

## References

- Beal, M. W., R. H. Poppenga, W. J. Birdsall, and D. Hughes. 1999. Respiratory failure attributable to moxidectin intoxication in a dog. *Journal of the American Veterinary Medical Association* **215**:1813-1817.  
**Abstract:** Moxidectin is a macrocyclic lactone of the milbemycin family used in veterinary medicine for the prevention and treatment of endoparasitism in horses and dogs. Moxidectin intoxication can cause various abnormal neurologic manifestations, including ataxia, weakness, lethargy, stupor, coma, seizures, and respiratory arrest. Intensive supportive care may be necessary for a dog to recover from moxidectin intoxication
- Bensignor, E., and D. N. Carlotti. 1999. Management of demodicosis in dogs. *Point Veterinaire* **30**:67-72.  
**Abstract:** When presented with demodicosis in dogs, considerations should include the case history (juvenile demodicosis or adult-onset demodicosis), clinical signs (localised or generalised demodicosis, dry or purulent demodicosis), in order to establish a prognosis. The principal agents used for canine demodicosis are: amitraz, ivermectin, milbemycin oxime, moxidectin: it is advisable to know the dosage, method of administration and side-effects of these. A treatment follow-up by skin scrapings is suggested (6 photos, 1 figure, 4 boxes, 1 table, 46 references)
- Beuing, G., and G. Erhardt. 2002. Influences on the frequency of estimated Collie Eye Anomaly (CEA) in Collies and Shelties in preventive examination-results of a breeding club organisation. *Kleintierpraxis* **47**:407-413.  
**Abstract:** Veterinary examination results from 1.612 Shelties and 2.514 Collies, as demanded in a program to reduce hereditary eye diseases, were analysed in a data set of in total 15.022 Collies and 6.209 Shelties of a German breeding club in respect to the total frequency of Collie Eye Anomaly (CEA) and possible effects on the frequency. 19.7 % of the Shelties and 22.6 % of the Collies were described as affected. Neither gender nor coat colour showed an effect on the CEA-frequency. Additionally, there was no trend over the last ten years to a higher or lower incidence. In contrast, there were significant differences in the CEA diagnosis depending on the dogs age at examination. Especially Collies examined up to an age of 10 weeks showed a significant higher frequency of CEA than the older dogs. The effect of the age at examination could be explained by a gonormal-rate of 52.9 % in Shelties and 62.5 % in Collies. Additionally there were significant differences in the CEA diagnosis depending on the level of the veterinarians practice. The frequency of CEA ranged between 3.5 % (veterinarians without further education in ophthalmology) and 34.7 % (members of DOK and AKVO). This shows the necessity within a breeding program to standardize the national and international frame conditions for CEA diagnostics
- Bishop, B. F., C. I. Bruce, N. A. Evans, A. C. Goudie, K. A. E. Gratton, S. P. Gibson, M. S. Pacey, D. A. Perry, N. D. A. Walshe, and M. J. Witty. 2000. Selamectin: a novel broad-spectrum endectocide for dogs and cats. *Veterinary Parasitology*

91:163-176.

**Abstract:** Selamectin, 25-cyclohexyl-25-de(1-methylpropyl)-5-deoxy-22,23-dihydro-5-(hydroxyimino)-avermectin B1 monosaccharide, is a novel endectocide with a unique combination of efficacy and safety in dogs and cats following both oral and topical administration. The compound is active against fleas and ticks, intestinal hookworms and ascarids, and immature heartworms. Also it is well tolerated at higher dosages than 22,23-dihydroavermectin B1a (DHAVM) or milbemycin oxime in Collies, which is a breed known to exhibit idiosyncratic sensitivity to avermectins. (C) 2000 Elsevier Science B.V. All rights reserved

Boissevain, I. 2003. Domitor unsuitable for collies? Tijdschrift Voor Diergeneeskunde **128**:316.

Boy, M. G., R. H. Six, C. A. Thomas, M. J. Novotny, C. D. Smothers, T. G. Rowan, and A. D. Jernigan. 2000. Efficacy and safety of selamectin against fleas and heartworms in dogs and cats presented as veterinary patients in North America. *Veterinary Parasitology* **91**:233-250.

