Safety Profile of Moxidectin (ProHeart 6) and Two Oral Heartworm Preventives in Dogs

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ABSTRACT
Medical records of a nationwide veterinary practice (Banfield, the Pet Hospital) were evaluated to determine the incidence of adverse events and particular health problems following administration of the sustained-release injectable heartworm preventive moxidectin (ProHeart 6), 2 oral monthly heartworm preventives, and/or vaccines in dogs. Similar information was reviewed for dogs receiving neither heartworm preventives nor vaccines. The safety profile of these products was comparable. However, ProHeart 6 was associated with a 27% increased risk of mast cell tumor (2.1 per 10,000 exposures), while one of the oral heartworm preventives was associated with a 23% increased risk of death (22.0 per 10,000 exposures). This analysis of medical records for more than 7 million office visits and over 2 million dogs demonstrates the feasibility of using large electronic databases to test hypotheses generated by spontaneous adverse event reports to the United States Food and Drug Administration Center for Veterinary Medicine. In addition, information can be generated on baseline occurrences of certain conditions in a large population of dogs presented to veterinary hospitals across the United States.

INTRODUCTION
ProHeart 6 (moxidectin) was launched by Fort Dodge Animal Health (Overland Park, KS) in June 2001 with an indication to prevent canine heartworm disease caused by Dirofilaria immitis for 6 months and to treat existing larval and adult stages of the canine hookworm Ancylostoma caninum. Since ProHeart 6 was introduced to the market, the United States Food and Drug...
Activity of an injectable, sustained-release formulation of moxidectin administered prophylactically to mixed-breed dogs to prevent infection with *Dirofilaria immitis*

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**Objective**—To test the ability of a single injection of a sustained-release formulation of moxidectin (moxidectin SR) to protect dogs against heartworm infection for 180 days after inoculation with infective third-stage larvae (L3) of *Dirofilaria immitis*.

**Animals**—32 adult mixed-breed dogs.

**Procedure**—Dogs were allocated to 4 groups on the basis of weight and sex. Dogs were injected SC with saline (0.9% NaCl) solution or moxidectin SR at the rate of 0.06, 0.17, or 0.5 mg/kg of body weight (day 0). Each dog was inoculated SC with 50 *D. immitis* L3 180 days later. On days 330 and 331, dogs were euthanized. The heart, lungs, and thoracic cavity were examined, and number and sex of heartworms were determined.

**Results**—A mean of 35.9 heartworms was recovered from untreated control dogs. Fourteen worms were recovered from 1 of 8 dogs given moxidectin SR at the lowest dosage, and none of the dogs in the 2 highest moxidectin treatment groups were infected. Small barely palpable granulomas were detected at injection sites of moxidectin-treated dogs. Frequency and size of granulomas were positively correlated with dose of moxidectin administered.

**Conclusions and Clinical Relevance**—A single dose of moxidectin SR at a dosage as low as 0.17 mg/kg can safely and reliably confer complete protection against infection after challenge-exposure with *D. immitis* L3, and protection lasts for at least 180 days. This mode of prophylactic treatment against infection with heartworms effectively eliminates failure of prophylaxis that results from erratic administration of medications designed for monthly administration. (Am J Vet Res 2001;62:1721–1726)

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*Dirofilaria immitis* can cause debilitating, potentially fatal cardiopulmonary disease in dogs and cats. Infection with *D. immitis* results when mature third-stage larvae (L3) gain entry to a host during feeding by vector mosquitoes. Dogs and cats are at risk when a reservoir of microfilaricemic hosts exists, there is a sufficient population of vector-competent mosquitoes, and there is a sufficient environmental temperature to allow maturation of L3 in these vectors. Because of the mobility of domestic dogs, which are the primary reservoir for infection, and the ubiquity of potential vector mosquitoes, the geographic range of *D. immitis* in North America is extensive. In the preceding 4 decades, it has expanded from the southeastern and gulf-coast states to encompass the Mississippi River basin; states in the mid-Atlantic, northeastern, and southwestern United States; and the southern tier of Canadian provinces.

Since the early 1960s, chemoprophylaxis for infection with heartworms has evolved in stages to reach a situation in which less frequent administration of drugs is required; this is achieved by the use of various dosing formulations created to facilitate administration. The first effective chemoprophylactic developed to prevent *D. immitis* infection of dogs was diethylcarbamazine citrate (DEC). Successful prophylaxis with DEC depends on consistent daily administration begun prior to infection and maintained for 60 days following the period of transmission. Omission of even a few doses can result in failure of protection.

Macrolide endectocides constitute a second generation of chemoprophylactics against infection with heartworms. These compounds are highly active against the tissue-migrating stage (L4) of *D. immitis* and are virtually 100% effective up to the sixth week of infection. The strategy underlying their use as chemoprophylactic agents does not involve maintaining lethal amounts of active compound in tissues or plasma, as is the situation for DEC. Rather, administration is aimed at periodically destroying all developing larvae early during infection prior to their entrance into the circulation and exertion of a pathogenic effect. Ivermectin, the first compound of this class to be licensed as a chemoprophylactic against infection with heartworms, was initially marketed in 1987 as an oral formulation designed to deliver an effective dose when administered at monthly intervals during the transmission season. Other members of this class, including milbemycin oxime, moxidectin, and selamectin, also are effective as oral or topical formulations administered on a monthly basis. Because of their broad spectrum of activity against various stages of heartworm larvae, macrolide endectocides generally offer a safety margin that enables an owner to miss administration of