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Original Contribution

A clinician's guide to statin drug-drug interactions

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Abstract: The statins are widely used worldwide to reduce risk for cardiovascular events in both the primary and secondary prevention settings. Although generally quite safe, the statins can be associated with a variety of serious side adverse effects, including myalgia, myopathy, and changes in plasma enzymes of hepatic origin. Although rare, the most serious of these is rhabdomyolysis. Several drugs can interfere with the metabolism and disposal of the statins, thereby increasing risk for adverse events. It is important that clinicians treating patients with statins be aware of the potential for drug-drug interactions between each statin and specific other drugs and take measures to prevent them. The prediction of potential drug-drug interactions derives from basic pharmacokinetic principles. Certain drug interactions are predicted by measuring the effect of interacting drugs on blood plasma concentrations of the statin. Individual patient variations resulting in part from polymorphisms in the metabolizing enzymes confound some of these predictions. Based on these known effects, a new classification for predicting statin drug interactions is proposed. This report discusses likely prescription and nonprescription interactions as well as potential alternatives for special populations.
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The metabolism of statins is described by basic pharmacokinetic principles. Pharmacokinetic measures involve the rate of absorption, distribution, metabolism, and excretion for these molecules. With the exception of lovastatin and simvastatin, which are given as prodrugs, all statins are administered in the active hydroxyl acid form (Fig. 1). Once ingested, various other factors affect their absorption, distribution, metabolism, and excretion. Statins are moderately to well absorbed, with the time to reach peak plasma concentration averaging about 4 hours. When consumed with food, lovastatin is more efficiently absorbed. Rosuvastatin, pitavastatin, and simvastatin are not affected by food, whereas fluvastatin, pravastatin, and atorvastatin have a reduced absorption with food. Once absorbed into the portal venous system, while all statins undergo extensive first-pass metabolism, the rate of this first-pass hepatic uptake inversely relates to the systemic bioavailability. Therefore, the lower systemic

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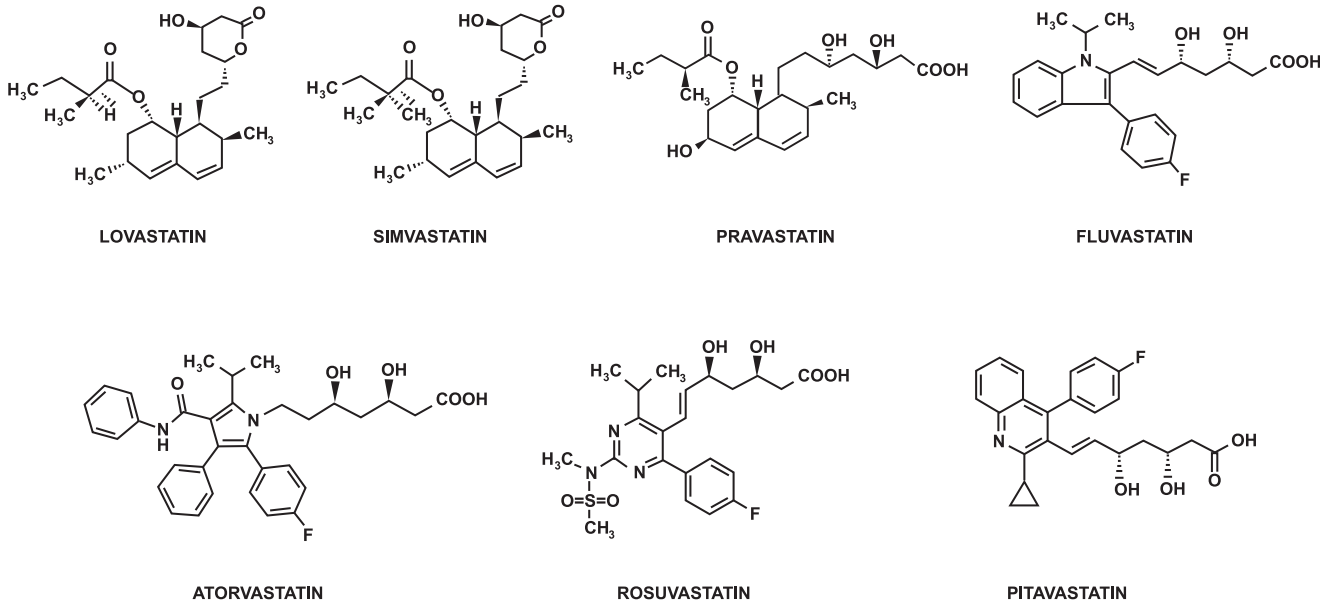

