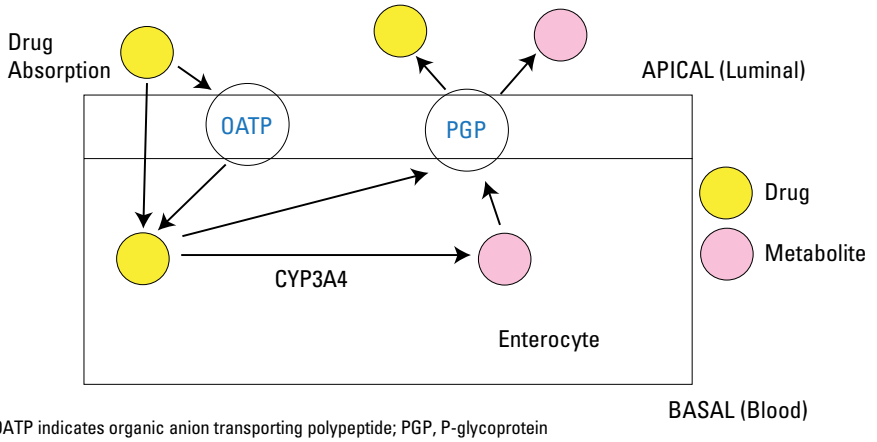
Drug Transporters: The Final Frontier for Drug Interactions

John R. Horn, PharmD, FCCP, and Phillip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.

Figure

Transporters in the Small Intestinal Enterocyte



OATP indicates organic anion transporting polypeptide; PGP, P-glycoprotein

The knowledge of the specific enzymes responsible for drug metabolism has expanded over the past 15 years. We now understand that many drugs are actively transported into and out of cells by a variety of transporter proteins susceptible to reduced or enhanced activity upon exposure to certain drugs.

Drug transporters are usually either uptake or efflux. The Figure shows some of the transporters found at the apical (luminal) side of the enterocytes in the small intestine. P-glycoprotein (P-gp) is an efflux transporter that takes drug molecules from the cell cytoplasm and transports them back into the intestinal lumen for excretion. For some orally administered drugs, this limits their bioavailability. The organic anion transporting polypeptide and organic cation transporter are uptake transporters that mediate the transport of molecules into the cell. In addition to the enterocyte, these and other transporters are found on the apical side of renal tubular cells and the bile canaliculi. Transporters can also be found on the luminal surface of capillary endothelial cells in the brain and in renal tubular cells.

P-gp transports many drugs that are substrates of CYP3A4. When a drug that is a substrate of P-gp and CYP3A4 is taken orally, it has to diffuse through the enterocytes to gain access to the systemic circulation. P-gp and CYP3A4 act as barriers to the systemic exposure of exogenous substances including drugs. Some drug molecules will be transported out of the enterocyte by P-gp and be eliminated without absorption. Other molecules will be metabolized by CYP3A4 in the enterocyte and lost to pharmacologic activity. P-gp helps modulate the number of drug molecules in the enterocyte and therefore helps to prevent saturation of CYP3A4. This results in an increase in the efficiency of first-pass drug metabolism. CYP3A4 concentrations decrease from the proximal to distal portions of the intestine. P-gp content increases from the proximal to distal intestine. Thus, where an excess of CYP3A4 is available for metabolism, less P-gp is present. Conversely, where CYP3A4 concentrations are lower, more P-gp is found to prevent saturation of the enzyme.

An inhibitor of P-gp will increase the bioavailability of a P-gp substrate, whereas induction of P-gp will reduce the bioavailability of a substrate drug. Digoxin is a drug that is a substrate of P-gp but is not metabolized by CYP3A4. P-gp inhibits its bioavailability and contributes to its renal and biliary secretion. The coadministration of the P-gp inhibitors erythromycin or clarithromycin to patients receiving chronic digoxin has been noted to result in an increase in serum digoxin concentrations.[1] In another study, clarithromycin increased the area under the plasma concentration-time curve (AUC) following oral digoxin administration by about 1.7-fold.[2] The AUC of digoxin administered intravenously was increased 1.2-fold during clarithromycin dosing. The ability of quinidine to increase digoxin concentrations has been well described. Quinidine not only increases the bioavailability of digoxin, it also reduces the biliary and renal secretion of digoxin by inhibiting P-gp activity. Because P-gp is present in the endothelium of capillaries in the brain and functions as part of the blood–brain barrier, a P-gp inhibitor may enable a greater percentage of digoxin to reach the brain causing increased central nervous system side effects. Conversely, P-gp inducers can reduce digoxin plasma concentrations.[3] ■

For a list of references, go to www.PharmacyTimes.com.

online For a table listing common drugs that are known to be substrates, inhibitors, or inducers of P-gp, please visit www.PharmacyTimes.com/DrugTransporters.

Table

Substrates, Inhibitors, and Inducers of P-glycoprotein

Substrates	Inhibitors	Inducers
Colchicine	Amiodarone	Carbamazepine
Cyclosporine	Clarithromycin	Rifampin
Digoxin	Erythromycin	St. John's wort
Fexofenadine	Ketoconazole	Tipranavir
Indinavir	Quinidine	
Morphine	Saquinavir	
Sirolimus	Verapamil	