Ivermectin treatment of naturally acquired and experimentally induced *Strongyloides stercoralis* infections in dogs

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Summary: *Treatment of* Strongyloides stercoralis *infection was investigated in 2 dogs with naturally acquired, chronic-active infections, and in 3 dogs with corticosteroid-enhanced, experimentally induced hyperinfections. A single oral dose of ivermectin was given to naturally infected (200 μg/kg of body weight) and experimentally infected (800 μg/kg) dogs. Five dogs with experimental hyperinfections served as controls. Dogs with naturally acquired infections ceased to shed first-stage larvae in the feces 1 week after treatment, but 1 dog had recrudescence and required a second dose. Ivermectin was 100% effective in removing adult* S stercoralis *from the intestinal tract of the experimentally infected dogs, but it was not effective in removing third-stage larvae from parenteral sites. Ivermectin-treated dogs had few intestinal parasites of any stage, whereas at necropsy, 4 of 5 experimentally infected dogs not treated had massive infections (>100,000 adults, >92,000 larvae) in the intestinal tract, and 3 of 5 had larvae (>2,500) in parenteral sites.*

Strongyloides stercoralis is a nematode parasite that can cause a variety of clinical syndromes in primates and dogs from self cure to severe disseminated disease.[1] The parasite has a complex lifecycle in which parthenogenetic females embedded in the intestinal mucosa lay embryonated eggs that hatch internally. The resultant first-stage larvae (L1) are passed in the feces and may develop directly to second-(L2) and third-stage larvae (L3) or may develop through 4 free-living larval stages to free-living adult males and females. The free-living adults reproduce sexually to produce L1, which also develop to L3. It is the L3 of both cycles that penetrate the skin of the host, undergo tissue migration, and develop to the adult stage in the intestinal tract. In most instances, dogs shed L1 of *S stercoralis* in the feces for a short period.[2] A few dogs continue to shed larvae indefinitely,[3] with clinical signs analgous to those of human beings with chronic-active strongyloidiasis.[1] Rarely, dogs develop fatal hyperinfections (disseminated infections) by autoinfection.[4] In autoinfection, larvae that have developed to the infective third stage within the gastrointestinal tract penetrate the intestinal mucosa and migrate to the definitive site in the small intestine or to parenteral sites.[5] Autoinfection may be induced by the administration of corticosteroids to dogs with active strongyloidiasis.[2,6]

Treatment of chronic-active strongyloidiasis in dogs is difficult. Thiabendazole is the only approved drug with activity against *S stercoralis* infection in dogs; however, thiabendazole treatment is not satisfactory for hyperinfected dogs. The purpose of the study reported here was to determine the efficacy of ivermectin treatment for naturally acquired and experimentally induced infections of *S stercoralis* in dogs.

Materials and Methods

Naturally acquired infections—A 3-month-old 1.1-kg sexually intact male Maltese dog (dog 1) was examined because of lethargy, listlessness, and unwillingness to play; but the dog was eating, drinking, urinating, and defecating normally. Physical examination revealed a serous nasal and ocular discharge. Tracheal palpation elicited a mild, moist cough, but lungs had normal bronchovesicular sounds. Several *S stercoralis* L1 were found in a direct smear of feces (Fig 1). Low normal values for total RBC numbers and hemoglobin content (3.91 × 106 and 9.0 g/dl, respectively) were determined, but the eosinophil count was normal (508 cells/dl).

The dog was treated with 20 mg of thiabendazole/kg of body weight, PO, once daily for 3 days, and this protocol was repeated in 7 days. After treatment, the owner was asked to return the dog in 25 days for reexamination. On reexamination, the dog's condition was clinically improved. The nasal and ocular discharge and moist cough had resolved, but the dog continued to shed larvae in

