# Cytochrome p450 Part 3: Drug Interactions

## Essential Concepts and Considerations

Stephen D. Krau, PhD, RN, CNE

**KEYWORDS**

• Cytochrome p450 • Inducers • Inhibitors • Drug interactions • Cancer therapy
• Grapefruit juice • Medication administration

**KEY POINTS**

- The most important consideration related to understanding cytochrome p450 enzymes is the appreciation that all drug effects vary among individuals and are strongly influenced by genes.
- The same enzyme may display a variety of functions and alterations, which can range from ultrarapid activity, to no activity.
- The science exists to improve patient outcomes and to improve understanding of drug response; however, clinical progress in implementing pharmacogenomics is lacking.
- The main challenges for the future are to identify among all of the polymorphisms those that contribute to idiosyncratic effects and adverse drug reactions.
- Technological efforts should also be focused on the development of tests that can easily be done in the clinic or at the bedside, which would remove one of the barriers to the use of pharmacogenomics in routine practice.

Cytochrome p450 enzymes have an important role in the metabolism of medications, and a critical function when it comes to drug-drug interactions. This is not just the result of administering the medications at the same time, but rather the physiologic effects of the medications on the enzymes caused by the bioavailability that can last for hours to months. This dynamic is not limited to prescribed or over-the-counter medications but also takes into account different foods or beverages the patient eats or drinks during drug therapy. Just as it is well known that many green leafy vegetables block the action of Coumadin, or drinking beverages with vitamin C enhances the absorption of oral iron preparations, there are food sources that affect the function of the cytochrome p450 (CYP) enzymes. For example, the effect of many

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Vanderbilt University Medical Center, School of Nursing, 461 21st Avenue South, Nashville, TN 37240, USA
*E-mail address:* steve.krau@vanderbilt.edt

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medications is altered when taken with grapefruit juice (GJ). The explanation given here will help nurses who administer medications, prescribe medications, and teach patients about their medications to understand how knowledge of CYP enzymes can ameliorate the incidence of adverse drug-drug interactions.

Two essential concepts in understanding the role of CYP in drug-drug interactions focus on the functional roles of the enzymes as inducers and/or inhibitors. Exposure to certain substances or drugs can induce the synthesis of the cytochrome p450 enzymes. This induction results in an acceleration of the metabolism of drugs that are substrates for the enzyme. Inducers increase the enzyme levels, increasing the metabolism of the drug. Depending on the drug, an inducer can decrease the effect of the drug and/or lead to toxic buildup of metabolites.[1] With a decrease in the therapeutic effect of a drug, a common practice is to increase the dose of the drug, which has the potential to increase toxic metabolites. The induction process is presented in **Fig. 1**.

Along with the allele phenotype that relates to the individual variation in the enzymes, it is important to consider polypharmacy and the impact that one medication may have on the enzyme that is the substrate of another. Some of the most important inducers of p450 enzymes include cigarette smoking, anticonvulsants, rifampin, glucocorticoids, and chronic alcohol consumption. As such, following cytochrome p450 induction, the enhanced metabolism of other drugs can impede the pharmacologic activity of the substrate and these effects may persist for a long time following cessation of the inducer drug.

In contrast, there are drugs that inhibit specific cytochrome p450 enzyme metabolism, which can result in an immediate decrease in the metabolism of the substrate, resulting in an accumulation and potential toxicity.[1] Inhibiting compounds for the specific enzyme blocks the activity of that enzyme. Depending on the drug, inhibition can lead to reduced therapeutic effects, or a buildup of unmetabolized compounds. The conundrum is that, when there is not a therapeutic effect, there can follow an increase in dosing, which results in a higher probability of toxicity. This process is shown in **Fig. 2**.

Some of the clinically important drugs for which there have been clinical toxicities caused by inhibitory drug interactions have included theophylline, warfarin, carbamazepine, benzodiazepines, phenytoin, cyclosporine, psychotropic drugs, calcium channel blockers, tacrolimus, and hydroxymethylglutaryl coenzyme A (HMG-CoA). Potent inhibitors for many medications are the furanocoumarins, which are found in GJ. A more complete list of inducers and inhibitors for the specific enzyme subfamilies is presented in **Table 1**. A cytochrome p450 inhibitor is not necessarily metabolized by the enzyme it is inhibiting. The mechanism of inhibiting is the result of competitive binding at the site of the enzyme, as conveyed in **Fig. 2**. The beginning and the ending

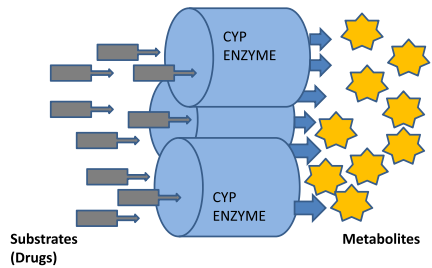


**Fig. 1.** Inducers of drug metabolism. Inducers increase the cytochrome p450 enzyme activity, resulting in increased drug metabolism. This process can lead to increase in toxic metabolites, and reduced therapeutic effect of the substrate.