Get to Know an Enzyme: CYP2C19

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In previous issues of *Pharmacy Times*, we discussed the cytochrome P450 (CYP450) enzymes CYP1A2 and CYP2C9. In this issue, we will discuss CYP2C19—an enzyme whose activity varies depending upon important genetic differences among people and also is involved in some clinically important drug interactions.

The enzyme CYP2C19 is found primarily in the liver, as are the previous enzymes we discussed (CYP1A2 and CYP2C9). CYP450 enzymes metabolize most medications, and the most important of these enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Genetic Influences

Racial background is an important factor in the likelihood of being deficient in CYP2C19. About 3% to 5% of Caucasians are poor metabolizers for CYP2C19—that is, they lack functioning genes for the synthesis of CYP2C19. In Asians, roughly 12% to 23% are poor metabolizers for CYP2C19. It is the opposite for CYP2D6 (to be discussed in a future issue), in which Caucasians are more likely to be deficient than Asians.

CYP2C19 Substrates

Drugs metabolized by CYP2C19 are called CYP2C19 substrates and are listed in Table 1. Many drugs are metabolized by more than one CYP450 enzyme, and this is especially true for CYP2C19, where it is often a secondary pathway. Nonetheless, in some drugs, CYP2C19 is known to be the primary pathway, and these are listed with an asterisk (*) in Table 1. Many of the other drugs in Table 1 are metabolized primarily by other CYP450 enzymes.

CYP2C19 Inhibitors

Drugs that inhibit CYP2C19 activity (Table 2) are likely to increase the plasma concentrations of the medications listed with an asterisk in Table 1, and in some cases adverse outcomes may occur. For the other drugs in Table 1 (where other enzymes may be more important), the outcome of the interaction is more difficult to predict.

CYP2C19 Inducers

Some drugs induce (stimulate) CYP2C9 (see Table 3), and they may reduce the efficacy of CYP2C9 substrates. Enzyme inducers tend to be "broad-spectrum," in that they often induce several CYP450 isozymes. Enzyme induction interactions may be hard to detect clinically, since reduced drug effect may be interpreted as simply a lack of patient drug response.

Importance of Drug Interactions Involving CYP2C19

Because drugs metabolized by CYP2C19 often have other pathways, if the patient is deficient in CYP2C19, the other pathways may become more important. For example, the primary pathway for omeprazole is CYP2C19, with CYP3A4 as a secondary pathway. So in a patient with normal CYP2C19 activity, inhibitors of CYP3A4 have little effect on omeprazole metabolism. If the patient is CYP2C19-deficient, however, CYP3A4 inhibitors may markedly increase omeprazole concentrations.

Drugs that stimulate CYP2C19 (enzyme inducers) often induce several drug metabolism pathways, so enzyme induction often markedly decreases in the plasma concentrations of drugs with multiple metabolic pathways. For example, if a drug is metabolized by CYP2C19, CYP1A2, and CYP3A4, the enzyme inducer may stimulate metabolism by all 3 of these pathways.

Summary

The CYP450 enzyme CYP2C19 is at least partly involved in the metabolism of many drugs, but inhibitors of CYP2C19 will tend to have the greatest effect on drugs for which CYP2C19 is the primary pathway (eg, those with an asterisk in Table 1). But CYP2C19 inhibition by itself does not frequently cause adverse consequences, compared with other CYP450 enzymes because: (1) not many of the CYP2C19 substrates have serious toxicity, and (2) the alternative pathways often take over. Nonetheless, inhibition or induction of CYP2C19 sometimes results in adverse drug interactions, so it cannot be ignored. PT

online For tables listing CYP2C9 substrates and inhibitors and inducers of CYP2C19, please visit www.PharmacyTimes.com/CYP2C19.