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Pharmacogenetic Variation Of CYP2C19 Affecting The Efficacy Of Anti-Platelet Therapy

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Abstract

Antiplatelet drugs used to treat and prevent platelet aggregation in conditions like stroke and cardiovascular events. Pharmacogenetics plays a vital role in affecting the treatment outcome due to its variation. Cytochrome P450 (CYP450) enzymes especially, CYP2C19 play in the metabolism of a variety of medications, including clopidogrel and genetic variation of CYP2C19 may affect clopidogrel metabolism which is a prodrug. Through encouraging a shift in antiplatelet therapy toward customized medicine, it improves the science of pharmacogenetics. More precise and effective patient care in the area of cardiovascular health is possible if doctors are encouraged to consider hereditary traits while prescribing antiplatelet medications.

Keywords: Anti-platelet, pharmacogenetics, CYP450, genetic variation in CYP2C19, clopidogrel, prasugrel and ticagrelor

INTRODUCTION

Antiplatelet medications are drugs that help prevent blood clot formation by inhibiting the aggregation of platelets, which are small cell fragments in the blood that play a key role in clot formation. These medications are prescribed to reduce the risk of cardiovascular events and stroke.[(1)]Platelets are activated if they are exposed to this highly thrombogenic environment, and severable soluble agonists, such as ADP, thromboxane A2, serotonin, and thrombin, recruit and activate additional platelets.[(2)] Platelet aggregation is mediated through glycoprotein (Gp) IIb/IIIa, and the thrombus is stabilised through the conversion of fibrinogen bridges to fibrin.[(3)] ADP signals are transduced through P2 purinergic receptors (P2Y1 and P2Y12) on the surface of platelets, contributing to thrombus growth and stability. Thromboxane A2, synthesized by cyclooxygenase (COX) from arachidonic acid, amplifies platelet activation and leads to micro-vessel contraction and thrombus propagation. [(4)] Thrombin is an enzyme that catalyses the cleavage of fibrinogen into soluble fibrin and is, therefore, a major mediator of the plasmatic coagulation system. It is also one of the most potent platelet activators through the interaction of protease-activated receptors (PARs) on the platelet surface. Interaction of PAR-1 and PAR-4 results in activation of platelets and smooth muscle cells and therefore contributes to platelet pro-coagulant activity and aggregation. [(5)]

Pharmacogenetics is the science of understanding how genetic variability influences drug treatment outcome. The terms pharmacogenetics and pharmacogenomics are often used interchangeably, pharmacogenetics generally refers to the effects of a single genetic marker, while pharmacogenomics is broader in context, referring to the collective influence of variability across the genome to modulate an individual's drug response profile. Pharmacogenetics may influence both the pharmacokinetics and pharmacodynamics of medications. This variability has relevance for dosing, therapeutic sensitivity, likelihood of side effects, and risk for hypersensitivity reactions.[6] The efficacy of anti-platelet therapy has been affected due to CYP2C19 pharmacogenetics and leads to recurrent heart problems

PHARMACOGENETIC VARIATION

Pharmacogenetic variability is likely another major source of inconsistency in therapeutic responses. Since the completion of the Human Genome Project, greater attention is turning to identifying genetic sources of variability in drug response, the clinical impact of variability in patients receiving the drug, and finally, altering therapy at an individual level to achieve a consistent therapeutic response for each patient. Termed "personalised medicine," this potentially represents a sea change in pharmacotherapeutics, where a genetic profile will determine the appropriate drug and/or dose the patient should receive for maximum therapeutic benefit with minimal risk of toxicity.[7]
Over 55% of the available drugs in human medicine are metabolized by cytochrome P450 (CYP450) enzymes. These enzymes are major contributors to phase I drug metabolism and catalyze oxidative, reductive, and hydrolytic reactions of endogenous and xenobiotic compounds. The resulting compounds are often more water-soluble and available for further phase II conjugation. The 57 functional CYPs, the isoforms belonging to the CYP1, CYP2, and CYP3 families, are responsible for the metabolism of around 80% of clinical drugs. These include CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5, with CYP3A4 and CYP2D6 contributing to over 50% of CYP-related drug metabolism. [8]

