How Should I Treat Dogs & Cats with *MDR1* Mutation?

Katrina Mealey, DVM, PhD, DACVIM, DACVCP
Washington State University

The Problem

✔ **Dozens of drugs** are transported by the *MDR1* (*ABCB1-1Δ*) gene product P-glycoprotein, but relatively few cause serious toxicity in animals with *MDR1* gene mutations.[1-3]

✔ **Homozygous vs heterozygous**
—In general, toxicity is most severe in homozygous animals, but toxicity can also occur in heterozygous animals.[4,5]

✔ ***MDR1* gene mutations** have been identified in both dogs (*ABCB1-1Δ*) and cats (*ABCB1*1930_1931del TC).[6,7]

Options & Solutions

The drugs detailed here can cause serious, even fatal, adverse drug reactions in animals with *MDR1* mutations unless dose reductions are made. In some situations, use of alternative drugs may be the only therapeutic option.[4,5,8-10]

Analgesic & Preanesthetic Agents

Acepromazine (as Tranquilizer & Preanesthetic)

✔ **In dogs with** *MDR1* mutation, acepromazine tends to cause profound and prolonged sedation.[11]

✔ ***MDR1* mutation**
—Dose reductions should provide the level of tranquilization and/or sedation expected to occur in a normal/normal dog receiving the full dose.
- **Mutant/mutant dog,** dose reduction of 30% to 50% (anecdotal)
- **Mutant/normal dog,** dose reduction of 25% (anecdotal)

Butorphanol (as Analgesic & Preanesthetic)

✔ **Butorphanol,** an opioid analgesic used most commonly as a cough suppressant or preanesthetic agent, can cause greater and more prolonged sedation in dogs with *MDR1* mutation.[12]

Homozygous = mutant/mutant
- Affected dogs and cats have 2 copies of the mutated *MDR1* gene and always pass 1 copy of the defective gene to offspring.
- Homozygotes have potentially fatal sensitivity to certain antiparasitic and chemotherapeutic agents.

Heterozygous = mutant/normal
- Affected dogs and cats have only 1 copy of the mutated *MDR1* gene, but there is a 50% chance of passing the defective gene to offspring.
- Compared with homozygotes, heterozygotes can react to the same agents when administered at higher doses.

✔ ***MDR1* mutation**[12]
- —Dose reduction should provide the level of tranquilization and/or sedation as that expected to occur in a normal/normal dog receiving the full dose.
- —**Mutant/mutant dog,** dose reduction of 30% to 50%
- —**Mutant/normal dog,** dose reduction of 25%

Antibacterial Agents

Doxycycline

✔ **Doxycycline is transported** by the *MDR1* gene product (P-glycoprotein). However, the drug has a wide therapeutic window.[13]

✔ ***MDR1* mutation**
- —The author is aware of **strong clinical evidence** supporting safe treatment of numerous *MDR1* mutant/mutant dogs at regular dosages.[12]

Erythromycin

✔ **Erythromycin may cause** neurologic signs in dogs with *MDR1* mutation.[12]

✔ ***MDR1* mutation**[12]
- —**Mutant/mutant collie** exhibited signs of neurologic toxicity shortly after receiving erythromycin.
  - After withdrawal of erythromycin, neurologic signs resolved completely.
  - No other potential causes of neurologic toxicity were identified.

Antiparasitic Agents

Emodepside + Praziquantel (Combination Anthelmintic)

✔ **FDA approved for use** in **cats only**
- —However, in certain countries (but ***not*** the United States), the oral formulation also is available for dogs.[14]

✔ ***MDR1* mutation**
- —Use of this anthelmintic combination can result in neurologic toxicity.
  - ***ABCB1*1930_1931del TC mutation in cats** would be expected to cause neurologic toxicity.
  - **In mutant/mutant dogs,** neurologic toxicity has been reported.[15,16]

Macrocyclic Lactones

✔ **If used according** to label doses
- —**In mutant/mutant & mutant/normal dogs,** all US FDA-approved heartworm preventives (ie, ivermectin, milbemycin, moxidectin, selamectin) are considered safe for use.
  - See specific trademark products for label indications.

