Complications of P-glycoprotein Deficiency in Dogs and Cats

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1. Review: P-glycoprotein's role in drug disposition

Several more thorough reviews of the influence P-glycoprotein (P-gp) has on drug disposition can be found elsewhere[1-3]. P-gp operates as a highly efficient drug efflux pump for substrate drugs (Table 1), actively driving the substrate drug out of cells or tissues that express P-gp. Whilst many mammalian tissues have been shown to express P-gp, only three sites seem to have a clinical impact on the disposition of substrate drugs. So, from a practicing companion animal veterinarian's perspective, the three sites to worry about in a patient with P-gp deficiency are the blood brain barrier (enhanced CNS penetration of P-gp substrate drugs), biliary canaliculi (decreased biliary excretion of P-gp substrate drugs) and T-lymphocytes (increased intracellular concentration of P-gp substrate immunosuppressants). Each of these sites, and the potential clinical consequences of administering a P-gp substrate to a P-gp deficient patient, is discussed in more detail below.

Table 1. Some P-gp substrate drugs/drug classes that are prescribed to canine and/or feline patients.

Acepromazine	Emodepside	Macrocyclic Lactones
Butorphanol	Grapiprant	Maropitant
Cyclosporine A	Ketoconazole	Methylprednisolone
Doxorubicin	Loperamide	Vinca alkaloids

2. What is P-glycoprotein deficiency

<u>"Intrinsic" P-gp deficiency</u>. "Intrinsic" or genetically mediated P-gp deficiency occurs in both dogs and cats. In dogs it is caused by a 4 base-pair deletion mutation in the canine ABCB1 (formerly MDR1) gene[4] and, in cats, by a 2 base-pair deletion mutation in the feline ABCB1 gene[5]. The canine and feline deletion mutations generate multiple premature stop codons such that animals inheriting 2 mutant alleles have no functional P-gp causing extreme susceptibility P-gp substrate drugs. Heterozygotes, animals inheriting 1 mutant and 1 normal allele, have partial P-gp function and are more susceptible to P-gp-mediated adverse reactions than animals inheriting 2 wildtype alleles, but generally less susceptible than animals with 2 mutant alleles as shown in Figure 1.

The canine MDR1 mutation is generally associated with herding breeds but can occur in mixed breed dogs and has even been identified purebred Siberian Huskies and Boxers. Maine Coon cats are the breed most affected by the feline MDR1 mutation (frequency of ~ 5%), with the frequency in non-purebred cats (i.e., domestic short-, medium-, and longhairs) at about 1%.[6]

<u>"Acquired" P-gp deficiency</u>. Acquired P-gp deficiency can result if two P-gp substrate drugs are concurrently administered as they can compete for P-gp-mediated efflux. Competition for P-gp-mediated efflux can increase CNS penetration, decrease biliary clearance and/or enhance intracellular lymphocyte concentrations of one or both drugs. Importantly, acquired P-gp deficiency has the potential to affect all dogs and cats (i.e., MDR1 normal/normal) and has caused fatal adverse drug reactions in both species.

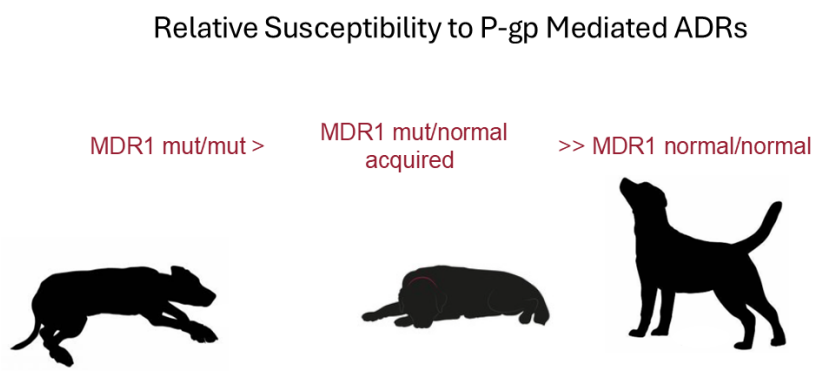

Figure 1. Schematic representation of the relative susceptibility of P-gp deficient animals to P-gp-mediated adverse drug reactions.

