Metabolic Inhibitors

Dose and Timing Affect Object Drug Response

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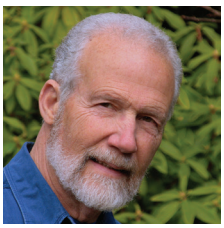

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MANY POTENTIAL DRUG INTERACTIONS are based on a precipitant drug that inhibits the metabolism of the object drug. The outcome of these interactions is a reduction in the systemic clearance of the object drug, which leads to the object drug accumulating in the plasma. It is possible to predict these interactions based on knowledge of the metabolic pathway of the object drug and the specific inhibitory properties of the precipitant drug. However, predicting the magnitude of the change in object drug clearance is difficult due to a large variation commonly seen among patients. Some of this is due to variation in patient factors, such as concurrent diseases, renal function, pharmacogenomics, gender, and laboratory values. Drug variables (dose, route, timing of doses, duration) also influence the response of the object drug. A recent study looked at the effects of drug variables on interaction outcomes.

EFFECTS OF PRECIPITANT DRUG VARIABLES ON THE INTERACTION BETWEEN KETOCONAZOLE AND MIDAZOLAM

Effect of Precipitant Drug Dose

A complex study was undertaken to describe the interaction between ketoconazole, a CYP3A4 inhibitor, and midazolam, the CYP3A4 substrate.[1] In the first phase, 9 subjects received a single 5-mg dose of oral midazolam alone and concomitantly with a single 100-, 200-, or 400-mg oral dose of ketoconazole. Drugs were administered 1 hour after a standard breakfast. Compared with the administration of midazolam alone, the 100-, 200-, and 400-mg doses of ketoconazole increased the mean area under the concentration time curve (AUC) of midazolam by 2.3-, 2.7-, and 4.2-fold, respectively, and the peak plasma concentration of midazolam by 1.9-, 1.7-, and 2.5-fold, respectively. The response was greatest as the ketoconazole dose increased from 200 mg to 400 mg; the 100- and 200-mg doses produced a similar degree of increase in midazolam plasma concentrations. This study is limited by the single doses of ketoconazole, but the trend observed would be expected to occur with multiple dosing, as well.

Effect of Precipitant/Object Drug Timing

The second phase involved administering a single 400-mg dose of ketoconazole 12 hours before, 2 hours before, concomitantly, 2 hours after, and 4 hours after a single, oral 5-mg dose of midazolam. A single 5-mg dose of midazolam was also administered alone to each subject. The administration of ketoconazole prior to midazolam produced the greatest increase in midazolam plasma concentration. The mean AUC of midazolam increased by 3.9-, 4.9-, and 5.4-fold when ketoconazole was administered 12 hours before, 2 hours before, and concurrently with midazolam, respectively. Administration of the ketoconazole dose 2 and 4 hours after midazolam produced an increase in midazolam's mean AUC by 2- and 1.2-fold, respectively. The peak midazolam concentrations were increased only by the administration of ketoconazole prior to midazolam.

Administering midazolam before a single dose of ketoconazole allows midazolam absorption to occur without interference of its enterocyte first-pass metabolism by ketoconazole. The finding that ketoconazole given 12 hours before midazolam results in a nearly 4-fold increase in AUC may be the result of its long half-life (8-10 hours) or noncompetitive inhibition of the CYP3A4 enzyme, which can extend the inhibition longer than the half-life of ketoconazole might suggest. Thus, multiple doses of ketoconazole may reduce the metabolism of midazolam throughout ketoconazole's once-daily dosing interval.

SUMMARY

The degree that a precipitant drug affects an object drug depends on the concentration of the precipitant drug at the interaction site. This primarily results from the dose, the route of administration, and the time between the administration of the 2 drugs. These differences often explain the variability in response seen in different studies of the same interacting drugs. For orally administered drugs, administration of the object drug concomitantly or shortly after the precipitant drug is likely to maximize the interaction magnitude. ◆