GENOMIC VARIATION IN CYP2C19

CYP2C19 is an essential member of the CYP450 superfamily, and it contributes about 16% of total hepatic content. CYP2C19 is the principal enzyme involved in the hepatic metabolism of drugs such as antimalarial (proguanil), oral anticoagulants (R-warfarin), chemo therapeutic agents (cyclophosphamide), anti-epileptics (S-mephenytoin, diazepam, phenobarbitone). Antiplatelets (clopidogrel), proton

phenobarbitone). antiplatelets (clopidogrel), proton pump inhibitors (omeprazole, pantoprazole, rabeprazole), antivirals (nelfinavir), and

Antide pressants (amitriptyline, clomipramine). Metabolizer status, such as normal or extensive (EM), intermediate (IM), rapid (RM), and ultra-rapid (UM), is defined by different diplotypes. Genetic variation in CYP2C19 impacts the metabolism of many drugs and has been associated with efficacy and safety issues for several commonly prescribed drugs. [9]

Over 50 CYP2C19 genomic variants have been identified. The CYP2C19 gene is located on chromosome 10q24.1q24.3, is composed of nine exons, and produces a medium-sized protein (55.93 kDa) from 490 aminoacids. Homozygosity for loss-of-function alleles confers poor metabolism; heterozygosity for loss-of-function (LOF) alleles confers intermediate metabolism; wild-type alleles (*1/*1) confer what may be considered 'normal' metabolism; and homozygosity for a gain-of-function (GOF) allele confers ultra-rapid metabolism. The four major phenotypes listed above correspond to selected permutations of the most common CYP2C19 genetic variants (*1, *2, *3, *17) in the dose-response relationship. The frequency of these phenotypes seems to differ with ethnicity. Approximately 2% of Europeans (the most widely studied population) are poor CYP2C19 metabolizers, while up to 20% of Asians are poor metabolizers, underscoring the need for further study in all populations. Poor or intermediate metabolism of clopidogrel may lead to persistently elevated platelet function in spite of treatment (i.e., high on-treatment platelet reactivity, or HTPR) in individuals treated for acute coronary syndromes (ACS). These individuals remain at high risk for ischemia, limited post-PCI myocardial flow, and adverse cardiovascular outcomes (e.g., stent thrombosis, myocardial infarction, stroke, and death). The most common SNPs responsible for the poor metabolizer phenotype result from premature stop codons due to the presence of adenine in lieu of guanine on nucleotide

681 of exon 5 (CYP2C19*2) and on nucleotide 636 of exon 3 (CYP2C19*2). While there are other alleles associated with CYP2C19 LOF (CYP2C19*4, *5, *6, *7, *8), they comprise less than one percent of the known CYP2C19 allele. Only one GOF variant (CYP2C19*17) has been identified. [10]

PREDICTED PHENOTYPE	GENOTYPE	EXAMPLES OF CYP2C19 DIPLOTYPES
CYP2C19 ultrarapid metabolizer	An individual function alleles carrying two increased	*17/*17
CYP2C19 rapid metabolizer	An individual carries one normal function allele and one increased function allele.	1*/*17
CYP2C19 is a normal metabolizer.	An individual carrying two normal function alleles	1*/*1, *38/38*
CYP2C19 is a likely intermediate metabolizer.	An individual carries one normal function allele and one decreased function allele. OR one increased function allele and one decreased function allele OR Two decreased function alleles	1*/*9, *9/*17, *9/*9
CYP2C19 intermediate metabolizer	An individual carries one normal function allele, one no function allele, one no function allele, and one increased function allele.	*1/*2, *1/*3, *2/*17
CYP2C19 is likely a Poor metabolizer.	An individual carries one decreased function Allele and one no function allele.	*2/*9, *3/*9
YP2c19 is a metabolizer.	An individual carrying two no-function alleles	*2/*2, *2/*3, *3/*3

