

IVERMECTIN & THE MACROCYCLIC LACTONES

SALVATION OR CURSE?

Why these drugs may not be every dog's best defense against heartworm and other parasites

When prevention and treatment can be worse than the disease

What veterinary research found that the drug companies couldn't

by Leslie Crane Rugg

Any pet owner visiting a veterinary clinic in the last 15 years will have been mesmerized by the prominently displayed poster or model of an animal heart. This organ, reproduced in vivid, gory, technical detail, shows the hostile takeover by *dirofilaria immitis*, more commonly known and feared as heartworms.

Tragic histories abound of once happy, carefree dogs, infected by mosquito bites, now reduced to radically sick shadows of their former active lives. Within their ravaged bodies, adult heartworms infested major organs, restricted blood flow in the arteries of the lungs, and produced thousands of larvae or *microfilaria*. Vigorous, healthy animals became weak vessels for proliferating spaghetti-like strands of voracious adult parasites; at the same time the larvae were marking time until another mosquito bit their host and carried them to yet another innocent victim to start the process all over again.

The only **cure** for adult heartworms has been drugs in the arsenic family. Although the poison itself vacates a dog's body within 24 hours, the dead worms often take two months or more to pass. Too often, a dog is so affected by the disease that the sheer mass of dead worms or the dog's own systemic immune reaction to the worms can hasten the end of the dog's life. The best chance for survival while under treatment for the disease has been to limit the animal's activity severely for at least one month. Only then will the dead worms decompose more safely and be efficiently absorbed by the immune system. Otherwise, the dog may die.

Which is worse? The disease or the treatment?

For the thousands of years since dogs have existed, the heartworm cycle has repeated itself, striking dogs initially in warm weather climates, eventually spreading worldwide. Only the cooler regions, where temperatures never climbed above 57° F, were spared.

Then the cycle was broken. As veterinary medicine progressed, a heartworm **preventive** was developed. Diethylcarbamazine (DEC) was given daily to dogs during mosquito season. However, if any of the daily doses were missed, the dog could still become infected with heartworms, and the potentially lethal, arsenic treatment was prescribed.

In 1983, the first major advancement in prevention was introduced. A leading pharmaceutical company, Merck AgVet, promoted its newest, most comprehensive anti-parasiticide. Originally a product for horses and secondarily formulated for cattle, its developers thought it might be applied to dogs as well. The product contained ivermectin

– the first macrocyclic lactone - similar in human medicine to erythromycin but without the antibiotic effect.

During the first few years of usage, a popular assumption was mistakenly made that these large animal formulations of ivermectin could be successfully given to dogs. Even though the off-label doses (inappropriate to species, size, and weight) were too high and too strong for dogs, few adverse incidents were reported. However, as off-label use became more widespread, a disturbing pattern emerged, particularly noticeable in one breed. Although many Collies were given high doses without the occurrence of toxic reaction, some Collies developed severe clinical signs, often resulting in death.

Toxicosis typically occurred within 8-24 hours. Initial signs included dilated pupils, apparent blindness, and staggering. In some cases, these symptoms did not worsen and resolved without further distress. Moderate clinical signs included those mentioned and progressed to include lack of coordination and lateral recumbence (inability to stand). Severe signs included all of the aforementioned and led to coma and/or death, usually due to respiratory arrest.

University studies investigated this phenomenon of erratic sensitivity, and results indicated that the pattern of toxicity was seen in families of Collies; clearly some sort of genetic link existed. Armed with the knowledge that extremely low doses of ivermectin were effective as a heartworm preventive, Merck AgVet, now known as Merial, Ltd., ordered further studies to ensure that a dog formulation would be safe for sensitive Collies as well. HEARTGARD® , containing ivermectin at a dose of 6 micrograms (mcg) per kilogram (kg) of body weight, was heralded as the most effective heartworm

preventive available. It completely eliminated migrating larval forms of heartworms when dosage instructions were properly followed.

Over time, other drug companies generated competitive heartworm preventives, each one with a different member of the macrocyclic lactone family as its active ingredient. INTERCEPTOR® contains milbemycin oxime. PROHEART® contains moxidectin. REVOLUTION® contains selamectin.

Pet owners and veterinarians alike heaved grateful sighs of relief. A simple diagnostic blood test and effective preventives finally provided the answer to the debilitating disease and to the toxic cure. A monthly tablet taken orally could truly eradicate the scourge of heartworm.

And it did, saving countless numbers of dogs from misery and death...except for the occasions when dogs received toxic doses of the preventives for which there is no known cure.

