CYP2C9: The Support Crew I

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Abstract

This chapter discusses the genetics, metabolic actions, substrates, inducers, and inhibitors of P450 CYP2C9.

Cytochrome P450 2C9 is an important member of the cytochrome P450 (CYP) enzyme superfamily. It accounts for approximately 20% of the hepatic P450 enzymes and metabolizes approximately 15% of current therapeutic drugs.[1] Included in these are several commonly used drugs in the perioperative period, some of which have a low therapeutic index (such as warfarin and phenytoin). In addition, commonly used pain medications, including certain nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and several anesthetics and anesthetic adjuncts, are substrates of the 2C9 enzyme.

The gene coding for CYP2C9 is located on chromosome 10 and is expressed primarily in the liver. CYP2C9 shows selectivity for the oxidation of small, lipophilic anions that tend to be weak acids with pKa values ranging from 3.8 to 8.1.[2] CYP2C9 is highly polymorphic, with 33 variants and several subvariants.[1] *CYP2C9*1* is the wild-type allele. One of the most common variants is the *CYP2C9*2*, which was the first polymorphism identified. This gene variant codes for the intermediate metabolizer phenotype in individuals homozygous for this allele. The *CYP2C9*3* allele codes for the poor metabolizer phenotype.[3] Both of these variants typically produce reduced enzyme activity. Drugs metabolized by an individual with an intermediate or poor metabolizer phenotype may be oxidized inadequately or not at all, causing

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an increase in plasma concentrations and thus increasing the risk for untoward effects. These pharmacogenetic polymorphisms cause significant interindividual variability in drug response. There can be a 10-fold difference in the pharmacokinetic parameters of 2C9 between individuals, which has led to genotyping as a method of ascertaining dosage parameters of drugs such as irbesartan.[4]

In addition to interindividual variability, there are significant ethnic variations in the allelic polymorphisms of CYP2C9. Approximately 1% of Caucasians are homozygotes and 22% are heterozygotes for *CYP2C9*2*. *CYP2C9*3* homozygosity in Caucasians is approximately 0.5% and heterozygosity is approximately 12%. In contrast, homozygosity in either variant is rare in the African-American and Asian populations. Heterozygosity for *CYP2C9*2* in the African-American population ~~is~~ roughly 9% and almost nonexistent in the Asian population; heterozygosity for the *CYP2C9*3* variant is roughly 4% for both populations.[5,6] Of course, the currently recognized polymorphisms only partially account for the ethnic variations. Despite a lack of *CYP2C9*2* in the Asian population, therapeutic warfarin dosing is much lower than in Caucasians.[3]

There are many drugs used in the perioperative period that are substrates of 2C9. In addition to warfarin and phenytoin, a number of these drugs are commonly found in the medication lists of preoperative patients, including carvedilol, clopidogrel, the sulfonylureas (glyburide and glipizide), angiotensin receptor II antagonists (irbesartan and losartan), sertraline, and fluvastatin. Pain medications, including celecoxib, hydromorphone, and several NSAIDs (ibuprofen, indomethacin, naproxen, and diclofenac), are also substrates for 2C9. Several agents commonly used for induction and maintenance are significantly influenced by alterations in the 2C9 enzyme, including propofol (a 30% to 50% metabolic contribution by 2C9), ketamine (30% to 40%), phenobarbital (30% to 40%), diazepam (5% to 10%), and halothane (10% to 20%).[1]

CYP2C9 activity is both induced and inhibited by several common perioperative drugs. In addition to being a substrate, barbiturates act as 2C9 inducers. There is a significant decrease in steady-state plasma concentration of warfarin with barbiturate administration. Unfortunately, the magnitude of the effect of barbiturate induction of 2C9 is unpredictable. A review of the literature suggests that in most instances, phenobarbitone administration produces inconsistent changes in the plasma concentration of phenytoin.[7,8] Amiodarone acts as an inhibitor of the 2C9 enzyme and is particularly significant because of its long half-life. Inhibition of the enzyme persists for several weeks following withdrawal of this drug leading to significantly elevated levels of both warfarin and phenytoin.[2] Antibiotics including fluconazole and several from the sulfa class are also inhibitors of 2C9. The inhibitors listed here are in addition to the competitive inhibition that may occur between substrates.

CYP2C9 is an important enzyme in the metabolism of numerous drugs. Genetic polymorphisms, ethnic variability, and interindividual expression of the gene

significantly affect the plasma levels of drugs metabolized by this enzyme. CYP2C9 is, and will continue to be, an important factor to consider in the perioperative arena.

Take-Home Points

- CYP2C9 plays a major role in the metabolism of approximately 15% of drugs, many of which can be found in the perioperative period.
- CYP2C9 genetic polymorphisms and interindividual expression of these genes can affect the metabolism of certain drugs.
- There are significant ethnic variations in the allelic polymorphisms.
- CYP2C9 activity can be significantly enhanced or decreased by several common perioperative medications.

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