Effect of Gender on Drug Interactions: Metoprolol-Diphenhydramine

John R. Horn, PharmD, FCCP; and Philip D. Hansten, PharmD

Over the years a number of studies have looked at the differences in pharmacokinetics and/or pharmacodynamics of drugs in men and women. In many cases, gender differences have been found. One obvious reason for these differences is that women tend to have lower body weight than men. Adults are often given the same dose of drug regardless of body weight, so women tend to have higher serum concentrations of drugs than men. Other gender differences, such as differences in bioavailability, metabolism, and renal elimination, may also be involved.

Relatively few studies, however, have looked at gender differences for drug interactions. In a recent, well-controlled study, interesting differences were found between men and women in the magnitude of the interaction between metoprolol and diphenhydramine.[1] Metoprolol is metabolized largely by cytochrome P450 (CYP) 2D6, and diphenhydramine is a CYP2D6 inhibitor. Patients given the combination, therefore, tend to have higher metoprolol plasma concentrations and greater pharmacodynamic effects from metoprolol. Although metoprolol is given as a racemic mixture, S-metoprolol exerts most of the beta-blocking effects of the drug.

HOW WAS THE STUDY PERFORMED?

Men and women were given a single oral dose of metoprolol 100 mg with and without concurrent diphenhydramine (50 mg 3 times per day for 5 days) in a randomized, double-blind, placebo-controlled, crossover study. Both gender groups had people with normal CYP2D6 activity (EMs) and people deficient in CYP2D6 activity (PMs). The researchers looked at both the pharmacokinetics and the pharmacodynamics of metoprolol with and without diphenhydramine.

WHAT WERE THE RESULTS?

Metoprolol alone with normal CYP2D6. When metoprolol was given with placebo in EMs, women had 62% higher S-metoprolol plasma concentrations than men. As expected, these higher plasma concentrations were associated with greater cardiovascular pharmacodynamic effects in women.

Metoprolol plus diphenhydramine with normal CYP2D6. Diphenhydramine coadministration increased S-metoprolol area under the plasma concentration–time curve by 84% in EM women, and by 45% in EM men. It was not possible to determine if the greater drug interaction in women was due to greater sensitivity to the interaction itself, or to higher plasma concentrations of the CYP2D6 inhibitor diphenhydramine. (Both men and women received the same dose of diphenhydramine, and the women had lower body weights.)

Subjects deficient in CYP2D6. As expected, diphenhydramine had virtually no effect on metoprolol pharmacokinetics in male or female PMs, because giving a CYP2D6 inhibitor to subjects deficient in CYP2D6 would not be expected to result in a drug interaction.

WHAT ARE THE IMPLICATIONS FOR PHARMACY PRACTICE?

Taken together, these results suggest the following precautions:

1. Women tend to have a greater pharmacodynamic effect from metoprolol alone, and are probably more likely to develop excessive cardiovascular responses. Consider adjusting metoprolol dosage for body weight, particularly if the patient is very small.
2. Compared with men, women appear to manifest larger increases in metoprolol plasma concentrations when CYP2D6 inhibitors are given concurrently. Female gender, therefore, can be considered a risk factor for adverse effects from the interaction between metoprolol and drugs that inhibit CYP2D6.
3. Both men and women PMs will tend to have higher metoprolol plasma concentrations and pharmacodynamic effects. Although the pharmacist will usually not know the CYP2D6 status of their patients, he or she can be alert for excessive beta-blockade (eg, bradycardia, hypotension, heart failure) in patients given metoprolol.
4. Other beta-adrenergic blockers that are metabolized by CYP2D6 include carvedilol, nebivolol, propranolol, and timolol. They are also likely to interact with diphenhydramine and other CYP2D6 inhibitors. ***PT***

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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.