Drug-Induced QT Prolongation in Women During the Menstrual Cycle

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Women have slower cardiac repolarization than men, which manifests as longer heart rate corrected QT intervals (QTc) on the electrocardiogram (ECG). This sex difference is apparent only after puberty. Furthermore, women are more prone than men to develop torsades de pointes ventricular arrhythmias after administration of drugs that prolong cardiac repolarization (eg, antiarrhythmic drugs, terfenadine, erythromycin, etc). These findings suggest a role for sex hormones in the response to drugs that alter cardiac repolarization, and animal studies have demonstrated that sex hormones can alter potassium channel expression, ion currents, cardiac repolarization, and QT response to drugs.

During the menstrual cycle there is a dynamic change in circulating levels of estrogen and progesterone. In the absence of a drug that alters cardiac repolarization, QTc does not change during the menstrual cycle, but the possibility that the variation in the hormonal milieu may cyclically modulate the action and/or disposition of drugs has not been studied.

Ibutilide is an antiarrhythmic agent that is used for termination of atrial fibrillation and flutter. It prolongs QTc in a dose-dependent manner with a rapid onset and return to near baseline within 2 to 6 hours. The plasma concentrations of the drug fall rapidly following intravenous infusion, and it has no known active metabolites, making ibutilide an excellent probe to study differences in drug-induced QT prolongation.

The purpose of this study was to compare QT prolongation after the administration of a dose of ibutilide in women during 3 phases of the menstrual cycle and to compare the degree of QT prolongation in response to ibutilide between women and men.

**METHODS**

We studied 58 healthy volunteers who were not taking any medications, 38 men and 20 women, between ages 21 and 40 years and within 10% of their ideal body weight (Metropolitan Life Table). All volunteers had normal clinical and laboratory evaluations and nor-
bacco; and current lactation. The study was approved by the institutional review board of Georgetown University Medical Center, Washington, DC, and all participants provided written informed consent.

**Experimental Protocol**

Participants were studied in the General Clinical Research Center of the Georgetown University Hospital. The women were studied 3 times coinciding with the menses, ovulation, and luteal phases of the menstrual cycle. Men were each studied once. Menses phase evaluation for women was performed within 24 to 60 hours after the onset of menses. Ovulation phase evaluation was done 24 to 48 hours after a urinary ovulation predictor test turned positive (OvuQuick, Quidel Corporation, San Diego, Calif). Luteal phase evaluation was performed 7 to 9 days after ovulation. Women entered the study at different phases of their menstrual cycle, but the majority (14/20) started with the menses phase visit.

After a supine rest period of 20 minutes, a baseline ECG was recorded using a MacVU ECG recorder (Marquette Electronics, Milwaukee, Wis). Then each participant received ibutilide (Corvert, The Upjohn Co, Kalamazoo, Mich) 0.003 mg/kg, diluted in 20 mL of normal saline and infused over a period of 10 minutes. Although this dose of ibutilide is only one third of the recommended antiarrhythmic dose,\(^1\) it is known to produce significant prolongation of the QT interval.

Timed ECGs were obtained from time = 0 (before ibutilide infusion) to at least time = 120 minutes (at 0, 5, 10, 15, 20, 30, 40, 50, 60, 90, and 120 minutes) and, for initial safety assessment in the first 39 subjects studied, to time = 300 minutes. All ECGs were 12 lead and were recorded on computer disk and on paper at 50 mm per second speed with the subject in a stationary resting supine position.

The ECGs were coded and randomized to allow blinded measurement of QT intervals using a validated computer-operator interactive method developed in our laboratory.\(^12\) Measured QT intervals were corrected for heart rate using the formulae of Bazett\(^1\) (QTc = QT/RR\(^{1/2}\)) and Fridericia\(^1\) (QTc = QT/RR\(^{2/3}\)).\(^1\)

**Measurement of Plasma Ibutilide Concentrations**

Ibutilide concentrations in plasma were measured using high-performance liquid chromatography and mass spectrometry detection (Agilent Technologies series 1100 LC/MSD system, Palo Alto, Calif) after liquid-liquid extraction. The extracted standard curve in plasma using this method was linear for ibutilide concentrations from 25 to 500 pg/mL. The percentage coefficient of variation (CV) at the lower limit of quantification of 50 pg/mL was 6.0; percentage CV for the higher limit of quantification of 500 pg/mL was 1.3 on 7 runs.

**Statistical Analysis**

Sample size was calculated to allow detection of a 30% difference in QTc prolongation between menstrual cycle phases and each sex, with \(\alpha = 0.05\) and power of .80. We used a 2-tailed, unequal \(t\) test to compare single time points among men and individual phase studies of women. Assessment of significance of difference in mean change in QTc interval between groups was performed using analyses of variance (ANOVA). To assess the cumulative “burden” of QTc increase over time after ibutilide infusion, we also compared the areas under the curve (AUC) of the change in QTc vs time over 60 minutes from onset of infusion. A similar AUC analysis with ANOVA was performed for ibutilide concentrations measured over time = 10 to 40 minutes. A \(P\) value < .05 was considered significant. The correlation of QTc prolongation with serum hormone levels was calculated using the Pearson correlation coefficient.

