**FOCUS ON DRUGS, HORMONES, AND THE QT INTERVAL**

# Influence of Oral Progesterone Administration on Drug-Induced QT Interval Lengthening

## A Randomized, Double-Blind, Placebo-Controlled Crossover Study

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**ABSTRACT**

**OBJECTIVES** This study tested the hypothesis that oral progesterone administration attenuates drug-induced QT interval lengthening.

**BACKGROUND** Evidence from preclinical and human investigations suggests that higher serum progesterone concentrations may be protective against drug-induced QT interval lengthening.

**METHODS** In this prospective, double-blind, crossover study, 19 healthy female volunteers (21 to 40 years of age) were randomized to receive progesterone 400 mg or matching placebo orally once daily for 7 days timed to the menses phase of the menstrual cycle (between-phase washout period = 49 days). On day 7, ibutilide 0.003 mg/kg was infused over 10 min, after which QT intervals were recorded and blood samples collected for 12 h. Before the treatment phases, subjects underwent electrocardiographic monitoring for 12 h to calculate individualized heart rate–corrected QT intervals ($QT_cI$).

**RESULTS** Fifteen subjects completed all study phases. Maximal serum ibutilide concentrations in the progesterone and placebo phases were similar (1,247 ± 770 pg/ml vs. 1,172 ± 709 pg/ml; p = 0.43). Serum progesterone concentrations were higher during the progesterone phase (16.2 ± 11.0 ng/ml vs. 1.2 ± 1.0 ng/ml; p < 0.0001), whereas serum estradiol concentrations in the 2 phases were similar (89.3 ± 62.8 pg/ml vs. 71.8 ± 31.7 pg/ml; p = 0.36). Pre-ibutilide lead II $QT_cI$ was significantly lower in the progesterone phase (412 ± 15 ms vs. 419 ± 14 ms; p = 0.04). Maximal ibutilide-associated $QT_cI$ (443 ± 17 ms vs. 458 ± 19 ms; p = 0.003), maximal percentage increase in $QT_cI$ from pre-treatment value (7.5 ± 2.4% vs. 9.3% ± 3.4%; p = 0.02), and area under the effect ($QT_cI$) curve during the first hour post-ibutilide administration (497 ± 13 ms·h vs. 510 ± 16 ms·h; p = 0.002) were lower during the progesterone phase. Progesterone-associated adverse effects included fatigue/malaise and vertigo.

**CONCLUSIONS** Oral progesterone administration attenuates drug-induced $QT_cI$ lengthening. (Influence of Progesterone Administration on Drug-Induced QT Interval Lengthening; NCT01929083). (J Am Coll Cardiol EP 2016;2:765–74) © 2016 by the American College of Cardiology Foundation.

**ABBREVIATIONS
AND ACRONYMS**

**ECG** = electrocardiogram

**HCG** = human chorionic gonadotropin

**ICRC** = Indiana Clinical Research Center

**IDS** = Investigational Drug Service

**IU** = Indiana University

**LQTS** = long QT syndrome

**QT$_c$ interval** = Bazett's corrected QT interval

**QTcI** = individualized heart rate-corrected QT interval

**QT$_F$** = Fridericia-corrected QT interval

**TdP** = torsades de pointes

Torsades de pointes (TdP) is a polymorphic ventricular tachycardia associated with QT interval prolongation [1], which may be induced by more than 100 medications available in the United States [2]. TdP can be catastrophic, often degenerating into ventricular fibrillation causing sudden cardiac arrest [3]. The risk of TdP increases as the heart rate-corrected QT (QT$_c$) interval increases [4,5], particularly if it exceeds 500 ms [6,7]. Consequently, QT$_c$ interval prolongation is commonly used as a marker of increased risk of TdP.

