Sex Differences in Drug-Induced Changes in Ventricular Repolarization

Vicente

Brief title: Sex Differences in ECG Drug-Induced Changes

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Abstract

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. This study assesses whether there are sex differences in the ECG changes induced by four different hERG potassium channel blocking drugs.

Methods and results: 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. ECGs and plasma drug concentrations were obtained at pre-dose and at 15 time-points post-dose. Dofetilide, quinidine and ranolazine prolonged QTc. There were no sex differences in QTc prolongation for any drug, after accounting for differences in exposure. Sex differences in any ECG biomarker were observed only with dofetilide, which caused greater J-T_{peak}c prolongation (p=0.045) but lesser T_{peak}-T_{end} prolongation (p=0.006) and lesser decrease of T wave amplitude (p=0.003) in women compared to men.

Conclusions: There were no sex differences in QTc prolongation for any of the studied drugs. Moreover, no systematic sex differences in other drug-induced ECG biomarker changes were observed in this study. This study suggests that the higher torsade risk in women compared to men is not due to a larger concentration-dependent QTc prolongation.

Keywords: sex differences; QTc prolongation; T wave morphology; torsade de pointes; drugs; hERG block

Introduction

Women are at higher risk for drug-induced torsade de pointes, a potentially fatal ventricular arrhythmia [1]. The reason for the higher drug-induced torsade risk in women is not entirely clear. It might be because women are smaller than men and thus are exposed to higher drug concentrations, there may be sex differences in the electrophysiology of the heart that make women more susceptible or there may be sex differences in drug metabolism and transport that make women more susceptible.

Almost all drugs that cause torsade block the human ether-a-go-go related gene (hERG) potassium channel [2] and prolong the heart rate corrected QT interval (QTc) on the electrocardiogram (ECG) [3]. Previous clinical studies with different drugs (e.g. quinidine [4], ibutilide [5], rac-sotalol [6]) have shown greater drug-induced QTc prolongation relative to serum drug concentration in women compared to men. However, it has been shown recently that sex differences in the delay between serum quinidine concentration and ECG changes (hysteresis [7]) in a study of intravenous quinidine may have contributed to observed sex differences in quinidine-induced QTc prolongation [8].

Sex- and age-differences in ventricular repolarization at baseline have been reported since the 1920s [9-11]. Specifically, longer QTc in women compared to men is explained by longer early repolarization (J-T_{peak}), despite women having shorter depolarization (QRS) and shorter late repolarization (T_{peak}-T_{end}) than men do [11]. The shorter J-T_{peak} interval in men is likely due to reduced calcium current by testosterone [11]. Testosterone-induced calcium block may prevent occurrence of early after depolarizations [12, 13], which are the triggers for torsade, and

therefore may lower the risk for torsade in men. However, it is still not clear how other physiological mechanisms contribute to these baseline differences and how they might be related to drug-induced torsade risk.

Sex differences in drug-induced ECG changes may provide insights for the higher risk for drug-induced torsade in women. In this study we assesses whether there are sex differences in the ECG changes (QTc, but also QT subintervals and T wave morphology) induced by a selective hERG potassium channel drug (dofetilide) and three drugs that block hERG but also block calcium or late sodium inward currents (quinidine, ranolazine and verapamil).

Methods

Clinical Study design

The design of this clinical study has been described previously [14]. Briefly, 22 healthy subjects (11 women) received a single oral dose of dofetilide, quinidine, ranolazine, verapamil and placebo in a double-blind 5-period crossover study at a clinical research unit (Spaulding Clinical, West Bend, Wisconsin, USA). ECGs and plasma drug concentrations were obtained pre-dose and at 15 time-points post-dose (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 14, 24 h), during which the subjects were resting in a supine position for 10 min. Continuous 12-lead ECGs were recorded at 500 Hz and with an amplitude resolution of 2.5 μV using the Mason-Likar electrode configuration [15]. Plasma drug concentration was measured using a validated liquid chromatography with tandem mass spectroscopy method by Frontage Laboratories (Exton, Philadelphia, PA). The study was approved by the U.S. Food and Drug Administration Research

Involving Human Subjects Committee and the local institutional review board. All subjects gave written informed consent.

