

## The Multi Drug Resistance Gene Defect and Collie Dogs

### Summary

- Problems associated with this genetic defect are rare in our practice.
- The defect is **restricted to Rough and Smooth Collies, Australian Shepherd dogs and Shetland Sheepdogs** (although other herding breeds can rarely be affected e.g. Border Collie, Old English Sheepdog). The defect is not recognised in terriers, spaniels, retrievers, setters, toy and hunting breeds and many more.
- Affected dogs are very sensitive to the effects of certain drugs, causing neurological signs.
- Very few drugs are of concern e.g. some 'flea and worm' drugs.
- Advocate (a drug we strongly recommend to control roundworms, lungworms and fleas) is **SAFE** in susceptible breeds as long as it is used at the manufacturer's recommended dose and via the correct route of administration. A 5 times overdose can cause problems. In line with Woodcroft Vets current working practices, Advocate should not be used in conjunction with other similar drugs e.g. Milbemax.
- Affected dogs can be identified with a genetic test so that problems can be avoided – ask us for more details.
- Please read on for more information.



### What is MDR1?

MDR stands for Multi Drug Resistance. A gene is a set of instructions animals use to make parts of their bodies e.g. hair colour. MDR1 is the name given to a gene, which is responsible for building a drug transport molecule (called a "P-glycoprotein transport molecule" or "P-gp pump") inside many mammals. This transport molecule is responsible for removing potentially harmful substances (e.g. drugs and toxins) from the body. Of relevance in this situation is the ability of the transport molecule to keep substances including drugs out of the brain. In sensitive dog breeds, it is too little MDR1 (and therefore too little transport molecule), which causes drugs to accumulate in the brain causing (potentially fatal) toxicity.

Each mammal has two copies of this gene = "gene pair". Each gene in this pair can be:

- functional (written as "MDR1", responsible for building the functional P-gp pumps) or
- mutated/abnormal (written as "mdr1" (using lower case to distinguish it from the functional MDR1), unable to build transport molecules).

The MDR1 defect is inherited as what is called a recessive gene but with partial expression. What that means is that:

- a dog with 2 copies of functional MDR1 has the correct number of transport molecules and will be normal (i.e. 'unaffected') and
- a dog with 2 copies of mutated mdr1 has non-functional transport molecules and will have marked problems with drug sensitivity (i.e. affected)

These individuals are known as homozygous as both the genes are the same.

But if a dog has one of each gene (i.e. MDR1 + mdr1 - what is known as a carrier or heterozygous) the normal MDR1 gene, although dominant, doesn't completely have its own way and you get a halfway house where the individual is still likely to have problems albeit to a lesser degree than the completely affected individuals.

### **Which breeds can be affected the mutation? How common is the mutation?**

A UK survey in 2012 showed that the main breeds to be concerned about are Smooth Collies, Rough Collies, Australian Shepherds and Shetland Sheepdogs. The incidence of the gene mutation in Border Collies and Old English Sheepdogs is much lower. The mutation was not recognised in German Shepherd dogs, Bearded Collies and many other breeds.

### **Which drugs do we need to be concerned about?**

1. *Selamectin (Stronghold), milbemycin (Milbemax), and moxidectin (Advocate) (antiparasitic agents)* – these drugs have better safety profiles than the older drug, Ivermectin, and are **SAFE** in dogs with two copies of the mutation if used at the manufacturer's recommended dose and via the correct route of administration. Higher doses (generally 5 times higher than the recommended dose) have been documented to cause neurological toxicity in dogs with two copies of the MDR1 mutation.

However, some of the preparations are considered so safe in the general canine population that they often have very wide dose ranges and therefore a limited number of tablet/pipette sizes. In such cases there are potential implications for sensitive dogs with the mutation. If, for example, a dog suspected of having the MDR1 mutation weighs 10 kg and the dose of a hypothetical drug is one tablet for a dog weighing from 10 to 50 kg then, by giving such a tablet to a 10kg dog you will be close to the five fold increase in dose at which adverse reactions might be expected. So here either the tablet would need to be divided (which would possibly go against data sheet guidelines), find another class of drug to do the job or, ideally, have such a dog tested for the presence or absence of the MDR1 gene defect so that a fully informed decision can be made.

Currently, even at the recommended doses, we do not advise concurrent use of Advocate and Milbemax in any breed.

2. *Loperamide (Imodium; antidiarrheal agent)*
3. *Acepromazine (a drug used in most routine anaesthetic protocols)*
4. *Butorphanol (analgesic and pre-anaesthetic agent)*
5. *Chemotherapy drugs*

Restricting the type of drugs used in dogs suspected of having the MDR1 defect is mere crisis management. By making a blanket ban for certain drugs we run the risk of denying MDR1 normal dogs safe, effective treatment for some serious conditions (e.g. canine lungworm caused by *Angiostrongylus Vasorum*).

### **What is the next step?**

#### Pet owner

If your dog belongs to one of the breeds listed above and you are worried about the potential adverse effects of one of the drugs also listed, please talk to one of our vets. There are numerous options available:

- Reducing the dose of the drug in question (although this may mean using the drug outwith the manufacturers recommendations).
- Choosing an alternative drug to do the job (although in practice if there was a better and safer drug, this would be our first line therapy for our stated aim e.g. control of lungworm in your dog).
- Test for the presence or absence of the MDR1 gene defect so that a fully informed decision can be made.

#### Dog breeders

A Kennel Club official testing scheme is in existence and comes with appropriate breeding advice.

