Get to Know an Enzyme: CYP1A2

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The cytochrome P450 enzymes are found primarily in the liver, although some (eg, CYP3A4) are also found in substantial amounts in the intestine. They are involved in the metabolism of most medications and are the mechanism by which most pharmacokinetic drug interactions occur. Cytochrome P450 3A4 (CYP3A4) is the superstar; it gets attention because a majority of drugs are metabolized by CYP3A4. Other important CYP450 enzymes include CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Here we will focus on a rising star: CYP1A2.

CYP1A2 Substrates

The importance of CYP1A2 for drug interactions has been increasing over the past decade due to the growing number of drugs metabolized by this enzyme.[1] Drugs metabolized by CYP1A2 are called CYP1A2 substrates.

CYP1A2 Inhibitors

Drugs that inhibit CYP1A2 will predictably increase the plasma concentrations of the medications listed in Table 1, and in some cases adverse outcomes will occur. Of particular note is fluvoxamine, which is a potent CYP1A2 inhibitor and also inhibits other CYP450 enzymes, such as CYP2C19, CYP3A4, and to some extent CYP2C9. Thus, fluvoxamine may prevent other metabolic pathways from compensating for the CYP1A2 inhibition. The fluoroquinolone antibiotics, enoxacin and ciprofloxacin, also substantially inhibit CYP1A2.

CYP1A2 Inducers

Other drugs may stimulate CYP1A2, and they may reduce the efficacy of CYP1A2 substrates. Of particular note is cigarette smoking, which can substantially increase CYP1A2 activity.[2] Thus, smoking may reduce the efficacy of any of the CYP1A2 substrates. For example, it has been known for many years that smoking substantially increases theophylline dosage requirements. More recently, smoking has been shown to reduce the serum concentrations and efficacy of the atypical antipsychotics, clozapine and olanzapine.

online For lists of CYP1A2 substrates, inhibitors, and inducers, go to www.PharmacyTimes.com/enzymeCYP1A2.

Important Drug Interactions Involving CYP1A2

Some CYP1A2 interactions have limited clinical importance; for example, most patients can withstand an elevated caffeine concentration due to ciprofloxacin without significant adverse consequences. Others, however, can be serious. Historically, the most important CYP1A2 drug interactions were probably severe theophylline toxicity due to concurrent use of theophylline with CYP1A2 inhibitors such as ciprofloxacin or fluvoxamine. These still occur occasionally, even with reduced use of theophylline, but the many newer CYP1A2 substrates now present drug-interaction problems with CYP1A2 inhibitors. For example, tizanidine plasma concentrations increased over 30-fold when the potent CYP1A2 inhibitor fluvoxamine was given concurrently.

Assessing CYP1A2 Activity in Patients

For some CYP450 enzymes such as CYP2D6, genetic factors dictate most of the activity of the enzyme, and genotyping of patients may be useful. This is not true for CYP1A2, however, where the activity of the enzyme is dictated largely by environmental, dietary, and other factors in addition to genetics.[1] In this case, phenotyping is more useful, where, instead of genetic testing, a probe compound is given to the patient and the actual enzyme activity is determined. One proposed phenotyping method for CYP1A2 is to obtain a saliva sample following a test dose of caffeine. One drawback of such testing is that the subject must abstain from coffee, many teas and soft drinks, and chocolate for a day or so before the test.

Summary

The enzyme CYP1A2 increasingly is involved in drug interactions as new medications metabolized by this enzyme are released. Some of the substrates that warrant particular attention are theophylline, clozapine, olanzapine, and tizanidine. Some of the more potent CYP1A2 inhibitors include cimetidine, ciprofloxacin, enoxacin, and fluvoxamine. Among CYP1A2 inducers, smoking is probably the most important, but the usual enzyme inducers such as rifampin and barbiturates can also substantially increase CYP1A2 activity. PT

For a list of references, go to: www.PharmacyTimes.com.