✔ ***MDR1* mutation**
- —Although the label heartworm prevention doses of the following drugs are safe to use in dogs with *MDR1* mutation, higher doses can result in adverse neurologic effects in mutant/mutant and mutant/normal dogs (anecdotal).
- —**Ivermectin** at doses higher than those for heartworm prevention
  - **Mutant/mutant dogs:** Doses used for treating mange (300-600 µg/kg) can cause severe (potentially fatal) neurologic toxicity.[6,17]
  - **Mutant/normal dogs:** The author has been able to use ivermectin to treat sarcoptic mange and generalized demodicosis in ***some*** mutant/normal dogs, depending on several factors (eg, other drugs or supplements the dog is receiving, ability of owner to monitor for early signs of toxicity).[12]
- —**Milbemycin, moxidectin, selamectin** at higher doses and/or more frequent administration
  - In **mutant/mutant dogs,** higher doses

Use of an emodepside–praziquantel combination can result in neurologic toxicity in cats with *MDR1* mutation, as well as in mutant/mutant dogs.[15,16]

FDA = Food and Drug Administration

Until more information is available, use of taxanes in animals with *MDR1* mutation should be carefully considered.

CNS = central nervous system, GI = gastrointestinal

(generally, 10-20 times higher than heartworm prevention dose) or more frequent use (ie, daily rather than monthly) have been documented to cause neurologic toxicity in dogs with *MDR1* mutation.[8,17]

Chemotherapeutic Agents

Doxorubicin, Actinomycin D (Antibiotic Antineoplastic Agents)

✔ **Compared with normal/normal dogs,** dogs with *MDR1* mutation (mutant/mutant and mutant/normal)[12,18] are at increased risk for neutropenia, thrombocytopenia, and GI adverse effects

✔ ***MDR1* mutation**

—Initial and subsequent doses recommended by author[12]

- **Mutant/mutant dogs,** initial dose reduction of 50%, with subsequent doses increased as tolerated
- **Mutant/normal dogs,** initial dose reduction of 25%, with subsequent doses increased as tolerated

Paclitaxel, Docetaxel (Taxanes)

✔ **There are no approved formulations** of these agents for use in dogs or cats with *MDR1* mutation.

—Paclitaxel caused severe myelosuppression in a **mutant/normal dog** treated with a reduced dose of this agent.[12]

- Additional research is being conducted. Until more information is available, use of taxanes in animals with *MDR1* mutation should be carefully considered.

✔ ***MDR1* normal/normal dose recommendations**

—One source cites anecdotal (paclitaxel) protocols in presumed *MDR1* normal/normal dogs.[19]

Vinblastine, Vincristine, Vinorelbine (Vinca Alkaloids)

✔ **Compared with normal/normal dogs** receiving these agents, dogs with *MDR1* mutation are at increased risk for[5,9,18]

—Neutropenia and thrombocytopenia

—GI and neurologic adverse effects

—Neurologic toxicity

✔ ***MDR1* mutation**

—Current recommendations (anecdotal)

- **Mutant/mutant dogs,** dose reduction of 50%
- **Mutant/normal dogs,** dose reduction of 25%

—Additional research is ongoing.

Gastrointestinal Agents

Loperamide

✔ **An opioid excluded** from the central nervous system (CNS) by P-glycoprotein

✔ ***MDR1* mutation**

—**In mutant/mutant dogs,** loperamide can achieve high CNS concentrations, resulting in neurologic toxicity (ie, CNS depression).[10,20]

- Can be reversed in short-term by opioid antagonists (eg, naloxone)

Ondansetron

✔ **The author is aware** of several homozygous dogs with *MDR1* mutation experiencing mild-to-moderate CNS depression after receiving this agent.[12]

—Because ondansetron is a known P-glycoprotein substrate alternate, antiemetics may be more appropriate choices, particularly for cancer patients receiving chemotherapeutic agents that are P-glycoprotein substrates (see **Chemotherapeutic Agents**).[12]