ECG Analysis

From the continuous recording and within the 10 min resting supine period at each of the 16 predefined time-points, triplicate non-overlapping 10-second ECGs with more stable heart rates and maximum signal quality were extracted using Antares software (AMPS-LLC, New York City, NY, USA)[16]. The extracted ECGs were up-sampled from 500 Hz to 1,000 Hz and semi-automatically evaluated by ECG readers blinded to treatment and time as described elsewhere [14, 17]. Briefly, global measures of PR, QT, QRS, J-T_{peak} and T_{peak}-T_{end} intervals were semi-automatically measured in the vectormagnitude lead. In addition to these ECG intervals, different T wave morphology (e.g., T wave amplitude, flatness, asymmetry and notching) and vectorcardiographic biomarkers were automatically measured [18]. T wave flatness, asymmetry and presence of notch [19] were assessed with QTGuard+ (GE Healthcare, Milwaukee, Wisconsin, USA). All the other T wave morphology (30% of repolarization duration [20]) and vectorcardiographic biomarkers (QRS-T angle, ventricular gradient, maximum magnitude of the T vector [T wave amplitude] and total cosine R-to-T [TCRT][21]) were automatically assessed with ECGlib [22].

Heart rate corrected QT (QTc) was computed using Fridericia's correction formula [23]. All heart rate dependent ECG biomarkers were corrected using an exponential model ($biomarker_c = biomarker/RR^{\alpha}$), allowing the relationship to be sex dependent as previously described [18]. No sex-specific differences in the heart rate dependency were found [18] and the values of α

coefficient were 0.58 for J-T_{peak}, 0.96 for T wave amplitude (measured as the maximum magnitude of the T vector), 0.85 for ventricular gradient and 0.58 for T wave flatness.

Statistical Analysis

Unpaired Student's *t*-tests were computed to assess baseline differences between women and men in each ECG biomarker using R version 3.1.2 (Vienna, Austria). The placebo-corrected change from baseline was computed using PROC MIXED in SAS 9.3 (SAS institute, Cary, North Carolina, USA), where the change from baseline for each ECG biomarker by time-point was the dependent variable. Sequence, period, time, drug, and an interaction between treatment and time were included as fixed effects, and subject was included as a random effect. Afterwards, we performed an exposure-response analysis similar to the one proposed for early QT assessment [24] but for a single-dose placebo-controlled randomized crossover study design. Briefly, a linear-mixed effects model was used to evaluate the relationship between each ECG biomarker (except notch) and plasma drug concentrations. This was done using PROC MIXED in SAS 9.3, and having a random effect on both intercept and slope (i.e., allowing each subject to have his own drug concentration-biomarker relationship). A logistic regression model was used to evaluate the relationship between presence of notch and drug concentration including a random effect on intercept in SAS (PROC GLIMMIX). Sex differences were evaluated by the interaction between slope and intercept of effect by drug level (to adjust for differences in exposure) and sex in a linear mixed effects model with PROX MIXED in SAS. P-values <0.05 were considered statistically significant without adjustment for multiplicity.

Results

Twenty-two healthy subjects (11 females) with a mean age of 26.9 ± 5.5 years participated in this randomized controlled clinical trial. All subjects completed the study except for one subject who withdrew prior to the last treatment period (quinidine period for that subject). This resulted in 5,232 of the 5,280 planned ECGs. There were no unexpected treatment related adverse events.

At baseline (supplementary table S1), women had higher heart rates, but shorter QRS duration (p=0.010), late repolarization interval (T_{peak}-T_{end} , p=0.044), 30% of early ($ERD_{30\%}$, p=0.002) and late ($LRD_{30\%}$, p=0.011) repolarization duration and smaller ventricular gradient (p =0.009) than men did. Early repolarization interval (J-T_{peak}c) was longer (p = 0.001) in women compared with men. There were trends toward women having longer QTc (p = 0.065), greater TCRT (p = 0.064) and smaller T wave amplitude (p = 0.064) than men at baseline. No additional sex differences were observed at baseline.