Figure 1 Chemical structures of statins. Type I naphthalene statins (lovastatin, pravastatin, simvastatin); type II non-naphthalene (atorvastatin, pitavastatin, rosuvastatin, fluvastatin). Lovastatin and simvastatin are prodrugs.

bioavailability of fluvastatin (19%–29%) may suggest a more efficient first-pass metabolism. Pravastatin is the only statin not protein bound, which imparts a low systemic exposure to the medication.[1]

Statins undergo a complex metabolic fate, beginning with absorption, followed by hepatic uptake, metabolism, and eventually elimination from the liver into either the systemic circulation or the biliary tract (Fig. 2).[2] During the absorption process, most statins are substrates for the P-glycoprotein (P-gp) efflux transporter, which reduces absorption into the portal circulation. Enterocyte cytochrome P450 (CYP) may metabolize some statins before eventual absorption into the portal circulation. Hepatic uptake is mediated by several transporters, including organic anion transporting polypeptide 1B1 (OATP1B1), which facilitates metabolism by additional CYP enzymes (phase I metabolism) and glucuronidation (phase II metabolism). Additional efflux transporters on the canalicular membranes of hepatocytes facilitate biliary excretion.

Some interacting drugs, such as cyclosporine, inhibit multiple sites of statin disposition (Table 1),[3] resulting in larger increases in serum concentrations and subsequent risk for myopathy. Cyclosporine is an inhibitor of OATP1B1, OATP1B3, P-gp, and adenosine triphosphate

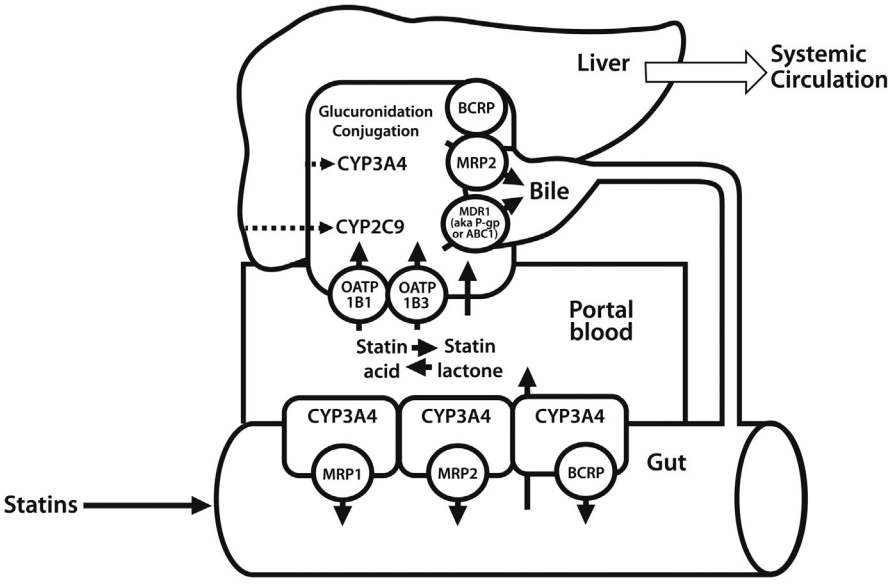

Figure 2 Metabolic fate of statins. BCRP, breast cancer–resistant protein, encoded by gene ABCG2; MDR1, multidrug-resistant protein 1; MRP2, multidrug-resistant–associated protein 2, encoded by gene ABCC2; OATP1B1, organic anion transporter protein 1B1, formerly known as OATP2, encoded by SLCO1B1 gene; OATP1B3, organic anion transporter protein 1B3, encoded by the SLCO1B3 gene; P-glycoprotein, P-gp, encoded by the ABCB1 gene. Adapted from Niemi et al.[2]