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Lomitapide Drug Interactions

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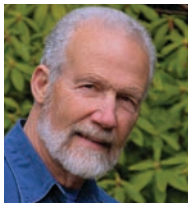

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Familial hypercholesterolemia is a difficult disease to treat, usually requiring multiple medications to reduce low-density lipoprotein cholesterol. A new drug, lomitapide (Juxtapid), has been approved for this disorder, and the drug is susceptible to many drug–drug interactions. Although lomitapide is only available through a restricted access program, patients on lomitapide may obtain prescriptions for potentially interacting drugs from other providers, so we all must be aware of lomitapide interactions.

Interactive Properties

Lomitapide is a substrate for CYP3A4, and it also inhibits CYP3A4 and P-glycoprotein (P-gp). These properties suggest that lomitapide will have many drug interactions. Given that lomitapide can produce dose-dependent hepatotoxicosis, it is imperative that close attention be given to potential lomitapide drug–drug interactions.

CYP3A4 Inhibitors

In a pharmacokinetic study, ketoconazole (a strong CYP3A4 inhibitor) produced a 27-fold increase in lomitapide plasma concentrations, suggesting that lomitapide is highly susceptible to inhibitors of CYP3A4.[1] Because lomitapide has dose-dependent hepatotoxicity, the product information for lomitapide states that strong or moderate CYP3A4 inhibitors are contraindicated in patients receiving lomitapide. Even weak CYP3A4 inhibitors are a concern because oral contraceptives (weak CYP3A4 inhibitors) approximately doubled lomitapide exposure. Thus, it is recommended that the maximum dose of lomitapide be 30 mg/day in patients on weak CYP3A4 inhibitors. These stringent precautions regarding CYP3A4 inhibitors are appropriate given how sensitive lomitapide is to inhibition of metabolism and the potential severity of the adverse outcomes.

CYP3A4 Substrates

Because lomitapide inhibits CYP3A4, one would expect it to increase the plasma concentrations of CYP3A4 substrates.

Simvastatin

Lomitapide approximately doubles the plasma concentrations of simvastatin. When lomitapide is used with simvastatin, the simvastatin dose should not exceed 20 mg daily (or up to 40 mg daily if, prior to lomitapide administration, the patient has tolerated 80 mg daily of simvastatin without muscle toxicosis). Lovastatin and simvastatin have very similar drug interactions, so one should expect lovastatin to interact similarly with lomitapide. Atorvastatin is also metabolized by CYP3A4, but lomitapide increased atorvastatin area under the curve by about 50%. The product information does not recommend dosage reductions for atorvastatin if it is used with lomitapide, but it is possible that an occasional patient on the combination may develop muscle toxicosis. Patients should be monitored accordingly.

> The properties of lomitapide suggest that it will have many drug interactions.

Other CYP3A4 Substrates

Although few other CYP3A4 substrates have been studied in combination with lomitapide, given that lomitapide is a CYP3A4 inhibitor, one should expect drug interactions. Particular attention should be given to CYP3A4 substrates with substantial dose-dependent toxicity, such as calcium channel blockers, carbamazepine, colchicine, certain corticosteroids (eg, budesonide, dexamethasone, fluticasone, methylprednisolone, mometasone), ergot alkaloids, immunosuppressants (eg, cyclosporine, sirolimus, tacrolimus), certain opioids (eg, alfentanil, fentanyl, methadone, oxycodone, sufentanil), pimozide, ranolazine, and vinca alkaloids (vinblastine, vincristine, vinorelbine).

P-glycoprotein Substrates

Since lomitapide inhibits P-gp, it would be expected to increase plasma concentrations of P-gp substrates such as colchicine, digoxin, imatinib, lapatinib, ranolazine, saxagliptin, and many others. It would be prudent to use conservative doses of P-gp substrates in patients receiving lomitapide.

Other Drugs

Although the mechanism of interaction has not been established, lomitapide increased warfarin plasma concentrations by about 30%. The warfarin dose may need adjustment if lomitapide is started or stopped or the dosage is changed. Because bile acid sequestrants can bind with other medications, it is recommended to separate them by at least 4 hours from administration of lomitapide.

Summary

Lomitapide has properties that predispose it to drug–drug interactions: it is a substrate for CYP3A4, and it inhibits CYP3A4 and P-gp. It also has demonstrated serious dose-dependent hepatotoxicity, so it is important that plasma concentrations not become elevated. Careful attention to drug interactions is required to minimize the risk of adverse outcomes. 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.