Time-dependent Analysis

Results of the pharmacokinetic analysis are shown in Figure 1 for each drug: (a) dofetilide, (b) quinidine, (c) ranolazine and (d) verapamil. There were no differences between women and men in the pharmacokinetic profiles of dofetilide and ranolazine. However, the maximum plasma drug concentration of quinidine and verapamil were higher in women than in men (2074 [95% confidence interval 1897 to 2268] vs. 1506 [1340 to 1693] ng/mL, p < 0.001 and 156.9 [11.5 to 220.9] vs. 82.21 [66.4 to 101.9] ng/mL, p = 0.002 respectively, Figure 1).

Figure 2 shows the time-matched placebo- and baseline-corrected drug-induced QTc changes (ΔΔQTc) for each drug: (a) dofetilide, (b) quinidine, (c) ranolazine and (d) verapamil. There were no differences between women and men in the ΔΔQTc prolongation induced by dofetilide, quinidine or ranolazine (Figure 2). Verapamil increased the heart rate and PR interval, but did not cause ΔΔQTc prolongation or any other changes in the additional ECG biomarkers assessed in this study.

Concentration-dependent Analysis

There were no sex differences in the relationship between plasma drug concentration and ΔΔQTc prolongation induced by dofetilide (Figure 3), quinidine (supplementary Figure 1) or ranolazine (supplementary Figure 2). Sex differences were observed only with dofetilide, which caused greater concentration dependent ΔΔJ-T_{peak}c prolongation (17 [95% confidence interval: 13 to 21.1] vs. 11.1 [7 to 15.2] ms·ng/mL, p = 0.045), but a lesser increase in ΔΔT_{peak}-T_{end} (10.1 [6 to 14.2] vs. 18.8 [14.7 to 23] ms·ng/mL, p = 0.006) and lesser decrease of ΔΔT wave amplitude (-35.9 [-52.3 to -19.6] vs. -73.9 [-90.6 to -57.2] μV·ng/mL, p = 0.003) in women compared with men (Figure 3). There were no other sex-specific differences in the exposure-response relationships between any of the drugs and ECG biomarkers (supplementary tables S2-S5 and supplementary Figure S1-S8).

Discussion

This study showed no sex differences in the QTc prolongation caused by dofetilide, quinidine and ranolazine. Additional assessment of other ECG subintervals and morphology biomarkers

showed sex-specific differences only with dofetilide (selective hERG potassium channel block). Specifically, women had greater dofetilide-induced increase in J-T_{peak}c (early repolarization), but a lesser increase in T_{peak}-T_{end} (late repolarization) and lesser decrease of T wave amplitude. No other sex differences in the exposure-response relationship were observed for any of the other drugs and ECG biomarkers. While sex differences with dofetilide were consistent with differences between women and men in the absence of drug, these few sex differences were not present with other drugs. Therefore, few-to-no sex differences in drug-induced changes in ventricular repolarization were observed consistently across the study drugs.

Sex differences in ECG changes induced by dofetilide

There was no difference in dofetilide-induced prolongation of repolarization (QTc) between women and men in this study. However, dofetilide caused greater increase of early repolarization (J-T_{peak}c) but lesser prolongation of late repolarization (T_{peak}-T_{end}) and lesser T wave amplitude decrease in women than in men. Adult women have longer QTc than men at baseline, but this difference diminishes with age [10]. These sex- and age-differences in the QTc interval are fully explained by women having longer J-T_{peak}c. The shorter J-T_{peak}c in men is likely due to the block of L-type calcium current by testosterone, which may shorten the plateau phase of the ventricular action potential [11] but also may prevent the occurrence of early after depolarizations [12, 13], which are the triggers for torsade de pointes. Therefore, in this study selective hERG potassium channel block (dofetilide) increased the sex differences in early and late repolarization intervals without increasing the sex differences in QTc.

Previous studies reporting sex differences in drug-induced QTc prolongation

Previous clinical studies have shown greater drug-induced QTc prolongation relative to serum drug concentration in women compared to men with different drugs. Benton and colleagues found greater intravenous quinidine-induced QTc prolongation in women [4]. However, a recent retrospective analysis [8] of that study showed no sex differences in quinidine-induced QTc or T_{peak}-T_{end} prolongation when accounting for sex differences in the delay between serum quinidine concentration and ECG changes (hysteresis [7]). This is consistent with the lack of sex differences in quinidine-induced ECG changes observed in this study.

