Spartan

CYP2C19 Testing: Opportunity to Improve Patient Care

Contents

Introduction

The CYP2C19 enzyme metabolizes approximately 15 percent of all prescribed drugs.[1] About 30% of Caucasians and Africans, and 50% of Asians and Indians carry CYP2C19 gene variants that reduce response to drugs metabolized by CYP2C19.[2,3,4,5] Identifying a patient's CYP2C19 genotype may provide insight into drug response and adverse drug reactions.

Cytochrome P450 2C19 (CYP2C19) Enzyme

The cytochrome P450 (CYP) genes encode the cytochrome P450 class of metabolic enzymes found mainly in the human liver. Many of these enzymes are important for drug metabolism and clearance. The CYP2C19 gene is particularly important because the CYP2C19 enzyme metabolizes widely-used drug classes such as anti-platelet therapies, beta blockers, antidepressants, proton pump inhibitors, and antiepileptics.

Drugs metabolized by CYP2C19 are called substrates (Table 1).[6] Drugs that decrease CYP2C19 activity are called inhibitors, and drugs that increase activity are called inducers (Table 2). Inhibitors can increase the plasma concentrations of certain medications. In some cases, this can lead to adverse drug reactions (ADRs). Inducers can decrease the plasma concentration of medications, and potentially make them ineffective.

Table 1. Common Drugs Metabolized by CYP2C19

Common Drugs Metabolized by CYP2C19	
Antibiotics	• Chloramphenicol
Anticancer	• Nilutamide • Cyclophosphamide
Antidepressants	• Amitriptyline • Citalopram • Clomipramine • Imipramine • Moclobemide
Antiepileptics	• Diazepam • Phenobarbitone • Phenytoin • Primidone • S-mephenytoin
Antifungals	• Voriconazole
Antiplatelet agents	• Clopidogrel
Beta blockers	• Propranolol
Proton pump inhibitors	• Lansoprazole • Omeprazole • Pantoprazole • Rabeprazole
Other	• Carisoprodol • Hexobarbitol • Indomethacin • Nelfinavir • Progesterone • Proguanil • R-mephobarbital • R-warfarin

Table 2. Common Inhibitors and Inducers of CYP2C19

Therapy	Inhibitors	Inducers
Antibiotic	Chloramphenicol	Rifampicin
Antifungal	Ketoconazole	
Antiepileptic	Felbamate Oxycarbazepine Topiramate	Carbamazepine
Antiplatelet	Ticlopidine	
Corticosteroid		Prednisone
Contraceptive		Norethindrone
Eugeroic	Modafinil	
Histamine H2-receptor antagonist	Cimetidine	
Proton pump inhibitor	Lansoprazole Omeprazole Pantoprazole Rabeprazole	
SSRI	Fluvoxamine	
Fluoxetine		
NSAID	Indomethacin	
Uricosuric	Probenicid	

Genetics of CYP2C19

Humans carry two copies of the CYP2C19 gene, with one inherited from each parent. Some people carry mutations in one or both of their CYP2C19 genes. These alternative forms of the gene are called alleles. The CYP2C19*1 allele is considered the wild-type, or "normal" allele, with "normal" enzyme activity. The CYP2C19*2 and CYP2C19*3 alleles are the most common loss-of-function alleles (Table 3).[7] Carriers of these alleles have reduced CYP2C19 enzyme activity. The CYP2C19*17 allele is a gain-of-function allele.

Table 3. CYP2C19 Carriers in Different Ethnic Groups

CYP2C19 Allele	CYP2C19 Enzyme Activity	Carriers of 1 or 2 alleles (% of population)				
		African American	Asian	European	Indian	Middle Eastern
*2	None	28	50	28	58	23
*3	None	1	17	<1	5	2
*17	Increased	29	5	38		

Carriers of this allele have increased CYP2C19 enzyme activity. There are alleles other than *2, *3, and *17, but these alleles are carried by less than 0.5% of the individuals in most ethnic groups.

The genotype of a heterozygous individual is written as *1/*2 for a *2 carrier and *1/*3 for a *3 carrier. Similarly, a homozygous individual has a genotype of *2/*2 or *3/*3. Wild-type individuals have normal enzyme activity, whereas heterozygotes have intermediate activity, and homozygotes have poor activity. Compound heterozygotes such as *2/*3 also have poor enzyme activity because they carry two loss-of-function alleles like a homozygote.

