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Update: Acute Coronary Syndromes (V)

Personalized Antiplatelet Therapy

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ABSTRACT

It is well established that high on-treatment platelet reactivity to adenosine diphosphate during clopidogrel therapy is an independent risk factor for ischemic event occurrences in a postpercutaneous coronary intervention patients. However, the precise role of platelet function testing remains debated. Platelet function testing to ensure optimal platelet inhibition has been recommended by some authorities to improve outcomes in patients treated with clopidogrel. Recent prospective, randomized trials of personalized antiplatelet therapy have failed to demonstrate a benefit of platelet function testing in improving outcomes. In this review article, we discuss the mechanisms responsible for clopidogrel nonresponsiveness, recent trials of platelet function testing, and other new developments in the field of personalized antiplatelet therapy.

Tratamiento antiagregante plaquetario personalizado

Palabras clave:
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RESUMEN

Actualmente está bien establecido que la alta reactividad plaquetaria a la adenosina difosfato durante el tratamiento con clopidogrel es un factor independiente predictivo del riesgo de eventos isquémicos en pacientes a los que se ha practicado una intervención coronaria percutánea. Sin embargo, el papel exacto de las pruebas de la función plaquetaria sigue siendo objeto de controversia. Las pruebas de la función plaquetaria para asegurar una inhibición plaquetaria óptima han sido recomendadas por algunos autores para mejorar los resultados en los pacientes tratados con clopidogrel. En ensayos prospectivos y aleatorizados recientes sobre tratamiento antiagregante plaquetario personalizado, no se ha podido demostrar un efecto favorable de las pruebas de la función plaquetaria en cuanto a mejora de los resultados clínicos. En este artículo se analizan los mecanismos de la falta de respuesta a clopidogrel, los ensayos recientes de las pruebas de la función plaquetaria y otros nuevos avances en el campo del tratamiento antiagregante plaquetario personalizado.

Abbreviations

ACS: acute coronary syndrome
ADP: adenosine diphosphate
HPR: high on-treatment platelet reactivity
PCI: percutaneous coronary intervention
PFT: platelet function testing
PRU: $P2Y_{12}$ reaction units

INTRODUCTION

Adenosine diphosphate (ADP)-$P2Y_{12}$ receptor interaction plays a pivotal role in platelet-rich thrombus generation at sites of plaque rupture and subsequent ischemic event occurrence in patients with coronary artery disease. The clinical efficacy of dual antiplatelet therapy consisting of acetylsalicylic acid and a $P2Y_{12}$ receptor blocker has been demonstrated in a wide range of high-risk coronary artery disease patients.[1] However, clopidogrel therapy, the most widely used $P2Y_{12}$ receptor blocker, is associated with widely variable pharmacodynamic response and approximately 1 in 3 clopidogrel-treated patients will have high on-treatment platelet reactivity (HPR). This complication has been strongly linked to postpercutaneous coronary intervention (PCI) ischemic event occurrence in observational studies of thousands of patients. Despite the fundamental importance of unblocked $P2Y_{12}$ receptors in the genesis of thrombosis, the clear demonstration of clopidogrel nonresponsiveness, and even the identification of genes associated with resistance—*CYP2C19*2* and **3*—and their strong link to increased post-PCI ischemic risk, cardiologists do not usually determine platelet function or genetic polymorphisms in

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their high risk patients treated with clopidogrel. Coompared with the objective assessments and adjustments frequently made during treatment with most other cardiovascular drugs, this "nonselective" or "one-size-fits all" approach to clopidogrel, the most widely used $P2Y_{12}$ inhibitor to prevent a catastrophic thrombotic event occurrence, is paradoxical.[2,3]

There has been long-term reluctance to assess platelet function due to the potential introduction of artifacts by laboratory methods, incomplete reflection of the actual *in vivo* thrombotic process, and failure to unequivocally establish a causal relation between the results of the test and thrombotic event occurrence. In the last decade, understanding of platelet receptor physiology has markedly improved, more potent $P2Y_{12}$ receptor blockers that can overcome some of the limitations of clopidogrel have been developed, and cheaper generic clopidogrel is available. The introduction of more user-friendly platelet function assays that can reliably determine the antiplatelet effect of $P2Y_{12}$ receptor blockers and point-of-care genetic assay that can readily determine genetic polymorphisms associated with the metabolism of $P2Y_{12}$ receptor blockers (particularly clopidogrel and prasugrel) have stimulated strong interest in antiplatelet therapy monitoring and personalized antiplatelet therapy.[3,4]

MECHANISMS RESPONSIBLE FOR CLOPIDOGREL NONREPONSIVENESS

Multiple lines of evidence strongly suggest that variable and insufficient active metabolite generation are the primary explanations for clopidogrel response variability and nonresponsiveness where negligible or no antiplatelet effect of clopidogrel is observed.[5] Variable levels of active metabolite generation following clopidogrel administration could be explained by: *a)* variable or limited intestinal absorption that may be influenced by *ABCB1* gene polymorphism, and *b)* functional variability in CYP (cytochrome P450) isoenzyme activity that is influenced by drug-drug interactions and single nucleotide polymorphisms in genes encoding CYP isoenzymes.[5]