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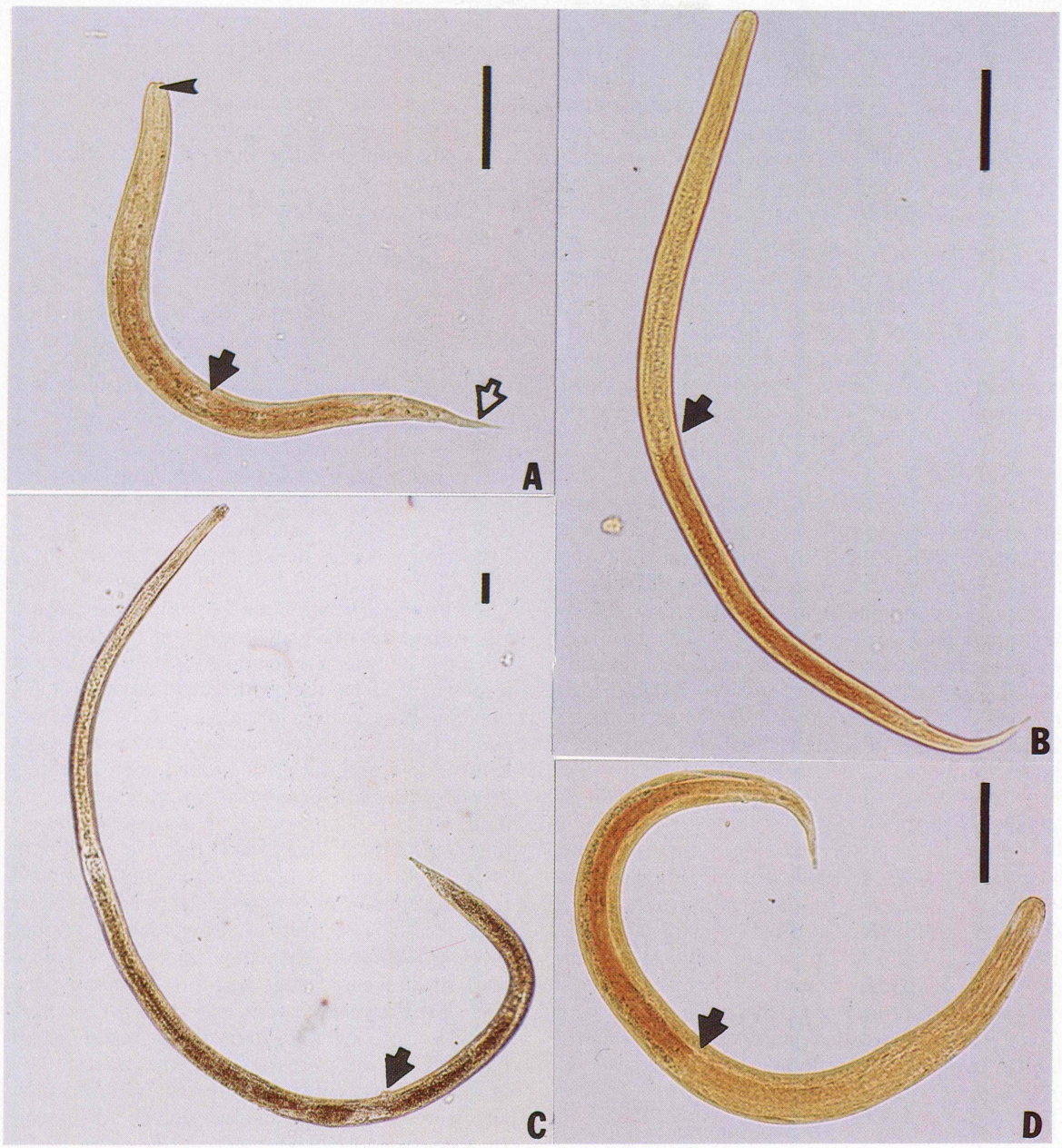

Figure 1—Strongyloides stercoralis *parasites recovered from infected dogs. Lugol's Iodine stain, bar = 50 μm.*
A—First-stage larva recovered by Baermann examination of feces from dogs with naturally acquired, chronic-active infections. The mouth tube (small closed arrow), genital primordium (closed arrow), and conical tail (open arrow) differentiate this larva from those of Filaroides spp *or hookworm.*
B—Third-stage larva recovered from tracheal washings of dog 2, which acquired its infection naturally. This larva was identical to those recovered from tracheal washings of experimentally infected dogs. Notice the filariform esophagus (closed arrow).
C—Adult female recovered from feces of an experimentally infected dog 24 hours after treatment with ivermectin. Notice the vulva (closed arrow) and lack of eggs in the uterus.
D—Third-stage larva recovered from tracheal washings of a hyperinfected dog. Notice the filariform esophagus (closed arrow).

the feces (72 L1/g). The owner reported that the dog had been vomiting from treatment with thiabendazole.

