Title of Disease:  MDR1 Mutation

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Synonyms:  Ivermectin sensitivity; ABCB1-1Δ mutation

Disease Description:  The MDR1 mutation causes 2 distinct problems in affected dogs—(I) susceptibility to adverse drug reactions and (II) relative adrenal insufficiency. Details of both are provided below

I. Many different drugs and drug classes have been reported to cause problems in Collies and other herding breed dogs that carry the MDR1 mutation. We and other researchers have documented the toxicity that occurs with several of these drugs.

Drugs that have been documented to cause problems in dogs with the MDR1 mutation include:

- **Acepromazine** (tranquilizer and pre-anesthetic agent). In dogs with the MDR1 mutation, acepromazine tends to cause more profound and prolonged sedation. We recommend reducing the dose by 25% in dogs heterozygous for the MDR1 mutation (mutant/normal) and by 30–50% in dogs homozygous for the MDR1 mutation (mutant/mutant).

- **Butorphanol** (analgesic and pre-anesthetic agent). Similar to acepromazine, butorphanol tends to cause more profound and prolonged sedation in dogs with the MDR1 mutation. We recommend reducing the dose by 25% in dogs heterozygous for the MDR1 mutation (mutant/normal) and by 30–50% in dogs homozygous for the MDR1 mutation (mutant/mutant).

- **Emodepside** (Profender®)–is a deworming drug approved for use in cats only in the U.S., but is approved for use in dogs in some other countries. Use of this drug in dogs with the MDR1 mutation has resulted in neurological toxicity.
- **Erythromycin.** Erythromycin may cause neurological signs in dogs with the MDR1 mutation. A mutant/mutant collie exhibited signs of neurological toxicity after receiving erythromycin. After withdrawal of the drug, the dog's neurological signs resolved. There were no other potential causes of neurological toxicity identified in the dog.

- **Ivermectin** (antiparasitic agent). While the dose of ivermectin used to prevent heartworm infection is SAFE in dogs with the mutation (6 micrograms per kilogram), higher doses, such as those used for treating mange (300–600 micrograms per kilogram) will cause neurological toxicity in dogs that are homozygous for the MDR1 mutation (mutant/mutant) and can cause toxicity in dogs that are heterozygous for the mutation (mutant/normal).

- **Loperamide** (Imodium™; antidiarrheal agent). At doses used to treat diarrhea, this drug will cause neurological toxicity in dogs with the MDR1 mutation. This drug should be avoided in all dogs with the MDR1 mutation.

- **Selamectin, milbemycin,** and **moxidectin** (antiparasitic agents). Similar to ivermectin, these drugs are safe in dogs with the mutation if used for heartworm prevention at the manufacturer's recommended dose. Higher doses (generally 10–20 times higher than the heartworm prevention dose) have been documented to cause neurological toxicity in dogs with the MDR1 mutation.

- **Vincristine, Vinblastine, Doxorubicin** (chemotherapy agents). Based on some published and ongoing research, it appears that dogs with the MDR1 mutation are more sensitive to these drugs with regard to their likelihood of having an adverse drug reaction. Bone marrow suppression (decreased blood cell counts, particularly neutrophils) and GI toxicity (anorexia, vomiting, diarrhea) are more likely to occur at normal doses in dogs with the MDR1 mutation. To reduce the likelihood of severe toxicity in these dogs (mutant/normal or mutant/mutant), we recommend reducing the dose by 25–30% and carefully monitoring these patients.

**Drugs that are known to be pumped out of the brain by the protein that the MDR1 gene is responsible for producing but appear to be safely tolerated by dogs with the MDR1 mutation:**

- **Cyclosporin** (immunosuppressive agent). While we know that cyclosporin is pumped by P-glycoprotein (the protein encoded by the MDR1 gene), we have not documented any increased sensitivity to this drug in dogs with the MDR1 mutation compared to "normal" dogs. Therefore, we do not recommend altering the dose of cyclosporin for dogs with the MDR1 mutation, but we do recommend therapeutic drug monitoring.
Digoxin (cardiac drug). While we know that digoxin is pumped by P-glycoprotein (the protein encoded by the MDR1 gene), we have not documented any increased sensitivity to this drug in dogs with the MDR1 mutation compared to "normal" dogs. Therefore, we do not recommend altering the dose of digoxin for dogs with the MDR1 mutation, but do recommend therapeutic drug monitoring.

Doxycycline (antibacterial drug). While we know that doxycycline is pumped by P-glycoprotein (the protein encoded by the MDR1 gene), we have not documented any increased sensitivity to this drug in dogs with the MDR1 mutation compared to "normal" dogs. Therefore, we do not recommend altering the dose of doxycycline for dogs with the MDR1 mutation.

Drugs that may be pumped out by the protein that the MDR1 is responsible for producing, but appear to be safely tolerated by dogs with the MDR1 mutation:

- Morphine, buprenorphine, fentanyl (opioid analgesics or pain medications). We suspect that these drugs are pumped by P-glycoprotein (the protein encoded by the MDR1 gene) in dogs because they have been reported to be pumped by P-glycoprotein in people, but we are not aware of any reports of toxicity caused by these drugs in dogs with the MDR1 mutation. We do not have specific dose recommendations for these drugs for dogs with the MDR1 mutation. The following drugs have been reported to be pumped by P-glycoprotein (the protein encoded by the MDR1) in humans, but there is currently no data stating whether they are or are not pumped by canine P-glycoprotein. Therefore we suggest using caution when administering these drugs to dogs with the MDR1 mutation.
  - Domperidone
  - Etoposide
  - Mitoxantrone
  - Ondansetron
  - Paclitaxel
  - Rifampicin

There are many other drugs that have been shown to be pumped by human P-glycoprotein (the protein encoded by the MDR1 gene), but data is not yet available with regard to their effect in dogs with the MDR1 mutation.

