Top 5 Breed-Specific Considerations to Avoid Adverse Drug Effects

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Adverse drug effects can increase morbidity and mortality in dogs, cause emotional stress for pet owners, and increase cost of care. Many (but not all) adverse drug effects can be predicted and therefore prevented. Genetic testing can be used to help identify possible drug effects and determine whether dose adjustments or alternative drug therapies are needed.

Following are the top 5 adverse drug effects that are more likely to occur in specific dog breeds, according to the author.

1 *MDR1* Mutation & Enhanced Susceptibility to CNS Toxicity (Primarily in Herding Breeds)

P-glycoprotein, encoded by the multidrug sensitivity gene (*MDR1* gene, also known as *ABCB1* gene), functions as a drug transport pump at the blood-brain barrier, preventing potentially toxic compounds from gaining access to the brain.[1] The *MDR1* gene mutation (*ABCB1-1*Δ) results in production of dysfunctional

TOP 5 BREED-SPECIFIC CONSIDERATIONS TO AVOID ADVERSE DRUG EFFECTS

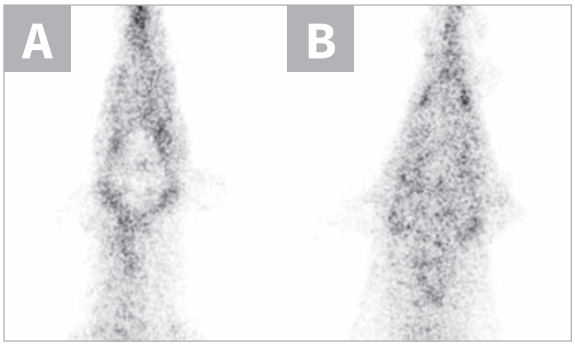
1. *MDR1* Mutation & Enhanced Susceptibility to CNS Toxicity (Primarily in Herding Breeds)
2. *CYP2B11* Deficiency in Greyhounds & Other Sighthounds
3. *MDR1* Mutation & Enhanced Susceptibility to Drugs Eliminated via Biliary Excretion (Chemotherapeutics & Other Drugs)
4. Delayed Postoperative Bleeding in Greyhounds & Other Sighthounds
5. Sulfonamide Hypersensitivity in Doberman Pinschers

TABLE 1

DOG BREEDS KNOWN TO CARRY THE *MDR1* MUTATION[24-26]

Breed	Approximate Frequency (%)
Collie	70
Windsprite*	65
Australian shepherd (all sizes)	50
McNab	30
Silken windhound	30
English shepherd	15
Shetland sheepdog	15
German shepherd dog	10
Herding crossbreed	10
Crossbreed	5
Old English sheepdog	5
Border collie	<5

*Formerly longhaired whippet



▲ **FIGURE 1** Nuclear scintigraphic images of the brain and surrounding tissue in collies after IV injection of the radiolabeled P-glycoprotein substrate sestamibi (^{99m}Tc-sestamibi). P-glycoprotein restricts ^{99m}Tc-sestamibi entry into brain tissue of the *MDR1* wild-type dog (***A***), whereas lack of P-glycoprotein allows ^{99m}Tc-sestamibi to enter brain tissue of the *MDR1* mutant/mutant dog (***B***).

P-glycoprotein and affects many herding breed dogs (***Table 1***) and some nonherding breeds.[2] Drugs that are P-glycoprotein substrates achieve higher brain concentrations in dogs with the *MDR1* mutation (heterozygous or homozygous) than in dogs without the mutation.[1] When P-glycoprotein substrate drugs exert CNS effects, those effects are more pronounced in dogs with the *MDR1* mutation unless the dosage is decreased appropriately.[1,3] Thus, dose reductions should be made when possible or an alternative drug should be selected. A nuclear scintigraphy study demonstrated that wild-type *MDR1* homozygotes (*MDR1* normal/normal) have a fully functional blood-brain barrier with essentially no radioactivity in the brain, whereas *MDR1* mutant homozygotes (*MDR1* mutant/mutant) have brain radioactivity levels comparable with surrounding tissue, demonstrating a dysfunctional blood-brain barrier with respect to P-glycoprotein substrates (***Figure 1***).[1] Although many P-glycoprotein substrate drugs (***Table 2***) exert CNS effects and cause neurologic toxicity in dogs with the *MDR1* mutation, some do not and can therefore be administered at usual dosages. *MDR1* genotyping should be performed to identify at-risk dogs prior to treatment with P-glycoprotein substrate drugs.[4]

