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Effect of CYP2C19 Polymorphisms on the Platelet Response to Clopidogrel and Influence on the Effect of High Versus Standard Dose Clopidogrel in Carotid Artery Stenting

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WHAT THIS PAPER ADDS

This report covers an important topic in the field of endovascular surgery. Studies assessing the influence of genetic polymorphisms on high on-treatment platelet reactivity in cerebrovascular disease patients are limited, and need validation in large multicenter studies. Similar larger studies have been performed in coronary artery disease patients but not in CAS. Their role in CAS is based only on that indirect experience but has never been specifically tested. The effects of CYP2C19 gene phenotypes and dose adjustment of clopidogrel on platelet reactivity in patients undergoing CAS, which have not been assessed before, were investigated. For patients with high on-treatment reactivity who were intermediate–poor metabolizers, the use of high dose clopidogrel compared with standard dose was not significantly different. Probably, in the near future, the use of systematic CYP2C19 genotyping and other SNPs in patients undergoing platelet function testing could help selecting the appropriate P2Y12 inhibitor by identifying patients with high on-treatment reactivity who are intermediate –poor metabolizers.

Objectives: Genetic background has been identified to be a major predictor of post-clopidogrel platelet inhibition in patients undergoing coronary stenting. However, there is a lack of data on clopidogrel response regarding genotype in patients undergoing carotid artery stenting (CAS). The influence of the most common allelic variants of CYP2C19 phenotypes and genotypes on response to baseline clopidogrel and on the pharmacodynamic effect of dose adjustment (high or standard dose of clopidogrel) in patients with high on-treatment reactivity after CAS was investigated.

Methods: Platelet reactivity was assessed before and 30 days after carotid stenting using the VerifyNow P2Y12 assay to obtain P2Y12 reactivity unit (PRU) values.

Results: A total of 209 patients (79.4% male, 44.1% currents smokers) were treated by CAS. Smokers improved responsiveness to clopidogrel ($p = .034$). With respect to CYP2C19 enzymatic function, 61 subjects (29.1%) were ultra-rapid metabolizers, 95 patients (45.5%) were extensive metabolizers, 51 (24.4%) were intermediate metabolizers, and two (0.96%) were poor metabolizers. Baseline PRU was significantly higher among intermediate–poor metabolizers compared with ultra-rapid ($p = .001$) or extensive metabolizers ($p = .005$). At 30 days follow up, in non-responding patients with the intermediate–poor metabolizer phenotype, the PRU value and inhibition percentage were significantly reduced with standard dose ($p = .008$; $p = .0029$) and high dose of clopidogrel ($p = .00\ 0$; $p = .000$). However, high dose clopidogrel did not achieve a more intense pharmacodynamic effect at 30 days ($p = .994$) compared with standard dose.

Conclusions: In patients undergoing carotid stenting, those with the CYP2C19*2 allele had increased basal PRU values and in fact clopidogrel non-responders increased significantly among intermediate–poor metabolizers.

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Although high dose and standard dose clopidogrel therapy was effective in lowering the 30 day PRU values in patients with high on-treatment reactivity who are intermediate—poor metabolizers, the use of high dose clopidogrel did not result in statistically significantly greater reductions in reactivity compared with the standard dose.

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INTRODUCTION

Clopidogrel, in combination with aspirin, is effective in preventing recurrent vascular events, such as myocardial infarction (MI) or stroke.[1] Like all thienopyridines, clopidogrel is a pro-drug that must undergo hepatic biotransformation (via cytochrome P450 [CYP]) to convert the active metabolite (R130964) that inhibits platelet aggregation. Approximately 85% of the clopidogrel absorbed into the bloodstream from the intestine is hydrolyzed to an inactive carboxylic acid derivative by esterases.[2,3] The remaining 15% is metabolized in the liver by a double oxidation process (Fig. 1). The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor.[4]

