Adverse Drug Reactions in Veterinary Patients Associated with Drug Transporters

Katrina L. Mealey, DVM, PhD

KEYWORDS

• ATP-binding cassette transporters • ABCB1 • ABCG2 • Solute carrier
• Pharmacogenetics

KEY POINTS

- Because drug transporters play an important role in drug absorption, distribution, and excretion, alterations in drug transporter function can result in adverse drug reactions.
- The ABCB1 polymorphism in dogs and drug interactions involving P-glycoprotein can enhance the toxicity of many drugs.
- The species-wide ABCG2 defect in cats is responsible for fluoroquinolone-induced retinal toxicity.
- Because drug transporters play an important role in drug disposition, a thorough understanding of drug transporters in companion animals is critical in drug discovery and development.

INTRODUCTION

Most veterinarians consider an adverse drug reaction to be something that happens when excessive drug accumulation results in drug toxicity. Another type of adverse drug event, lack of efficacy, occurs when a drug fails to reach effective concentrations at the site of action. Both types of adverse drug events (lack of drug efficacy or drug toxicity) can be deleterious to the patient, so both should be avoided. Optimal drug therapy is achieved when drugs reach effective concentrations at the site of action but do not reach toxic concentrations in susceptible tissues.

Any factor that influences plasma and/or tissue drug concentrations will influence the optimization of drug therapy. Some obstacles to achieving optimal drug therapy have been discussed in previous articles. Alterations in the function of drug-metabolizing enzymes, whether due to genetic polymorphisms or drug-drug

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Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Washington State University, Pullman, WA 99164-6610, USA
E-mail address: kmealey@vetmed.wsu.edu

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interactions, can increase or decrease plasma and tissue drug concentrations. Other factors that may influence plasma and tissue drug concentrations include liver disease, renal disease, patient age, dietary interactions, and interactions with nondrug supplements such as herbals and so-called nutraceuticals (nutritional supplements).

For many drugs used in veterinary practice, plasma and tissue concentrations are also highly dependent on the activity of drug transporters. These transporters are large transmembrane proteins that function as either drug efflux or uptake pumps.[1] The transporters are expressed to some degree on a variety of tissues while being highly expressed on the surface of tissues that are responsible for drug absorption, metabolism, and excretion, such as liver, intestinal lumen, biliary canaliculi, and renal tubular epithelium.[2] In addition, these transporters are expressed on the endothelium of "sanctuary" or protected sites, including brain, retina, testes, and placenta (**Fig. 1**).[3,4]

Two superfamilies of drug transport proteins are considered to be of major importance in determining drug disposition in human patients: the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily and the solute carrier (SLC) superfamily. Research in human patients and/or knockout mice models have demonstrated clinically significant changes in drug disposition resulting from altered function of these drug transporters.[4] Although specific examples of drug transporter defects in veterinary species are scarce, those that have been documented dramatically illustrate the importance of the ABC transporter family in drug disposition. Altered function of drug transporters either intrinsically (ie, genetic polymorphisms) or extrinsically (ie, drug-drug interactions) can result in decreased drug efficacy or increased risk of toxicity in affected patients. Whether one can extrapolate data from human or mouse studies and apply it to other species depends on the specific transporter and drug involved, because there may be species differences in tissue expression and/or substrate specificity of the transporter.

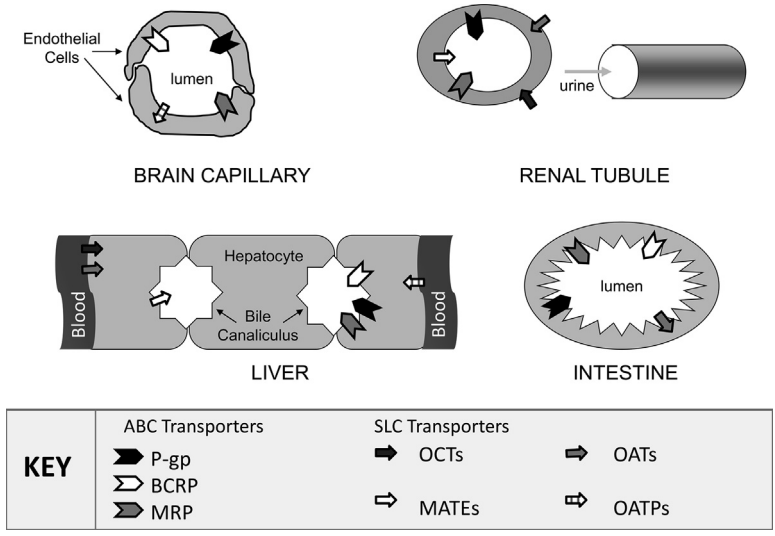

Fig. 1. Major drug transporters of the ABC and SLC superfamilies, their tissue localization, and direction of drug transport. ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; MATEs, multidrug and toxin extrusion transporters; MRP, multidrug resistance–related protein; OATs, organic anion transporters; OATPs, organic anion–transporting polypeptides; OCTs, organic cation transporters; P-gp, P-glycoprotein; SLC, solute carrier.