2 *CYP2B11* Deficiency in Greyhounds & Other Sighthounds

Greyhounds recover more slowly than other dog breeds after receiving certain injectable anesthetic drugs (eg, thiopental, thiamylal, propofol).[5,6] Accumulating evidence suggests this is largely due to decreased liver expression of cytochrome P450 2B11 (CYP2B11; a major drug-metabolizing enzyme) in affected dogs.[7] CYPB11 metabolizes a range of anesthetic drugs, including propofol, ketamine, midazolam, and medetomidine.[7-9] A mutation in the *CYP2B11* gene (*CYP2B11-H3*) that decreases CYP2B11 expression in vitro was recently identified in greyhounds and certain other sighthound breeds.[10] The mutation has higher prevalence in American Kennel Club-registered greyhounds than in National Greyhound Association-registered greyhounds.[10] This difference may be a consequence of selective breeding for

different purposes (ie, conformation vs racing speed). *CYP2B11-H3* was also identified in >50% of the sighthound breeds that were evaluated, as well as in some nonsighthound breeds at a lower prevalence (***Table 3***, next page).[10] Although in vivo validation studies are still needed, *CYP2B11* genotyping might aid in identification of individual dogs likely to demonstrate prolonged effects when receiving drugs that require the CYP2B11 enzyme for efficient elimination.

3 *MDR1* Mutation & Enhanced Susceptibility to Drugs Eliminated via Biliary Excretion (Chemotherapeutics & Other Drugs)

Adverse drug effects caused by the *MDR1* gene mutation are not limited to neurologic toxicity. Because P-glycoprotein actively transports substrate drugs into the bile, dogs with the *MDR1* mutation have decreased biliary clearance of those drugs normally eliminated via biliary excretion

TABLE 2

DRUGS & THEIR POTENTIAL ADVERSE EFFECTS IN DOGS WITH THE *MDR1* MUTATION[1-3,12,13]

Drug Category	Specific Agent
Neurologic toxicity	
Analgesic	Butorphanol
Sedative	Acepromazine
Antiparasitic (macrocyclic lactones)*	Doramectin Eprinomectin Ivermectin Milbemycin Moxidectin Selamectin
Antiparasitic (octadepsipeptide)	Emodepside
GI (antidiarrheal)	Loperamide
GI (antiemetic)	Ondansetron
Other toxicities (eg, myelosuppression, GI)	
Chemotherapeutic (antibiotic/antineoplastic agents)	Doxorubicin Actinomycin D
Chemotherapeutic (vinca alkaloids)	Vincristine Vinblastine Vinorelbine
Chemotherapeutic (taxanes)	Paclitaxel Docetaxel
Immunosuppressant	Cyclosporine

*Should only be administered at label doses; label doses for heartworm prevention undergo safety studies in dogs with the *MDR1* mutation as required by the FDA.

TABLE 3

DOG BREEDS KNOWN TO HARBOR THE *CYP2B11-H3* MUTATION[10]

Breed	*CYP2B11-H3* Frequency (%)
Sighthounds	
Greyhound (American Kennel Club-registered)	59
Rhodesian ridgeback	28
Borzoi	26
Greyhound (National Greyhound Association-registered)	17
Italian greyhound	11
Whippet	11
Scottish deerhound	11
Silken windhound	7
Spanish sighthound	6
Windsprite*	5
Ibizan hound	3
Other breeds	
Golden retriever	12
Border collie	8
Labrador retriever	6
Crossbreed	2

*Formerly longhaired whippet

CYB5R3 = cytochrome b_5 reductase
EACA = epsilon aminocaproic acid

(***Figure 2***), resulting in increased overall drug exposure.[11] Affected dogs experience susceptibility to associated adverse effects when the drugs are administered at recommended dosages. This effect has been documented with vincristine (bone marrow suppression),[12] cyclosporine A (immunosuppression),[13] doxorubicin (bone marrow suppression, GI toxicity; anecdotal), and others. Affected dogs should receive decreased dosages of these drugs as previously described.[14] *MDR1* genotyping should be performed to identify at-risk dogs prior to treatment with P-glycoprotein substrate drugs.[4]