Sex differences in ibutilide-induced QTc prolongation have been previously reported [5]. Ibutilide prolongs the QTc interval by blocking the hERG potassium channel and increasing the late sodium inward current. Enhancement of late sodium current may result in early repolarization interval (J-T_{peak}c) prolongation, which is seen in long QT syndrome type 3 patients [25]. Whether hysteresis effects and additional late sodium current enhancement contributed to the sex differences in QTc prolongation observed with intravenous ibutilide deserves further investigation.

Darpo and colleagues reported women having higher rac-sotalol plasma levels as well as a steeper concentration dependent QTc prolongation [6]. While we did not study rac-sotalol, which blocks the hERG potassium channel, we observed women having higher plasma concentration of quinidine, which also blocks the hERG potassium channel. However, there were no sex differences in the quinidine concentration dependent response in this study. While there were

few-to-no sex differences in the four drugs of this study, sex differences in drug-induced changes might be present with other drugs.

Sex differences in dofetilide-induced torsade de pointes risk

Recent studies have shown that female sex, longer baseline QTc and greater drug-induced QTc prolongation are significant risk factors for torsade in patients taking dofetilide [26, 27]. The few sex differences in drug-induced ECG changes in this study suggest that, in patient populations, women may have longer ΔΔQTc prolongation because women are exposed to higher plasma drug concentrations than men. This, together with women having longer baseline QTc [9-11], may partially explain the higher risk for drug-induced torsade in women. However, this should be interpreted with caution because the reduced sample size of this study and the differences between populations (e.g. age or healthy vs. not healthy subjects) participating in this vs. other studies.

Limitations

The difference between women and men in dofetilide-induced J-T_{peak}c prolongation was statistically significant (p=0.045), however this result should be interpreted with caution because p-values were not adjusted for multiple comparisons and the reduced sample size of this study (11 women vs. 11 men). Lower p-values would be required to consider a finding statistically significant when adjusting for multiple comparisons. Therefore, adjusting for multiplicity could

minimize or even result in no sex differences in the drug-induced changes in the present study. The study sample size was similar to cohorts used in a previous quinidine study (12 women vs. 12 men) [4]. In addition, retrospective assessment showed that the study was powered to detect sex differences in the drug concentration vs. QTc slope similar to those reported previously with rac-sotalol [6]. The use of other heart rate correction formulas for QT might produce different results [28]. However, sensitivity analysis using either a study based heart rate correction and the so-called model-based QT correction (QTcMod= QT(120 + HR)/180)[29] did not change the observed sex differences in drug-induced ECG effects (results not shown).

Conclusions

There were no sex differences in the relationship between plasma drug concentration and ΔΔQTc prolongation induced by dofetilide, quinidine and ranolazine. In addition, no systematic sex differences of other drug-induced ECG biomarker changes were observed in this study. This study suggests that the higher torsade risk in women compared to men is not due to a larger concentration-dependent QTc prolongation. However, women have a longer QTc at baseline and are often exposed to higher drug concentrations than men, which likely contribute to their higher torsade risk.

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Figure legends

Figure 1: Measured plasma drug concentration (mean ± 95% confidence intervals) in women (red open circles) and men (closed blue circles) for (a) dofetilide, (b) quinidine, (c) ranolazine and (d) verapamil.

Figure 2: Pharmacodynamic time profiles of mean baseline- and placebo-corrected drug-induced QTc changes in women (red open circles) and men (closed blue circles) for (a) dofetilide, (b) quinidine, (c) ranolazine and (d) verapamil. The errors bars denote the ±95% confidence intervals.

Figure 3: Mean baseline- and placebo-corrected plasma dofetilide concentration-dependent changes (PK/PD response) in women (red solid line) and men (blue dashed line) in (a) QTc, (b) J-T_{peak}c, (c) T_{peak}-T_{end}, and (d) T wave amplitude measured as the maximum magnitude to the T vector. Shaded areas show the 95% confidence intervals from the model predictions. For clarity, the observed data is grouped in 10 bins (deciles) represented by the circles (median concentration and mean ΔΔ ECG change) and error bars (95% confidence intervals) for women (red open circles) and men (blue closed circles). See supplementary table S2 for the

population and sex-specific slopes values, and supplementary figure S5 for the observed data. Sex-specific PK/PD relationships for quinidine, ranolazine and verapamil are shown in supplementary figures S1-S3.

