Neurologic complications after melarsomine dihydrochloride treatment for *Dirofilaria immitis* in three dogs

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An 11-year-old spayed female Dalmatian weighing 30 kg (66 lb) was evaluated by the neurology service at Texas A&M University because of progressive hind limb ataxia of 1 week's duration. Two months previously, heartworm infection (unassociated with clinical signs) was diagnosed in this dog. Treatment of this dog for *Dirofilaria immitis* was undertaken by the referring veterinarian and consisted of an injection of melarsomine dihydrochloride (2.5 mg/kg [1.14 mg/lb], IM) into the left epaxial muscles. This was followed by a second injection into the same muscular region 6 weeks later and a third injection into the right epaxial muscles the day after the second injection. During the third treatment, the dog struggled and had to be restrained by several people to complete the injection. Within hours of the last injection, the dog became ataxic and had marked signs of pain. During the next week, no improvement was detected in these clinical signs; the dog was ataxic, had difficulty rising, and remained recumbent for most of the time. During that period, treatment involved supportive care and administration of aspirin every 4 hours (dosage unknown).

On physical examination at the time of referral, the dog was obese, paraparetic, and had signs of anxiety and depression. Auscultation revealed a grade III/VI systolic murmur over the left apex of the heart. Results of a neurologic examination indicated severe paraparesis. Proprioceptive deficits were detected in the hind limbs (greater in the right hind limb), and postural reactions were delayed. Segmental spinal reflex evaluation revealed slightly increased patellar and gastrocnemius reflexes and decreased flexor withdrawal reflexes in both hind limbs. The cutaneous trunci reflex was absent caudal to the L3 vertebral body on the right side. Paraspinal hyperesthesia was induced on palpation of the lumbar spine and dorsal flexion of the tail.

A lesion of spinal cord segments T3 through L3 was suspected because of the increased patellar and gastrocnemius reflexes. There also appeared to be involvement of spinal cord segments L4 through S2, because of the decreased flexor reflex and the signs of pain that were elicited via dorsal flexion of the tail. Differential diagnosis included intervertebral disk disease, neoplasia, inflammatory or infectious disease, vascular compromise, and trauma.

A CBC, serum biochemical profile, urinalysis, and bacteriologic culture of urine were performed. Abnormal findings detected via the CBC were an inflammatory leukogram and mild anemia. Results of serum biochemical analyses and urinalysis indicated no notable abnormalities. Thoracic radiography was performed and revealed normal findings. A sample of CSF was obtained from the cerebromedullary cistern; the fluid was colorless and clear, with concentrations of 2 WBC/µL (reference limit, < 5 WBC/µL), 4 RBC/µL (reference limit, < 5 RBC/µL), and 39 mg of protein/dL (reference limit, < 25 mg/dL). Cytologic analysis revealed many macrophages with heavily vacuolated cytoplasm, which suggested that they were activated.

Survey radiographs of the vertebral column revealed spondylitis deformans ventrally and degenerative changes involving the articular processes throughout the cervical, thoracic, and lumbar regions of the vertebral column. Sclerosis of the vertebral body endplates at L7 through S1 was detected; 2 vestigial, partially mineralized ribs at T13 were also found. Myelography was performed after iohexol [0.45 mL/kg (0.2 mL/lb)] was injected via the L5-6 intervertebral space into the ventral subarachnoid compartment. Thinning of the dorsal column of contrast media was noted from T12 through L2; the spinal cord was shifted to the left from the level of T12 vertebra caudally along its entire length. A focal compressive lesion was not noted throughout this section of spinal cord. The cauda equina was deviated dorsally by a ventral extradural compression at the L7-S1 disk space.

