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Effect of CYP2D6 Genetic Polymorphism on the Pharmacokinetics and ECG Pharmacodynamics after Single Oral Administration of Flecainide in Healthy Subjects

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Background: Drug-induced QT/QTc prolongation may lead to development of cardiac arrhythmias including Torsade de Pointes. Flecainide is a class Ic antiarrhythmic agent and is metabolized by CYP2D6. Our objective was to evaluate the effect of CYP2D6 genetic polymorphism, and also drug interaction with paroxetine as a CYP2D6 inhibitor, on flecainide pharmacokinetics (PK) and electrocardiographic QTc intervals after single oral administration in healthy subjects.

Methods: An open label, two period cross-over study was performed in 16 healthy male volunteers (4 for CYP2D6*1/*1 or *1/*2, genotype group 1; 6 for *1/*10, group 2; 6 for *10/*10 or *10/*36, group 3). Subjects were administered 200 mg of flecainide on day 1 (period 1). After a seven-day washout period, subjects were administered 20 mg of paroxetine from day 8 to 14, and 200 mg of flecainide on day 15 (period 2). Blood sampling and 12-lead electrocardiograms were performed up to 72 hours after flecainide administration. QT intervals were corrected by individual QT-RR regression (QTcR). PK parameters were obtained by using NONMEM?? (version V, level 1.1, Globomax, Ellicott City, MD). Repeated measures ANOVA was applied to QT and QTcR interval change from baseline.

Results: A one-compartment model with first order absorption well fitted the flecainide PK profile. Apparent total clearance was significantly lower with genotype group 2 (28.3%) and group 3 (26.6%) in period 1, but significantly lower with genotype group 2 only in period 2 (18.1%) compared to genotype group 1. Post-hoc analysis of variance (ANOVA) showed significant differences of clearance between wild type and other two variant genotype groups (p=.033). Change from time-matched baseline of QT intervals were significantly different among genotype groups ($p < .001$), but QTcR intervals were not significantly different probably due to large inter-individual variability and small number of subjects.

Conclusion: The CYP2D6*10 allele was associated with lower apparent total clearance after single administration of flecainide to healthy subjects. However, effects of CYP2D6 polymorphism on the electrophysiologic markers were not definite due to large variability.