Effects of dermal application of 10.0% imidacloprid-0.08% ivermectin in ivermectin-sensitive Collies

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Objective—To evaluate the safety of dermal application of 10.0% imidacloprid-0.08% ivermectin in ivermectin-sensitive Collies at dose rates of 3 to 5 times the proposed maximum therapeutic dose.

Animals—15 Collies (5 males and 10 females) that were confirmed as ivermectin-sensitive dogs.

Procedure—Dogs were assigned to 3 treatment groups (control, 3X, or 5X group) in a randomized block design on the basis of the maximal ivermectin-sensitivity score obtained during preliminary screening. Dogs in groups 3X and 5X were treated at 3 and 5 times the maximum label dose, respectively. Control dogs received an application of an equal volume of a nonmedicated solution. Observation and scoring on all days were conducted to specifically include neurologic signs typical of ivermectin toxicosis, including lethargy, ataxia, abnormal mydriasis, and abnormal salivation.

Results—None of the dogs had clinical abnormalities during the study period.

Conclusions and Clinical Relevance—Analysis of results of this study indicates that dermal application of 10.0% imidacloprid-0.08% ivermectin is safe for use in ivermectin-sensitive Collies at dose rates of 3 or 5 times the proposed maximum therapeutic dose. (*Am J Vet Res* 2004;65:277–278)

Ivermectin, a macrocyclic lactone, has been used widely in veterinary medicine to treat and control parasitic infections. In most dogs, ivermectin can be administered at a dosage of 2.5 mg/kg without evidence of toxic effects.[1,2] However, results of several clinical studies[1,3-5] have indicated a wide range of sensitivity to the effects of avermectins among Collies. Although signs of toxicosis have not been observed in Collies treated repeatedly with ivermectin at dosages of ≤ 60 µg/kg,[6] approximately one-third of all Collies treated at a dosage of 120 µg/kg developed mild to moderate signs of toxicosis.[7] The repeatable and consistent response seen in ivermectin-sensitive Collies to dosages ranging from 120 to 200 µg of ivermectin/kg has resulted in the use of ivermectin-sensitive Collies to determine the potential for toxic effects of avermectin and milbemycin analogues at various dosages.[4,6,8,9]

Ivermectin toxicosis has been observed most commonly in Collies. It has also been reported[10] that Australian Shepherds, Border Collies, Shetland Sheepdogs, and Old English Sheepdogs may also be sensitive to ivermectin. The purpose of the study reported here was to evaluate the safety of dermal application of 10.0% imidacloprid-0.08% ivermectin in ivermectin-sensitive Collies at dosage rates of 3 to 5 times the proposed maximum therapeutic dose.

Materials and Methods

Animals—Fifteen Collies (5 males and 10 females) that were identified as ivermectin-sensitive dogs were used in the study. Dogs ranged from 8 months to 7 years of age and weighed between 16.8 and 37.3 kg. Dogs were selected from a pool of privately owned Collies[a] that were related to known ivermectin-sensitive Collies.

A physical examination and complete hematologic and biochemical analyses were performed to evaluate general health status. All dogs entering the study were considered healthy and had results of hematologic and biochemical analyses that were within reference ranges. Dogs were screened for ivermectin-sensitivity and heartworm-negative status prior to inclusion in the study. Heartworm status was determined by use of the modified Knott's test and an antigen heartworm test.[b]

Each dog was identified with a unique ear tattoo and corresponding number on its collar and cage card. Dogs were housed in 1.83 × 1.37-m, raised stainless-steel dog pens with plastic-coated metal floors and a resting board. Dogs were fed daily by use of separate feed hoppers, and water was provided ad libitum via automatic waterers. Informed consent was obtained from the owners prior to use of the dogs in the study. The study protocol was approved by a university institutional animal care and use committee.

Screening for ivermectin toxicosis—Dogs that had the potential for ivermectin sensitivity were screened by oral administration of ivermectin at the rate of 120 µg/kg. Dogs were observed for ivermectin toxicosis at 0, 2, 4, 6, 8, 12, and 24 hours after the time of oral dosing. Observations were performed within 30 minutes of the scheduled time points. Dogs were observed for clinical signs of ataxia, lethargy, mydriasis, and salivation. Only dogs that had clinical signs of ivermectin toxicosis were selected for subsequent use in the study. Severity of clinical signs was ranked on a scale of 0 to 3 (0, no reaction; 1, mild reaction; 2, moderate reaction; and 3, severe reaction).[5-8] In the study reported here, a minimum washout period of 28 days was allowed between screening for ivermectin toxicosis and the first day of acclimation.