✔ ***MDR1* mutation**
—**In mutant/mutant and mutant/normal dogs,** competition for P-glycoprotein–mediated biliary or renal excretion among P-glycoprotein substrates may delay clearance and consequently increase toxicity.[21]

Meeting the *MDR1* Challenge

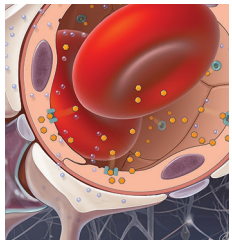
Author Insights

✔ **The hypothalamic–pituitary–adrenal axis**
—Is suppressed in **mutant/mutant dogs,** as compared to wild-type dogs
—In situations of stress (eg, severe illness, adverse drug reaction), physiologic doses of corticosteroids are indicated.[22]

✔ **Concurrent use of drugs** (in particular, ketoconazole and spinosad)
—Can inhibit P-glycoprotein function, causing a phenotype similar to an *MDR1* mutation

✔ **Cats with this mutation**
—Are likely to have drug sensitivities similar to those in dogs with *MDR1* mutation

✔ **Additional information**
—Methods for testing patients for the canine and feline *MDR1* mutation can be found at Washington State University Veterinary Clinical Pharmacology Laboratory.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Cats with *MDR1* mutation are likely to have drug sensitivities similar to those in dogs with the mutation.

KATRINA MEALEY, DVM, PHD, DACVIM, DACVCP, is professor and Richard L. Ott Endowed Chair in Small Animal Medicine and Research at Washington State University (WSU) in Pullman. Her primary research interest is pharmacogenetics, specifically the study of genetic determinants of response to drug therapy. Most of Dr. Mealey's current laboratory work focuses on *MDR1* polymorphism in canine herding breeds (eg, collie, Australian shepherd, Shetland sheepdog) and its implications for multidrug sensitivity. In addition, the Veterinary Clinical Pharmacology Laboratory at WSU recently started investigating other breed-related adverse drug reactions in dogs. Dr. Mealey received her DVM from Colorado State University and PhD from Texas A&M University. She also completed a small animal internship at University of Minnesota, along with 2 residencies (small animal internal medicine and veterinary clinical pharmacology) at Texas A&M University.

REFERENCES

1. Kim RB. Drugs as P-glycoprotein substrates, inhibitors and inducers. *Drug Metab Rev*. 2002; 34(1-2):47-54.
2. Yu DK. The contribution of P-glycoprotein to pharmacokinetic drug-drug interactions. *J Clin Pharmacol*. 1999;39(12):1203-1211.
3. West CL, Mealey KL. Assessment of antiepileptic drugs as substrates for canine P-glycoprotein. *Am J Vet Res*. 2007;68(10):1106-1110.
4. Barbet JL, Snook T, Gay JM, Mealey KL. *ABCB1-1Δ* (*MDR1-1Δ*) genotype is associated with adverse reactions in dogs treated with milbemycin oxime for generalized demodicosis. *Vet Dermatol*. 2009;20(2):111-114.
5. Mealey KL, Fidel J, Gay JM, Impellizeri JA, Clifford CA, Bergman PJ. *ABCB1-1Δ* polymorphism can predict hematologic toxicity in dogs treated with vincristine. *JVIM*. 2008;22(4):996-1000.
6. Mealey KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the *MDR1* gene. *Pharmacogenetics*. 2001;11(8):727-733.
7. Mealey KL, Burke NS. Identification of a nonsense mutation in feline *ABCB1*. *J Vet Pharmacol Ther*. 2015;38(5):429-433.
8. 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 (San Antonio)*. 2011;21(6): 666-672.
9. Krugman L, Bryan JN, Mealey KL, Chen A. Vincristine-induced central neurotoxicity in a collie homozygous for the *ABCB1Δ* mutation. *J Small Anim Pract*. 2012;53(3):185-187.
10. Mealey KL, Greene S, Bagley R, et al. P-glycoprotein contributes to the blood-brain, but not blood-cerebrospinal fluid, barrier in a spontaneous canine P-glycoprotien knockout model. *Drug Metab Dispos*. 2008;36(6):1073-1079.

