Be on the Alert for Increasing Drug Interactions with Statins

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The availability of generic versions of simvastatin and lovastatin will encourage health care providers to place these 2 statins on their preferred-drug lists. This move, combined with the increased focus on the importance of lowering lipid levels, undoubtedly will result in more patients being prescribed 1 of these 2 statins. Simultaneously, the seemingly endless downward revisions of target low-density lipoprotein (LDL) levels inevitably will result in statin-dose escalation.

Statins are very safe drugs that occasionally produce adverse events. Toxicity involving skeletal muscles most commonly results in pain, weakness, or cramps with or without creatine kinase elevations (myalgia or myopathy), but it usually is not associated with long-term sequelae. Rhabdomyolysis is a much more severe form of muscle toxicity that is quite rare. Both types of statin toxicity, however, appear to be drug-dose– and plasma-concentration–related. The coadministration of drugs that interact with statins can increase the risk of muscle toxicity by up to 10-fold.[1,2]

Who Is at Risk?

Patients Taking Simvastatin and Lovastatin

Both of these drugs have very low bioavailability (~5%) and are primarily dependent on CYP3A4 for their metabolism. Due to presystemic metabolism, patients given a 20-mg dose may absorb only 1 mg into their systemic circulation. The remaining 19 mg are metabolized. If a CYP3A4 inhibitor, however, is coadministered with the simvastatin or lovastatin, the amount of drug absorbed may increase dramatically. As a consequence, potent inhibitors of CYP3A4 (eg, itraconazole) can produce 10-fold increases in the plasma concentrations of these statins. Even modest CYP3A4 inhibitors (eg, diltiazem) can cause a 4- to 6-fold increase.[3-5] This increase would be the equivalent of taking a 100- to 200-mg daily dose of the statin.

The large potential magnitude of this interaction explains why nearly all cases of rhabdomyolysis occur in patients taking drugs known to interact with statins.

Patients Taking >20-mg Doses of Simvastatin and Lovastatin

Larger doses of statins will be required as target LDL levels are set lower. Patients on higher doses (eg, 80 mg) of simvastatin appear to be at an increased risk of toxicity. Patients taking 20 or 40 mg daily exposed to an interacting drug need only a 4- or 2-fold increase, respectively, in plasma concentration to be in the high-risk group. Drinking a glass of grapefruit juice daily will produce this degree of increase.[6] If high doses of simvastatin or lovastatin are required to reach lipid goals, the clinician should consider switching the patient to a more potent statin (eg, atorvastatin or rosuvastatin) or adding a second lipid-lowering agent (eg, ezetimibe).

Patients Taking Any Statin Plus Other Lipid-lowering Agents

Although the mechanisms have not been completely elucidated, the administration of fibrates (gemfibrozil > fenofibrate) and rarely niacin has been associated with muscle toxicity, both when used alone and with statins.[5] It is likely that a combination of pharmacokinetic and pharmacodynamic effects is responsible.

Table

Commonly Prescribed CYP3A4 Inhibitors

Amprenavir	Indinavir
Atazanavir	Itraconazole
Clarithromycin	Ketoconazole
Cyclosporine	Nefazodone
Diltiazem	Quinupristin
Erythromycin	Ritonavir
Fluconazole	Telithromycin
Fluvoxamine	Verapamil
Grapefruit juice	Voriconazole

Adapted from reference 8.

What Should You Recommend to Patients Taking Statins?

- Patients should alert a health care professional if they experience muscle pain or weakness
- Patients taking simvastatin or lovastatin who are prescribed CYP3A4 inhibitors should stop taking the statin during the time the inhibitor is administered. If the inhibitor is to be administered over a long term, one should consider switching to an alternative statin that is not metabolized by CYP3A4 (eg, pravastatin, fluvastatin, rosuvastatin) or to low-dose atorvastatin.
- Patients who experience muscle toxicity should discontinue all statins until the symptoms clear, which may require 6 to 8 weeks. A trial of an alternative statin has been demonstrated to be effective in avoiding muscle symptoms about 50% of the time[7] (Table[8]). PT

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