Was the question going to be asked again? Was the disease or the prevention worse?

The American Board of Veterinary Toxicology (ABVT) has recognized a series of clinical signs related to ivermectin toxicity including “mydriasis (pupil dilation), depression, coma, tremors, ataxia (loss of coordination), stupor, emesis (vomiting), drooling, and death.” Merial Ltd. itself also reported in product information other adverse reactions such as “lethargy, anorexia (loss of appetite), diarrhea, convulsions (seizures), paresis (paralysis), recumbency (immobile leaning/lying down), and excitability.”

Merial technical support veterinarian, Dr. Doug Carithers, attributes greater than 99% of reported canine toxic reactions to the result of individuals administering large

animal formulations in an off-label manner. Extremely rarely, he says, have such reactions resulted when farm dogs ingest the feces of cattle, sheep or horses that have also been given ivermectin as an anti-parasiticide. Exposure to livestock-sized doses, even when fully metabolized by farm animals, may be strong enough to produce side effects in dogs that ranged from mild to lethal, from abnormal dilation of eye pupils to death.

Dr. Carithers states, “Merial has never had a documented case of ivermectin toxicosis from appropriately administered HEARTGARD® dosages. Adverse reactions typically occur when people give the wrong dose or misuse large animal formulations for small animals. It’s like taking a whole bottle of aspirins instead of the recommended one or two.”

But problematic, unexplainable cases of toxic reactions persist, in which individual dogs of certain breeds don’t tolerate doses specified by some as safe. The breeds most affected are closely related herding breeds. Along with the Collie, anecdotal statistics claim Australian Shepherds, Bearded Collies, Border Collies, Old English Sheepdogs, and Shetland Sheepdogs as those breeds at high risk for ivermectin toxicity. Similar suspicious events have added a variety of other breeds to this list from Whippets to Irish Water Spaniels to Bullmastiffs. Many of these breeds were ones already documented in veterinary journals as either proven or suspected to be hypersensitive to or intolerant of an assortment of medications including particular anesthetics and wormers.

According to ABVT, the contrast between a sensitive breed such as the Collie and a tolerant breed such as the Beagle (the standard breed used in most animal trials) reveals the extraordinarily low dosage that elicits signs of ivermectin toxicity. Collies are

affected at a mere “0.1-0.2 mg/kg or 15-30 times the therapeutic dose” whereas Beagles only begin to be affected at “2.5-40 mg/kg or greater than 200 times the therapeutic dose.” Collie sensitivity appears consistently with other macrocyclic lactones as well. In studies done by Drs. William Tranquilli, Alan Paul and Kenneth Todd at the University of Illinois, mild signs of toxicity to milbemycin oxime were seen in Collies at 10 times the therapeutic dose for INTERCEPTOR®.

Despite the fact that drug companies responsible for mectin-based products had complied with Food and Drug Administration (FDA) regulations for adequate testing to certify safe usage by all breeds, the FDA further mandated that product labels caution about certain breeds’ extreme sensitivity. For example, the HEARTGARD® label warns: “Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels...”

The relationship between pharmaceutical companies and the FDA attempts to unite science with legal and ethical requirements. Given the limitations of scientific technology at the time when HEARTGARD®, for example, was tested and approved, Carithers indicates that Merial researchers “had recognized the breed-specific sensitivity and even realized that it was a familial trait. But our techniques weren’t advanced enough to identify the specific genetic cause.” Even so, the company was convinced of the safety of its product, if only because of the wide margin between a recommended dose and any adverse reactions caused at higher doses.

Today, when pet owners search for definitive information on their computers, they read at Merial’s website: “Tablets have a wide margin of safety for all sizes and breeds of dogs. It is approved for use in puppies as young as 6 weeks, small dogs

regardless of weight, pregnant or breeding bitches, stud dogs, and Collies.” With FDA permission, Merial has removed any cautionary information. Yet ivermectin is only considered to be safe and approved for dogs when given the appropriate dose of the appropriate formulation. Otherwise, some Collies and some dogs of other breeds will continue to be adversely affected.

So what is at the root of this sensitivity? Why can some dogs tolerate the drug, even at larger than recommended doses, while others cannot? Is it the drug or is it the dog? And how can a pet owner or a veterinarian know before a tragic mistake is made?