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Female sex is an independent risk factor for TdP in patients with acquired or congenital long QT syndrome (LQTS) [6,8-10]. QT$_c$ intervals are longer in women than in men [11], a difference that becomes apparent only after puberty [12], suggesting that sex hormones may be responsible. Post-pubertal differences in QT$_c$ intervals may be partially caused by a reduction in QT$_c$ intervals in male individuals as a result of testosterone and dihydrotestosterone production [11]. However, other factors may also contribute to the difference in risk of TdP. Some studies have reported that hormone replacement therapy with estrogen resulted in QT$_c$ interval lengthening [13,14].

Progesterone is a testosterone precursor [15] and has a similar androgenic structure [16]. Higher serum progesterone concentrations are associated with shorter QT$_c$ intervals [17] and may exert protective effects against lengthening of ventricular repolarization [18]. Preclinical data suggest that exogenous progesterone administration may protect against drug-induced prolongation of ventricular repolarization [19-21], ventricular early afterdepolarizations [21], and arrhythmias [22,23]. However, the influence of exogenous progesterone administration on response to QT$_c$ interval-prolonging drugs in humans has not been determined.

Few effective strategies have been developed to reduce the risk of drug-induced QT$_c$ interval prolongation and TdP. We tested the hypothesis that oral administration of progesterone attenuates drug-induced QT interval lengthening in young healthy women.

## METHODS

**STUDY SUBJECTS.** Healthy pre-menopausal female volunteers age 21 to 40 years were enrolled. Exclusion criteria included serum potassium <4.0 mEq/l; serum magnesium <1.8 mg/dl; hemoglobin <9.0 mg/dl; hematocrit <26%; history of hypertension, coronary artery disease, heart failure, or liver or kidney disease; serum creatinine >1.5 mg/dl; use of hormonal contraceptives; baseline Bazett's corrected QT interval >450 ms; personal or family history of LQTS, arrhythmias, or sudden cardiac death; concomitant use of any QT interval-prolonging drugs; pregnancy; weight <45 kg; and unwillingness to use nonhormonal forms of birth control during the study period. This study was approved by the Institutional Review Board at Indiana University (IU) Purdue University Indianapolis. All subjects provided written informed consent.

**STUDY PROCEDURES.** This was a prospective, randomized, double-blind, placebo-controlled, crossover study conducted in the Indiana Clinical Research Center (ICRC). Subject recruitment began in April 2013, and study procedures were completed on the last enrolled subject in February 2014. The study consisted of 3 phases: a pre-randomization phase to determine each subject's individual QT interval heart rate correction and randomized double-blind progesterone and placebo phases. Before inclusion, all subjects underwent a screening physical examination, and blood was obtained for determination of serum potassium, magnesium, creatinine, and transaminase concentrations, as well as hemoglobin and hematocrit values. A urine human chorionic gonadotropin (HCG) test was performed to rule out pregnancy, and a 12-lead electrocardiogram (ECG) was obtained. Each study phase was conducted during the menses phase of the menstrual cycle (defined as 24 to 60 h after menses onset), when serum estradiol and progesterone concentrations are at their lowest, to minimize the effects of endogenous sex hormones [18].