**RESULTS**

The mean ages of the women and men were similar (Table 1). Mean weight and height of the women were both less than those of the men, but body mass index was similar. Baseline heart rate was the same in both sexes, but men had shorter QTc intervals than women.

Sex hormone levels fluctuated as expected with low levels of estradiol and progesterone during menses, a peak of estradiol during ovulation, and the highest values of progesterone during the luteal phase (Table 2). Men had the lowest estradiol serum levels, and their testosterone was 15 times higher than that of the women. There were no significant differences in the baseline QTc intervals during the 3 phases of the women’s menstrual cycle (Figure 1).

After ibutilide infusion there were no significant changes in the heart rate or blood pressure and the only adverse effect observed was a self-terminating short run (10 seconds) of asymptomatic bigeminal premature ventricular contractions at the end of the infusion in 1 woman. All QTc results shown used the Bazett\(^1\) correction for heart rate.

<table>
<thead>
<tr>
<th>Women (n = 20)</th>
<th>Men (n = 38)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25.5 (4.3)</td>
<td>27.6 (5.7)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.65 (0.07)</td>
<td>1.78 (0.07)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.7 (9.1)</td>
<td>78.0 (9.8)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>23.4 (3.2)</td>
<td>24.6 (3.1)</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>65 (9)</td>
<td>64 (10)</td>
</tr>
<tr>
<td>Corrected QT interval, ms</td>
<td>410 (15)</td>
<td>391 (21)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD). BMI indicates body mass index.

<table>
<thead>
<tr>
<th>Table 2. Serum Sex Hormone Levels*</th>
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<tr>
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<tr>
<td>Estradiol, pg/mL</td>
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<tr>
<td>Progesterone, ng/mL</td>
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<tr>
<td>Testosterone, pg/dL</td>
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</table>

*Data are presented as mean (SD). Ellipses indicate not applicable.

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Analyses using Fridericia\textsuperscript{4} correction were qualitatively the same and quantitatively very similar (data not shown).

**Changes in QT Interval With Ibutilide**

Ibutilide infusion induced an increase in QTc in all subjects, typically peaking within 5 minutes (t=15 minutes) of completion of the 10-minute infusion. In women, there was a trend, which did not reach statistical significance. In women, there was a trend, of completion of the 10-minute infusion. Error bars indicate SEMs. For comparison of all 3 phases of menstrual cycle compared with men (Figure 2). The mean QTc change over 0 to 60 minutes was significantly smaller in men than in women studied at both the menses (P = .03) and ovulatory (P = .04) phases (Figure 3). Similarly, women in the luteal phase of their menstrual cycle had the least QTc prolongation secondary to ibutilide infusion compared with the other 2 phases (P = .06 vs menses, P = .02 vs ovulatory). For comparisons of menses phase with ovulatory phase (P = .91) and of luteal phase with men (P = .75), there was no difference in mean QTc change over 0 to 60 minutes.

**Plasma Ibutilide Concentrations**

Concentrations of ibutilide were the same in men and women (mean [SD] 563 [291] pg/mL in men vs 507 [160] pg/mL in women; P = .76 at t = 15 minutes; 187 [79] pg/mL in men vs 186 [37] pg/mL in women; P = .72 at t = 40 minutes). Comparison of AUCs of concentrations did not show the same pattern as the QTc AUCs. In increasing order, the values (pg × min/mL) were 1444 for menses, 1531 for luteal, and 1658 for ovulatory, with no significant differences between phases (repeated measures ANOVA, P = .23).

**Sex Hormone Analysis**

In women, both progesterone levels (r = −.40) and the progesterone-to-estradiol ratio (r = −.41) were inversely correlated with the ibutilide-induced QT interval prolongation (P = .001 for both). Neither testosterone (r = 0.09, P = .46) nor estradiol (r = 0.14, P = .28) serum levels showed any significant correlation with the mean change in QTc.

**COMMENT**

This is the first study to compare QT-prolonging effects of a drug during phases of the menstrual cycle. It yielded the novel finding that the QTc prolongation seen after a single infusion of a relatively low dose of ibutilide varies with a greater response found during the first half of the cycle. Furthermore, we found an inverse correlation between progesterone level and mean QTc change after ibutilide but no such correlation for estradiol concentration nor for testosterone. Our results also demonstrate a sex difference in ibutilide response with a greater QT prolongation in women than in men, as described for other QT-prolonging drugs.\textsuperscript{3,15} The lack of difference between plasma ibutilide concentrations does not support a pharmacokinetic explanation for greater QT response to ibutilide in women and suggests sex dif-
ferences in cardiac sensitivity to the drug. It is important to note that in our protocol, we infused only one third of the clinically used initial dose of ibutilide and due to the dose-dependent characteristics of this drug, it is possible that the full clinical dose would exhibit even larger differences. Our results confirmed the well-known sex difference in baseline QTc and are in agreement with those found by Burke et al, in which no differences in the baseline QTc intervals were seen during the 3 phases of the menstrual cycle.