Although several mechanisms have been proposed for the inter-patient variability[5] in response to clopidogrel, genetic polymorphisms have been identified to be major predictors of post-clopidogrel platelet inhibition and adverse clinical events in patients undergoing percutaneous coronary stenting (PCI).[6–8] This gene is highly polymorphic, with ≥34 identified polymorphisms, some of which result in loss of function (LOF). CYP2C19*2 and CYP2C19*3 are the most common LOF alleles.[6]

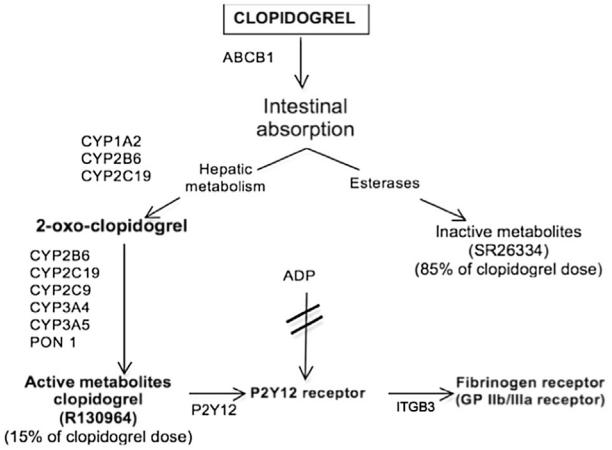
Studies have shown that patients with one or two LOF CYP2C19 alleles have reduced conversion to the clopidogrel active metabolite, decreased platelet inhibition, and increased cardiovascular events compared with patients with normal CYP2C19 function.

The relationships between single nucleotide polymorphisms (SNPs) and clopidogrel effects using different dosing strategies (standard vs. high dose) have been examined in PCI, but not in carotid artery stenting (CAS). However, their role in CAS is based only on that indirect experience but has never been specifically tested. As such, they might not apply to CAS.[7,8]

Therefore, the main aim of this study was to investigate whether genetic backgrounds of patients were relevant to the response to clopidogrel in the CAS setting, by studying the prevalence of the most common allelic variants of CYP2C19 phenotypes and genotypes (*2, *3, and *17) and to evaluate at 30 days after CAS if treatment intensification strategies (doubling the clopidogrel dose) in intermediate—poor responders patients could potentially provide a more intense antiplatelet effect than standard dose therapy by providing a larger amount of substrate for biotransformation into the active metabolite.

MATERIALS AND METHODS

The design and clinical results of the study have been described previously.[9] Two hundred and nine patients (79.4% male, 44.1% currents smoker) were treated by CAS and had adequate DNA recovered and were available for



Genotype	Polymorphism	dbSNP ID*	SNP
CYP2C19[11-13]	CYP2C19*2	rs4244285	681G>A
	CYP2C19*3	rs4986893	636G>A
	CYP2C19*17	rs12248560	-806C>T
CYP2C9[14]	CYP2C9*2	rs1799853	3608C>T
	CYP2C9*3	rs1057910	42614A>C
CYP2B6[15]	CYP2B6*5	rs3211371	1459C>T
	CYP2B6*9	rs3745274	516G>T
CYP3A4[16-18]	CYP3A4*1	rs2242480	13871>G
CYP3A5[17]	CYP3A5*3	rs776746	6986 G>A
PON1[19]	Q192R	rs662	672 A>T
ABCB1[5,21]	C3435T	rs1045642	3435 C>T
P2RY12[21,22]	G52T	rs6809699	52T>G
	C34T	rs6785930	34C >T
CYP1A2[23]	CYP1A2*1F	rs762551	-164 C>A
ITGB3[22]	L196P	rs5918	196T>C

* Ref SNP accession ID number (*http://www.ncbi.nlm.nih.gov/snp/*).

Figure 1. Clopidogrel metabolism, evaluated genes, and single nucleotide polymorphisms that have been previously associated with clopidogrel response in cardiovascular diseases.