Flibanserin: Hypotension and Syncope with Drug Interactions

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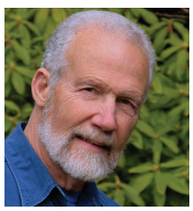

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Flibanserin (Addyi) has been approved by the FDA for the treatment of hypoactive sexual desire disorder in premenopausal women.[1] Primarily metabolized by CYP3A4 and, to a smaller extent, by CYP2C19, flibanserin appears to be an inhibitor of P-glycoprotein and perhaps CYP3A4. Adverse effects (AEs) associated with the administration of flibanserin include sedation, hypotension, and syncope. These AEs can be exacerbated by drug interactions with flibanserin.

CYP3A4 Inhibitors

The administration of ketoconazole 400 mg daily for 5 days increased the mean area under the concentration time curve (AUC) by more than 4.5-fold. The half-life of flibanserin was increased from a mean 11 hours to more than 18 hours following ketoconazole administration. Itraconazole 200 mg daily for 8 days produced a 2.6-fold increase in the AUC of flibanserin. Full therapeutic doses of itraconazole would likely produce a larger increase in AUC. Fluconazole inhibits both CYP3A4 and CYP2C19. When a fluconazole 400-mg loading dose followed by 200 mg daily for 3 days was administered with flibanserin, the mean AUC increased 7-fold and its half-life increased by 13 hours. During this study, several subjects became hypotensive, with one of the subjects becoming unresponsive with a blood pressure of 64/41 mm Hg and a heart rate of 50 beats per minute. The subject responded to fluid administration.

Other drugs that inhibit both CYP3A4 and CYP2C19 (delavirdine, fluvoxamine, INH, and voriconazole) would likely produce similarly large increases in flibanserin plasma concentrations. Patients who are poor metabolizers of CYP2C19 may demonstrate an exaggerated response to CYP3A4 inhibitors. Grapefruit juice (8 oz regular strength) increased the AUC of flibanserin by 40%. With all of these interactions, inhibition of the CYP3A4 metabolism of flibanserin resulted in increased serum concentrations. It would be prudent to avoid administering CYP3A4 inhibitors (eg, clarithromycin, erythromycin, cyclosporine, imatinib, miconazole, posaconazole, ritonavir, and voriconazole) to patients taking flibanserin.

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CYP3A4 Inducers

Rifampin 600 mg daily for 7 days reduced the mean AUC of flibanserin by 95%. Etravirine, a modest CYP3A4 inducer and weak CYP2C19 inhibitor, reduced the AUC of flibanserin by about 20%. Based on these study results, other inducers of CYP3A4—such as barbiturates, carbamazepine, bosentan, phenytoin, rifabutin, and St. John's wort—are likely to reduce the efficacy of flibanserin. CYP3A4 inducers should also be avoided in patients taking flibanserin.

Alcohol

In several studies, the administration of alcohol with flibanserin resulted in hypotensive episodes or syncope. The reduction in systolic blood pressure exceeded 45 mm Hg in some subjects. Doses of alcohol ranged from 0.4 to 0.8 g/kg (about 2 to 4 drinks); higher doses of alcohol tended to increase the hypotensive response. As expected, alcohol also increased the central nervous system depression associated with flibanserin. Alcohol administration did not alter the pharmacokinetics of flibanserin. However, patients taking flibanserin should be counseled to avoid alcohol.

Oral Contraceptives

Based on a meta-analysis of pharmacokinetic data, patients taking oral contraceptives (OCs) had an average 40% increase in flibanserin concentration compared with patients not taking OCs. Pending a controlled trial, patients on OCs should be monitored for increased flibanserin AEs.

Digoxin

The administration of flibanserin 100 mg daily for 5 days increased the AUC of a single 0.5-mg dose of digoxin almost 2-fold. Based on this study's results, it appears that flibanserin has P-glycoprotein-blocking activity. Patients taking digoxin should be monitored for AEs (arrhythmia, bradycardia, anorexia) if flibanserin is added to their dosage regimen.

Simvastatin

In a study of 12 subjects, flibanserin 50 mg twice daily for 4 days caused the mean AUC of simvastatin, following a single 40-mg dose, to increase 2.6-fold. Lovastatin and atorvastatin plasma concentrations would be expected to increase with flibanserin administration. Monitor patients receiving these statins plus flibanserin for complaints of muscle weakness or pain.

Summary

Patients taking flibanserin are at risk of a number of potential drug interactions. The hypotension and syncope outcomes prompted the FDA to require a risk evaluation and mitigation strategy for flibanserin patients. Pharmacists should be vigilant in monitoring for potential interactions with flibanserin to mitigate the risk of AEs in patients taking the drug.

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.