Procedure—Baseline body weights were obtained on the first day of acclimation, and all dogs were weighed 7 days later immediately before application of treatments.

Received July 28, 2003.
Accepted September 29, 2003.
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Accuracy of the scale[c] was verified by use of certified weights before and after each weigh period. During the acclimation period, dogs were observed twice daily to determine evidence of clinical signs of disease, food consumption, and voiding of feces.

Treatments—Dogs were assigned to 3 treatment groups (control, 3X, and 5X groups) in a randomized block design on the basis of the maximal ivermectin-sensitivity score determined during the prestudy screening. Randomization was performed by use of a random-number generator[d] 1 day before treatments were administered.

In this study, the 1X dose was defined as the maximum recommended dosage of imidacloprid-ivermectin solution (26 mg of imidacloprid/kg and 210 µg of ivermectin/kg). On the first day of the study (day 0), 3 dogs received an application of 3 times the dose of test solution (ie, 10.0% imidacloprid-0.08% ivermectin) to screen for unexpected signs of toxicosis. The remaining 12 dogs received an application of an equivalent volume of control solution (baby oil[e]). Clinical signs of toxicosis were not observed in the 3 dogs treated with the 3X dose.

Those 3 dogs were treated again with the test solution (3X dose) on days 28 and 56. In addition to the test solution, those 3 dogs received a small volume of control solution; thus, the total solution applied (3X dose and baby oil) was equivalent to the volume for the 5X group. On day 28, the remaining 12 dogs were equally allocated to the 5X or control groups. Dogs in the 5X group received the test solution at 5 times the maximum recommended dosage on days 28, 56, and 84. Dogs in the control group received an application of an equivalent volume of control solution on days 28, 56, and 84.

Test or control solutions were applied to each dog by separating the hair between the shoulder blades and placing the solution directly on the skin. Care was taken to ensure that the solution remained in contact with the skin and did not splash or run onto the hair. When necessary to accommodate the volume, solution was also applied to the dorsal area of each dog. Investigators wore latex gloves when applying solutions. Gloves were changed between dogs.

Observations—Because the same volume of solution was applied to each dog, investigators were not aware of the treatment group of the dogs. Clinical observations were made on the days of administration (days 0, 28, 56, and 84) at approximately 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours after application. On the remaining days of the study, dogs were observed twice daily. Observations and scoring on all days specifically included neurologic signs typical of ivermectin toxicosis, including lethargy, ataxia, abnormal mydriasis, and abnormal salivation. Scores were assigned for specific clinical signs on a scale of 0 to 3 (0, clinically normal; 1, mild reaction; 2, moderate reaction; and 3, severe reaction),[5-8] similar to the scoring performed during the prestudy screening.

Results

None of the dogs had clinical abnormalities during the study period. There were no adverse reactions in ivermectin-sensitive dogs resulting from dermal application of 10.0% imidacloprid-0.08% ivermectin at rates of 3 or 5 times the proposed maximum therapeutic dose. Statistical analysis of the clinical observations was not conducted because we did not detect adverse reactions to treatment.

Discussion

It is known that certain breeds of dogs, especially Collies, are sensitive to the toxic effects of high doses of macrocyclic lactones. It has been documented that this is attributable to a mutation of the MDR1 gene, which causes premature termination of p-glycoprotein synthesis and results in a defective blood-brain barrier.[11] Sensitivity to macrocyclic lactones is a dose-related phenomenon, and the severity of signs varies among ivermectin-sensitive Collies.[4]

Because of the potential sensitivity of certain breeds, it is required that any new formulation is clinically tested in ivermectin-sensitive Collies before the compound can be approved for use. In the study reported here, 3 or 5 times the recommended therapeutic dose of 10% imidacloprid-0.08% ivermectin was topically applied to ivermectin-sensitive Collies. These dogs had clinical signs of toxicosis when orally administered ivermectin at a rate of 120 µg/kg. Thus, all dogs used in this study probably had mutations of the MDR1 gene. The fact that none of them had clinical signs of toxicosis after dermal application of 10% imidacloprid-0.08% ivermectin would suggest that the plasma concentrations obtained after dermal application are not high enough to induce clinical signs of toxicosis in ivermectin-sensitive Collies.

[a]Wil-O-Lane Kennels, Allegan, Mich.
[b]Dirochek, Synbiotics Corp, San Diego, Calif.
[c]Vet-Tec 300, Technidyne Scale Inc, Howell, NJ.
[d]Microsoft Excel, Microsoft Corp, Redmond, Wash.
[e]Baby oil (mineral oil and fragrance), Johnson & Johnson Consumer Products Co, Skillman, NJ.

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