Numerous studies have evaluated the influence of single nucleotide polymorphisms of the gene encoding CY2C19 as well as single nucleotide polymorphisms of the p-glycoprotein transporter *(ABCB1)* gene on clopidogrel response variability and clinical outcomes.[5] The most widely analyzed and most frequent single nucleotide polymorphisms are *CYP2C19*2* (loss-of function [LoF] allele), which is associated with complete absence of enzyme activity, and *17 (gain-of-function allele), which is associated with increased expression and increased enzymatic activity.[6] Less exposure to plasma clopidogrel active metabolite (32% relative reduction; $P < .001$) and less platelet inhibition (9% absolute reduction from baseline; $P < .001$) were demonstrated in healthy carriers of at least 1 *CY2C19 LoF* allele compared with noncarriers.[7] In the first genome-wide association study, conducted in healthy Amish subjects, *CYP2C19*2* was the only single nucleotide polymorphism associated with clopidogrel response variability and accounted for only 12% of the variation in platelet aggregation to ADP after clopidogrel treatment. In a replication study of PCI patients, carriers of the *CYP2C19*2* allele had a $\sim$ 2.4-fold higher cardiovascular event rate than noncarriers.[8] In a collaborative meta-analysis of various clinical trials primarily involving patients who underwent PCI (91%, 55% had acute coronary syndrome [ACS]), there was an increased risk of the composite end point occurrence of cardiovascular death, myocardial infarction or stroke among carriers of 1 *LoF* allele (hazard ratio [HR] = 1.55; 95% confidence interval [95%CI], 1.10–2.17; $P = .01$), as well as among carriers of 2 *LoF* alleles (HR = 1.76; 95%CI, 1.24–2.50; $P = .002$), compared with noncarriers. A significantly increased risk of stent thrombosis was observed in both carriers of 1 *LoF* allele (HR = 2.67; 95% CI, 1.69–4.22; $P < .0001$ and) and 2 *LoF* alleles (HR = 3.97; 95%CI, 1.75-9.02; $P = .001$) than in noncarriers.[9]

Subsequent retrospective analyses of trials involving non-PCI patients failed to demonstrate a significant association between *CYP2C19 LoF* allele carriage and adverse clinical outcomes. The relation of the gain of function allele (*CYP2C19*17*) carrier status, and *ABCB1* and paraoxonase-1 genotypes to antiplatelet response and clinical outcomes in clopidogrel-treated patients are inconclusive at this time.[9–12] In addition, *LoF* allele carrier status is an important independent predictor of the pharmacodynamic response to clopidogrel and the outcomes of high-risk clopidogrel-treated patients who have undergone PCI. In 2009, the Food and Drug Administration noted that healthcare professionals should be aware that tests are available to determine genotype and that the antiplatelet response in poor metabolizers is increased by high-dose clopidogrel. The Food and Drug Administration also recommended the use of other antiplatelet medications or alternative dosing strategies for clopidogrel in poor metabolizers.[13]

Finally, it should be noted that the CYP2C19 isoenzyme is not the only factor determining the antiplatelet response to clopidogrel, as even in poor metabolizers, some degree of platelet inhibition has been observed when no enzyme activity is expected. In a study of healthy persons with homozygous CYP2C19 extensive metabolizer genotype, clopidogrel 75 mg/day was administered for 9 days. In this study, all identified factors together accounted for only 18% of interindividual variation in pharmacokinetic parameters and 32% to 64% of interindividual variation in platelet function as measured by VASP-P (vasodilator-stimulated phosphoprotein phosphorylation) assay, VerifyNow $P2Y_{12}$ assay, and ADP-induced platelet aggregation by conventional assay.[14] Stimulation of CYP3A4 activity by rifampin and St. Johns Wort, and CYP1A2 activity by tobacco smoking have been shown to enhance platelet inhibition induced by clopidogrel.[15–17] The effect of smoking on the antiplatelet effect of clopidogrel has been associated with clinical outcomes and may, in part explain the "smoker's paradox".[18] Conversely, agents that compete with clopidogrel for CYP and/or inhibit CYP, attenuate the antiplatelet effect of clopidogrel. A diminished pharmacodynamic response to clopidogrel has been observed with coadministration of proton pump inhibitors such as omeprazole, lipophilic statins, and calcium channel blockers that are metabolized by the CYP2C19 and CYP3A4 isoenzymes.[19–21] Although a diminished level of platelet inhibition induced by clopidogrel has been demonstrated in some *ex vivo* studies following coadministration of these agents, the effect of these interactions on the risk of ischemic event occurrence remains controversial. In addition to the above mechanisms explaining clopidogrel pharmacodynamic variability, old age, increased body mass index, renal insufficiency, diabetes mellitus, and ACS have also been associated with a diminished antiplatelet response to clopidogrel (Figure).[22] Finally, noncompliance is an obvious factor that must be excluded in the diagnosis of clopidogrel nonresponsiveness. When attempting to define causality for high platelet reactivity related to the occurrence of clinical events in patients receiving clopidogrel, all of the aforementioned mechanisms should be considered. The advantages and disadvantages of platelet function testing (PFT) and genotyping are given in Table 1.

Platelet Function Testing

Based on the vast amount of accrued observational data, the recent 2011 American and European guidelines have given a class IIb recommendation in the high-risk patient for PFT or genotyping if the results of testing could alter management