A 5-month-old 1.5 kg female Maltese dog (dog 2) was admitted to the medicine department because of a 2-month history of lethargy, coughing, and diarrhea, which had continued despite treatment with numerous antibiotics and antidiarrheal drugs at a local veterinary clinic.

On physical examination, the dog had signs similar to those of dog 1, except that on auscultation of the thorax, increased bronchovesicular

sounds were heard throughout the lungs. The rectal temperature was normal and the stool was soft but not liquid. Abnormalities were not detected on CBC or serum biochemical analysis. Thoracic radiography revealed a generalized interstitial pattern, with a bronchoalveolar pattern in some areas. Several L3 of *S stercoralis* were recovered from tracheal washings (Fig 1). Baermann examination of the feces revealed 48 L1 of the parasite/g of feces.

Experimentally induced infections—Eight 8-week-old Beagle-type dogs were housed in stainless steel cages, which were washed daily in a cage washer at 100 C to prevent reinfection of dogs with the parasite. Dogs were inoculated subcutaneously with 5,000 L3 of *S stercoralis*, which were obtained by mixing L1 from the feces of experimentally infected Beagles with charcoal, and maintaining the larvae at 25 C for 7 days.

Monitoring experimentally induced infections—Feces from each dog were examined by use of the Baermann technique[a] 3 times/wk throughout the study. When dogs ceased to shed L1 in the feces (as judged by 3 consecutive negative Baermann examinations), daily corticosteroid (0.5 mg of prednisolone/kg, PO) treatment was initiated to induce development of hyperinfections. When dogs began to shed 3 times the number of larvae given in the infective dose/g of feces (15,000 larvae/g), they were considered to be hyperinfected with the parasite, and were either treated with ivermectin or saved as control dogs.

After the fecal shed of L1 indicated hyperinfection, dogs were sedated with thiopental sodium (10 to 20 mg/kg, IV, to effect), intubated, and a 3-mm catheter was passed to the tracheal bifurcation. Sterile 0.9% NaCl (saline) solution (10 ml) was infused and then aspirated. Recovered material was centrifuged, and the pellet was stained with Lugol's iodine, and then observed with a microscope, using Nomarski interference optics.[b]

Treatment—Dogs with naturally acquired infections and those with experimentally induced infections were given ivermectin[c] (200 and 800 μg/kg, PO, respectively), which was diluted in sterile saline.

Necropsy—Five days after ivermectin treatment, dogs were euthanatized with an overdose of barbiturate anesthesia, and their skin was removed and laid in a pan of warm (37 C) saline to retrieve parenteral larvae. The intestines were removed, slit longitudinally, and hung in cylinders containing warm saline solution for 3 hours. Parasites were allowed to sediment by gravity, and the total number of larvae and adults were determined, using 10× magnification. Other internal organs were minced, placed on sieves in saline solution, and the fluid was allowed to sediment by gravity. Total numbers of parasites emerging from the samples were determined either directly or by dilution counting.

Active autoinfection was demonstrated in experimentally infected dogs on the basis of a total fecal shed of L1 exceeding 200,000, which was the maximal possible shed from the infective dose. Additionally, autoinfection was demonstrated in these dogs and suspected in naturally infected dogs by recovering L3 from tracheal washes.

Results

Disseminated infection was detected in 1 experimentally infected dog by recovering L1 from a tracheal wash sample, and in another experimentally infected dog by recovering 2 adult parasites in tissues outside the lumen of the gastrointestinal tract.

