

Safety of moxidectin in avermectin-sensitive Collies

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Objective—To evaluate the safety of moxidectin administration at doses of 30, 60, and 90 $\mu\text{g}/\text{kg}$ of body weight (10, 20, and 30 times the manufacturer's recommended dose) in avermectin-sensitive Collies.

Animals—24 Collies.

Procedure—Collies with mild to severe reactions to ivermectin challenge (120 mg/kg; 20 times the recommended dose for heartworm prevention) were used. Six replicates of 4 dogs each were formed on the basis of body weight and severity of reaction to ivermectin test dose. Within replicates, each dog was randomly allocated to treatment with oral administration of 30, 60, or 90 μg of moxidectin/kg or was given a comparable volume of placebo tablet formulation. Dogs were observed hourly for the first 8 hours and twice daily thereafter for 1 month for signs of toxicosis.

Results—Signs of toxicosis were not observed in any control group dog throughout the treatment observation period. Likewise, signs of toxicosis were not observed in any dog receiving moxidectin at 30, 60, or 90 $\mu\text{g}/\text{kg}$.

Conclusions and Clinical Relevance—The moxidectin formulation used in the study reported here appears to have a wider margin of safety than ivermectin or milbemycin in avermectin-sensitive Collies. (*Am J Vet Res* 2000;61:482–483)

Results of several clinical studies indicate a wide range of sensitivity to the effects of avermectins among Collies.^{1,4} Although signs of toxicosis have not been observed in Collies treated repeatedly with ivermectin at doses $\leq 60 \mu\text{g}/\text{kg}$ of body weight,⁵ approximately 35% of all Collies treated with 120 μg of ivermectin/kg develop mild to moderate signs of toxicosis.⁶ The consistent and repeatable response of individual sensitive Collies to doses of ivermectin ranging from 120 to 200 $\mu\text{g}/\text{kg}$ has resulted in the development of an avermectin-sensitive Collie model, which has been used to assess the potential for toxicity of avermectin and milbemycin analogues at different doses.^{3,5,7,8} By use of this model, results have indicated that Collies sensitive to the effects of 120 μg of ivermectin/kg (20 times the recommended dose) are similarly affected by milbemycin oxime administered at 10 mg/kg (20 times the manufacturer's recommended dose). From these results it was concluded that ivermectin and milbemycin commer-

cial formulations have similar potential for toxicity at 10 to 20 times the manufacturer's recommended dose for prevention of heartworm infection.⁷ The purpose of the study reported here was to evaluate the safety of moxidectin administration at doses of 30, 60, and 90 $\mu\text{g}/\text{kg}$ of body weight (10, 20, and 30 times the manufacturer's recommended dose) in avermectin-sensitive Collies.

Materials and Methods

Dogs—Twenty-four clinically normal, heartworm-free, ivermectin-sensitive Collies (8 males, 8 females, 8 puppies; age range, 6 months to 8 years) weighing between 10 and 40 kg were used.^a Dogs were screened for heartworm infection before inclusion in the study, which eliminated the possibility of inducing a shock-like reaction with resultant confusion as to the cause of signs of toxicosis after moxidectin or ivermectin administration. All Collies used in the study had previously been identified as sensitive to this class of compounds by observation of mild, moderate, or severe signs of toxicosis after oral administration of 120 μg ivermectin/kg (20 times the label dose [6 $\mu\text{g}/\text{kg}$] recommended for prevention of heartworm infection) at least 2 months prior to the study. To establish a direct dose response comparison of the potential toxicity of moxidectin, dogs were administered a lower (10X), an equivalent (20X), and a higher (30X) multiple oral dose of moxidectin; the recommended moxidectin dose for prevention of heartworm infection is 3 $\mu\text{g}/\text{kg}$. Dogs had fully recovered from the effects of pretrial sensitivity testing before inclusion in the moxidectin study. In a similarly tested group of avermectin-sensitive Collies, plasma ivermectin concentration after a 100 $\mu\text{g}/\text{kg}$ dose was $< 3 \mu\text{g}/\text{ml}$ 21 days after oral administration.⁶ Considering these data, residual effects from pretrial sensitivity testing conducted at least 2 months before moxidectin administration could be discounted.

Each dog was identified by an ear tattoo and housed in a run measuring 4 \times 8 ft with metal walls and a raised, coated, metal screen floor. Facilities exceeded the minimal requirement specified by USDA guidelines. The study protocol was approved by the University Office of Laboratory Animal Care prior to initiation of the trial. Dogs were fed daily via metal feeders, and water was provided ad libitum through automatic waterers.