After the myelogram was completed, a computed tomographic scan of the vertebral column from vertebra T12 through L2 was performed. Abnormal atten-
uation of the epaxial musculature was identified bilaterally (worse on the right; Fig 1). The spinal cord was observed along the left side of the vertebral canal. A space-occupying soft tissue mass was evident on the right side of the spinal canal throughout this region. Measurements of x-ray attenuation (in Hounsfield units [HU]) for this mass were suggestive of an extensive paraspinal soft tissue mass inconsistent with normal epidural fat (normal epidural fat: –10 to –100 HU; soft tissue mass: +34.7 to +75.6 HU). A biopsy specimen of the spinal mass was obtained via a right hemilaminectomy at intervertebral space T12-13. During dissection, brownish, opaque fluid was observed originating from the epaxial muscles. A sample of the fluid was submitted for aerobic bacteriologic culture but yielded no growth after 72 hours. Within the vertebral canal, the epidural fat was firm and adhered to the dura. The dura mater was normal in appearance. Samples of the epidural tissue and bony fragments of the adjacent vertebrae were submitted for histologic evaluation. The surgical site was closed in a routine manner, and the dog recovered from anesthesia without complications.

Histologic examination of the epidural tissue revealed adipose tissue with chronic supplicative inflammation and fibroplasia; no neoplastic cells were detected, and special stains yielded no evidence of fungal or bacterial organisms. The spinal bone fragments were composed of mature lamellar bone with no apparent abnormalities.

Pain management consisted of oxymorphone (0.05 mg/kg [0.023 mg/lb], IM, q 4 to 6 h) for the first 24 hours postoperatively and, after that, butorphanol (0.34 mg/kg [0.023 mg/lb], PO, q 8 to 12 h) for 4 days. Because bacteriologic culture of urine yielded growth, broad-spectrum antimicrobial treatment was initiated; the dog received amoxicillin (20 mg/kg [9 mg/lb], PO, q 8 h) and enrofloxacin (4.5 mg/kg [2 mg/lb], PO, q 12 h) for 10 days. Three days after surgery, carprofen (2.5 mg/kg, PO, q 12 h, for 10 days) was added to the pain management. At this time, conscious proprioception and motor function were slightly improved, and the dog was discharged to the owner. Two weeks later, the owner reported that the dog appeared to be normal, with no apparent signs of ataxia or difficulty climbing up and down stairs. Fourteen months after discharge, the owner reported that the dog had remained very active with normal motor function and no apparent proprioceptive deficits.

A 1.5-year-old sexually intact male terrier mixed-breed dog weighing 6.2 kg (13.6 lb) was evaluated at the Louisiana State University Veterinary Teaching Hospital and Clinic for staging and treatment of heartworm disease. During a routine health maintenance appointment, tests performed on the dog had yielded positive results for adult heartworms and circulating microfilariae. The owner had noted no signs of systemic illness in the dog, except for an occasional cough. Before treatment, tests to determine the stage of the disease were performed; these included a CBC, serum biochemical analyses, urinalysis, an ECG, and thoracic radiography. With the exception of a low-grade inflammatory leukogram, laboratory results for urine, blood, and serum samples were within reference limits. The lead-II ECG tracing was normal. Thoracic radiography revealed slight enlargement of the left caudal mainstem pulmonary artery, with mildly increased bronchial and interstitial markings throughout all lung fields. These findings were consistent with heartworm disease.

Adulticide treatment was performed; 2 injections of melarsomine dihydrochloride (2.5 mg/kg, IM) were administered deep in the lumbar epaxial musculature at an interval of 24 hours. Both injections appeared to cause pain on the basis of vocalization by the dog during and after the injections as well as the subsequent observation of its altered gait and hunched posture. Moderate paraparesis, urine retention, and fecal incontinence were detected within hours after the second injection. Findings of a complete neurologic examination indicated that the dog was paraparetic (signs worse on the right side). Marked motor and proprioceptive deficits were noted in both hind limbs. Anal tone was diminished, and the urinary bladder was distended and difficult to express. Segmental spinal reflexes of the hind limbs were normal to exaggerated on the left side, and there was a diminished patellar reflex on the right side. These findings were consistent with a neuroanatomic lesion located between spinal cord segments L4 through S2.

Because of monetary reasons, a complete diagnostic workup was not performed at that time. Management consisted of cage rest, manual bladder expression, intermittent urinary catheterization, administration of corticosteroids, and physical therapy. Corticosteroid treatment consisted of a single injection of methylprednisolone sodium succinate* (30 mg/kg [13.6 mg/lb], IV) followed by oral administration of prednisone (0.8 mg/kg [0.36 mg/lb], PO, q 24 h, for 5 days and then every other day). Upper motor neuron urinary bladder signs were treated
with phenoxybenzamine (10 mg, PO, q 12 h) and bethanecol (10 mg, PO, q 8 h). Physical therapy consisted of passive range-of-motion exercises and hydrotherapy in a whirlpool tub.