Ivermectin was 100% effective at removing L1, L2, and adults of *S stercoralis* from the intestinal tract of hyperinfected dogs and 99.95% effective in removing L3 from the gastrointestinal tract. A significant ($P = 0.001$) difference was detected between the number of parasites recovered from control dogs and that from treated dogs. Ivermectin was not effective, however, at removing parenteral L3. At necropsy, 4 of 5 experimentally infected control dogs had massive infections (>100,000 adults, >92,000 larvae) in the intestinal tract, and 3 of 5 had larvae (>2,500 L3) in parenteral sites (Table 1). One control dog had 1,000,000 intestinal parasites, but only 4 in parenteral sites. Treated dogs had few intestinal parasites, but L3 were found in parenteral sites. Adult *S stercoralis* collected from the feces of treated dogs had no eggs within the reproductive tract.

The 2 dogs with naturally acquired infections also were treated with ivermectin. The dogs were each given 1 dose of ivermectin (200 μg/kg, PO) after obtaining permission from the owner for extra label use of the drug. Forty-eight hours after treatment, the feces of dog 1 were free of L1 as judged by Baermann examination. Two weeks later, 2 larvae/g were found in the feces of dog 1, thus, a second dose of ivermectin (200 μg/kg, PO) was given. Subsequent fecal examinations were negative for *S stercoralis*. Twenty-four hours after treatment, dog 2 passed several adult *S stercoralis* in the feces as well as numerous L1. Ten days after treatment, dog 2 was reexamined and found to be bright and alert. The diarrhea and cough had resolved, and the feces were negative for the parasite by Baermann examination. Subsequent fecal examinations for the parasite were negative.

Adverse effects of ivermectin treatment were not detected during the 24-hour period after

[a]Baermann technique—Feces to be examined are placed in a tea strainer or other wire mesh, which is placed over a small glass cup. The cup is filled with tap water until the feces are barely covered. After one hour incubation, the sediment in the cup is examined for nematode larvae.

[b]Nomarsky interference optics, Zeiss, Opto-Systems Inc, Jenkintown, Pa.

[c]IvomecR, MSD-AGVET Inc, Rahway, NJ.

Table 1—Total numbers of Strongyloides stercoralis *adults and larvae recovered from dogs at necropsy*

Parasite stage and location	Hyperinfected controls*					Ivermectin treated		
	1	2	3	4	5	6	7	8
Intestinal tract parasites								
L1 and L2	1,159,313	86,490	36,120	ND	976,185	0	0	0
L3	11,240	10,080	56,140	4,560	40	2	0	26
Adults	573,065	1,041,750	473,860	100,000	56,556	0	0	0
Parenteral parasites†								
L1 and L2	0	0	0	ND	2	0	0	0
L3	25,333‡	75	17,302‡	2,555‡	0	3	50,373‡	464‡
Adults	1	0	3	0	2	0	0	0

*Experimentally induced hyperinfections; †parenteral sites included lungs, brain, liver, kidney, spleen, bladder, heart, lymph nodes, skin, and muscle; ‡Greater than 90% found in the skin and muscle.

Numbers of parasites in all control dogs were significantly ($P < 0.001$) higher than those in treated dogs, except for numbers of L3 in parenteral sites.

administration of the drug to either naturally-infected dogs given 200 μg/kg or experimentally infected dogs given 800 μg/kg.

Discussion

Ivermectin given orally at 200 μg/kg decreased parasite burdens in 2 dogs with naturally acquired, chronic-active infections of *S stercoralis,* but a second dose was required in 1 dog to effect apparent parasitologic cure. Ivermectin given at 800 μg/kg was highly effective against adult (100%) and larval (99.95%) stages of *S stercoralis* in the gastrointestinal tract of hyperinfected dogs, but was not effective against tissue-dewelling stages. This was contradictory to another study[7] in which negligible numbers of parenteral larvae were collected from extraintestinal sites in 1 treated dog. Despite the remaining parenteral larvae, ivermectin was substantially better for treatment of *S stercoralis* than thiabendazole, which is the only approved drug with activity against *S stercoralis* available for use in dogs. When thiabendazole was given to immunosuppressed, strongyloides-infected dogs, there was only a transient decrease in larvae in the feces, and large numbers of adults were found in the gastrointestinal tract on necropsy.[8]

Ivermectin given orally at 200 μg/kg and 800 μg/kg to heartworm-negative dogs caused no detectable adverse effects, despite the killing and elimination of large numbers of *S stercoralis* adults and larvae. These results were consistent with those from a toxicity study in Beagles.[7] In that study, toxic signs included mydriasis, lethargy, tremors, ataxia, stupor, emesis, drooling, and coma.[7] The highest single oral dose without toxic effects was 2.0 mg/kg,[7] which was considerably higher than the effective dose used in our study. Idiosyncratic reactions to ivermectin have been documented in collies,[9] and another report[10] described a case of ivermectin toxicosis in a Doberman Pinscher that accidentally ingested ivermectin (2.8 mg/kg) formulated for use in horses.