Until Dr. Katrina Mealey at Washington State University’s College of Veterinary Medicine became fascinated by this puzzle, all that veterinary medical experts had figured out was the possible existence of an autosomal recessive trait (a particular matched set of genes from both parents) that might cause Collies and perhaps a few other breeds to be “idiosyncratically sensitive to the drug,” as summarized in the most current veterinary source, Clinical Neurology in Small Animals – Localization, Diagnosis and Treatment (Ithaca, International Veterinary Information Service, 2002). Editor K.G. Braund records the source of toxicosis as “perhaps associated with the blood-brain barrier acting as an ineffective ivermectin barrier,” thereby setting off a potential chain reaction of central nervous system dysfunction. He concludes, “It has been reported 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.”

In the course of her research, begun only a few years ago with those minimal clues, Dr. Mealey has succeeded in pinpointing the mechanism and its gene that cause

Collies and potentially other breeds to react so erratically when administered ivermectin. Solid medical evidence validates the presence or absence of a single protein, *P-glycoprotein* (P-gp). When P-gp is present and functional, ivermectin cannot remain in the brain, and a dog can tolerate the heartworm preventive. When P-gp is absent, ivermectin penetrates the brain and stays there, thus setting in motion the circumstances for toxic reaction. Dr. Carithers describes the difference by contrasting a river in motion with a stagnant swamp.

Both Mealey and Carithers agree that ivermectin is safe for Collies at the six mcg per kg **heartworm preventive** dose, administered once a month. Mealey adds, “Even a large number of sensitive Collies do not show signs of toxicity at that dosage.” The problem occurs, says Mealey, when “you get to doses - usually in the range of 100-300 mcg per kg - used for **treating** mange, heartworm larvae, or endoparasites such as lungworms.”

Prevention vs. treatment is the key. Ivermectin is not approved by the FDA for these particular treatments, but the drug is often used for those purposes because of its effectiveness on those and other parasites. Like Carithers, Mealey also cites owner or veterinary miscalculation in diluting the more concentrated strength of ivermectin suitable for horses or cattle as causes for toxicosis.

Dr. Mealey is one of the new generation of veterinary researchers who considers herself fortunate to have been in the right place at the right time. She had always wanted to be a veterinarian but went to pharmacy school first, which, she says “was extremely valuable to me as a veterinarian.” Although she originally planned on going into small animal private practice, she decided to pursue a different career path. Taking her

internship and residency in small animal internal medicine and clinical pharmacology, she also had to complete a Ph.D. program. “I found myself intrigued by unanswered questions such as what causes a certain disease, why does one breed seem predisposed to a certain disease process, why is this drug toxic in some animals but not in others, etc.” Academic research provided Mealey with the setting that allowed her to seek these vital answers.

On a personal level, Mealey had always had a love for Collies, fostered by her parents’ choice of pet. In fact, one family Collie did get infected with heartworm in an area not considered endemic for the disease. At Texas A&M University, where she completed her veterinary residencies and Ph.D. program, a Collie was the university mascot. Whether a conscious or serendipitous convergence of interests, Mealey and Collies and heartworm seemed fated to interact.

As a young veterinary student at Colorado State University learning about oncology (cancer), Mealey first became interested in P-gp as a chemotherapy resistance pump. Her initial interest was further fanned by a veterinary oncologist, Dr. Jeff Klausner, during her internship at the University of Minnesota. Finally, at Texas A&M, she dived into researching P-gp’s role in causing chemotherapeutic drug resistance in cancer cells and received two National Institute of Health (NIH) grants to continue her investigation.

Having read that P-gp was a critical component of the blood-brain barrier, Mealey began to realize its connection with ivermectin, she says, “when I came across an article about ivermectin being a substrate (a substance that is acted on) for P-gp. Previous research suggested how P-gp might be responsible for chemotherapeutic failure in the

treatment of human tumors because the protein pumped chemotherapeutic agents out of tumor cells, protecting them from exposure to potentially toxic agents. It seemed to me that if such a protein were absent at the blood-brain barrier in certain animals – for example, Collies - these animals might be more susceptible to neurologic effects of drugs – for example, ivermectin. I came up with the hypothesis that ivermectin-sensitive Collies lack functional P-gp at the blood brain barrier.”

For five years, she expected to come upon a report in a scientific or veterinary journal that already proved her point, but nothing surfaced. In a race against time and the possibility of competition, Mealey completed her preliminary work and published the results, thanks to the support she received from her WSU department chair, Dr. Richard DeBowes, and to the molecular biology skills of her research lab technician, Steve Bentjen. Says Mealey, “We were able to do the initial study on a very small budget, most of which came from a Washington State University faculty start-up package.”