**Abstract:** A series of randomized, controlled, masked field studies was conducted to assess the efficacy and safety of selamectin in the treatment of flea infestations on dogs and cats, and in the prevention of heartworm infection in dogs. In addition, observations were made on the beneficial effect of selamectin treatment on dogs and cats showing signs of flea allergy dermatitis (FAD). In all studies selamectin was applied topically, once per month, in unit doses providing a minimum dosage of 6 mg kg<sup>-1</sup>. Dogs and cats with naturally occurring flea infestations, some of which also had signs associated with FAD, were assigned randomly to receive three months of topical treatment with selamectin (220 dogs, 189 cats) or a positive-control product (dogs: fenthion, n=81; cats: pyrethrins, n=66). Selamectin was administered on days 0, 30, and 60. Day 0 was defined as the day that the animal first received treatment. Flea burdens were assessed by flea comb counts and clinical evaluations of FAD were performed before treatment, and on days 14, 30, 60, and 90. On days 30, 60, and 90, mean flea counts in selamectin-treated dogs were reduced by 92.1, 99.0, and 99.8%, and mean flea counts in fenthion-treated dogs were reduced by 81.5, 86.8, and 86.1%, respectively, compared with day 0 counts. Also, on days 30, 60, and 90, mean flea counts in selamectin-treated cats were reduced by 92.5, 98.3, and 99.3%, and mean flea counts in pyrethrin-treated cats were reduced by 66.4, 73.9, and 81.3%, respectively, compared with day 0 counts. Selamectin also was beneficial in alleviating signs in dogs and cats diagnosed clinically with FAD. A total of 397 dogs free of adult heartworm infection from four heartworm-endemic areas of the USA were allocated randomly to six months of treatment with selamectin (n=298) or ivermectin (n=99). Selamectin achieved a heartworm prevention rate of 100%, with all dogs testing negative for microfilariae and adult heartworm antigen on days 180 and 300. Selamectin was administered to a total of 673 dogs and 347 cats having an age range of 6 weeks to 19 years (3954 doses). The animals included 19 purebred or crossbred Collies (Bearded, Border, and unspecified). There were no serious adverse events. Results of these studies indicated that selamectin was highly effective in the control of flea infestations in dogs and cats

without the need for simultaneous treatment of the environment or of in-contact animals and also was beneficial in alleviating signs associated with FAD. Selamectin also was 100% effective in preventing the development of canine heartworms and was safe for topical use in dogs and cats. (C) 2000 Elsevier Science B.V. All rights reserved

Clark, J. N., J. D. Pulliam, and C. P. Daurio. 1992. Safety Study of A Beef-Based Chewable Tablet Formulation of Ivermectin and Pyrantel Pamoate in Growing Dogs, Pups, and Breeding Adult Dogs. *American Journal of Veterinary Research* **53**:608-612.

**Abstract:** To determine the safety of a new combination of ivermectin and pyrantel (as pamoate salt) in a novel beef-based chewable tablet formulation, 3 tolerance trials were conducted and included growing dogs, pups, and breeding adult dogs. Growing dogs, given the combination orally for 5 consecutive days at recommended dosages (5 mg of pyrantel/kg of body weight, 6- $\mu$ -g of ivermectin/kg) or at twice the pyrantel dosage in combination with the recommended dosage of ivermectin, had no adverse effects. The combination also was administered to 6-week-old pups at 1, 3, and 5 times the recommended dose on 3 successive days for 3 times in 1 month. Compared with age-matched controls, treatment had no effect on clinical status, growth rate, or gross or histologic features. Breeding male and female dogs given the combination at 3 times the recommended dose for extended periods had no adverse effects, and prevalence of abnormalities in the offspring was not greater than that in nonmedicated controls

Dejaham, C., and C. J. Henry. 1995. Treatment of Canine Sarcoptic Mange Using Milbemycin Oxime. *Canadian Veterinary Journal-Revue Veterinaire Canadienne* **36**:42-43.

Fassler, P. E., W. J. Tranquilli, A. J. Paul, M. D. Soll, J. A. Dipietro, and K. S. Todd. 1991. Evaluation of the Safety of Ivermectin Administered in A Beef-Based Formulation to Ivermectin-Sensitive Collies. *Journal of the American Veterinary Medical Association* **199**:457-460.

**Abstract:** Twenty-four Collies sensitive to the toxic effects of ivermectin, when administered at high dosages, were studied to evaluate the effects of repeated monthly treatment with an ivermectin beef-based formulation at amounts up to 10 times the dosage recommended for heartworm prevention in dogs. Collies were treated 3 times at 30-day intervals at rates of 12, 36, or 60- $\mu$ -g of ivermectin/kg of body weight, or with vehicle. Complete physical and neurologic examinations were performed on all dogs prior to the first treatment and after the final treatment. Clinical observations and ivermectin reaction scores were recorded daily for each dog throughout the study. Clinical or neurologic signs characteristic of ivermectin toxicosis were not observed for any dog during the study. Single episodes of vomiting were recorded for 2 vehicle-treated dogs and 2 dogs treated with ivermectin at 12- $\mu$ -g/kg from 6 to 21 days after treatment. At the end of the study, all dogs were challenge-exposed with ivermectin at 120- $\mu$ -g/kg to reconfirm their sensitivity to this class of compounds. All dogs developed signs

typical of ivermectin toxicosis during the subsequent 48- to 72-hour period. Results of this study demonstrated that ivermectin can be administered repeatedly without adverse effects at rates up to 60- $\mu$ -g/kg (10 times the recommended use level) to Collies known to be sensitive to this drug

