogs (330 dogs treated with COMFORTIS and 140 dogs treated with an active control), no serious adverse reactions were observed with COMFORTIS. All reactions were regarded as mild and did not result in any dog being removed from the study. The most frequently reported adverse reaction in dogs in the COMFORTIS and active control groups was vomiting. The occurrence of vomiting, most commonly within 48 hours after treatment, decreased with repeated doses of COMFORTIS.
Percentage of Dogs (%) with Adverse Reactions

	Month 1		Month 2		Month 3	
	COMFORTIS Chewable Tablets (N=330)	Active Topical Control (N=139)*	COMFORTIS Chewable Tablets (N=282)	Active Topical Control (N=124)	COMFORTIS Chewable Tablets (N=260)	Active Topical Control (N=125)
Vomiting	12.7	12.2	7.8	3.2	5.8	4.8
Decreased Appetite	9.1	5	2.8	1.6	1.9	0.8
Lethargy	7.6	5	3.5	4	1.2	0.8
Diarrhea	6.7	5	4.3	0.8	1.2	0
Cough	3.9	5	0.4	2.4	0	0
Polydipsia	2.4	1.4	0.7	0	0.4	0
Vocalization	1.8	0	0.4	0	0.4	0
Increased Appetite	1.5	0	0.4	0.8	0.4	0
Erythema	1.5	0	0.4	0	0.4	0
Hyperactivity	1.2	1.4	0	0	0.4	0
Excessive Salivation	1.2	0	0.4	0	0	0

* This number (n=139) is less than the total number of dogs in the safety population for the active control group (n=140) because one dog joined the study late and was only dosed at Month 3. In US and European field studies, no dogs experienced seizures when dosed with COMFORTIS at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of COMFORTIS, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

Post Approval Experience (June 2009):
The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, anorexia, ataxia, diarrhea, pruritus, trembling, hypersalivation and seizures.
Following concomitant extra-label use of ivermectin with COMFORTIS, some dogs have experienced the following clinical signs: trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation. Post approval experience continues to support the safety of COMFORTIS when used concurrently with heartworm preventatives according to label directions.
For technical assistance or to report an adverse drug experience, call Elanco at 1-888-545-5973. Additional information can be found at www.comfortis.com. For a complete listing of adverse reactions for spinosad reported to the Center for Veterinary Medicine, see Adverse Drug Experience Reports under <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation>.

Effectiveness:
In a well-controlled laboratory study, COMFORTIS began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. COMFORTIS kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with COMFORTIS. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis and pruritus as a direct result of eliminating the fleas.
Storage Information:
Store at 20-25°C (68-77°F), excursions permitted between 15 to 30°C (59 to 86°F).
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