Neurologic examinations were performed daily for 2 weeks. Improvements in hind limb function were first noted on day 12 of hospitalization. Strength and coordination improved readily, and the dog was soon able to walk and run with moderate ataxia. The dog was able to posture to urinate and defecate without assistance by day 20, at which time it was discharged from the hospital. Decreased anal tone and fecal incontinence persisted. On day 30, the dog received a microfilaricidal dose of ivermectin (100 µL/kg [45 µL/lb], PO) without complication. The owner discontinued phenoxybenzamine and bethanecol treatments on day 45. The dog continued to do well at home with only mild clinical signs of ataxia and incontinence. Elective castration was performed on day 80 without complication. The dog was examined on day 97 for inappropriate urination that consisted of voiding a steady stream of urine during normal physical activity (especially if excited). Additional diagnostic testing was declined. Treatment with phenylpropanolamine was effective in temporarily abolishing clinical signs. On day 363, the dog was presented for routine vaccinations; on that occasion, the result of an occult heartworm test was negative, and on physical examination, mild hind limb paresis that was exacerbated by exercise was noted.

A 1-year-old 5-kg (2.3-lb) sexually intact female mixed-breed dog was submitted to the Texas Veterinary Medical Diagnostic Laboratory for postmortem examination. The dog had been evaluated by its veterinarian as part of a yearly health examination. The result of an occult heartworm test was positive. Findings of routine bloodwork and thoracic radiography were reportedly normal. An ECG documented a mild sinus tachycardia (heart rate, 190 beats/min). Five days later, the veterinarian treated the dog with an injection of melarsomine dihydrochloride (2.5 mg/kg, IM) into the right paralumbar epaxial musculature. Immediately after the injection, the dog vocalized and had difficulty with locomotion of the hind limbs. Treatment included administration of methylprednisolone sodium succinate (10 mg PO, q 12 h) and bethanecol (10 mg, PO, q 8 h). Physical therapy consisted of passive range-of-motion exercises and hydrotherapy in a whirlpool tub.

Additional treatment with corticosteroids and administration of fluid SC were undertaken. At 34 hours after the melarsomine injection, the dog was referred to an external cardiac compression. Overall, lesions associated with heartworm disease were minimal.

Figure 2—Photomicrograph of a section of the L1 spinal cord segment in a dog with neurologic complications secondary to an IM injection of melarsomine dihydrochloride. Notice the neutrophilic perivascular cuffing, axon degeneration, and neutrophilic infiltration into rarefied tissue. H&E stain; bar = 20 µm.
The L3 larvae, which enter the subcutaneous tissue of dogs (definitive hosts); during a period of 4 months, the L3 larvae molt to the L4 stage while migrating to the small pulmonary arteries. The L4 larvae enter the arteries, become L5 larvae, mature, and mate over the next 2 to 3 months. In most cases, microfilariae can be detected in the peripheral blood approximately 6 months after infection.5 In dogs, common clinical signs of heartworm disease include coughing, hemoptysis, dyspnea, tachypnea, weakness, and exercise intolerance. Severe clinical signs may occur secondary to pulmonary hypertension, pulmonary thromboembolism, and right-sided congestive heart failure. However, many affected dogs do not have clinical signs for long periods. In dogs, neurologic signs resulting from heartworm disease are rare, but severe paresis has been reported in association with aberrant larval migration in the epidural space.4 Other neuromuscular signs including hind limb lameness, paresthesia, and seizures may develop in dogs with systemic arterial dirofilariasis and thromboembolism.2,3 The disease severity is classified on the basis of clinical findings and either results of immunodiagnostic assessment (ELISA) or testing for microfilariae.1,10,11 Disease severity is classified on the basis of clinical signs, history, findings on physical examination, results of laboratory tests, and evaluation of radiographs. Four classes of heartworm disease have been established: subclinical or mildly clinical disease (class 1); moderate disease (class 2); severe disease (class 3); and caval syndrome, a very severe form of disease (class 4). Before treatment, a CBC (including platelet count), serum biochemical analyses, and urinalysis should be performed. Thoracic radiography and echocardiography are useful to characterize the degree of cardiopulmonary compromise and the severity of heartworm disease.

