Drug Transporters: The Final Frontier for Drug Interactions—Part 2

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In the first article on drug transporters, we focused on the efflux transporter P-glycoprotein (December 2008 *Pharmacy Times*; see www.PharmacyTimes.com/DrugTransporters). This time we are going to examine the uptake transporters. These transporters actively pump drugs into cells, including hepatocytes and renal tubular cells. Drugs can then be secreted into the bile, metabolized (hepatocyte), or secreted into the urine (renal tubular cell). These uptake transporters are generally divided into those that transport anionic molecules (organic anion transporters [OATs] or organic anion transporting polypeptides [OATPs]) and those that transport cationic molecules (organic cation transporters [OCTs]). OATPs are primarily found in the liver, while OATs and OCTs can be found in the liver, kidney, and brain.

Examples of OAT substrates include methotrexate and nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are secreted by the renal tubular cells as their primary method of elimination. When 2 drugs that are both substrates for the same OAT are coadministered, the possibility for competitive inhibition of the transporter, and hence of drug elimination, will be present. Numerous reports have described an interaction between NSAIDs and methotrexate that can result in severe methotrexate toxicity. This outcome is the result of the NSAID competing for OATs and reducing the renal clearance of methotrexate.[1] Several HMG-CoA reductase inhibitors including pravasta-

tin and cerivastatin are partially eliminated by OATs. Cyclosporine is an inhibitor of OAT and has been demonstrated to increase the plasma concentrations of these statins by over 5-fold.[2,3] The ability of probenecid to reduce the renal clearance of penicillins and cephalosporins is at least partially due to competition for OATs in the renal tubule.[4]

OCTs transport a number of drugs including cimetidine, metformin, procainamide, and triamterene from the plasma into hepatocytes and renal tubular cells. As with cytochromes, a variety of different OAT and OCT transporters exist. Metformin's uptake into the liver, where it exerts its pharmacologic effect, is mediated by OCT1, while its elimination via the kidney is primarily due to OCT2. The capacity of OCT2 to transport metformin is at least 10 times greater than OCT1. Thus, OTC2 and the renal elimination of metformin are primarily responsible for its pharmacologic properties.[5] Cimetidine also is a substrate for OCT and can compete with metformin for both OCT1 and OCT2. Because OCT2 is primarily responsible for metformin's elimination, competition from cimetidine will result in reduced renal clearance of metformin and elevated plasma concentrations.[6,7] Procainamide is another known OCT substrate. Its renal clearance has been reduced following coadministration with several drugs, including amiodarone,[8] levofloxacin,[9] and cimetidine.[10]

The clinical outcome of drug interactions based on OAT or OCT inhibition will depend on the pharmacologic properties of the object drug. For example, inhibiting the hepatic uptake of a drug may reduce its metabolism, leading to higher plasma concentrations. If the site of action of the object drug is intrahepatic (eg, HMG-CoA reductase inhibitors or oral hypoglycemic drugs), how-

ever, a reduction in the desired pharmacologic effect also may occur, despite increased plasma concentrations.

Nevertheless, the resulting increase in the drug's plasma concentration may lead to an increase in side effects unrelated to the drug's therapeutic effect. Relating to the examples given above, patients taking statins might have an increased risk of myopathy, whereas those on metformin could have a greater risk of developing lactic acidosis. The effect of inhibited object drug renal clearance will depend on the percent of drug eliminated via the kidney and its therapeutic window. In general, clinically significant effects will occur with drugs having at least 50% of their elimination via renal secretion and demonstrate a narrow therapeutic window.

Finally, although a large number of drugs have been shown in vitro to be potential inhibitors of OAT and OCT, their concentrations in vivo are often too low to produce significant competition for transport with other drugs. ∎