Hadrick, M. K., S. E. Bunch, and J. N. Kornegay. 1995. Ivermectin Toxicosis in 2 Australian Shepherds. *Journal of the American Veterinary Medical Association* **206**:1147-1150.

Hernandez, J., and S. Blot. 2001. Loperamide poisoning in a Collie. *Point Veterinaire* **32**:58-+.

**Abstract:** A Collie was presented with howling, partial loss of consciousness and bradycardia, following administration of loperamide for treatment for gastroenteritis. After administration of naloxone, the specific morphinomimetic antidote, there was rapid and complete cessation of symptoms. Loperamide is a potentially toxic substance in Collies and similar breeds and its use is therefore contra-indicated in these dogs

Hopper, K., J. Aldrich, and S. C. Haskins. 2002. Ivermectin toxicity in 17 Collies. *Journal of Veterinary Internal Medicine* **16**:89-94.

**Abstract:** Ivermectin is widely used in veterinary medicine as an anthelmintic and generally has a wide margin of safety, but Collies are prone to ivermectin toxicity. Two groups of Collies were presented to the University of California Veterinary Medical Teaching Hospital (VMTH) with ivermectin toxicity. The medical records of the 2 groups of Collies were reviewed retrospectively. Group I comprised 5 adult Collies that received at least 400  $\mu$ g/kg ivermectin PO and were presented to the VMTH 3 hours after intoxication. These Collies showed marked clinical signs on presentation. Three of these dogs required mechanical ventilation and were euthanized for financial reasons; the remaining 2 dogs were comatose but recovered in 5-7 days. Group II was comprised of 12 adult Collies presented to the VMTH 2 days (n = 10) and 5 days (n = 2) after subcutaneous injection of 200-250  $\mu$ g/kg ivermectin. These animals showed greater variation in severity of illness among individuals; 5 animals progressed to stupor or coma, whereas 4 animals remained ambulatory. Most of these dogs' clinical signs deteriorated from the day of intoxication until approximately day 6, from which time they showed gradual but steady improvement. All of the Collies in this group survived, but it took 3 weeks for most of them to recover. Collies suffering from ivermectin toxicity can have a severe and prolonged clinical course requiring intensive nursing care. Respiratory, cardiovascular, and nutritional support may all be required. With appropriate care, however, the prognosis for complete recovery is good

Kim, J. S., and E. C. Crichlow. 1995. Clinical Signs of Ivermectin Toxicity and the Efficacy of Antigabaergic Convulsants As Antidotes for Ivermectin Poisoning in Epileptic Chickens. *Veterinary and Human Toxicology* **37**:122-126.

**Abstract:** The clinical signs of ivermectin toxicity were determined in 6 groups of 10 epileptic and 8 nonepileptic chickens for 72 h after dosing with sc Injections of

5.0, 7.5, 10.0, 12.5 or 15.0 mg ivermectin/kg bw. At the 5.0 mg/kg dose, mild diarrhea developed 4 h post-dosing and lasted until the end of the 72-h monitoring period. With higher doses of ivermectin body weight, egg production and feed and water consumption were markedly reduced. Severe diarrhea, mydriasis, bradypnea, ataxia, sedation coma and death occurred with the highest dose of ivermectin. No differences in the signs of ivermectin toxicity were observed between epileptic and non-epileptic chickens. To assess the efficacy of the antiGABAergic convulsants, methyl-beta carboline-carboxylate (beta-CCM), picrotoxin and pentylentetrazol (PTZ), as antidotes for ivermectin toxicity, 8 epileptic and 6 non-epileptic chickens/treatment group were given dosages of each convulsant which previously induced convulsions in 50% (ED(50)) and again in 100% (ED(100)) of treated chickens. These convulsants were given 6 h after dosing with 15.0 mg ivermectin/kg. The ED(100) dosages of picrotoxin and PTZ alleviated mydriasis and sedation, but did not reduce the diarrhea. The ED(50) dose convulsants were not effective in reducing or alleviating ivermectin toxicity, nor was alleviation of any sign of ivermectin toxicity obtained with any dosage of beta-CCM. Although the dosages of these antiGABAergic convulsants used normally produced convulsions in epileptic and non-epileptic chickens, no convulsions were observed in chickens with ivermectin toxicity. These findings suggest that some of the signs from high ivermectin dosages in epileptic and non-epileptic chickens can be alleviated by treating with picrotoxin and PTZ. These compounds may serve as antidotes in the treatment of ivermectin toxicity

Kitagawa, H., Y. Sasaki, K. Ishihara, and K. Ishizako. 1988. Plasma Milbemycin-D Concentrations in Collies, Shelties and Japanese Mongrel Dogs. *Japanese Journal of Veterinary Science* **50**:1184-1191.