On the basis of results of these tests, heartworm disease is classified by stage, and treatment is tailored to meet the individual needs of affected dogs. In general, initial treatment with an adulticide is followed by a period of rest; administration of a microfilaricide is performed after a period of time. Effective adulticidal treatment may result in pulmonary hypertension, pulmonary thromboembolism, and focal pneumonitis associated with the death of adult heartworms and their embolization to the caudal lobar pulmonary arteries.1,13 The severity of these pulmonary and vascular changes is related to the number and location of heartworms.14 In addition, the level of exercise plays an important role in these changes.15,16 Coughing, depression, anorexia, fever, and signs of congestive heart failure may occur following adulticidal treatment. In some dogs, severe coagulopathy and thromboembolic complications may result in disseminated intravascular coagulopathy or death.1,2,17 Consequently, dogs with very severe disease (ie, caval syndrome [class 4]) are considered poor candidates for routine adulticidal treatment.

The cardiopulmonary consequences of treatment for adult heartworms are well recognized. Likewise, injection site reactions associated with use of melarsomine have been reported.2,18 However, neurologic complications as a result of treatment for heartworms have been rarely reported. In 1 report,2 progressive distal polyneuropathy in a 3-year-old male Setter-type dog that was treated for heartworm disease and secondary disseminated intravascular coagulopathy with thiacytarasamide and long-term administration of heparin was described. In that report, weakness, muscle atrophy, and signs of decreased sensation were noted in the dog 5 weeks after its discharge from the hospital. The cause of the neuropathy was not determined.18

To the authors’ knowledge, neurologic complications associated with IM injection of melarsomine dihydrochloride for treatment for heartworm disease in dogs have not been reported. Although there was no direct evidence of melarsomine-induced spinal cord injury, the close temporal association between drug administration and development of neurologic deficits in all 3 dogs of this report strongly supports this hypothesis.

Melarsomine dihydrochloride is an organic arsenical agent that is highly effective against both sexes of adult Dirofilaria immitis.18-21 The drug was introduced into the United States’ market in September 1995. Predictive formulas used by the manufacturer suggest that > 500,000 dogs have been treated in the United States since the product was launched.5 During the time that the drug has been available commercially, there have been no product formulation changes, and no problems have been associated with any particular component of the formulation. The manufacturer’s recommended treatment regimen for dogs with limited clinicopathologic abnormalities (ie, dogs with class 1 or 2 disease) consists of 2 injections of melarsomine dihydrochloride (2.5 mg/kg [1.13 mg/lb], IM) into the deep epaxial lumbar musculature (1 injection in right and left sides) at an interval of 24 hours.1 Dogs with marked clinical abnormalities (ie, dogs with class 3 disease and certain dogs with class 2 disease) should be treated with a single injection of melarsomine (2.5 mg/kg, IM) that is followed 1 month later by 2 consecutive injections given at an interval of 24 hours.1 This regimen is designed to reduce the severity of thromboembolic complications associated with treatment with this adulticide. Melarsomine is not approved for dogs with caval syndrome (ie, class 4 heartworm disease). For all treated dogs, strict activity restriction is recommended for ≥ 1 month after the first and last injections. The most common adverse reaction associated with the use of melarsomine is irritation at the injection site with resultant signs of pain, swelling, tenderness, and reluctance to move. Sterile granulomas or abscesses may form at the injection site. Injection site reactions may appear clinically as firm nodules and can persist indefinitely.18

In 1996, the manufacturer received reports of 2 cases of paresis or paralysis after administration of melarsomine dihydrochloride, but whether these reactions were related to the use of melarsomine dihydrochloride was not conclusively determined. However, in 1997, standardized questioning of veterinarians and diagnostic evaluation of affected dogs were instituted to better define any possible association between treatment with melarsomine dihydrochloride
and paresis or paralysis. Such neurologic deficits were not reported after use of the drug by practitioners internationally, nor were these signs observed in any of the clinical trials that were conducted prior to registration of the agent in the United States. To date, < 80 reports of paresis or paralysis that developed in dogs after treatment with melarsomine dihydrochloride have been submitted to the manufacturer in the United States. At present, the approved label statement for melarsomine dihydrochloride indicates that paresis or paralysis in dogs after administration may occur rarely.

