

Health Matters - MDR1

What is MDR1?

Readers of the Shetland Sheepdog breed notes in the UK dog papers over the last 30 years may recall references to our breed suffering adverse reactions to an anti-parasitic drug called Ivermectin. Research started in the 1980s has discovered that some breeds of dog, mainly, but not exclusively, varieties of collie, are unable to produce a protein (P-glycoprotein 1 or Pgp for short) which is essential for pumping drugs and toxins out of the central nervous system. As a result the drugs accumulate and produce neurological symptoms ranging from tremors, loss of appetite, and excessive salivation, through to blindness and coma, and sometimes death. Ivermectin is just one of several drugs which it is now known can cause this reaction, and the condition is generally referred to as MDR1 because the protein Pgp is also called the Multi-Drug Resistance protein.

MDR1 is not a disease, and as long as a dog with the sensitivity is not exposed to any of the dangerous drugs then it will not be at risk of a reaction.

Which are the problem drugs?

The problem drugs are broken down into three categories:

Class A

Drugs which should **NOT** be given to dogs with MDR1 sensitivity

Ivermectin related substances (Anti parasites): (Diapec®, Ecomectin®, Equimax®, Eqvalan®, Ivomec®, Noromectin®, Paramectin®, Qualimec®, Sumex®, Virbamec®)

Doramectine substances "Anti parasites": (Dectomax®)

Loperamide substances "anti diarrhoeal ": (Imodium®)

Moxidectine substances "Anti Parasites" (Cydectin®, Equest®)

Flagyl (Metronidazole®)

Class B

Drugs which should only be used under strict veterinary supervision

Cytostatics "Chemotherapy": (Vinblastine, Vincristine, Doxorubicine, Paclitaxel, Docetaxel, Methotrexat, Vincristine)

Immunosuppressive: (Cyclosporine A)

Heart glycosides: (Digoxine, ethyldigoxine)

Opioids: (Morphium)

Antiarrhythmics: (Verapamil, Diltiazem, Chinidine)

Antiemetics: (Ondansetron, Domperidon, Metoclopramide)

Antibiotics: (Sparfloxacin, Grepafloxacin, Erythromycin)

Antihistamines: (Ebastin)

Glucocorticoid: (Dexamethason)

Acepromazine: (tranquilizer and pre-anesthetic agent)

* **Butorphanol** : (analgesic and pre-anesthetic agent) *

Class C

Drugs which should only be given in the strict application form and dosage

Selamectin (Stronghold®), Milbemax® and Advocate®

* In dogs with the MDR1 mutation, acepromazine and butorphanol tend to cause more profound and prolonged sedation in dogs . It is recommended to reduce the dose by 25% in dogs which are carriers for the MDR1 mutation and by 30-50% in dogs which are positive for the MDR1 mutation.

Is it inherited?

The inability to produce the Pgp protein is a genetic mutation, and therefore it is an inherited characteristic. The gene responsible is what is known as an autosomal recessive – that means it can occur in either dogs or bitches, and a defective copy of the gene has to be passed down from both parents for a dog to be fully susceptible to the problem drugs. However, a dog inheriting one defective copy of the gene from a parent will be a carrier, and even carriers may show sensitivity to avermectins and other drugs.

How likely is it that my Sheltie has the MDR1 mutation?

Most of the work on the MDR1 mutation has been done in the USA where the incidence is quite low, and it was not until 2008 that a study looked at the prevalence of the mutation in the UK dog population. The sample sizes were quite small, but of the 49 Shetland Sheepdogs tested 6 of them (12%) were positive for the mutation - i.e. would be hypersensitive to the problem drugs, 23 (47%) were carriers and 20 (41%) were normal. Further investigation is required to confirm the findings, but these initial results suggest that more than half of UK Shelties could experience a reaction, albeit minor, if one of the problem drugs were administered.

How do I know if my dog could be affected?

There is a DNA test available which will tell you whether your Sheltie has two defective copies of the gene which means it is sensitive to the problem drugs, or whether it is a carrier which could pass the sensitivity on to its progeny. The test can be done at any age. All laboratories accept either blood samples, which should be taken by a veterinary surgeon, or cheek swabs which can be taken by the owner. Your dog will need some form of permanent identification, normally a microchip. There are currently four laboratories which offer the test:

- Laboklin Europe – website <http://www.laboklin.co.uk/laboklin/showGeneticTest.jsp?testID=8032> (cost £72.50 at the time of writing)
- Animal Genetics UK – website <http://www.animalgenetics.eu/Canine/Canine-disease/canine-MDR1-Multi-drug-Resistance.html> (cost £32 or Euros 40)
- Genomia – website <http://www.genomia.cz/en/test/mdr1/> (cost Euros 58.33 for one test or 54.17 for 5 or more tests)
- Veterinary Medical Pharmacology Lab (USA) - <http://www.vetmed.wsu.edu/depts-VCPL/> (cost US\$70 for 1 test or US\$60 for 5 or more)

Full instructions and application forms for submitting samples can be found on the above websites.

Why should I worry about MDR1?

Many of the drugs on the MDR1 danger list (Class A) are ones which are commonly prescribed by veterinary surgeons, for example Metronidazole is frequently given for tummy upsets. Also some of the drugs on the “use with care” list, such as Stronghold® or Advocate® , are now available over the counter and no veterinary consultation is necessary, so extreme care needs to be taken in their application and dosage.

What should I do?

1. Most veterinary surgeons are aware of MDR1 and will not prescribe any of the dangerous drugs to susceptible breeds like Shelties. However it will do no harm to raise their awareness of the problem. Whenever one of your own dogs needs medication, check with your vet to ensure that they do not administer one of the above drugs unless the dog has been DNA tested for MDR1 and proven not to carry the defective gene. There are effective alternative treatments which can be given instead.
2. Have your Sheltie DNA tested if you want to be 100% certain of its genetic status for MDR1. This is important if you intend to use the dog for breeding purposes, as it will give you an idea of the likely genetic status of any puppies your Sheltie produces. The results of the test can be submitted to the Kennel Club for inclusion in the quarterly Breed Records Supplement and publication on their website <http://www.the-kennel-club.org.uk/services/public/mateselect/test/Default.aspx>
3. Before mating a bitch, check the Kennel Club Health Test Results website to find out if a stud dog you are interested in using has been DNA tested for MDR1. Again this will help you in determining the likelihood of producing puppies with multi drug resistance.
4. When you sell a puppy or adult Sheltie, make sure you tell the purchaser about MDR1 and suggest that they let their veterinary surgeon know that Shelties can be hypersensitive to certain drugs. Include this information in your puppy sales information packs, along with the usual feeding and other advice.
5. Be aware that a hypersensitive dog can suffer a reaction if it is exposed to a problem drug from any source, not just having one prescribed by a vet. Farmers routinely treat their livestock with anti-parasitic medications, and it has been known for a dog which ate grass in a cow pasture to die as a result of this. Take care when exercising your Sheltie on farm land and try to prevent it from ingesting any grass or dung in these areas.

Where can I find out more about MDR1?

Further information can be found on a number of websites, but a useful starting point is Washington State University where much of the research was carried out and the genetic test developed: <http://www.vetmed.wsu.edu/depts-VCPL/index.aspx>

The Rough Collie Breed Council also produced a booklet on the subject, and this can be downloaded from: <http://www.roughcolliebreedcouncil.co.uk/rcbcmrleaflet.pdf>