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SPECIAL POINTS OF INTEREST:

- Mutations in the MDR1 gene can result in adverse drug reactions in affected pets
- Increased testing and screening can help veterinarians make adjustments in drug doses to prevent drug reactions
- MDR1 testing should be considered at wellness examinations for high risk breeds

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MDR-1 Mutation

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Fig 1: A cheek swab is obtained for MDR1 testing



Fig 2: The Australian shepherd is considered a high risk breed for MDR1 mutation



Dear Colleague,

Ever wonder why some dogs or some breeds tolerate drugs better? We have all heard about collies and adverse reaction to ivermectin, but there are many other breeds and drugs that can have similar problems. A readily available screening test may be able to help identify patients at risk for adverse drug reactions.

What is the MDR1 gene?

MDR1 is a gene which encodes for P-glycoprotein. This drug transport system is designed to protect cells by limiting absorption and distribution of drugs along with enhancing excretion of others. Dogs with mutations in the MDR1 pathway have a deficient or defective g-glycoprotein allowing for increased toxicity of drugs processed through this pathway. Although the most commonly reported breed is Collies (approximately 70% carry the mutation), many other breeds such as Australian shepherds, English shepherds, German shepherds, whippets and sheepdogs can have mutations in this pathway.

How can I use pharmacogenetics in my patients?

Pharmacogenetics is the study of how genetic variability in animals can influence the absorption, activation and elimination of drugs. We can now test for the MDR1 mutation to determine which patients are at risk of increased drug toxicity. Research is ongoing to determine which drugs are affected and how to adjust dosing in high risk patients. Dogs and humans have two alleles or copies of the MDR1 gene. A simple cheek swab or blood sample is used to look for mutation status and the results are reported as normal/normal, normal/mutant, and mutant/mutant. Patients reported as normal/normal should be able to tolerate standard doses of these medications with no dose adjustment. If the results are normal /mutant (heterozygous) then dosing may be reduced and the patient should be watched more closely for side effects. If a patient is reported as mutant/mutant (homozygous) then dose adjustments or elimination of certain medications may be recommended.

What drugs are affected and how to I adjust therapy?

Many drugs are affected by this pathway. The most commonly reported is ivermectin but other antiparasitides such as selamectin, milbemycin and moxidectin can also have increased risk of neurotoxicity if this pathway is mutated. These agents are typically safe when included in heartworm preventions but higher doses should be avoided. Acepromazine dosing should be reduced by 25% in heterozygous dogs and 30-50% in homozygous patients. Butorphanol can still be used in these tolerated despite mutation and these include: cyclosporine, digoxin and doxycycline.

patients but the dose should be reduced by 25% for heterozygous animals and 30-50% in these patients. There are also other medications processed through this pathway that may still be homozygous animals. Loperamide should be avoided due to a significant risk of neurotoxicity in these patients. There are also other medications processed through this pathway that may still be tolerated despite mutation and these include: cyclosporine, digoxin and doxycycline.

How is MDR1 mutation testing used in Oncology patients?

In oncology this pathway plays a major role in the elimination of chemotherapy agents such as vincristine, vinblastine and doxorubicin to name a few. In high risk breeds we delay the use of these agents until the mutation status can be determined. Once we can confirm a patients mutation status we can safely adjust the chemotherapy doses to still provide an effective dose while minimizing toxicity. In some cases this can delay more aggressive chemotherapy by 1 to 2 weeks until we can prove a patients status. Routine testing during a wellness visit could eliminate treatment delays and unnecessary toxicity in these high risk breeds.

How can I use MDR1 mutation testing in General Practice?

Veterinarians can easily include genetic testing as part of an initial puppy visit or routine wellness exam. Patients can be tested as soon as a puppy has been weaned. I would encourage any high risk breed, and any patient with previous drug reactions to be tested. There are many known drugs affected by this pathway but there may be more medications we have not found yet. This test is simple, inexpensive, easy to perform and one day may save an animal's life.

Information on drugs affected, breeds affected, dosing information and testing can be found on through the Veterinary Clinical Pharmacology Lab at Washington State University. The website is <http://www.vetmed.wsu.edu/depts-VCPL>

If you would like to discuss MDR1 testing further with one of our Oncology team members, please don't hesitate to call us at (713)-693-1166.

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