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Statins and Macrolide Antibiotics: Defining the Risk

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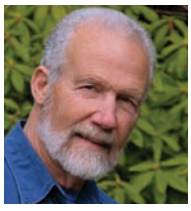

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In 2006, this column discussed the risk of drug interactions with statins, particularly lovastatin and simvastatin, combined with drugs that inhibit CYP3A4.[1] The availability of generic simvastatin and its subsequent listing on formularies as a preferred drug would increase the number of patients exposed to high doses of statins or the concurrent administration of CYP3A4 inhibitors.[2] Our recommendation to avoid lovastatin and simvastatin during coadministration of CYP3A4 inhibitors was echoed in a labeling change in 2011. While the magnitude of potential interactions and the potential risk of muscle toxicity supported the recommendations, no specific risk data were available.

Risk of Adverse Outcomes

A recent study evaluated the risk of statin toxicity during the coadministration of macrolide antibiotics.[3] The investigators examined the records of patients older than 65 years who were regularly taking statins (lovastatin, simvastatin, atorvastatin) and who received clarithromycin or erythromycin (>75,000 patients)—macrolides known to inhibit CYP3A4—and about 70,000 patients receiving azithromycin, which does not inhibit CYP3A4. The primary outcome for the study was hospitalization with rhabdomyolysis, with secondary outcomes including hospitalization for acute kidney disease, hyperkalemia, and mortality. The occurrence of each outcome in patients taking azithromycin plus a statin was compared with patients taking clarithromycin or erythromycin plus a statin. Patients in both groups were well matched for demographics, comorbidities, statin dose, and concurrent medications. The administration of clarithromycin or erythromycin resulted in a higher risk of rhabdomyolysis (relative risk: 2.17), with the absolute risk being quite small (0.03% vs 0.01% of patients). The occurrence of acute kidney disease was also increased (0.26% vs 0.46%) when erythromycin and clarithromycin were administered with statins compared with azithromycin plus a statin. It is likely that the incidences of the outcomes are underestimated because disease codes were used to identify patients.

Management of the Interaction

The interaction between macrolides that inhibit CYP3A4 and statins metabolized by this enzyme infrequently produces a serious adverse event. It is not known how often the macrolide–statin combination would produce less severe muscle toxicity, such as weakness or pain, but the occurrence would be expected to be more frequent. The incidence of a severe outcome from this interaction is uncommon and appears to be easily avoided. The study by Patel et al demonstrates that choosing to use an antibiotic that does not inhibit CYP3A4 (eg, azithromycin) is a simple way to avoid the potential interaction with statins that are CYP3A4 substrates. Other antimicrobial agents that inhibit CYP3A4 include fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral), posaconazole (Noxafil), voriconazole (Vfend), telithromycin (Ketek), quinupristin/dalfopristin (Synercid), and isoniazid. In addition, many antiviral agents inhibit CYP3A4, including amprenavir (Agenerase), atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase), boceprevir (Victrelis), telaprevir (Incivek), and tipranavir (Aptivus). None of these agents should be administered to patients taking statins metabolized by CYP3A4.

The most commonly prescribed statin in Patel's study was atorvastatin. Unfortunately, the authors were unable to assess the risk of adverse outcomes for each statin because of limited sample size. However, CYP3A4 inhibitors such as macrolides increase the plasma concentrations of lovastatin and simvastatin by up to 10-fold while only increasing the concentration of atorvastatin by up to 4-fold. This difference in the magnitude of the interaction effect is most likely due to the greater first-pass metabolism of lovastatin and simvastatin (>95%) compared with atorvastatin (~85%).[4] Although atorvastatin is likely to have a lower risk of adverse interaction than lovastatin or simvastatin, it is not possible to declare it free of risk. Using a statin that is not a CYP3A4 substrate (pravastatin [Pravachol], fluvastatin [Lescol], or rosuvastatin [Crestor]) may lessen the risk of an interaction with the macrolides. One should also consider stopping the statin during the time of antimicrobial administration and for a few days afterward.

Summary and Recommendations

The risk of a serious adverse event caused by the coadministration of erythromycin or clarithromycin with statins that are substrates for CYP3A4 is small but the potential severity is great enough that an attempt should be made to avoid the interaction. Temporarily withholding the statin, selecting a statin that is not a CYP3A4 substrate, or selecting a macrolide antibiotic that is not a CYP3A4 inhibitor are all reasonable alternatives. n

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.