

Sex-Differences in Drug-Induced Changes in Ventricular Repolarization

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Introduction: Heart rate corrected QT (QTc) interval prolongation is a predictor of drug-induced torsade de pointes, a potentially fatal ventricular arrhythmia that disproportionately affects women. The reason for this higher risk is not clear and may be multifactorial. Longer QTc in women compared to men at baseline is explained by longer early repolarization (JT_{peak}), despite women having shorter depolarization (QRS) and shorter late repolarization ($T_{peak}-T_{end}$) than men do. Previous clinical studies with different drugs (e.g. quinidine, ibutilide, rac-sotalol) have shown greater drug-induced QTc prolongation relative to serum drug concentration in women compared to men. This study assesses whether there are sex differences in the ECG changes induced by 4 different drugs.

Methods: Twenty-two healthy subjects (11 women) received a single oral dose of dofetilide, quinidine, ranolazine, verapamil and placebo in a double-blind 5-period crossover study. Plasma concentrations and ECGs were obtained pre-dose and at 15 time-points post-dose. From the ECGs, PR, QTc (Fredericia's), QRS, $T_{peak}-T_{end}$ and rate corrected J-T_{peak} ($J-T_{peakC}$, study-specific exponential model with correction factor=0.58) were measured as well as T-wave morphology (e.g., flatness, asymmetry and notching). Sex-differences were evaluated by the interaction between slope of effect by drug level (to adjust for differences in exposure) and sex in a linear mixed effects model, using a significance level of 0.05.

Results: Dofetilide, quinidine and ranolazine caused concentration dependent QTc prolongation ($p<0.01$ for all). Verapamil increased PR ($p<0.01$) but did not cause changes in any other ECG interval or T-wave morphology biomarker. Sex-differences were observed only with dofetilide, which caused greater JT_{peakC} prolongation (interaction $p=0.045$) but lesser $T_{peak}-T_{end}$ prolongation (interaction $p<0.01$) and lesser decrease of heart rate corrected maximum magnitude of the T vector (interaction $p<0.01$) in women compared to men. No other sex differences were observed.

Discussion: No sex differences in drug-induced QTc prolongation were observed for any of the 4 drugs. This is in contrast to previous studies, which observed greater QTc prolongation in women than men. With dofetilide, a pure hERG potassium channel blocker, women had a greater increase in $J-T_{peakC}$, but a lesser increase in $T_{peak}-T_{end}$, which is consistent with differences between women and men in the absence of drug. There were no differences in T-wave flatness, asymmetry or notching between women and men. The mechanism for higher torsade de pointes risk in women versus men deserves further study.