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The Effect of CYP2C19 Genotype on the Platelet Responsiveness to Clopidogrel in Korean Healthy Subjects

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Variable inhibition of platelet aggregation in response to clopidogrel has been reported recently, but the underlying mechanisms remain unclear yet. We investigated the influence of cytochrome P450 (CYP) isozymes and MDR1 genetic polymorphisms on the platelet responsiveness to clopidogrel. Forty Korean healthy subjects were given a loading dose of 300 mg clopidogrel and followed by daily doses of 75 mg for 6 days. CYP2C19, 3A5, 2B6 and MDR1 genotypes of subjects were analyzed. ADP-induced platelet aggregation and plasma concentrations of clopidogrel were measured. Baseline levels of platelet aggregation were not significantly different among groups in relation to specific CYP or MDR1 genotype. However, at steady state, platelet aggregation was significantly associated with the CYP2C19 genotype and the absolute values in group with wild-type (CYP2C19*1/*1), group with heterozygous mutation (CYP2C19*1/*2 and *1/*3) and poor metabolizers (CYP2C19*2/*2, *2/*3 and *3/*3) were 31.3% ± 11.6%, 33.6% ± 10.5% and 56.7% ± 13.5%, respectively ($P < 0.0001$). Peak plasma concentration and area under the plasma concentration-time curve (AUC) of clopidogrel were not influenced by the MDR1 C3435T genotype. Peak plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of clopidogrel were not associated with MDR1 C3435T genotype. This results suggest that platelet responsiveness to clopidogrel was diminished significantly in CYP2C19 poor metabolizers in relation to CYP2C19*2 and *3, and CYP2C19 genotype seems to be a major determinant of clopidogrel resistance.