Lowe, J. K., A. V. Kukekova, E. F. Kirkness, M. C. Langlois, G. D. Aguirre, G. M. Acland, and E. A. Ostrander. 2003. Linkage mapping of the primary disease locus for collie eye anomaly. *Genomics* **82**:86-95.

**Abstract:** Collie eye anomaly (cea) is a hereditary ocular disorder affecting development of the choroid and sclera segregating in several breeds of dog, including rough, smooth, and Border collies and Australian shepherds. The disease is reminiscent of the choroidal hypoplasia phenotype observed in humans in conjunction with craniofacial or renal abnormalities. In dogs, however, the clinical phenotype can vary significantly; many dogs exhibit no obvious clinical consequences and retain apparently normal vision throughout life, while severely affected animals develop secondary retinal detachment, intraocular hemorrhage, and blindness. We report genetic studies establishing that the primary cea phenotype, choroidal hypoplasia, segregates as an autosomal recessive trait with nearly 100% penetrance. We further report linkage mapping of the primary cea locus to a 3.9-cM region of canine chromosome 37 (LOD = 22.17 at theta = 0.076), in a region corresponding to human chromosome 2q35. These results suggest the presence of a developmental regulatory gene important in ocular embryogenesis, with potential implications for other disorders of ocular vascularization. (C) 2003 Elsevier Science (USA). All rights reserved

Mealey, K. L., S. A. Bentjen, J. M. Gay, and G. H. Cantor. 2001. Ivermectin sensitivity in collies is associated with a deletion mutation of the *mdr1* gene. *Pharmacogenetics* **11**:727-733.

**Abstract:** A subpopulation of collie dogs is extremely sensitive to neurotoxicity induced by ivermectin. The aim of this study was to determine the mechanistic basis for this phenomenon. The multi-drug-resistance gene (*mdr1*) encodes a large transmembrane protein, P-glycoprotein (P-gp), that is an integral part of the blood-brain barrier. P-gp functions as a drug-transport pump at the blood-brain barrier, transporting a variety of drugs from the brain back into the blood. Since ivermectin is a substrate for P-gp, we hypothesized that ivermectin-sensitive collies had altered *mdr1* expression compared with unaffected collies. We report a deletion mutation of the *mdr1* gene that is associated with ivermectin sensitivity. The 4-bp deletion results in a frame shift, generating several stop codons that prematurely terminate P-gp synthesis. Dogs that are homozygous for the deletion mutation display the ivermectin-sensitive phenotype, while those that are homozygous normal or heterozygous do not display increased sensitivity to ivermectin. *Pharmacogenetics* 11:727-733 (C) 2001 Lippincott Williams & Wilkins

Mealey, K. L., S. A. Bentjen, and D. K. Waiting. 2002. Frequency of the mutant MDR1 allele associated with ivermectin sensitivity in a sample population of Collies from the northwestern United States. *American Journal of Veterinary Research* **63**:479-481.

**Abstract:** Objective To determine the frequency of the MDR1 gene mutation (polymorphism) associated with ivermectin sensitivity in a sample population of Collies in Washington and Idaho. Animals-40 healthy client-owned Collies. Procedure A blood sample (8 ml) was collected from each dog and used for RNA extraction. Reverse transcriptase was used to generate MDR1 cDNA. Polymerase chain reaction (PCR) primers were designed to amplify a 1,061-base pair region of the MDR1 gene. The PCR products were sequenced to determine whether the Collies had 0, 1, or 2 mutant alleles, Pedigrees of some dogs were available for analysis to determine relatedness of affected dogs, Results-Of the 40 Collies, 9 (22%) were homozygous for the normal allele (normal), 17 (42%) were heterozygous (carrier), and 14 (35%) were homozygous for the mutant allele (affected). Pedigree analysis revealed that some, but not all, affected dogs were related to each other within the 4 most recent generations. Conclusions and Clinical Relevance-A high percentage of a sample population of Collies in Washington and Idaho are affected or carriers of the mutant MDR1 allele associated with ivermectin sensitivity. A similar frequency of this mutation may be detected in dogs from other geographic areas. Pharmacologic treatment with ivermectin, loperamide, vincristine, and other drugs that are substrates of P-glycoprotein, the MDR1 gene product, may result in neurologic toxicosis in a high percentage of Collies

Mealey, K. L., N. C. Northrup, and S. A. Bentjen. 2003. Increased toxicity of P-glycoprotein-substrate chemotherapeutic agents in a dog with the MDR1 deletion mutation associated with ivermectin sensitivity. *Journal of the American*

Veterinary Medical Association **223**:1453-+.

