



Get to Know an Enzyme: CYP2C9

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Our column in November 2007 (please visit www.PharmacyTimes.com/EnzymeCYP1A2) discussed the cytochrome P450 (CYP450) enzyme CYP1A2, which has increased in importance following the release of several drugs metabolized by this enzyme. In this issue, we will discuss an old standby, CYP2C9, an enzyme involved in many clinically important drug interactions.

CYP450 enzymes, found primarily in the liver, are involved in the metabolism of most medications; the most important of these enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

CYP2C9 Substrates

Drugs metabolized by CYP2C9 are called *CYP2C9 substrates*. Keep in mind that many drugs are metabolized by more than 1 CYP450 enzyme, and CYP2C9 may represent only 1 pathway. CYP2C9 is the primary enzyme responsible for metabolizing nonsteroidal anti-inflammatory drugs (NSAIDs), oral antidiabetic agents, and angiotensin II receptor blockers (ARBs). CYP2C9 also is the major enzyme involved in the disposition of warfarin.

CYP2C9 Inhibitors

Drugs that inhibit CYP2C9 activity will increase the plasma concentrations of certain medications and, in some cases, adverse outcomes will occur. Any drug that inhibits CYP2C9, for example, will almost certainly increase the hypopro-

thrombinemic response to warfarin. Generally, it is preferable to use a noninteracting alternative to the CYP2C9 inhibitor; however, if the CYP2C9 inhibitor is necessary, appropriate monitoring of the international normalized ratio and warfarin dosage adjustments usually can prevent adverse outcomes.

Note that phenytoin is a CYP2C9 substrate, inhibitor, and inducer. Clinically, however, adverse outcomes primarily have been due to phenytoin's susceptibility to toxicity when combined with CYP2C9 inhibitors and its ability to act as an inducer of CYP2C9 and other CYP450 enzymes, thus reducing the effect of many other medications.

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

CYP2C9 Inducers

Some drugs induce CYP2C9, and they may reduce the efficacy of CYP2C9 substrates. Such interactions tend to be insidious, because they result in lack of efficacy, rather than more apparent adverse effects. One of the dangers is that, not knowing that an interaction is occurring, the dose of the CYP2C9 substrate is increased to compensate for the CYP2C9 induction, and then the CYP2C9 inducer is discontinued. This sequence of events can result in a substantial increase in the plasma concentrations of the CYP2C9 substrate, leading to toxicity.

Drug Interactions with CYP2C9

Warfarin continues to be a serious concern with regard to CYP2C9 drug interactions. Many cases of phenytoin toxicity due to concurrent therapy with CYP2C9 inhibitors have been reported, although such reports have been decreasing, at least in part because

fewer patients are on chronic phenytoin therapy.

Also of concern are oral hypoglycemic drugs. As with warfarin, the effect of CYP2C9 inhibitors or inducers can be compensated for with dosage adjustments of the CYP2C9 substrate. If the CYP2C9 substrate dose has been increased to compensate for a CYP2C9 inducer, however, stopping the inducer can result in severe hypoglycemia.

For other CYP2C9 substrates, such as NSAIDs or ARBs, adverse consequences from concurrent administration of CYP2C9 inhibitors or inducers have not been widely reported. Nonetheless, one should still be alert for evidence of possible adverse drug interactions.

CYP2C9 Activity in Patients

Genetic variation in CYP2C9 activity has been described, with some people having greater-than-normal activity and others having decreased activity.

Pharmacogenetic testing for CYP2C9 may be indicated for some patients to achieve optimal dosing and to predict the likely outcome of drug interactions. Investigations are under way to determine if genetic testing for CYP2C9 is useful prior to warfarin therapy in order to better select initial dosing.

Summary

CYP2C9 is involved in many drug interactions. Some of the substrates that warrant particular attention are warfarin, phenytoin, and oral hypoglycemics. Some of the more potent CYP2C9 inhibitors include amiodarone, fluoroaracil, metronidazole, miconazole (especially systemic use), and sulfamethoxazole (usually combined with trimethoprim). All of the usual enzyme inducers, such as barbiturates, carbamazepine, and rifampin, can substantially increase CYP2C9 activity. 