The mechanism of action of ibutilide has been attributed to both activation of a slow inward sodium current and inhibition of the potassium delayed rectifier (I_k). It prolongs the action potential and hence the QT interval in a dose-dependent manner. After intravenous infusion, plasma concentrations decline multiexponentially. Proarrhythmia is the major adverse event with a reported incidence that ranges up to 8% or even 36% in some reports. Most subjects enrolled in ibutilide studies have been men, but the proportion of patients who have developed ibutilide-induced polymorphic tachyarrhythmias is higher in women (eg, 17.5% vs 5.7% in men). In our study, we used a relatively small dose of ibutilide, which was sufficient to induce moderate short-lived repolarization changes. The sex difference in QT interval prolongation found in our study is consistent with the reported incidence of ibutilide-induced proarrhythmia and was seen despite adjusting dose by body weight to avoid higher plasma concentrations in smaller participants. The absolute dose of ibutilide administered to women in our study was 25% lower than that given to men (0.19 mg in women vs 0.25 mg in men; P = .001), and the plasma concentrations of ibutilide were similar in both sexes. These findings indicate that the greater response in women in this study is not attributable to differences in dosage or pharmacokinetics.

The first 60 minutes after initiation of ibutilide infusion are of prime interest for many reasons: (1) ibutilide is in wide-spread use clinically, (2) its maximum effect on QT is usually seen immediately after the end of infusion with rapid declines in blood levels and in QT, (3) there are no known active metabolites that could produce a delayed response, and (4) most ibutilide-induced arrhythmias have been found within the first 30 minutes after infusion. Previous observations such as a greater drug-induced QTc interval and a higher incidence of torsades de pointes in women and a shorter QTc interval in men after puberty have led to the hypothesis that sex hormones influence cardiac repolarization. To date much of the research in this field has focused on the effect of estradiol on ion currents and cardiac repolarization, although its role has not been completely defined. It is more clear that testosterone may exert a protective role, enhancing potassium currents, shortening the action potential duration, and diminishing the QT response to potassium channel blockers (eg, quinidine). Little is known about the direct or indirect effects of progesterone on cardiac repolarizing currents and/or the effects of progesterone on the QT interval prolongation secondary to drugs. This requires further study.

In agreement with our results, Burke et al reported that, after autonomic blockade, both women during the luteal phase and men have a shorter QTc interval compared with women in the menstrual and ovulation phases of their menstrual cycles (univariate analysis P < .005). Of note, after controlling for covariates, Burke et al found that only the difference between sexes continued to be statistically significant. In another study, Rashba et al demonstrated that the postpartum period is associated with a significant increase in risk of cardiac events among women with congenital long QT syndrome. Since there is an abrupt decline in estradiol and progesterone after delivery, this finding may also reflect a role of these sex hormones.

Conclusions
Our study supports the observation that women are more likely than men to develop ibutilide-induced torsades de pointes. Women during the menstrual and ovulation phases of the menstrual cycle had the greatest QTc response, and the findings support a complex role of sex hormones in this regard, possibly including a protective effect of progesterone. These are novel findings that require further investigation and confirmation. Physicians caring for patients who are receiving drugs with potential actions on cardiac repolarization currents should closely monitor the QT interval and beware of other risk factors for the development of torsades de pointes. These risk factors may include the phase of the menstrual cycle and recent pregnancy, in addition to female sex, serum electrolyte levels (especially low potassium and/or magnesium), ischemia, and concurrent use of other drugs with the ability to potentiate QT-prolonging effects.

Author Contributions: Study concept and design: Rodriguez, Kilborn, and Liu. Acquisition of data: Rodriguez, Kilborn, and Liu. Analysis and interpretation of data: Rodriguez, Kilborn, and Pezzullo. Drafting of the manuscript: Rodriguez, Kilborn, and Liu. Critical revision of the manuscript for important intellectual content: Kilborn, Pezzullo, and Woosley. Statistical expertise: Pezzullo. Obtained funding: Woosley. Administrative, technical, or material support: Woosley. Study supervision: Woosley. Funding/Support: This study was sponsored by grants from the Office of Women’s Health at the Food and Drug Administration, the Office for Research on Women’s Health of the National Institutes of Health, the Centers for Education and Research on Therapeutics, and grant 1 M01-RR13297 from the General Clin-
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REFERENCES

I should have no objection to go over the same life from its beginning to the end: requesting only the advantage authors have, of correcting in a second edition the faults of the first.
—Benjamin Franklin (1706-1790)