**Abstract:** Collies and Australian Shepherds with the MDR1 deletion mutation associated with ivermectin sensitivity may also be more susceptible than expected to the toxic effects of P-glycoprotein-substrate chemotherapeutic agents. The pharmacokinetics and pharmacodynamics of P-glycoprotein-substrate drugs may be altered in dogs with functional P-glycoprotein defects

Meiser, H., H. W. Hagedorn, M. Majzoub, and R. Schulz. 2001. Detection of levamisole and ivermectin in organ samples from a perished Collie. *Berliner und Munchener Tierarztliche Wochenschrift* **114**:210-215.

**Abstract:** A collie, known for its breed-dependent adverse reaction to ivermectin, was without any clinical signs. The dog was prophylactically treated with 3 mg/kg KG (s.c.) of levamisole. Within 15 minutes, the dog showed convulsions, vomitus, and dyspnoe, and perished 2.5 hours after injection of the drugs. The pathological findings were not informative as to the cause of death, and with regard to the adverse reactions, additional application of ivermectin was not excluded. Therefore, organ samples were submitted for toxicological analysis of both levamisole and ivermectin. For detection of levamisole and ivermectin, modified GC/MS and HPLC procedures were developed. Concentrations up to 535 mug levamisole and up to 26 ng ivermectin were found per g tissue. Both analytical methods are sensitive enough to detect these drugs after application of low doses. This study elucidates that combination of low-dosed ivermectin and levamisole is no recommendable means against adverse effects of ivermectin, with respect to collies. Moreover, the synergistic effects of ivermectin and levamisole suggests the same drug incompatibility in other dog breeds and animal species

Mueller, R. S., K. Hastie, and S. V. Bettenay. 1999. Daily oral ivermectin for treatment of generalised demodicosis in 23 dogs. *Australian Veterinary Practitioner* **29**:132-+.

**Abstract:** Twenty-seven dogs with generalised demodicosis were treated with daily oral ivermectin at a dose of 300mcg/kg body weight. Treatment was continued for two months after the first negative skin scraping. Twenty-three dogs responded to treatment and were in remission for longer than 12 months. One intact bitch relapsed several times during oestrus. In two dogs, ivermectin was discontinued due to side effects. One dog failed to improve on therapy. Two dogs relapsed 13 months and one dog 18 months after discontinuing ivermectin. Oral daily ivermectin at 300mcg/kg body weight was considered useful in the treatment of generalised demodicosis

Mueller, R. S., and S. V. Bettenay. 1999. A proposed new therapeutic protocol for the treatment of canine mange with ivermectin. *Journal of the American Animal Hospital Association* **35**:77-80.

**Abstract:** Ivermectin was used orally for the treatment of generalized demodicosis or scabies in 222 dogs. The dose was increased gradually from 50 mu g/kg body weight on day one, 100 mu g/kg body weight on day two, 150 mu g/kg body weight on day three, 200 mu g/kg body weight on day four, to the final

dose of 300  $\mu$ g/kg body weight on day five. This dose was continued daily until resolution for demodicosis and given four times at seven-day intervals for scabies. Two patients developed clinical ivermectin toxicity after two and 10 days, respectively, and recovered once the drug was discontinued. A gradual increase of the ivermectin dose into the therapeutic range and thorough monitoring of patients during treatment are recommended when using this drug to treat patients with generalized demodicosis or scabies

Nelson, O. L., E. Carsten, S. A. Bentjen, and K. L. Mealey. 2003. Ivermectin toxicity in an Australian shepherd dog with the MDR1 mutation associated with ivermectin sensitivity in collies. *Journal of Veterinary Internal Medicine* **17**:354-356.

Novotny, M. J., M. J. Krautmann, J. C. Ehrhart, C. S. Godin, E. I. Evans, J. W. McCall, F. Sun, T. G. Rowan, and A. D. Jernigan. 2000. Safety of selamectin in dogs. *Veterinary Parasitology* **91**:377-391.

