

# NEWS FROM THE WORLD OF ONCOLOGY

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## P-glycoprotein, Multi-drug Resistance Gene-1 (PGP, MDR1)

This month I will share information regarding the MDR1 gene that is important not only for cancer treatment but also for the use of many other drugs. It is well recognized that certain breeds are sensitive to some drugs when compared to other breeds. For example Collies and other herding breeds are often more sensitive to ivermectin.

The cause of this increased sensitivity has recently been determined to be due to a mutation in the multi-drug resistance gene (MDR1). This gene codes for a protein, P-glycoprotein (PGP), that is responsible for pumping many drugs out of the brain. This pump exists on the cell surface. Dogs with the mutant gene cannot pump some drugs out of the brain as efficiently as a normal dog, which may result in neurological signs. Mutant dogs are at risk of becoming ill and may even die.



A test has recently been developed that is able to screen for the presence of the mutant gene. This test determines if a dog is normal (PP), a carrier (Pp) or a mutant (pp). The gene's inheritance pattern is based on simple Mendelian genetics. This test allows veterinarians to make drug choices based on quantitative data. We are now able to determine if a dog is normal, in which case drugs of interest can be administered or abnormal, in which case an alternative treatment must be given.

Approximately 3 of every 4 Collies in the North America have the mutant MDR1 gene. The MDR1 mutation has also been found in Shetland Sheepdogs (Shelties), Australian Shepherds, Old English Sheepdogs, German Shepherds, Long-haired Whippets, Silken Windhounds, and a variety of mixed breed dogs.

Many drugs have been demonstrated to be MDR1 substrates, and they include:

- |               |                         |             |              |
|---------------|-------------------------|-------------|--------------|
| -Ivermectin   | -Selamectin             | -Milbemycin | -Moxidectin  |
| -Acepromazine | -Loperamide (Immodium™) |             | -Butorphanol |

**Vincristine, Vinblastine, Doxorubicin:** Dogs with the MDR1 mutation have increased sensitivity to these drugs and are more likely to have an adverse reaction. Adverse reactions include myelosuppression, GI toxicity and even death. Drug doses must be reduced in carrier and mutant dogs. For doxorubicin consideration must be given to complete avoidance of this drug.

The following drugs seem to be pumped by MDR1 but appear to be tolerated by dogs with the mutation:

- |                |           |              |           |
|----------------|-----------|--------------|-----------|
| -Cyclosporin   | -Digoxin  | -Doxycycline | -Morphine |
| -Buprenorphine | -Fentanyl |              |           |

The following drugs have been reported to be pumped by PGP, MDR1 in humans, but have no veterinary data available. Therefore they must be used with caution or avoided in carrier and mutant dogs:

- |              |             |               |              |
|--------------|-------------|---------------|--------------|
| -Domperidone | -Etoposide  | -Mitoxantrone | -Ondansetron |
| -Paclitaxel  | -Rifampicin |               |              |

The only way to know if an individual dog has the mutant MDR1 gene is to have the dog tested. Testing is simple and involves the submission of cheek cell samples. Results tend to be available within in one to two weeks. I now consider this test Standard of Care for any at risk breed and for any dog demonstrating an unexpected drug reaction.

***Dr. Kevin Finora is a board certified Oncologist and Small Animal Internist. He sees patients Wednesday (including evenings) to Saturday at VEC/RC South. Please do not hesitate to contact Dr. Finora if you have any cancer related questions.***

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