Procedures—Dogs were acclimated to trial facilities for at least 7 days prior to administration of trial medications. Dogs were given complete physical examinations and weighed on an electronic scale^b on day -1. Within severity of reactions to pretreatment ivermectin sensitivity testing (ie, mild, moderate, severe), all dogs were ranked according to sex and body weight as measured on day -1. Within sex, replicates of 4 adult dogs were formed, beginning with the most sensitive dogs. Puppies were ranked according to sensitivity and weight, but not sex. Within replicates, all dogs were randomly allocated to 1 of 4 treatment groups by drawing lots.

Treatments—Dogs were allocated to 4 oral administration treatment groups: 30 μg of moxidectin/kg, 60 μg of mox-

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idectin/kg, 90 µg of moxidectin/kg, and placebo tablets. The commercial formulation of moxidectin was used. Each dog was dosed with an appropriate number of tablets, and the final tablet was tailored to ensure accuracy of the dose administered. Dosing was accomplished by placing the tablets on the back of the tongue and observing that they were swallowed.

Observations—Each dog was observed daily from day -7 to day 30. In addition, each dog was examined for signs typical of avermectin toxicosis on an hourly basis for the first 8 hours after dosing and every 12 hours thereafter for the duration of the study. Scores were assigned for specific clinical signs,⁵⁻⁸ and scaled 0 to 3 with 0 = clinically normal, 1 = mild reaction, 2 = moderate reaction, and 3 = severe reaction. Clinical signs scored were signs of depression, ataxia, mydriasis, and salivation or drooling.⁵⁻⁸ Each dog was observed at rest in its cage and encouraged to stand and walk at the time of each clinical evaluation and scoring. Pupillary response was evaluated by shining light onto the optic fundus of each eye. Individuals examining dogs and assigning scores were unaware of treatment sequence and dose administered.

On day 31 all dogs were orally administered a liquid dose of ivermectin (120 µg/kg) to reconfirm sensitivity of each dog to avermectin toxicosis. Reactions were again scored and recorded twice daily for 6 days after ivermectin administration.

Statistical analyses—Confidence limits of sample size were calculated for each treatment group as described.⁹ Analyses of results were not performed, because reactions to treatment were not detected.

Results

Signs of toxicosis were not observed in any control group dog throughout the treatment observation period. Similarly, signs of toxicosis were not observed in any dog following moxidectin treatment with 10, 20, or 30 times the manufacturer's recommended dose for heartworm prevention. Although clinical signs of moxidectin toxicosis were not detected, statistical analysis of sample size revealed that 95% confidence intervals (CI) of detecting a reaction were moderately high (for ≤ 30 µg moxidectin/kg, CI = 0 to 0.17; for ≤ 60 µg/kg, CI = 0 to 0.24; for ≤ 90 µg/kg, CI = 0 to 0.44).

After oral administration of ivermectin (120 µg/kg) on day 31, dogs were scored for avermectin toxicosis twice daily. By 24 hours, all dogs had developed signs typical of mild to moderate toxicosis. By 36 hours, all dogs were or had been mildly ataxic or had signs of depression; approximately 50% of the adult dogs also had increased salivation or drooling. Signs of toxicosis had abated in all dogs by day 6 (120 hours after dosing). Mean cumulative scores attained were ataxia, 6.33; depression, 4.97; mydriasis, 0.00; and salivation/drooling, 1.25. The mean cumulative scores were determined by dividing the total cumulative score for each sign from 12 examinations by the number of dogs treated.

Discussion

The results of the study reported here indicate a wide margin of safety for moxidectin when used in

Collies known to be sensitive to the effects of a high dose of ivermectin (120 µg/kg). In a similar study assessing the potential toxicity of milbemycin, ivermectin solution for oral administration and milbemycin oxime (tablet formulation), when administered at 20 times the manufacturer's recommended dose for heartworm prevention, induced similar dose-dependent signs of toxicosis.⁷ Consequently, these 2 compounds appear to have similar margins of safety. Results of the study reported here indicate that moxidectin has a larger therapeutic index (calculated as the dose required to elicit an undesired effect divided by the dose required for the desired effect as heartworm preventative) and safety margin than ivermectin or milbemycin. Signs of toxicosis were not evident in any avermectin-sensitive dog at doses up to 30 times (90 µg/kg) the manufacturer's recommended heartworm preventative dose of moxidectin. These results are consistent with another study that did not detect any signs of moxidectin toxicosis at up to 5 times the heartworm preventative dose.⁸ Despite wide confidence intervals of detecting a rare toxic reaction, these results are valid in comparing the toxicity of moxidectin with that of ivermectin. All dogs had clinical signs of toxicosis after administration of ivermectin at 20 times the heartworm preventative dose before and after administration of moxidectin.

^aWil-O-Lane Kennels, Allegan, Mich.

^bTechnidyne Scale Inc, Howell, NJ.

^cMoxidectin, American Cyanamid Co, Princeton, NJ.

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