OUTCOME OF PHARMACOGENETIC VARIATION IN ANTIPLATELET THERAPY

Clopidogrel is an inactive prodrug that requires hepatic bioactivation via several cytochrome P450 enzymes, including CYP2C19. There are three major CYP2C19 genetic polymorphisms: CYP2C19*1 corresponds to normal function; CYP2C19*2 (c.681G>A; rs4244285); and CYP2C19*3 (c.636G>A; rs4986893) are loss-of-function alleles that cause most of the reduced function associated with "poor metabolizers." Poor metabolizers demonstrate two loss-of-function alleles, whereas intermediate metabolizers have one copy of a loss-of-function allele and may also demonstrate. [11]
In contrast, the CYP2C19*17 allele (c.-806C>T; rs12248560) results in increased activity due to enhanced transcription. Individuals carrying this allele may be categorised as ultra- rapid metabolizers (e.g., 17/17). Some studies indicate that this allele results in enhanced platelet inhibition and clopidogrel response, and carriers are possibly at higher risk of bleeding complications.[12] However, other studies have not identified the effects of CYP2C19*17, and adequate evidence of the independent effects of this allele on clinical outcomes is lacking. On March 12, 2010, the US Food and Drug Administration approved a new label for clopidogrel that includes a "boxed warning."[13] The boxed warning was issued primarily because of concerns that the antiplatelet effects of clopidogrel require activation by the CYP system. Patients with decreased CYP2C19 function due to genetic polymorphisms poorly metabolize clopidogrel and demonstrate higher rates of cardiovascular events, including acute coronary syndrome and the need for PCI, than patients with normal CYP2C19 function. [14]

A meta-analysis reported that among patients treated with clopidogrel following PCI, carrying even one reduced-function CYP2C19 allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis. The prevalence of the 2 and 3 alleles varies by ethnicity. In Asians, the proportion of patients who carry at least one copy of 2 is higher by about 50%, [15] resulting in decreased active metabolite levels and reduced antiplatelet effects when treated withclopidogrel, while only 7% of Asians carry the 3 allele. Another meta-analysis reported a higher risk of adverse clinical events in Asians with loss-of-function CYP2C19 variants in comparison with Western populations. [16]

STRATEGY TO TREAT CYP2C19 POOR METABOLIZAERS

Therefore, alternative treatment strategies for patients identified as "poor CYP2C19 metabolizers" should be considered. Increasing the clopidogrel dose is one way to overcome clopidogrel-response deficits.[17] However, Mega's study reported that tripling the daily clopidogrel maintenance dose to 225 mg achieved levels of platelet reactivity in CYP2C19*2 heterozygous patients that were similar to non-carriers who received the standard 75-mg dose; in contrast, daily doses as high as 300 mg did not demonstrate comparable levels of platelet inhibition in CYP2C19*2 homozygous patients.[18] Price's study reported that administering 150-mg clopidogrel maintenance dosing to PCI patients with CYP2C19 gene mutation could not improve prognosis in comparison to patients who received 75-mg clopidogrel daily. Another strategy is to administer newer, more potent platelet inhibitors (e.g., prasugrel, ticagrelor) instead of clopidogrel.[19] The Clinical Pharmacogenetics Implementation Consortium Guidelines for cytochrome CYP2C19 and clopidogrel therapy recommend standard clopidogrel dosing, as recommended in the product insert, for patients with the CYP2C19 extensive metabolizer or ultra-rapid metabolizer phenotype (e.g., 1/ 1, 1/ 17, 17/17). The current literature supports the use of alternative agents (e.g., prasugrel, ticagrelor) if clinical genotyping identifies a patient as a poor CYP2C19 metabolizer (e.g., 2/ 2, 2/ 3, 3/ 3). The most challenging patients are those with CYP2C19 intermediate phenotypes (e.g., 1/ 2, 1/ 3, 2/ 17), and the data also support administering alternative antiplatelet agents.[20] Another approach is to add a third drug (e.g., cilostazol) to aspirin and clopidogrel in order to further enhance platelet inhibition. However, these strategies are often associated with higher risks of bleeding, possibly due to the inhibition of the thromboxane A2 (TXA2) and adenosine diphosphate (ADP) platelet activation pathways that are essential for normal haemostasis. [21]
In accordance with unified therapy, adding the clopidogrel dose or switching to prasugrel or ticagrelor may not only increase the economic burden but also increase the risk of bleeding and other adverse reactions associated with these drugs. Further studies are needed to assess the effects of individualised clopidogrel treatments in patients with various CYP2C19 genotypes. [22]

CONCLUSION:

The genetic polymorphisms CYP2C19 emphasis their important influence on medication metabolism and consequent clinical results.The connection between poor CYP2C19 metabolizers and adverse cardiovascular event has been explained.It offers insights into alternate therapeutic approaches while navigating the challenges of managing individuals with various CYP2C19 phenotypes. It also highlights the difficulties in implementing these strategies and the need for more research to evaluate the efficaciousness of clopidogrel therapy in patients with different CYP2C19 genotypes.
It advances the field of pharmacogenetics by promoting a move in antiplatelet therapy towards personalized medicine. Encouraging physicians to take genetic characteristics into account when writing prescriptions for antiplatelet drugs opens the door to more accurate and efficient patient care in the field of cardiovascular health.

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