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 to 40 years and within 10% of their ideal body weight (Metropolitan Life Table). All volunteers had normal clinical and laboratory evaluations and normal ECG with QTc no more than 440 milliseconds. Women had regular menstrual cycles and were neither pregnant nor taking hormonal contraceptives. Exclusion criteria included family history of long QT syndrome, arrhythmias or sudden death; concomitant use of any licit or illicit drug, including tobacco.

Context
Women have a higher incidence of torsades de pointes than men, but it is not known if the risk of drug-induced torsades de pointes varies during the menstrual cycle.

Objectives
To determine if the degree of QT prolongation in response to ibutilide varies with the menstrual cycle phase and to compare QT prolongation between women and men.

Design and Setting
Cohort study of men and women who received the same intervention conducted between November 1998 and November 2000 at a general clinical research center of a university hospital.

Participants
A volunteer sample of 58 healthy adults (38 men and 20 women) aged 21 to 40 years.

Intervention
A low dose of ibutilide (0.003 mg/kg), infused intravenously for 10 minutes. Subjects were monitored for 120 minutes. Women received the intervention on 3 separate occasions to correspond with menstrual cycle phases, which were verified by using hormonal assays.

Main Outcome Measure
QT interval, recorded from electrocardiogram at timed intervals during and after ibutilide infusion and standardized for variations in heart rate (QTc).

Results
Maximum (mean [SD]) millisecond increase in QTc after ibutilide infusion was greater for women during menses (63 [13]) and the luteal phase (59 [17]) compared with women during the luteal phase (53 [14]) and compared with men (46 [16]; \( P = .002 \) vs menses and \( P = .007 \) vs ovulation). Progesterone (\( r = -0.40 \)) and progesterone-to-estradiol ratio (\( r = -0.41 \)), but not estradiol (\( r = 0.14 \)) or testosterone (\( r = 0.09 \)), were inversely correlated with ibutilide-induced QT prolongation.

Conclusions
Menstrual cycle and sex differences exist in QTc responses to ibutilide, with the greatest increase in QTc corresponding to the first half of the menstrual cycle.
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, it is known to produce significant pro-arrhythmic bigeminal premature ventricular contractions at the end of the infusion.

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. Measured QT intervals were corrected for heart rate using the formula of Bazett: *(QTc = QT/RR^1/2)* and Fridericia: *(QTc = QT/RR^2/3).* The extracted standard curve in 7 runs had a correlation coefficient of .995. 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 α of .05 and power of .80. We used a 2-tailed, unpaired 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 correction for heart rate.

**Table 1. Baseline Characteristics of Subjects**

<table>
<thead>
<tr>
<th></th>
<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>
<td>.15</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.65 (0.07)</td>
<td>1.78 (0.07)</td>
<td>.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.7 (9.1)</td>
<td>78.0 (8.8)</td>
<td>.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4 (3.2)</td>
<td>24.6 (3.1)</td>
<td>.16</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>65 (9)</td>
<td>64 (10)</td>
<td>.85</td>
</tr>
<tr>
<td>Corrected QT</td>
<td>410 (15)</td>
<td>391 (21)</td>
<td>.001</td>
</tr>
<tr>
<td>interval, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Table 2. Serum Sex Hormone Levels**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Menses</td>
<td>Ovulation</td>
</tr>
<tr>
<td>Estradiol, pg/mL</td>
<td>37.1 (15)</td>
<td>122 (42.0)</td>
</tr>
<tr>
<td>Progesterone, ng/mL</td>
<td>0.6 (0.2)</td>
<td>3.8 (4.0)</td>
</tr>
<tr>
<td>Testosterone, pg/dL</td>
<td>27.2 (11)</td>
<td>37.4 (10.0)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD). Ellipses indicate not applicable.
Analyses using Fridericia’s 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.

**FIGURE 1.** Baseline QTc Intervals (Bazett correction) in Women During the 3 Phases of the Menstrual Cycle and in Men

<table>
<thead>
<tr>
<th>Phase</th>
<th>Women</th>
<th>Menses</th>
<th>Ovulation</th>
<th>Luteal</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc, ms</td>
<td>410</td>
<td>408</td>
<td>411</td>
<td>391</td>
<td></td>
</tr>
</tbody>
</table>

Error bars represent SEMs. For comparison of all 3 phases of menstrual cycle compared with men, P=.001.

