

## Effect of CYP2D6 Genetic Polymorphism and Metabolic Inhibition on the Pharmacokinetics and QTc Intervals 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. 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 and QTc intervals after single oral administration in healthy subjects.

**Methods:** An open label, two period cross-over study was performed in ten healthy male volunteers (two for CYP2D6\*1/\*1, two for \*1/\*10, and six for \*10/\*10). Subjects were administered 200 mg of flecainide on day 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. Blood sampling and 12-lead electrocardiograms were performed up to 72 hrs after flecainide administration. QT intervals were corrected by individual QT-RR regression.

**Results:** There were significant differences of QTc change between genotype groups ( $-9.0 \pm 3.4$ ,  $11.3 \pm 3.4$ , and  $17.3 \pm 2.0$  msec for \*1/\*1, \*1/\*10, and \*10/\*10, respectively). QTc change also differed between periods, but this change was statistically significant in only the \*1/\*1 (extensive metabolizer; EM) group.

**Conclusions:** The CYP2D6\*10 allele was characterized to have a substantially greater increasing effect on QT/QTc than the wild-type (\*1) allele after single administration of flecainide to healthy subjects. The paroxetine-flecainide interaction augmented QT/QTc changes in the EM group.