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Genetics and Enzyme Inhibitor Interactions

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

John R. Horn, PharmD, FCCP

Philip D. Hansten, PharmD

The activities of several drug-metabolizing enzymes are under genetic control. The genetic variations in the activity of cytochrome P450 (CYP) 2D6, CYP2C9, and CYP2C19 have been widely studied.

Patients are characterized as homozygous extensive metabolizers (homEMs), heterozygous extensive metabolizers (hetEMs), or poor metabolizers (PMs) based on the activity of the enzyme. Patients receiving a drug metabolized by only 1 of these enzymes will have higher plasma concentrations if they are deficient in the enzyme responsible for its metabolism.

Enzyme Genetics and Interaction Risk

Genetic variations in drug metabolizing enzymes can modify the response to a potential drug interaction. One of the most common observations is that patients who are PMs for an enzyme are not very susceptible to drugs that inhibit the enzyme, because there is little enzyme to inhibit. On the other hand, patients who are extensive metabolizers of an object drug will usually demonstrate a large magnitude interaction when an inhibitor is coadministered.

For object drugs with multiple pathways for elimination, inhibition of 1 pathway by an interacting drug may not produce a large change in the object drug concentration because the other pathway(s) of elimination may compensate for the one that is inhibited. The possible magnitude of the change in the object drug will be limited to the proportion of the total drug metabolism that is attributable to the inhibited enzyme pathway.

Genetic Inhibition with Drug Interaction

When a drug is metabolized by 2 enzymes and the patient is genetically a PM for 1 enzyme pathway and a drug is administered that inhibits the other enzyme pathway, the magnitude of the interaction will be increased. Voriconazole is an antifungal drug that is metabolized by both CYP2C19 and CYP3A4, with CYP2C19 appearing to be the primary pathway. Inhibitors of either enzyme would decrease the elimination of voriconazole and produce increased plasma concentrations.

In a study to determine the effect of a CYP3A4 inhibitor on voriconazole pharmacokinetics, 20 subjects who were genotyped for CYP2C19 received a single voriconazole dose on the second day of 2 days of ritonavir 300 mg or placebo twice daily.[1] Ritonavir is known to acutely inhibit CYP3A4 but does not inhibit CYP2C19.

The effect of CYP2C19 genotype on voriconazole elimination was apparent, as the area under the concentration-time curve (AUC) of voriconazole increased by 200% in the CYP2C19 PMs compared with the homEM subjects during the placebo phase of the study. When ritonavir was coadministered, its influence on voriconazole elimination via CYP3A4 inhibition was fairly equal in each of the subjects.

However, as CYP3A4 became the primary pathway for voriconazole metabolism (eg, in the subjects that were CYP2C19 PMs), the relative effect of ritonavir on voriconazole clearance increased. In the homEMs, inhibition of CYP3A4 by ritonavir resulted in a 54% increase in voriconazole AUC compared with placebo. However, in subjects who were PMs for CYP2C19, the administration of ritonavir resulted in a 9-fold increase in the AUC of voriconazole.

With ritonavir, the half-life of voriconazole increased by 3 hours in the homEMs and by more than 80 hours in the PM subjects. In the homEM subjects, inhibition of CYP3A4 by ritonavir caused a modest increase in voriconazole concentration because CYP2C19 was available to metabolize the voriconazole. With the absence of CYP2C19 in the PM subjects, there was no alternative pathway for voriconazole metabolism, and the inhibition of CYP3A4 resulted in a large increase in voriconazole AUC.

Proton pump inhibitors are metabolized primarily by CYP2C19 and, to a lesser extent, CYP3A4. When the CYP3A4 inhibitor clarithromycin was administered with lansoprazole, the AUC of lansoprazole increased 38% in subjects genotyped as homEM for CYP2C19.[2] In CYP2C19 PM subjects, clarithromycin administration resulted in an 80% increase in lansoprazole AUC.

Drugs that have multiple pathways of elimination are often cited as having less potential to cause an adverse outcome when subjected to a single interacting drug. This is generally correct. However, the genetic lack of an enzyme supporting the alternate pathway will result in a larger increase in the object drug concentration and greater risk of patient harm.

The coadministration of a second precipitant drug that inhibits another pathway can lead to a similar large magnitude interaction. Drugs that have multiple metabolic pathways, particularly if 1 or more pathway is genetically variable, require a more complete evaluation of their potential to interact.

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.