Dogs shedding L1 of *S stercoralis* in the feces are infected with the parasite. Chronic-active status may be assumed in adult dogs shedding the parasites periodically in the feces. Hyperinfection, however, is more difficult to ascertain in the living host. The presence of L3 in a tracheal wash may only indicate active infection with the parasite, although it is suggestive of autoinfection in a dog shedding larvae in the feces for long periods that exceed the prepatent period of the parasite. Recovery of L1 from a tracheal wash confirms disseminated infection, because this finding requires the presence of adults in extraintestinal sites.[11] One dog experimentally infected in our study harbored a disseminated infection, because L1 were recovered from a tracheal wash. Another dog in the same group also had a disseminated infection, because 2 adult parasites were found in the brain.

Dogs with confirmed *S stercoralis* infection treated with ivermectin or other drugs are not necessarily cleared of infection just because they cease to shed detectable numbers of larvae in the feces. Baermann examination of feces, although the most reliable technique for confirming infection with the parasite, has low sensitivity. The output of larvae in the feces of infected dogs varies,[1] and severity of infection is best established by repeated Baermann examinations. Additionally, tissue-dwelling larval stages may act as storage forms of the parasite and cause recrudescence at a later time. In dog 1, the L1 found in the feces 2 weeks after treatment with ivermectin could have resulted from previously dormant larvae migrating to the duodenum and resuming development to the adult stage, with subsequent production of L1. The minimal prepatent period of the parasite is 12 to 14 days.[1] Alternatively, adult worms lying deeply embedded in fibrotic, connective tissue tunnels in the mucosa[11] may escape the effect of most anthelmintics, and go on to shed larvae. An interesting observation was that adult worms collected in the feces of treated dogs had no eggs within the uterus, suggesting an additional effect of the drug.

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Book Review: Atlas of Radiographic Anatomy and Diagnosis of Cage Birds

The *Atlas of Radiographic Anatomy and Diagnosis of Cage Birds* is an excellent reference book for avian practitioners. The original text is in German, with superb translation into English.

The book proceeds in an orderly manner, beginning with a broad discussion of handling methods and anatomic considerations and concluding with specific radiographic interpretation of pathologic conditions seen in pet-bird practice. Between these sections, a thorough review of radiographic positioning and technique, including contrast radiography, provides a detailed and usable reference for veterinarians and veterinary technicians. Normal radiographic anatomy is amply illustrated, with a heavy emphasis on the parrot group. Radiographs of normal birds of prey, racing pigeons, and mynah birds help round out species-specific information. Radiographs are clarified through the use of clear and concise diagrams opposite or adjacent to the film. Overall, the text emphasizes radiographic procedures and normal radiographic anatomy with less emphasis on pathologic conditions.

It should be stressed, under the discussion on sedation and restraint, that the preferred method of chemical restraint in caged birds is isoflurane. When compared with injectable drugs and other gas anesthetics, isoflurane provides superior safety and predictability.

The authors have done an excellent job of placing a lot of valuable information in the hands of beginning avian practitioners, but also provide the detail and depth that experienced clinicians will appreciate. With the importance of radiology in caged bird medicine, this book will certainly be pulled from the shelves on a frequent basis.—*[Atlas of Radiographic Anatomy and Diagnosis of Cage Birds. By Maria Elisabeth Krautwald, B. Tellhelm, G. Hummel, et al. 216 pages; illustrated. Paul Parey Scientific Publishers, PO Box 1815, New York, NY 10156-0610. 1992. Price $135.00.]*—ROBERT A. IRMIGER