Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy.

Abstract:

BACKGROUND: With the cytochrome P450 CYP2C19*2 (*2) allelic variant resulting in complete loss of enzyme function and the CYP2C19*17 (*17) variant being linked to increased transcriptional activity with extensive metabolism of CYP2C19 substrates, two common variants of the CYP2C19 gene have been explored recently. Currently, the isolated and interactive impacts of both variants on the antiplatelet effects of chronic clopidogrel therapy are unknown.

OBJECTIVES: The aim of this study was to assess the isolated and interactive impacts of *2 and *17 on clopidogrel responsiveness in patients under clopidogrel maintenance treatment. Methods: Patients (n=986) eligible for this study were under therapy with coronary stent-related chronic treatment with aspirin and clopidogrel. The ADP-induced platelet aggregation was measured on a Multiplate analyzer (in AU*min), and genotypes were determined with a TaqMan assay. RESULTS: Platelet aggregation values were significantly higher in carriers of at least one *2 allele than in homozygous wild-type allele carriers (P<0.001). For *17, platelet aggregation values were significantly lower in carriers of at least one *17 allele than in homozygous wild-type patients (P=0.01). A gene-dose effect was observed for both variants, with a pronounced effect of the mutant allele (*2 or *17) in
homozygous patients being seen. For the interactive effect of both variants on platelet aggregation values, a gradual increase in platelet aggregation values was observed from (+)*17/(-)*2 patients, who exhibited the lowest values (median of 207 AU*min) to (-)*17/(-)*2, (+)*17/(+)*2 and (-)*17/(+)*2 patients, who exhibited the highest values (median of 309 AU*min) (P<0.001). CONCLUSIONS: *2 and *17 allele carriage are independent predictors for the antiplatelet effect of chronic clopidogrel therapy.

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