**Abstract:** Selamectin is a broad-spectrum avermectin endectocide for treatment and control of canine parasites. The objective of these studies was to evaluate the clinical safety of selamectin for topical use in dogs 6 weeks of age and older, including breeding animals, avermectin-sensitive Collies, and heartworm-positive animals. The margin of safety was evaluated in Beagles, which were 6 weeks old at study initiation. Reproductive, heartworm-positive, and oral safety studies were conducted in mature Beagles. Safety in Collies was evaluated in avermectin-sensitive, adult rough-coated Collies. Studies were designed to measure the safety of selamectin at the recommended dosage range of 6-12 mg kg<sup>-1</sup> of body weight. Endpoints included clinical examinations, clinical pathology, gross and microscopic pathology, and reproductive indices. Selected variables in the margin of safety and reproductive safety studies were subjected to statistical analyses. Pups received large doses of selamectin at the beginning of the margin of safety study when they were 6 weeks of age and at their lowest body weight, yet displayed no clinical or pathologic evidence of toxicosis. Similarly, selamectin had no adverse effects on reproduction in adult male and female dogs. There were no adverse effects in avermectin-sensitive Collies or in heartworm-positive dogs. Oral administration of the topical formulation caused no adverse effects. Selamectin is safe for topical use on dogs at the recommended minimum dosage of 6 mg kg<sup>-1</sup> (6-12 mg kg<sup>-1</sup>) monthly starting at 6 weeks of age, and including dogs of reproducing age, avermectin-sensitive Collies, and heartworm-positive dogs. (C) 2000 Elsevier Science B.V. All rights reserved

Paradis, M. 1998. Ivermectin in small animal dermatology. Part I. Pharmacology and toxicology. *Compendium on Continuing Education for the Practicing Veterinarian* **20**:193-+.

**Abstract:** Although the only Food and Drug Administration-approved use of ivermectin in small animals is prevention of heartworm infection, large-animal formulations of ivermectin are widely used to control various parasites in dogs and cats. This article, which is Part 1 of a two-part presentation, discusses the pharmacology and toxicology of ivermectin. Part II will discuss extralabel uses of ivermectin in small animal dermatology. Ivermectin is a GABA agonist. Because

mammals have GABA receptors only in the central nervous system, ivermectin is safe for mammals unless it crosses the blood-brain barrier (as it apparently does in many collies and related herding-breed dogs). Although the dose used for heartworm prevention (6  $\mu$ g/kg orally once a month) is safe for these dogs, they should not receive higher doses of ivermectin. When using large-animal formulations of ivermectin for small animals veterinarians should take care to ensure accurate dosing. As with any extralabel drug use, the veterinarian should obtain informed consent from the animal's owner before initiating treatment

Paul, A. J., W. J. Tranquilli, R. L. Seward, K. S. Todd, and J. A. Dipietro. 1987. Clinical Observations in Collies Given Ivermectin Orally. *American Journal of Veterinary Research* **48**:684-685.

Paul, A. J., W. J. Tranquilli, K. S. Todd, D. H. Wallace, and M. Soll. 1991. Evaluating the Safety of Administering High-Doses of A Chewable Ivermectin Tablet to Collies. *Veterinary Medicine* **86**:623-625.

Paul, A. J., W. J. Tranquilli, and D. E. Hutchens. 2000. Safety of moxidectin in avermectin-sensitive collies. *American Journal of Veterinary Research* **61**:482-483.

**Abstract:** Objective-To evaluate the safety of moxidectin administration at doses of 30, 60, and 90  $\mu$ g/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  $\mu$ g 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  $\mu$ g/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

Paul, A. J., D. E. Hutchens, L. D. Firkins, and C. M. Keehan. 2004. Effects of dermal application of 10.0% imidacloprid-0.08% ivermectin in ivermectin-sensitive Collies. *American Journal of Veterinary Research* **65**:277-278.