As the research bore out, a strong heritability factor does play into ivermectin sensitivity. Dr. Mealey found three categories within the study’s Collie population. One group inherits the gene that produces P-gp from both parents; these dogs will not be affected by ivermectin and will not pass on a gene for sensitivity. Another group inherits the gene for P-gp from one parent but not both; these dogs are also not ivermectin-sensitive but do carry the gene for sensitivity. If bred to a dog with that same inheritance factor, the next-generation puppies will be sensitive to ivermectin. The final group does not inherit the gene that produces P-gp from either parent; these dogs will definitely be affected by ivermectin. Extrapolated to the general Collie population, that results in only

23% being non-sensitive non-carriers. 35% will prove to be sensitive and react toxically, and 42% will be carriers, perpetuating the problem.

Mealey says, “I expected to find that collies had a quantitative difference in P-gp expression at the blood brain barrier, but they really have a qualitative difference. The protein itself is defective. We were surprised at how frequently we found the mutant gene in the collie populations we have studied so far.”

The blood samples used for Dr. Mealey’s study came from Collies whose owners are members of Washington’s Inland Empire Collie Club. One of the club members, Dorothy Newkirk, conducts research in dairy cow mastitis at WSU’s College of Veterinary Medicine and just happens to work in the same building as Dr. Mealey. Mealey approached Newkirk, explained the research she was doing, and asked permission to take blood samples from Newkirk’s Collies to help perfect the study’s testing technique.

As Newkirk puts it, “Of course I agreed. My dogs provided skin cells from the insides of their cheeks and blood for DNA testing. I also told my breed club about the research and Dr. Mealey’s need for a larger sample to test. The members were very enthusiastic about helping and provided 42 dogs. Because some of the dogs were related, Dr. Mealey was also able to figure out the transmission of this gene.” Dr. Mealey adds, “The Inland Empire Collie Club’s donation of blood samples and pedigrees was invaluable in helping us determine the prevalence of the mutation in Collies.”

The results of the research were particularly helpful to Newkirk. Now she has learned that one of her Collies possesses the gene and can tolerate ivermectin. Two of her other Collies don’t; they will never be given an ivermectin product. In the past, Newkirk

had used heartworm medication only when traveling south to California or back east. It was her custom to treat with a non-ivermectin product for a month before and after the trips. She says, “My vet and I agreed on not tempting fate.”

In the future, the risk of tempting fate will be over for all Collies. Dr. Mealey is in the process of developing and licensing a screening test kit that will be accessible to all pet owners through their veterinarians. Mealey estimates the process will take a couple of years in order to create a reliable and accurate test, market and distribute it. In the meantime, she is busy gathering more data on other suspected breeds, working with several breed organizations. Recently, she reports having attended an agility trial. “I sampled Shelties, Border Collies and Australian Shepherds - this time using cheek swabs - and was overwhelmed by the response. I received an incredible amount of cooperation from the individual dog owners. No one said no!” And why would they when Dr. Mealey has solved the puzzle of ivermectin sensitivity, at least for Collies?

By her own estimation, much more work needs to be done. She would like to screen large populations of Collies, Australian Shepherds, Border Collies, and Shelties, but at this point funding has not yet been obtained. From her initial start-up grant, some funds have been reserved for specific cases such as investigating a non-Collie breed that has experienced ivermectin toxicity and a Collie (or other breed) that has experienced toxicity to other drugs.

While the results of her initial research have focused on ivermectin-sensitivity, P-gp is the key agent, responsible for creating the circumstance for drug sensitivity and related toxic reactions. “Any drug – not just ivermectin - crossing the blood-brain barrier in the absence of P-gp,” warns Dr. Mealey, “can cause problems.” For example,

anecdotal reports of Collies dying after being treated with Imodium have begun to surface. Defective P-gp could again be the culprit. Mealey is prepared to investigate loperamide (Imodium), chemotherapy agents such as doxorubicin, vincristine and vinblastine, digoxin (digitalis used as a heart medication), and other ivermectin-like wormers such as milbemycin, moxidectin and selamectin in her pursuit to provide answers for seemingly unexplainable questions.

From the corporate pharmaceutical viewpoint, Merial can only benefit from Katrina Mealey's findings. Dr. Carithers applauds her efforts, giving her credit for providing "a better understanding of the genetic basis we knew existed but couldn't isolate." He credits her accomplishment as a breakthrough not only valuable to Collies but to veterinary medicine. For those dogs of any breed that prove to be P-gp deficient, choosing appropriate drugs across the veterinary spectrum will now be possible. No longer will the treatment or the preventive be worse than the disease.

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