**FIGURE 2.** Change in QTc Intervals After a 10-Minute Infusion of Ibutilide at a Dose of 0.003 mg/kg

![Figure 2. Change in QTc Intervals After a 10-Minute Infusion of Ibutilide at a Dose of 0.003 mg/kg](image)

Figure depicts different responses of women during 3 phases of their menstrual cycle over 4 hours and men over 2 hours. Time=0 represents the start of the infusion. Error bars indicate SEMs.

**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=−0.40) and the progesterone-to-estradiol ratio (r=−0.41) 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. 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 ibuti-
lide and due to the dose-dependent
characteristics of this drug,\textsuperscript{11} it is pos-
sible that the full clinical dose would
exhibit even larger differences. Our re-
results confirmed the well-known sex dif-
fERENCE in baseline QTc and are in
agreement with those found by Burke
et al,\textsuperscript{10} in which no differences in the
baseline QTc intervals were seen dur-
ing the 3 phases of the menstrual cycle.

The mechanism of action of ibutil-
de has been attributed to both activa-
tion of a slow inward sodium current and
inhibition of the potassium de-
layed rectifier (I\textsubscript{k}\textsubscript{s}).\textsuperscript{16-17} It prolongs
the action potential and hence the QT in-
terval in a dose-dependent manner.\textsuperscript{11,18}

After intravenous infusion, plasma con-
centrations decline multiexponentially.\textsuperscript{18} Proarrhythmia is the major ad-
verse event with a reported incidence
that ranges up to 8\% or even 36\% in
some reports.\textsuperscript{19,20} Most subjects en-
rolled in ibutilide studies have been men,
but the proportion of patients who have
developed ibutilide-induced polymor-
phic tachyarrhythmias is higher in
women (eg, 17.5\% vs 5.7\% in men).\textsuperscript{19}

In our study, we used a relatively small
dose of ibutilide, which was sufficient
to induce moderate short-lived repolar-
ization changes. The sex difference in QT
interval prolongation found in our study
is consistent with the reported inci-
dence of ibutilide-induced proarhythm-
y and was seen despite adjusting dose
by body weight to avoid higher plasma
conzentations in smaller participants.

The absolute dose of ibutilide adminis-
tered 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 ibuti-
lide were similar in both sexes. These
findings indicate that the greater re-
sponse in women in this study is not at-
tributable 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 imme-
diately 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 arrhyth-
mas have been found within the first 30
minutes after infusion.\textsuperscript{19,20}

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 hy-
pothesis that sex hormones influence card-
iac repolarization. To date much of the
research in this field has focused on the
effect of estradiol on ion currents and
cardiac repolarization,\textsuperscript{7} although its role has
not been completely defined. It is more
clear that testosterone may exert a pro-
tective role, enhancing potassium cur-
rents, shortening the action potential du-
ration, and diminishing the QT response
to potassium channel blockers (eg, quinidine).\textsuperscript{9} Little is known about the di-
rect or indirect effects of progesterone on
cardiac repolarizing currents and/or the
effects of progesterone on the QT inter-
val prolongation secondary to drugs. This
requires further study.

In agreement with our results, Burke
et al\textsuperscript{21} reported that, after autonomic
blockade, both women during the lut-
eal 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\textsuperscript{22} dem-
ONSTRATED 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 es-
tradiol and progesterone after deliv-
ery, 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 de-
velop 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 proges-
terone. These are novel findings that re-
quire further investigation and confir-
mation. Physicians caring for patients
who are receiving drugs with potential
actions on cardiac repolarization cur-
rents should closely monitor the QT in-
terval 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 re-
cent pregnancy, in addition to female
sex, serum electrolyte levels (espe-
cially low potassium and/or magne-
sium), ischemia, and concurrent use of
other drugs with the ability to potenti-
ate QT-prolonging effects.

Author Contributions: Study concept and design:
Rodriguez, Liu, and Woosley.
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 in-
tellectual content: Kilborn, Pezzullo, and Woosley.
Statistical expertise: Pezzullo.
Obtained funding: Woosley.
Administrative, technical, or material support:
Woosley.
Study supervision: Woosley.
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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)