Effect of arsenical drugs on in vitro vascular responses of pulmonary artery from heartworm-infected dogs

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Objective—To test the effect of thiacetarsamide and melarsomine on vascular responses in isolated rings of pulmonary artery from heartworm-infected dogs.

Animals—18 heartworm-infected dogs.

Procedure—Isolated rings of pulmonary artery from heartworm-infected dogs were randomly treated with thiacetarsamide (30 µg/ml) or melarsomine dihydrochloride (30 µg/ml) for 30 minutes; untreated rings from the same dog served as control. Cumulative dose-response relations to norepinephrine, nitroglycerin, and methacholine were determined.

Results—Norepinephrine-induced constriction was not altered by treatment with either thiacetarsamide or melarsomine. Treatment with thiacetarsamide depressed nitroglycerin-induced relaxation, compared with values for untreated control rings and rings treated with melarsomine. Treatment of rings with thiacetarsamide or melarsomine depressed methacholine-induced relaxation, compared with values for untreated rings. Histologic examination of rings indicated that treatment with thiacetarsamide or melarsomine resulted in loss of endothelial cells.

Conclusion—Endothelial cell loss as a direct drug effect may be responsible for impaired endothelium-dependent relaxation in pulmonary artery from heartworm-infected dogs. Thiacetarsamide appears to have additional effects on vascular smooth muscle, which may explain why fewer complications are observed in dogs treated with melarsomine.

Clinical Relevance—Melarsomine may be a safer drug than thiacetarsamide and could be a better treatment for dogs with heartworm infection. (Am J Vet Res 1997;58:389–393)

A cute pulmonary complications in dogs after arsenical treatment for heartworm infection have been attributed to embolization of dead adult worms, followed by obstruction of pulmonary vessels and ischemic necrosis. However, it is difficult to ascribe all cardiopulmonary complications to embolization; pulmonary reactions that occur hours after treatment are unlikely to be a result of embolization of dead parasites, because worms are not killed by the drug until 6 to 15 days after treatment. Furthermore, side effects have been observed in clinically normal uninfected dogs after thiacetarsamide administration, and respiratory failure associated with pulmonary edema has developed in uninfected cats treated with thiacetarsamide. Such adverse reactions in the absence of parasites suggest that arsenical drugs directly influence arterial tone. Drug-induced alterations in vascular responsiveness may help explain the pathologic effects of arsenical drugs, and may have a role in pulmonary complications associated with treatment.

Since 1980, it has become evident that endothelial cells of all mammalian species have a role in control of vascular smooth muscle tone, and that pulmonary endothelial cells are likewise important in controlling pulmonary vascular resistance. Because endothelial cells release relaxing factors, as well as constricting and hyperpolarizing factors, alteration of endothelial cell behavior can be manifested in several ways. In pulmonary artery from heartworm-infected and noninfected dogs, there is an obligatory role for endothelial cells in the relaxation response to methacholine. The study reported here was conducted to test the hypothesis that the arsenical drugs thiacetarsamide sodium and melarsomine dihydrochloride impair vascular responsiveness in pulmonary artery from heartworm-infected dogs studied in vitro. Vascular responses to the endothelium-dependent vasodilator (methacholine), the endothelium-independent vasodilator (nitroglycerin), and the direct smooth muscle constricting agent (norepinephrine) were measured, in the absence and presence of thiacetarsamide or melarsomine.

Materials and Methods

Animal model—Eighteen random-source mixed-breed dogs, naturally infected with *Dirofilaria immitis*, were obtained from the university’s Laboratory Animal Resources. Presence of heartworm infection was determined by examining venous blood for microfilariae using a slide test, or testing for the adult worm antigen, or both. Heartworm infection was confirmed at necropsy; adult heartworms were counted and sexed, and used in other experiments. All 18 dogs used in these experiments had adult heartworms in the right side of the heart or pulmonary arteries, or both. The mean total number of adult heartworms was 19.8 ± 3.1 with a range of 2 to 74. In these dogs, the number of adult female worms (10.3 ± 10.2) was significantly greater than that of adult male worms (2.3 ± 2.8) (P < .001).