On the basis of the data received by the manufacturer, various degrees of neurologic deficits have been identified. Dogs may have mild unilateral lameness of the hind limbs or gait abnormalities localized to the hind limbs. More severe deficits may involve proprioceptive deficits and paresis, which may be bilateral in rare instances. These neurologic signs may be difficult to differentiate from soreness associated with the injection site because of their mild nature and often spontaneous resolution. The most commonly reported type of neurologic complication involves marked paresis to paralysis of the hind limbs (as observed in the first and second dogs of this report). In some dogs, paralysis begins unilaterally and progresses toward complete paraplegia in a matter of hours to days. Rarely, neurologic deficits involve all 4 limbs or lead to dementia, coma, and death. In the reports received by the manufacturer, all dogs with neurologic abnormalities in 4 limbs either died or were euthanized.

The pathophysiologic features of this variety of neurologic complications after treatment with melarsomine dihydrochloride are not known. Neurologic signs such as those observed in the first and second dogs of this report suggest epidural spinal cord compression. It is speculated that the compound migrates out of the injection site via fascial planes and causes an ascending inflammation along the nerve roots. The resulting extradural cord compression secondary to extensive inflammation and necrosis of fat surrounding the spinal cord (exemplified by findings in the first dog of this report) could produce various neurologic deficits. Alternatively, introduction of the compound in close proximity to the spinal vascular branches may result in vasospasm or vasculitis that induces ischemia of the corresponding spinal cord segment. Finally, inappropriate injection technique may result in direct contact of the agent with neural tissue. To initiate an inflammatory response as severe as that described in the third dog of this report, the compound may have been injected directly through the dura into the spinal cord.

Recognizing neurologic complications in the early phase after melarsomine dihydrochloride injection can be challenging. Intramuscular injections of melarsomine are known to create swelling of the epaxial muscle mass, especially if the compound is deposited in the fascial planes as a result of improper injection techniques. In treated dogs, severe pain that results in unwillingness to move and lameness could be interpreted as ataxia and needs to be carefully distinguished from neurologic deficits. Signs that indicate neurologic involvement include hind limb ataxia, decreased hind limb conscious proprioception, and decreased motor function. Hind limb paraparesis or paraplegia can occur within hours. Treatment of neurologic deficits associated with melarsomine injection involves supportive care and management of paraparesis or paraplegia; the use of corticosteroids is controversial.

Because the etiology of melarsomine-induced neurologic deficits is still poorly understood, it is difficult to predict long-term prognosis in affected dogs. Marked neurologic abnormalities do not necessarily carry a poor prognosis. The first dog of this report was paraparetic for several weeks before improvement was attained; eventually, that dog recovered completely, as reported by the owner. As observed in the second dog of this report, some affected dogs may incompletely recover. The most severe complications seem to carry a poor prognosis; complications that include deterioration and sudden death are most likely associated with an ascending process in the spinal cord and CNS.

A heightened awareness of proper injection techniques might prevent the occurrence of the majority of neurologic complications. Administration of melarsomine dihydrochloride should be only by deep IM injection into the center of the epaxial musculature in the region of L3 through L5. The drug should be deposited within the muscle belly; superficial or excessively deep injections should be avoided. Alternating sides for injections should be used. It is recommended to use a 23-gauge, 1-in needle for dogs weighing ≤ 10 kg (22 lb) and a 22-gauge, 1.5-in needle for dogs weighing > 10 kg. The utilization of specific needle sizes does not imply that the needle should be inserted to the hub at the injection site. Rather, the middle of the belly of the epaxial muscle group should be targeted. Strict adherence to the manufacturer's guidelines for drug administration is essential. Injection site reactions may develop more frequently because of deposition of the drug into fascial planes, leakage into the subcutaneous tissues, or traumatization of tissues as a result of lack of patient compliance. Although adverse effects are not necessarily associated with the volume of the injection, a general recommendation is to limit injection volumes to < 4 mL/injection site. In some instances, sedation of the dog may be indicated to assure appropriate administration of the drug.

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References