4 Delayed Postoperative Bleeding in Greyhounds & Other Sighthounds

Significant and occasionally life-threatening postoperative bleeding that starts 24 to 48 hours following surgery has been identified as a significant health concern in greyhounds.[15] Clinical studies suggest the incidence of delayed bleeding can range from 26% following routine gonadectomy[16] to ≤67% following limb amputation for osteosarcoma.[17] Current evidence indicates reduced α_2-antiplasmin activity in the plasma of affected dogs, suggesting that bleeding may be secondary to enhanced fibrinolysis of newly formed clots.[18,19] Both retrospective and placebo-controlled prospective studies have established the effectiveness of treatment with epsilon aminocaproic acid (EACA; ***Table 4***), an antifibrinolytic drug, for preventing delayed bleeding via increased clot strength.[16,17] Anecdotal evidence suggests Scottish deerhounds are also susceptible to delayed postoperative bleeding and may benefit from preventive antifibrinolytic treatment (EACA or tranexamic acid).[20] A breed-based predisposition to this condition has not yet been reported, but it

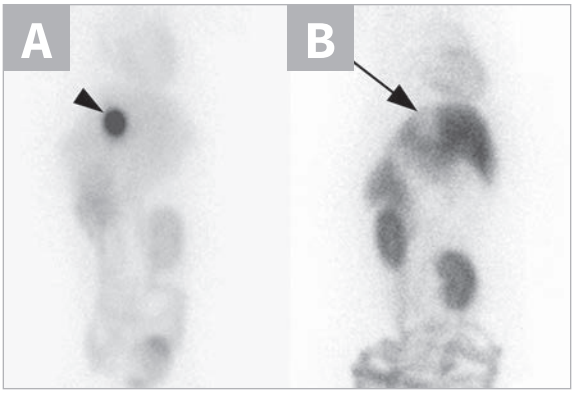
is likely caused by a mutation in a gene that regulates fibrinolysis. Although current recommendations are to treat all affected breed dogs, genetic testing for the putative mutation could be used to identify individual dogs that would benefit from prophylactic antifibrinolytic treatment. Identifying dogs of affected breeds that do not require treatment (ie, those that lack the mutation) could also minimize the potential risk for adverse effects of antifibrinolytic drugs (eg, thromboembolism).

5 Sulfonamide Hypersensitivity in Doberman Pinschers

Hypersensitivity to sulfonamides can manifest as fever, keratoconjunctivitis sicca, hepatotoxicity, skin eruptions, blood dyscrasias, and/or arthropathy and may lead to a mortality rate of 21% in Doberman pinschers.[21] Doberman pinschers have been reported to be particularly predisposed to sulfonamide hypersensitivity, but this is not limited to this breed.[22] A recent study identified an association between a mutation in the cytochrome b_5 reductase (*CYB5R3*) gene and sulfonamide hypersensitivity.[23] This mutation was determined to be overrepresented in Doberman pinschers and in dogs of other breeds that experienced sulfonamide hypersensitivity reactions. Although *CYB5R3* encodes a drug-metabolizing enzyme, this enzyme does not appear to be directly involved in the metabolism of sulfonamides.[23] Instead, it is likely to be linked to a polymorphism that is directly involved in sulfonamide clearance. When possible, sulfonamides should be avoided in Doberman pinschers.

Conclusion

The physical characteristics of certain dog breeds can provide clues for breed-specific susceptibility to certain adverse drug reactions. Genotyping for specific variants can be used to inform appropriate drug selection and/or dosage modifications. Preventive treatment with EACA or tranexamic acid should be considered in greyhounds and Scottish deerhounds undergoing major surgery after assessment of the risks and benefits to individual dogs.



▲ **FIGURE 2** Nuclear scintigraphic images of the ventral abdomen of an *MDR1* wild-type dog (***A***) and an *MDR1* mutant/mutant dog (***B***) 2 hours after IV injection of the radiolabeled P-glycoprotein substrate sestamibi (^{99m}Tc-sestamibi). P-glycoprotein efficiently pumps ^{99m}Tc-sestamibi into the gallbladder in the *MDR1* wild-type dog (***arrowhead***). In stark contrast, biliary excretion is essentially nonexistent in the *MDR1* mutant/mutant dog (***arrow***).

TABLE 4

EACA DOSE RATES CURRENTLY USED FOR THE PREVENTION OF DELAYED POSTOPERATIVE BLEEDING IN GREYHOUNDS[27] & SCOTTISH DEERHOUNDS[20]

Dog Weight	EACA Dose*
55-79 lb (25-35 kg)	500 mg (1 tablet)
80-104 lb (36-47 kg)	750 mg (1.5 tablets)
>105 lb (>47 kg)	1,000 mg (2 tablets)

*EACA tablets are administered PO every 8 hours for 5 days starting on the day of surgery.

See next page for references

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