CYP2C19 Metabolizer Phenotypes

A person's CYP2C19 genotype affects the level of CYP2C19 enzyme activity. This is known as the phenotype. CYP2C19 phenotypes are classified into four groups:

Metabolizer Phenotype	CYP2C19 Enzyme Activity	Examples of Genotypes
Extensive metabolizer (EM)	Normal	*1/*1
Intermediate metabolizer (IM)	Reduced	*1/*2, *1/*3
Poor metabolizer (PM)	Very low or absent	*2/*2, *3/*3, *2/*3
Ultra-rapid metabolizers (UM)	Increased	*1/*17, *17/*17

Clinical Significance

CYP2C19 alleles affect metabolism of many clinically important drugs. For example, the antiplatelet drug clopidogrel is metabolized to its active metabolite by CYP2C19. CYP2C19 intermediate metabolizers (IMs) and poor metabolizers (PMs) have reduced ability to produce the active metabolite, and this decreases the effectiveness of clopidogrel in heart attack patients receiving cardiac stents.[8] In 2010, the FDA added a black box warning to the label of clopidogrel stating that CYP2C19 PMs exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. The warning also states that tests are available to determine a patient's CYP2C19 genotype, and that alternative treatments should be considered in CYP2C19 PMs.

Proton pump inhibitors are affected by CYP2C19 genotype. For *Helicobacter pylori* eradication therapy, patients with the EM or UM phenotypes may require higher doses.[9] In contrast, patients with IM or PM phenotypes have higher plasma drug levels that increase the efficacy of treatment.

Many antidepressant drugs are partially metabolized by the CYP2C19 enzyme. For example, CYP2C19*2 carriers have lower tolerance to the side effects of citalopram, but remission rates are higher in those who can tolerate the drug.[10] For sertraline and imipramine, PMs may have a higher risk of adverse drug reactions (ADRs), and may require a lower dose. UMs may require a higher dose.[11]

Voriconazole is an antifungal with a narrow therapeutic range. CYP2C19*17 carriers are at risk of sub-therapeutic voriconazole levels and treatment failure.[12,13] CYP2C19 PMs may be at higher risk of voriconazole toxicity.[14]

Treatment Guidelines

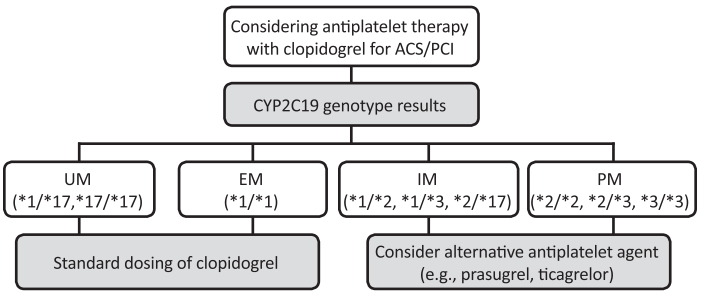
The PharmGKB is a pharmacogenomics knowledge resource that is managed by Stanford University and funded by the National Institutes of Health (NIH) and the National Institute of General Medical Sciences (NIGMS). The PharmGKB maintains a list of dosing guidelines for drugs metabolized by CYP2C19: https://www.pharmgkb.org/gene/PA124.

The list includes guidelines for the following drugs:

- Amitryptyline
- Citalopram
- Clomipramine
- Clopidogrel
- Doxepin
- Escitalopram
- Esomeprazole
- Imipramine

- Lansoprazole
- Moclobemide
- Omeprazole
- Pantoprazole
- Rabeprazole
- Sertraline
- Trimipramine
- Voriconazole

For example, PharmGKB lists guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) for CYP2C19 genotype and clopidogrel therapy.[15]



According to CPIC: "If pursuing CYP2C19 genotyping, one of the challenges is the need for rapid turnaround time of results. It would be advantageous to have the results before initiating antiplatelet therapy because the largest number of potentially preventable recurrent events occur early in treatment."

In another example, PharmGKB lists guidelines from the Dutch Pharmacogenetics Working Group (DPWG) for CYP2C19 homozygous ultra-rapid metabolizers (UMs) and proton pump inhibitor therapy:[16]

Proton pump inhibitor	Therapeutic dose recommendation for CYP2C19 *17/*17 genotype
Esomeprazole	• *Helicobacter pylori* eradication: increase dose by 50-100%. Be extra alert to insufficient response. • Other: be extra alert to insufficient response. Consider dose increase by 50-100%.
Lansoprazole	• *Helicobacter pylori* eradication: increase dose by 200%. Be extra alert to insufficient response. • Other: be extra alert to insufficient response. Consider dose increase by 200%.
Omeprazole	• *Helicobacter pylor*i eradication: increase dose by 100-200%. Be extra alert to insufficient response. • Other: be extra alert to insufficient response. Consider dose increase by 100-200%.
Pantoprazole	• *Helicobacter pylori* eradication: increase dose by 400%. Be extra alert to insufficient response. • Other: be extra alert to insufficient response. Consider dose increase by 400%.

Case Studies of CYP2C19 Testing

The clinical applications of CYP2C19 testing are highlighted in the following three peer-reviewed case studies.

Cardiology: Stent Thrombosis and Clopidogrel Resistance

Arima et al. (2012) reported the case of a 73-year-old female with stable angina who was treated with a drug-eluting stent and dual-antiplatelet therapy with aspirin and clopidogrel.[17] Five days later, she presented with persistent severe chest pain and was diagnosed with acute myocardial infarction due to stent thrombosis. The patient's CYP2C19 genotype was determined to be CYP2C19*2/*3, and she was classified as a poor metabolizer. Based on this genetic information, cilostazol was added as an additional antiplatelet medication to overcome the low responsiveness to clopidogrel. Four months later, the patient had experienced no further cardiac events.