II. Relative adrenal insufficiency.

P-glycoprotein, the product of the MDR1 gene, plays an important role in the negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis. As a P-
glycoprotein substrate, brain penetration of cortisol is limited in MDR1 wildtype dogs. However, because MDR1 mutant/mutant dogs lack P-glycoprotein, greater concentrations of cortisol enter the brain resulting in greater negative feedback of the HPA axis compared to MDR1 wildtype dogs. is suppressed compared with MDR1 wildtype dogs. Basal plasma cortisol concentrations and cortisol concentrations after ACTH administration are significantly lower in MDR1 mutant/mutant dogs compared to MDR1 wildtype dogs. Plasma ACTH concentrations after dexamethasone administration are significantly lower in MDR1 mutant/mutant dogs compared to MDR1 wildtype dogs. These research results are corroborated by some clinical observations in breeds known to harbor the MDR1 mutation including Collies, Shelties, Australian Shepherds, and others. Many of these dogs have worse outcomes in response to stress and, at times, respond poorly to appropriate therapy because of a state of relative adrenal insufficiency (RAI). These dogs may benefit from physiologic doses of prednisone during periods of stress.

**Description of Disease in specific Species: Dogs Only**

**Genetic Basis /Mode of Inheritance:** Autosomal Dominant (although heterozygotes have intermediate phenotype)

**Etiology:** Inherited condition

**Breed Predilection:**

<table>
<thead>
<tr>
<th>Breeds affected by the MDR1 mutation (frequency %)</th>
<th>Approximate Frequency</th>
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<tbody>
<tr>
<td>Australian Shepherd</td>
<td>50%</td>
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<tr>
<td>Australian Shepherd, Mini</td>
<td>50%</td>
</tr>
<tr>
<td>Border Collie</td>
<td>&lt; 5%</td>
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<tr>
<td>Collie</td>
<td>70 %</td>
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<tr>
<td>English Shepherd</td>
<td>15 %</td>
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<tr>
<td>German Shepherd</td>
<td>5 %</td>
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<tr>
<td>Herding Breed Cross</td>
<td>10 %</td>
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<tr>
<td>Long–haired Whippet</td>
<td>65 %</td>
</tr>
<tr>
<td>McNab</td>
<td>30 %</td>
</tr>
<tr>
<td>Mixed Breed</td>
<td>5 %</td>
</tr>
<tr>
<td>Old English Sheepdog</td>
<td>5 %</td>
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</tbody>
</table>
Clinical Findings / Signs: Depend on drug involved:
  - Neurological-macroyclic lactones (ivermectin, milbemycin, moxidectin, etc);
  - Loperamide; vincristine
    - Myelosuppression-vincristine, vinblastine, doxorubicin
    - Severe GI toxicity-doxorubicin, vincristine, vinblastine

Addisonian-like clinical signs (without electrolyte disturbances) can be seen in ‘stressed’ dogs that are MDR1 mutant/mutant. These dogs may benefit from physiologic doses of glucocorticoids. Examples of ‘stress’ include physical exertion, moderate to severe illness.

Diagnostic Procedures / Diagnostic Results: MDR1 genotyping

Genetic Control Because of the high frequency of the MDR1 mutation in many breeds (75% of Collies harbor at least 1 mutant allele; 50% of Australian Shepherds harbor at least 1 mutant allele), it is inadvisable to recommend breeding only MDR1 wildtype dogs.

Treatment/Management:
For loperamide, the opiate antagonist naloxone can be used to reverse clinical signs. For other drugs, there are no specific antidotes. Supportive care (including ventilator support) may be needed for weeks in some cases of macrocyclic lactone toxicity. The lipid rescue protocol that has been recommended for use in macrocyclic lactone toxicity is not helpful for dogs with the MDR1 mutant/mutant genotype (Wright et al, J Vet Emerg Crit Care epub 2011)

Veterinarians are encouraged to contact Katrina Mealey, DVM PhD, DACVIM, DACVCP (kmealey@vetmed.wsu.edu) for treatment or dosing information

Preventive Measures: Strict attention to drug doses used in affected animals.

Special Considerations:

Differential Diagnosis: Some drugs (those that inhibit P-glycoprotein function) can mimic the MDR1 mutation in dogs of any breed. P-glycoprotein is the protein...
encoded by the MDR1 gene. Drug that inhibit P-glycoprotein include ketoconazole, spinosad (Comfortis), and potentially cyclosporine. MDR1 wildtype dogs concurrently treated with ketoconazole or spinosad and extralabel doses of ivermectin (i.e., mange doses) have experienced neurological toxicity similar to that seen in dogs with the MDR1 mutation

Human Disease Homolog: None

Available Tests/Testing Facilities: MDR1 Genotyping test-Veterinary Clinical Pharmacology Laboratory at Washington State University.
www.vetmed.wsu.edu/vcpl  509-335-3745

References:

Wright HM, Chen AV, Talcott PA, Poppenga RH, Mealey KL. Intravenous fat emulsion as treatment for ivermectin toxicosis in three dogs homozygous for the ABCB1-1Δ gene mutation J Vet Emerg Crit Care 2011(epub)


Barbet J, Snook T, Gay JM, Mealey KL ABCB1 (MDR1) genotype is associated with adverse reactions in dogs treated with milbemycin oxime for generalized demodicosis; Vet Dermatol 2009; 20:111-114.


