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ISSN: 2153-0645
Journal of Pharmacogenomics & Pharmacoproteomics

Commentary

# Pharmacogenomics and Drug Interactions on Cytochrome P450 Metabolism

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## DESCRIPTION

Cytochrome P450 enzymes are essential for the metabolism of many drugs. There are more than 50 enzymes in this class, six of which metabolize 90% of the drug and the two most important enzymes are CYP3A4 and CYP2D6. The genetic diversity (polymorphisms) of these enzymes can affect a patient's response to commonly prescribed classes of drugs, such as beta-blockers and antidepressants. Cytochrome P450 enzymes can be inhibited or induced by drugs, causing clinically significant drug-drug interactions, which can lead to unexpected side effects and treatment failures. Interactions with warfarin, antidepressants, antiepileptic drugs, and statins usually involve the cytochrome P450 enzyme. Knowledge of the major drugs metabolized by the cytochrome P450 enzyme, as well as the most potent inhibitory and inducing drugs, helps minimize the potential for side effects and interactions of the drugs. Genotyping can determine if a patient has a particular enzyme polymorphism, but it has not been determined whether routine use of these tests will improve results. Cytochrome P450 (CYP450) enzymes are essential for the production of cholesterol, steroids, prostacyclin and thromboxane A2. It is also necessary for detoxification of foreign chemical substances and drug metabolism. The CYP450 enzyme is so named because it contains heme pigment (chromium and P) that attach to intracellular membranes (cells) and absorb light at wavelengths of 450 nm when exposed to carbon monoxide. There are over 50 CYP450 enzymes, but the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 metabolize 90% of the drug. These enzymes are expressed primarily in the liver, but are also found in the small intestine (which reduces the bioavailability of drugs), lungs, placenta, and kidneys.

### Pharmacogenomics

One in 15 whites or blacks may overreact to standard dose beta-blockers (e.g., metoprolol [Lopressor]) or the analgesic tramadol (Ultram). This is because CYP450 enzyme-mediated drug metabolism has genetic diversity (polymorphisms) that influences a patient's response to a particular drug. Each CYP450 enzyme is encoded by a specific gene. Everyone inherits one genetic allele from each parent. Alleles are called "wild-type" or "mutant", and the wild-type is the most common in the general population. "Wide" (i.e., normal) metabolic factors store two copies of the wild-type allele. Polymorphisms occur when a variant allele replaces one or both wild-type alleles. Variant alleles usually encode CYP450 enzymes with reduced or no activity. Individuals with two copies of the variant allele are poor metabolites, while individuals with one wild-type and one variant allele have reduced enzyme activity. Finally, some individuals inherit multiple copies of the wild-type allele, resulting in excessive enzymatic activity. This phenotype is called an "ultra-fast" metabolic factor. CYP450 enzyme polymorphisms are responsible for the differences in drug responses observed in patients of different races. For example, 7% of whites and 2-7% of blacks have inadequate metabolism of many beta blockers, antidepressants, and CYP2D6-dependent drugs that metabolize opioids. One in five Asians has inadequate metabolism of CYP2C19-dependent drugs that metabolize phenytoin (Dilantin), phenobarbital, omeprazole (Prilosec), and other drugs. Differences in drug response between individuals with different ethnic backgrounds can also be caused by genetic variation in other drug-metabolizing enzymes, drug transporters, and drug receptors.

### Drug interaction

Many drug-drug interactions are the result of altered CYP450 metabolism. The non-sedating antihistamines terfenadine (Seldane) and astemizole (Hismanal) and the gastrointestinal motility drug cisapride (Propulsid) have all withdrawn from the U.S. market as metabolic inhibition by other drugs caused life-threatening arrhythmias. The calcium channel blocker Mibefradil (Posicor) withdrew from the US market in 1998 because it was a potent enzyme inhibitor that provided toxicity levels for other cardiovascular drugs. The drug interacts with the CYP450 system in a variety of ways. The drug is metabolized by one CYP450 enzyme (e.g. from metoprolol to CYP2D6) or multiple enzymes (eg from wafarin

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**Received:** 03-Jan-2022, Manuscript No. JPP-22-1320; **Editor assigned:** 07-Jan -2022, PreQC No. JPP-22-1320 (PQ); **Reviewed:** 11-Jan -2022, QC No. JPP-22-1320; **Revised:** 14-Jan-2022, Manuscript No. JPP-22-1320 (R); **Published:** 24-Jan-2022, DOI:10.4172/2153-0645.1000004

**Citation:** Stuart M (2022) Pharmacogenomics and Drug Interactions on Cytochrome P450 Metabolism. J Pharmacogenom Pharmacoproteomics. 13: 004

[Coumadin] to CYP1A2, CYP2D6, CYP3A4). Drugs that cause metabolic interactions with CYP450s are called inhibitors or inducers. Inhibitors block the metabolic activity of one or more CYP450 enzymes. The extent to which an inhibitor affects drug metabolism depends on factors such as dose and the ability of the inhibitor to bind to the enzyme. For example, 50 mg of sertraline (Zoloft) is considered a mild inhibitor of CYP2D6, but increasing to 200 mg makes it a powerful inhibitor. The suppressive effect usually occurs immediately. In addition, the drug can be metabolized and inhibited by the same enzyme (e.g., erythromycin) or metabolized by one enzyme to inhibit another enzyme (e.g. terbinafine [Lamisil]). Drugs can be intentionally combined to take advantage of CYP450 inhibition. Ritonavir (Norvir), a protease inhibitor and potent CYP3A4 inhibitor, is added to Lopinavir (Kaletra) to increase serum levels in human immunodeficiency virus patients.