**Abstract:** 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

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- Roulet, A., O. Puel, S. Gesta, J. F. Lepage, M. Drag, M. Soll, M. Alvinerie, and T. Pineau. 2003. MDR1-deficient genotype in Collie dogs hypersensitive to the P-glycoprotein substrate ivermectin. *European Journal of Pharmacology* **460**:85-91. **Abstract:** Multidrug resistance (MDR) phenotypes in cancer cells are associated with overexpression of the drug carrier P-glycoprotein. The antiparasitic drug ivermectin, one of its substrates, abnormally accumulates in the brain of transgenic mice lacking the P-glycoprotein, resulting in neurotoxicity. Similarly, an enhanced sensitivity to ivermectin has been reported in certain dogs of the Collie breed. To explore the basis of this phenotype, we analyzed the canine P-glycoprotein-encoding MDR1 gene, and we report the first characterization of the cDNA for wild-type (Beagle) P-glycoprotein. The corresponding transcripts from ivermectin-sensitive Collies revealed a homozygous 4-bp exonic deletion. We established, by genetic testings, that the MDR1 frame shift is predictable. Accordingly, no P-glycoprotein was detected in the homozygote-deficient dogs. In conclusion, we characterized a unique case of naturally occurring gene invalidation. This provides a putative novel model that remains to be exploited in the field of human therapeutics and that might significantly affect tissue distribution and drug bioavailability studies. (C) 2003 Elsevier Science B.V. All rights reserved
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- Sasaki, Y., H. Kitagawa, Y. Kajita, H. Okachi, and K. Ishihara. 1986. Clinical-Application of Milbemycin-D As A Prophylactic Agent Against *Dirofilaria-Immitis* Infection in Dogs - Sensitivity for the Drug in Rough-Coated Collies. *Japanese Journal of Veterinary Science* **48**:1253-1256.
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Sasaki, Y., H. Kitagawa, S. Murase, and K. Ishihara. 1990. Susceptibility of Rough-Coated Collies to Milbemycin Oxime. *Japanese Journal of Veterinary Science* **52**:1269-1271.

Shanks, D. J., T. L. Mctier, T. G. Rowan, P. Watson, C. A. Thomas, D. D. Bowman, J. A. Hair, G. Pengo, C. Genchi, C. D. Smothers, D. G. Smith, and A. D. Jernigan. 2000. The efficacy of selamectin in the treatment of naturally acquired aural infestations of *Otodectes cynotis* on dogs and cats. *Veterinary Parasitology* **91**:283-290.

**Abstract:** The efficacy of a novel avermectin, selamectin, was evaluated against naturally acquired aural infestations of *Otodectes cynotis* on dogs and cats. In four controlled and masked studies conducted in the USA and Europe, animals were allocated randomly to treatment with either selamectin at a minimum dosage of 6 mg kg<sup>-1</sup> (range, 6-12.5 mg kg<sup>-1</sup>) or the vehicle only from the commercial formulation of selamectin (negative control). Treatments were administered topically in a single spot to the skin of each animal's back at the base of the neck in front of the scapulae. Cats were treated on day 0 only, and dogs were treated either on day 0 only or on days 0 and 30. The ears of dogs were examined otoscopically on day 14 for the presence of viable mites, Mite counts were conducted on day 30 for animals that had received one dose and on day 60 for animals that had received two doses. Percentage reductions in geometric mean mite counts for selamectin treatment compared with the vehicle were 100% for all animals on all count days. Analysis of variance, confirmed by Savage Scores, showed that  $\ln(\text{mite count}+1)$  values were significantly ( $P$  less than or equal to 0.0015) lower for selamectin than for the vehicle for all animals on all count days. Thus, selamectin administered topically at a minimum dosage of 6 mg kg<sup>-1</sup> was safe and 100% effective against naturally acquired aural infestations of *O. cynotis* in dogs and cats after a single dose or after two doses administered 1 month apart. (C) 2000 Elsevier Science B.V. All rights reserved

Shipstone, M., R. Mueller, and S. Bettenay. 1997. Milbemycin oxime as a treatment for canine scabies. *Australian Veterinary Practitioner* **27**:170-173.

**Abstract:** Twenty-three dogs with naturally acquired infections of *Sarcoptes scabiei* that were identified via positive superficial skin scrapings were treated with milbemycin oxime at a mean dose of 2mg/kg weekly for 4 weeks. Twenty of the dogs received a total of 4 doses, 3 received a total of 5 doses. At the revisit after 4 weeks 15/23 (65%) had complete resolution of clinical signs. Those animals that had residual pruritus or clinical signs compatible with *Sarcoptes* infestation were treated with additional doses of milbemycin oxime. This led to clinical resolution in 23/23 of the treated animals

Shoop, W. L., H. Mrozik, and M. H. Fisher. 1995. Structure and Activity of Avermectins and Milbemycins in Animal Health. *Veterinary Parasitology* **59**:139-156.