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demodicosis. Possibly I have been over-restrictive; however, I did this with the sole aim of avoiding any risk to patients.

—Lluis Ferrer, DVM, DECVD, PhD, Tufts University

REFERENCES

1. Liu Q, Arseculeratne C, Liu Z, et al. Simultaneous deficiency in CD28 and STAT6 results in chronic ectoparasite-induced inflammatory skin disease. *Infect Immun*. 2004;72(7):3706-3715.
2. Smith P, Zeiss CJ, Martin-Escalante D, Herrick CA, Bottomly K. Pruritic dermatitis associated with *Demodex musculi* in transgenic mice (abstract from Proceedings of AALAS National Meeting, 2003). *Contemp Top Lab Anim Sci*. 2003;424(4):111.

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11. Deshpande D, Hill KE, Mealey KL, Chambers P, Gieseg MA. The effect of the canine *ABCB1-1Δ* mutation on sedation after intravenous administration of acepromazine. *JVIM*. doi: 10.1111/jvim.13827.
12. Mealey KL. Unpublished observations, clinical data, and ongoing clinical/laboratory research; small animal medicine and research, Washington State University; accumulated clinical/laboratory evidence as of November 2015.
13. Mealey KL, Barhoumi R, Burhhardt RC, Safe S, Kochevar DT. Doxycycline induces expression of P-glycoprotein in MCF-7 breast carcinoma cells. *Antimicrob Agents Chemother*. 2002;46(3):755-761.
14. Plumb DC. Emodepside + praziquantel. In: Plumb DC, ed. *Plumb's Veterinary Drug Handbook*. 8th ed. Ames, IA: Wiley-Blackwell; 2015:505-507.
15. Elmshäuser S, Straehle LC, Kranz J, Krebber R, Geyer J. Brain penetration of emodepside is increased in P-glycoprotein-deficient mice and leads to neurotoxicosis. *J Vet Pharmacol Ther*. 2015; 38(1):74-79.
16. Hugnet C, Pineau X. Emodepside sensitivity in German shepherd dog is associated with deletion mutation of the *MDR1* gene. In: Proceedings of 22nd ECVIM-CA Congress. 2012; Maastricht, Netherlands.
17. Nelson OL, Carsten E, Bentjen SA, Mealey KL. Ivermectin toxicity in an Australian shepherd dog with the *MDR1* mutation associated with ivermectin sensitivity in collies. *JVIM*. 2003;17(3):354-356.
18. Mealey KL, Northrup NC, Bentjen SA. Increased toxicity of P-glycoprotein-substrate chemotherapeutic agents in a dog with the *MDR1* deletion mutation associated with ivermectin sensitivity. *JAVMA*. 2003;223(10):1453-1455.
19. Plumb DC. Paclitaxel. In: Plumb DC, ed. *Plumb's Veterinary Drug Handbook*. 8th ed. Ames, IA: Wiley-Blackwell; 2015:809-810.
20. Sartor LL, Bentjen SA, Trepanier L, Mealey KL. Loperamide toxicity in a collie with the *MDR1* mutation associated with ivermectin sensitivity. *JVIM*. 2004;18(1):117-118.
21. Coelho JC, Tucker R, Mattoon J, Roberts G, Waiting DK, Mealey KL. Biliary excretion of technetium-99m-sestamibi in wild-type dogs and in dogs with intrinsic (*ABCB1-1Δ* mutation) and extrinsic (ketoconazole treated) P-glycoprotien deficiency. *J Vet Pharmacol Ther*. 2009;32(5):417-421.
22. Mealey KL, Gay JM, Martin LG, Waiting DK. Comparison of the hypothalamic-pituitary-adrenal axis in *MDR1-1Δ* and *MDR1* wildtype dogs. *JVECC*. 2007;17(1):61-66.