3. Clinical examples of P-gp Deficiency

Increased CNS entry of P-gp substrate. Compared to animals with functional P-gp, those with complete P-gp deficiency have been shown to have up to 88 times higher concentrations of P-gp substrate drugs in brain tissue. Enhanced brain penetration of some P-gp substrates in a dog or cat with P-gp deficiency causes CNS depression which can be mild to moderate (maropitant, butorphanol, acepromazine) or severe and potentially fatal (loperamide, macrocyclic lactones). Even animals with acquired P-gp deficiency have experience severe neurological toxicity after concurrent treatment with P-gp substrates.[7] Clinical examples will be presented at the conference.

Decreased biliary excretion. An absolute lack of biliary excretion has been demonstrated experimentally in MDR1 mutant/mutant dogs. The same would be predicted for cats homozygous for ABCB11930_1931del TC. Prolonged clearance of P-gp substrates in P-gp deficient dogs and cats, would likely result in increased overall drug exposure. For example, grapiprant clearance from the central compartment of P-gp deficient dogs (MDR1 mutant/mutant) is 71% lower than that of dogs with normal P-gp function.[8] Not surprisingly, P-gp deficient dogs were more likely to experience gastrointestinal adverse effects from grapiprant than dogs with normal P-gp function. Similarly, P-gp deficient dogs (heterozygous or homozygous for the MDR1 mutation) are significantly more likely to experience vincristine-induced neutropenia and thrombocytopenia dogs with normal P-gp function.[9] Because the primary route of elimination for vincristine is P-gp-mediated biliary excretion of the parent compound, P-gp deficiency delays clearance and increases overall exposure to vincristine. Acquired P-gp deficiency results in similar defects in biliary clearance of vincristine and has caused fatal adverse reactions.[10]

Increased intracellular lymphocyte concentrations. Because immunosuppressants like cyclosporine function by inhibiting *intracellular* T-cell receptors, it is not the plasma drug concentration that predicts pharmacological response, but the intracellular drug concentration of T-cells. T-cell plasma membranes express P-gp, so P-gp deficient animals will accumulate higher concentrations of P-gp substrates (i.e., cyclosporine or tacrolimus) within their T-cells relative to animals with normal P-gp function. Clinically, this manifests as unexpectedly excessive immunosuppression despite treatment with a routine dose and despite plasma drug concentrations within the "therapeutic" range.[11]

4. How to Prevent P-gp-mediated Adverse Drug Reactions

First, the clinician must determine the P-gp status of the canine or feline patient, their overall health, and the P-gp substrate status of the drug(s) being administered. If a P-gp substrate drug is being administered to a patient with P-gp deficiency or if two or more P-gp substrate drugs are being

administered to any dog or cat, then either selecting alternative drugs or modifying drug doses may be necessary. Determining the P-gp status of dogs and cats is a straightforward and inexpensive process for pet owners and veterinarians but determining the P-gp substrate status of a drug may not be. While the P-gp substrate status of human drugs is often included in the label information, the corresponding information is not available for canine or feline drug products. Inclusion of P-gp substrate information on the label of drugs intended for canine and feline patients could prevent serious and potentially fatal adverse drug reactions in dogs and cats. Until then, our website (https://prime.vetmed.wsu.edu/) endeavors to provide a list of drugs that have been documented (and peer-reviewed) to be P-gp substrates. We also maintain a list of drugs off-line that we have studied and determined to be P-gp substrates but have not yet been peer-reviewed. For the latter we provide information on a case-by-case basis to pet owners and veterinarians.

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