**Abstract:** The avermectins and, to a lesser extent, the milbemycins, have revolutionized antiparasitic and antipest control over the last decade. Both avermectins and milbemycins have macrocyclic lactone structures that are superimposable, they are produced by the same genus of soil dwelling organisms,

they have the same mode of action, they exert this action against the same nematode/acarine/insect spectrum of targets, and they show the same mechanism-based toxicity in mammals. Reports suggesting that milbemycins have a different mode of action from avermectins with implications that there will be no mutual resistance to the groups have been shown to be false. Contributing to the belief that there were differences in mode of action between the two groups are the vague definitions of resistance presently in use which rely on the ability of the parasite to survive treatment at the manufacturer's recommended use level. More appropriately, drug resistance should be defined as 'a change in gene frequency of a population, produced by drug selection, which renders the minimal, effective dosage previously used to kill a defined portion (e.g. 95%) of the population no longer equally effective'. This type of definition would allow us to detect changes in susceptibility of a population earlier and is essential when comparing different chemicals to determine if there is mutual resistance to them. It is concluded that much effort has been expended by pharmaceutical, government, and academic scientists searching for broad-spectrum second generation avermectin and milbemycin products, but none has exceeded the original avermectin in any fundamental way. The newer avermectin and milbemycin compounds that have appeared claim niches in the market place based on emphasis of certain narrow parts of the overall spectrum. Consequently, there are no second generation avermectins and milbemycins at present and all newer compounds from this mode of action class are viewed as siblings of the first generation

Tranquilli, W. J., A. J. Paul, and R. L. Seward. 1989. Ivermectin Plasma-Concentrations in Collies Sensitive to Ivermectin-Induced Toxicosis. *American Journal of Veterinary Research* **50**:769-770.

Tranquilli, W. J., A. J. Paul, and K. S. Todd. 1991. Assessment of Toxicosis Induced by High-Dose Administration of Milbemycin Oxime in Collies. *American Journal of Veterinary Research* **52**:1170-1177.

**Abstract:** Fifteen Collies, previously having mild reactions to ivermectin challenge (120- $\mu$ -g/kg of body weight; 20 times the recommended dosage level), were studied to evaluate the effects of milbemycin oxime administration at 5 and 10 mg/kg (10 and 20 times the manufacturer's recommended dosage). Five replicates, comprising 3 dogs each, were formed on the basis of body weight. Within replicates, each dog was randomly allocated to treatment with 5 or 10 mg of milbemycin/kg or served as a untreated control. Dogs were examined repeatedly for signs of toxicosis for 4 days after treatment and daily thereafter. Two of 5 dogs treated at 5 mg/kg (10x) developed signs of mild depression on the day of treatment, but were normal 24 hours after treatment. All 5 dogs treated at 10 mg/kg (20x) developed signs of mild depression and ataxia by 6 hours. Signs persisted for 24 hours in 3 dogs. Two of these dogs also had mydriasis, whereas 3 salivated excessively. All dogs recovered completely by day 2 after treatment. The results of this study demonstrated that Collies sensitive to the effects of 120- $\mu$ -g of ivermectin (20x)/kg show similar sensitivity to the effects of milbemycin oxime administered at 10 mg/kg (20x). We conclude that ivermectin and milbemycin commercial formulations have similar margins of safety and that

milbemycin toxicosis appears to be dose-dependent in Collies with a demonstrated sensitivity to ivermectin

- Wallin-Hakanson, B., N. Wallin-Hakanson, and A. Hedhammar. 2000. Collie eye anomaly in the rough collie in Sweden: genetic transmission and influence on offspring vitality. *Journal of Small Animal Practice* **41**:254-258.  
**Abstract:** Between 1989 and 1997, 8204 rough collies were examined for collie eye anomaly (CEA) at up to 10 weeks of age. All dogs were positively identified and the results were registered under the Swedish Kennel Club genetic health programme. A significant decrease in litter size occurred if one of two affected parents had coloboma (3.8 pups) compared with litters from two chorioretinal dysplasia- (CRD-) affected collies (5.2 pups) or litters by two normal collies (5.0 pups), indicating an influence of the coloboma genotype on offspring vitality. The prevalence of CRD in pups from normal x normal matings and CRD x CRD matings was significantly different from that expected under simple autosomal recessive inheritance (43 per cent versus 25 per cent and 85 per cent versus 100 per cent), The results are compatible with polygenic inheritance but not with simple autosomal recessive inheritance. CRD prevalence in offspring of CRD x coloboma matings was significantly lower than in pups of CRD x CRD matings, reflecting effects of the coloboma genotype on vitality. These results have important implications for breeding programmes and the genetic control of CEA
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Ivermectin: Dangerous for dogs. *Tijdschrift Voor Diergeneeskunde* **121**:446-448.  
**Abstract:** Given that the National Poisons Control Centre is regularly contacted about ivermectin intoxication in dogs, we would like to emphasize the warning of Nap et al. (4) that the use of ivermectin in companion animals, and especially Collies and Bobtails, is not without risk. For this reason, the 'off-label' use of ivermectin for these dogs is not advised. There is currently a wide choice of selective drugs for the treatment of canine parasitic diseases