Figures

Figure 1

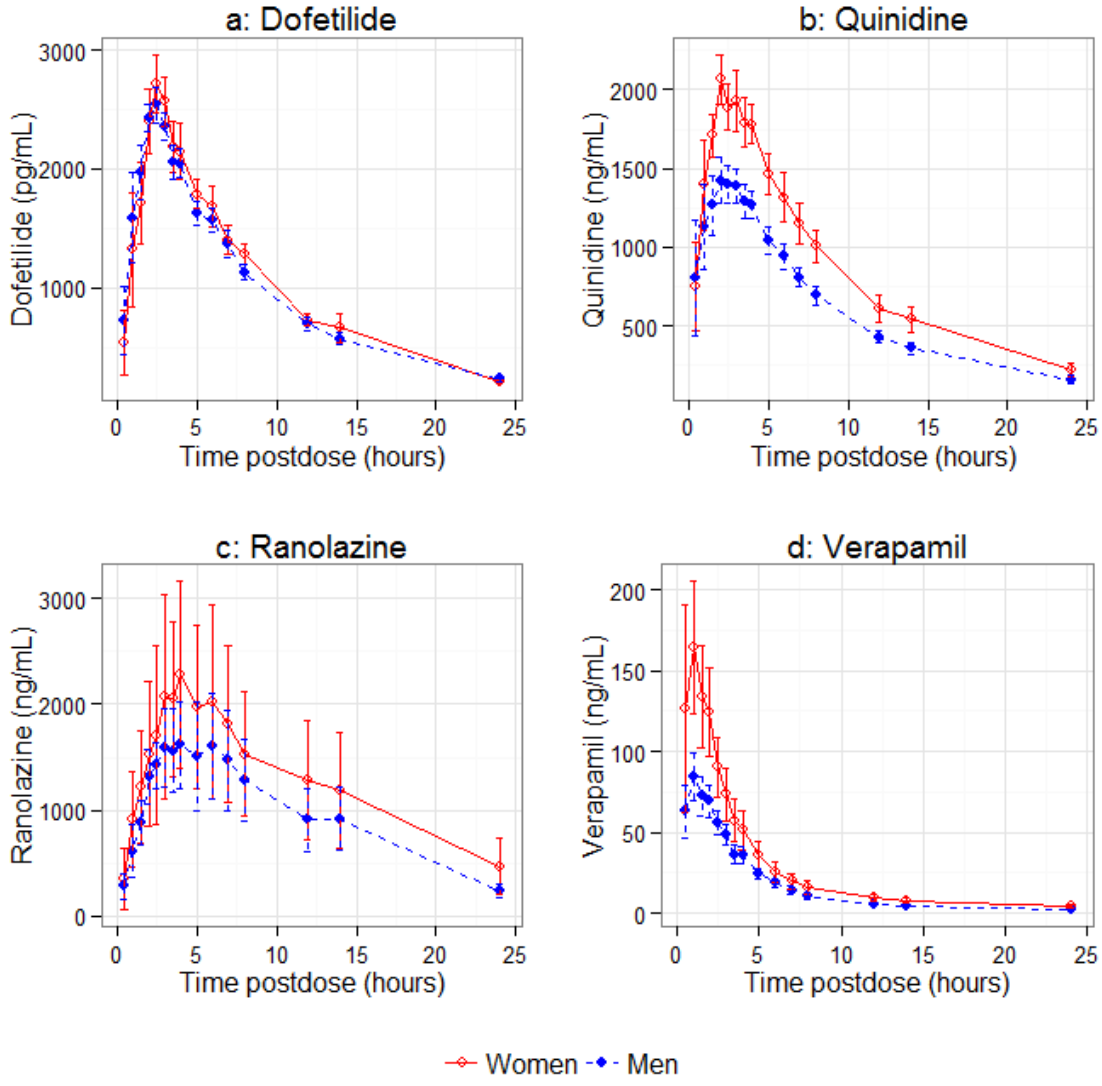


Figure 2

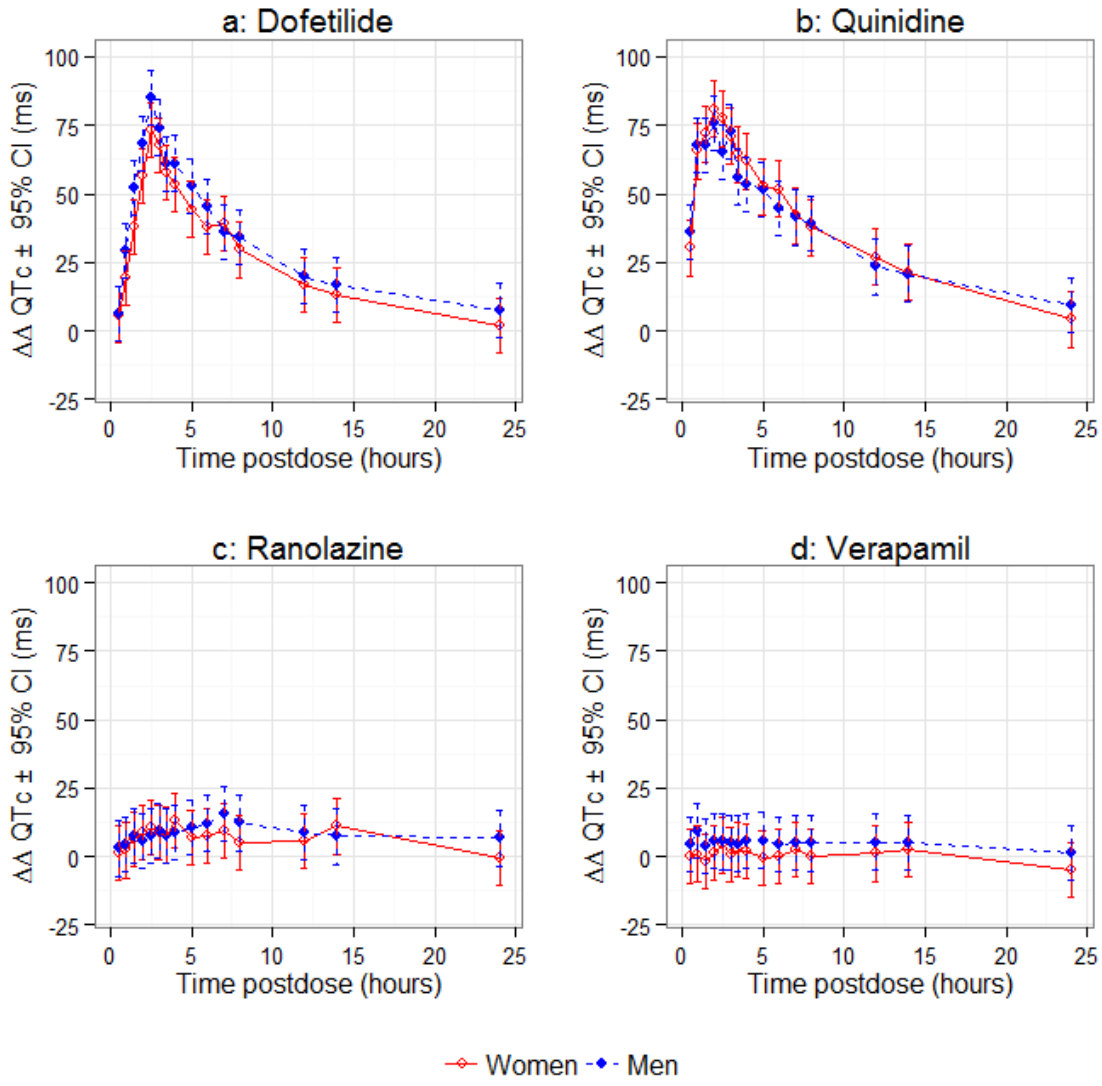
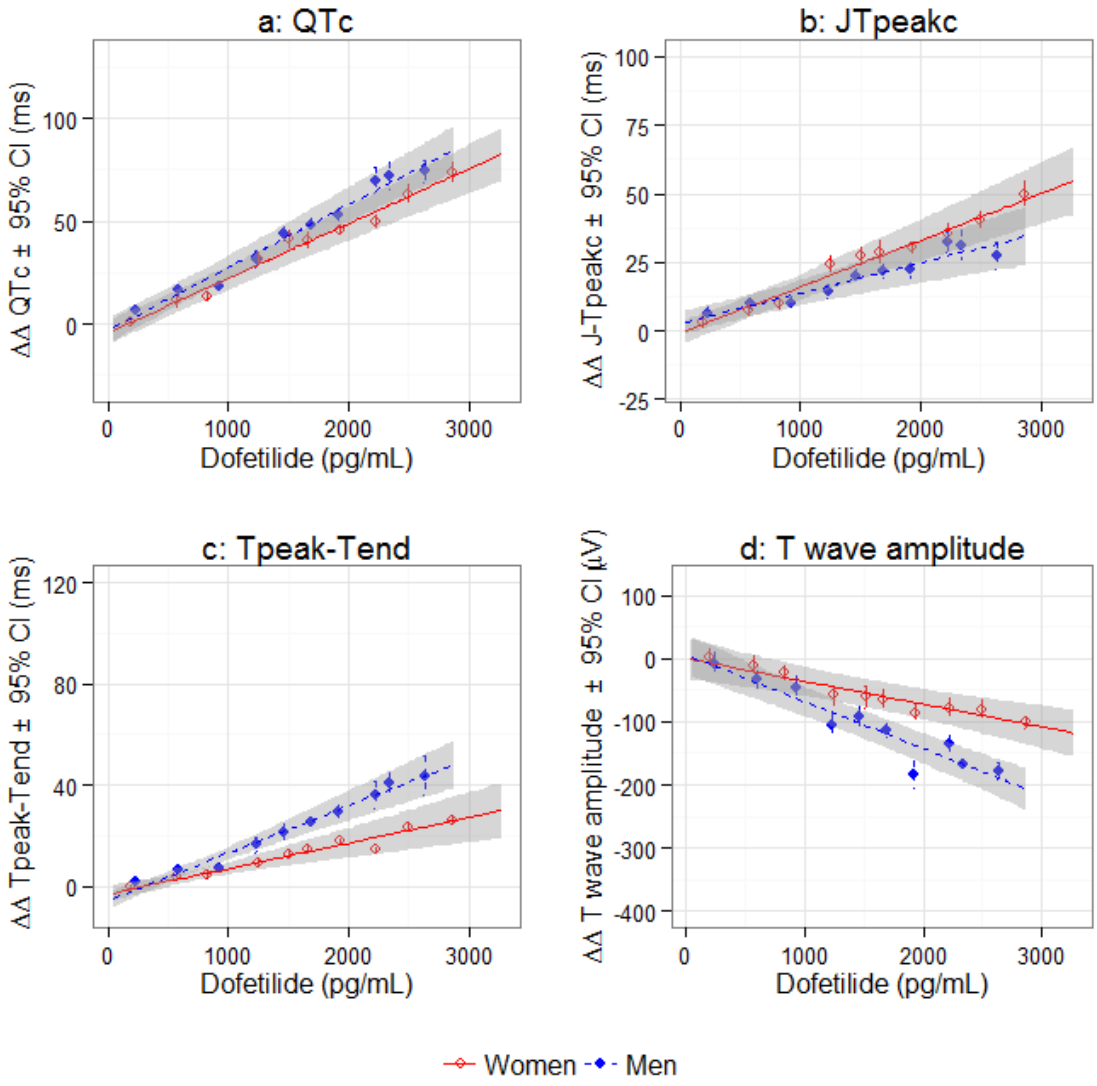

a: Dofetilide
b: Quinidine
c: Ranolazine
d: Verapamil
ΔΔ QTc ± 95% CI (ms)
Time postdose (hours)
Women
Men

Figure 3


a: QTc
ΔΔ QTc ± 95% CI (ms)
Dofetilide (pg/mL)
b: JTpeakc
ΔΔ J-Tpeakc ± 95% CI (ms)
Dofetilide (pg/mL)
c: Tpeak-Tend
ΔΔ Tpeak-Tend ± 95% CI (ms)
Dofetilide (pg/mL)
d: T wave amplitude
ΔΔ T wave amplitude ± 95% CI (μV)
Dofetilide (pg/mL)
Women
Men