

Fact Sheet - Multi-drug Resistance in Collies (MDR1)

It is now widely accepted that the Collie breeds (Rough Collies, Smooth Collies, Shetland Sheepdogs and Border Collies) appear to be hypersensitive to certain drug compounds.

The problem first came to light in 1983 when several Collies died from Ivermectin poisoning and, since then, the veterinary profession has accepted this drug should never be given to Collies. More recently a Rough Collie died from eating horse faeces (Ivermectin is used for worming horses and any excess drug passes out with their faeces).

Researchers have since found that approximately 60% of Rough and Smooth Collies appear to be susceptible not only to Ivermectin, but to a wide range of other drug substances. The MDR1 (multi-drug resistant) gene is responsible for enabling the body's blood-brain barrier to function normally. In healthy dogs the brain and central nervous system are protected by the 'blood-brain barrier', which prevents high drug concentration from circulating in the blood stream.

However, in MDR1-affected dogs the function of the blood-brain barrier is compromised allowing certain drug compounds to leak into major organs like the liver, or into the central nervous system, causing toxic reactions and even death. Symptoms include excessive salivation, ataxia, blindness, coma, and respiratory problems.

An **MDR1 Normal dog** (+/+) receives a healthy MDR1 gene from each of its parents and can therefore only pass on healthy genes to its offspring. The healthy + genes are dominant and such animals do not exhibit drug toxicity.

A **'Carrier'** (+/-) is a dog that has received a normal [dominant] MDR1 gene from one of its parents, and a defective gene [recessive] from the other parent which is 'carried' by the dominant + gene. Please bear in mind that a carrier can pass either a normal or a defective genes onto its offspring resulting in approximately 50% of the puppies inheriting a defective MDR1 gene. Theoretically the 'carrier' animal should not be susceptible to drug toxicity but unfortunately the dominance of the MDR1 + gene has been found to be incomplete as some 'carrier' animals also appear to be susceptible to high doses of those drugs that cause problems in MDR1-affected dogs, that is, those with two defective MDR1 genes (-/-).

An **Affected** dog (-/-) receives a defective or mutant MDR1 gene from both its parents, so such dogs are double recessive and will display toxic reactions to a wide range of drug compounds (see list below). In 2007 a genetic test was made available for MDR1 and so it is extremely important that breeders try and use Normal (+/+) dogs in their breeding programmes so as to eliminate the defective MDR1 genes as soon as possible.

If you have an MDR1-affected Collie (-/-) or carrier (+/-) you could be in a position to save its life by providing your veterinary surgeon with a copy of its MDR1 Certificate and the list of drug compounds that your Collie should never be given. Of those vets who have already been asked to put MDR1 test results onto a Collie's records, all have been aware of the Ivermectin problem but have had no idea about the broad spectrum of drug compounds that can severely threaten an MDR1-affected dog.

Case Study 1

Although full details are not known, a fatality occurred in 2010 in a collie (in France) that was given the drug Metaclopramide (other names - Reglan, Emeprid). This is used as an anti-emetic (i.e. anti sickness drug) for example in cases of gastro enteritis. The MDR1 status of this bitch was unknown but litter mates were affected and carriers (i.e. -/- and +/-). In all probability, she was also affected or a carrier.

The bitch was also given a sedative before going to the vet as she was not a good traveller. This sedative - Vetranquil (other names - Acepromazine), has a similar action to metaclopramide in decreasing dopamine levels in the brain and probably resulted in an overdose of sedation. Extreme caution is advised when sedating collies for any procedure as dosage may need to be reduced for *both* MDR1 carriers and those affected - i.e. -/- and +/-.

Case Study 2

A fatality was caused by a drug called metronidazole which may have significant risk as it is used in treatment of bowel and sexually transmitted infections and could be used by breeders worried about falling fertility in their bitches, especially if they have already had failing litters. One trade name for this is Flagyl.

The table here shows three classes of drug compounds: Class A includes substances that have been proven to pass through the blood-brain barrier in MDR1-affected dogs and cause problems; Class B lists substances which have shown interactions in animal tests, whereas Class C substances can be given without problems, even to affected dogs:

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Class A	<p>DO NOT USE in dogs with MDR1 defect (-/-)</p> <p><i>Affected dogs carry two mutant MDR1 genes and can therefore only pass on a mutant gene to their offspring. Affected dogs will experience drug toxicity following normal doses of certain drugs, listed here</i></p>	<p>Anti-Parasitic Drugs <u>Ivermectine substances:</u> Diapec®, Ecomectin®, Equimax®, Eqvalan®, Ivomec®, Noromectin®, Paramectin®, Qualimec®, Sumex® & Virbamec®</p> <p><u>Doramectine substances:</u> Dectomax®</p> <p><u>Moxidectine substances:</u> Cydectin® & Equest®</p> <p>(EU scientists commonly find residues of the above drugs in animal products - milk, cows, sheep, pigs & salmon).</p> <p><u>Loperamide substances:</u> Immodium® [anti-diarrhoeal]</p> <p><u>Metronidazole substances:</u> Flagyl</p>
Class B	<p>Interactions have been shown. Use only under close supervision of your vet</p>	<p><u>Cytostatics:</u>(Cancer treatment) Vinblastine, Doxorubicine, Paclitaxel, Docetaxel, Methotrexat & Vincristine</p> <p><u>Glucocorticoids</u> (Steroids commonly used to treat auto-immune diseases): Dexamethason</p> <p><u>Immuno-suppressives:</u> Cyclosporine A</p> <p><u>Heart glycosides:</u> Digoxine & Methyldigoxine</p> <p><u>Antiarrhythmics:</u> Verapamil, Diltiazem & Chinidine [Heart problems]</p> <p><u>Pain control:</u> Morphine & Butorphenol</p> <p><u>Anti-emetics:</u> Metoclopramide, Ondansetron & Domperidon [sickness/vomiting]</p> <p><u>Antibiotics:</u> Sparfloxacin, Grepafloxacin; Erythromycin</p> <p><u>Antihistamines:</u> Ebastin</p> <p><u>Tranquillisers & pre-anaesthetic agents:</u> Acepromazine</p> <p><u>Analgesic & pre-anaesthetic agent:</u> Butorphanol</p> <p><u>Other drugs:</u> Etoposide; Mitoxantrone; Ondansetron; Paclitaxel; Rifampicin.</p>
Class C	<p>Can be used</p>	<p>Stronghold®, Advocate® & Milbemax® can be used safely, but only in the recommended application form and dosage.</p>

***In dogs with an MDR1 mutant gene [-], Acepromazine and Butorphanol tend to cause deeper and more prolonged sedation. Vets are recommended to reduce the dosage by 25% in MDR1 carriers [+/-] and by 30 - 50% in MDR1 affected dogs [-/-]**