*In this case study, CYP2C19 genotype information was used to adjust the patient's antiplatelet therapy following stent thrombosis. Several clinical trials have shown that CYP2C19 genotype influences the effectiveness of clopidogrel treatment in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).[18,19] In these studies, carriers of CYP2C19*2 and *3 alleles had an increased risk of stent thrombosis and Major Adverse Cardiac Events (MACE) such as cardiac death, stroke, and myocardial infarction. The FDA boxed warning on the clopidogrel label states that alternative treatments should be considered in patients who are CYP2C19 poor metabolizers.*

Psychiatry: Serotonin Syndrome and Drug Interactions

Lorenzini et al. (2012) reported the case of a 46-year-old female with HIV and Hepatitis C who was hospitalized for bacterial peritonitis.[20] She had been taking escitalopram, a selective serotonin re-uptake inhibitor (SSRI), for 5 years to treat depression. In hospital, the patient was started on esomeprazole to treat symptoms of gastro-esophageal reflux. Three days later, her antiretroviral therapy was changed to darunavir, ritonavir, and emtricitabine/tenofovir. Four days following this change, the patient became nauseous and confused. Physical examination showed diaphoresis, mydriasis, myoclonus, deep tendon hyper-reflexia, and rigidity. Escitalopram elimination half-life was measured at two to three times higher than normal, and serum levels were twelve times higher. Based on these observations, her physicians suspected serotonin syndrome and stopped the escitalopram. The patient's condition improved within 24 hours.

Laboratory investigations revealed that the patient's genotype was *1/*2 for CYP2C19, with a predicted phenotype of Intermediate Metabolizer. Due to esomeprazole's inhibitory effect on CYP2C19, the actual phenotype was determined to be Poor Metabolizer. In addition to CYP2C19, escitalopram is metabolized by the CYP2D6 and CYP3A4 enzymes. The patient's CYP2D6 genotype was identified as *5/*10, with a predicted and actual phenotype of Poor Metabolizer. The patient's CYP3A4 phenotype showed reduced activity due to potent and irreversible CYP3A4 inhibition by both ritonavir and darunavir.

This patient's potentially fatal adverse event was explained by drug inhibition of CYP2C19 and CYP3A4, and CYP2C19 and CYP2D6 genetic polymorphisms.

Infectious Disease: Voriconazole Failure in a CYP2C19 Ultrarapid Metabolizer

Autmizguine et al. (2012) reported the case of a 19-year-old male with a primary immunodeficiency disease (chronic granulomatous disease) who was admitted for with sepsis secondary to a bacterial infection.[21] The infection initially presented as an acute pneumonia and rapidly evolved into multiorgan failure with acute respiratory distress syndrome, shock and acute renal failure, and disseminated intravascular coagulation. The bacterial infection was treated with intravenous antibiotics: cefotaxime, meropenem, ceftazidime, trimethoprim/sulfamethoxazole, doxycycline, levofloxacin, and ciprofloxacin.

For prophylaxis against invasive aspergillosis, the patient was started on intravenous voriconazole. Three days later, the first measurement of voriconazole plasma levels showed a very high level and the dose was decreased. Two days later, the patient was started on daily pulses of methylprednolisone and this resulted in dramatic improvement in multiorgan function and significant decrease in systemic inflammatory response. At this time, voriconazole plasma levels became undetectable despite repeated dose escalations. CYP2C19 testing indicated that the patient was *1/*17 for CYP2C19, with a predicted Ultrarapid Metabolizer phenotype. Based on this information, the patient was switched to oral itraconazole.

The initial high voriconazole plasma levels were attributed to the severe systemic inflammatory response, which is a known inhibitor of CYP2C19 enzyme activity. Once the inflammation was reduced, the patient's CYP2C19 Ultrarapid Metabolizer phenotype was expressed, and this led to undetectable levels of voriconazole.

Fungal infection prophylaxis was ineffective with voriconazole due to the patient's CYP2C19 Ultrarapid Metabolizer phenotype. Instead, the patient was switched to itraconazole.

Conclusion

The three case studies show the usefulness of CYP2C19 testing. CYP2C19 genetic results enable physicians to personalize drug treatment to the patient's genotype. This helps maximize drug efficacy and minimize adverse reactions. CYP2C19 testing is reimbursed by Medicare and most private insurers.

There are several CYP2C19 genotyping assays that are cleared by the FDA. The Spartan RX CYP2C19 System is the fastest and easiest of these assays. It provides results in less than 60 minutes from a non-invasive cheek swab.

Intended Use

The Spartan RX CYP2C19 System is a qualitative *in vitro* diagnostic test for the identification of a patient's CYP2C19 *2,*3, and *17 genotypes determined from genomic DNA obtained from a buccal swab sample. For prescription use only.

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