**FIGURE 1  Study Design**

ECG = electrocardiogram.
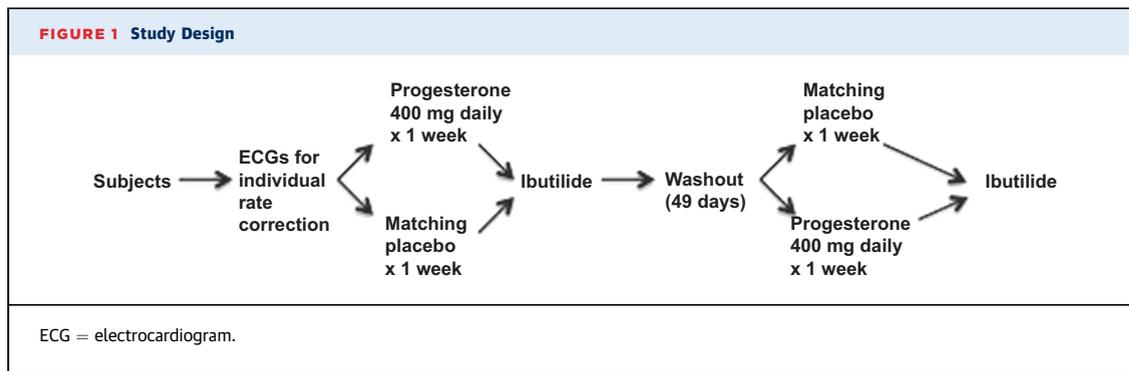
During the pre-randomization phase, subjects underwent a 12-h stay in the ICRC. Each subject underwent 3 12-lead ECGs (Marquette Mac 5500, GE Healthcare Bio-Sciences, Pittsburgh, Pennsylvania) 1 min apart, at 0, 15, and 30 min, and 1, 2, 4, 6, 8, and 12 h. ECGs were initiated between 7:00 AM and 9:00 AM and were completed between 7:00 PM and 9:00 PM. QT and RR intervals were used to determine each subject's individual heart rate-corrected QT interval ($QT_cI$) using the parabolic model $\beta \bullet RR^{\alpha}$ (24), where RR is the interval between adjacent QRS complexes, $\beta$ is the regression coefficient, and $\alpha$ is the slope.
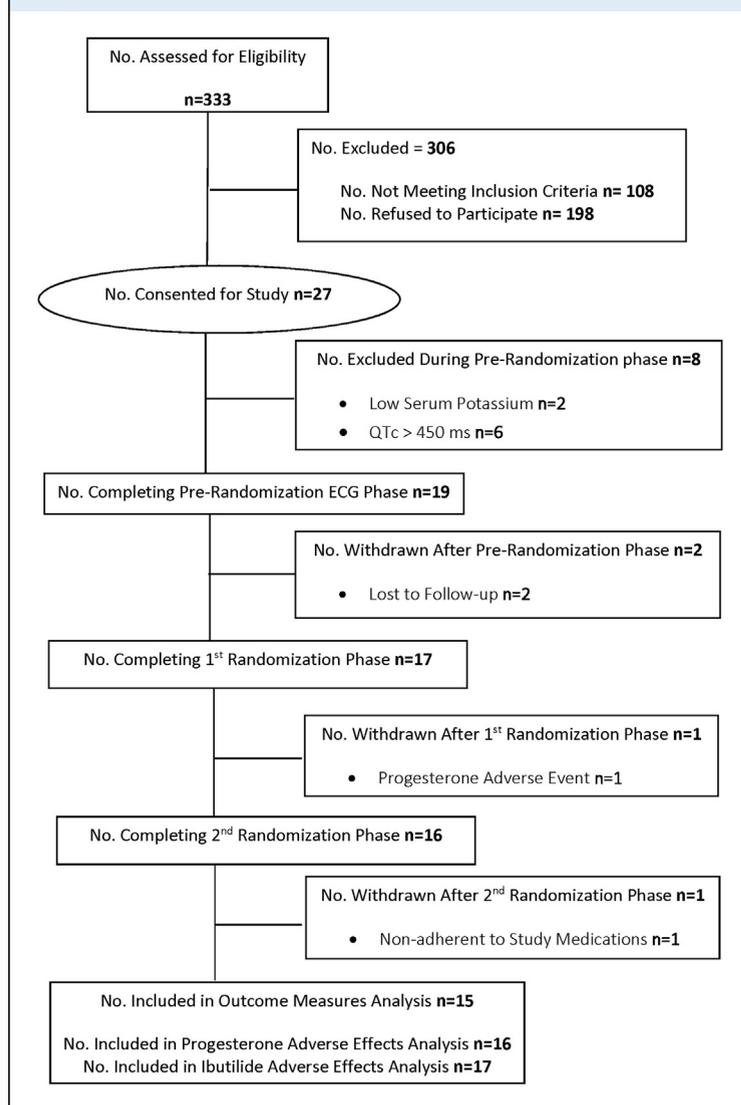
The study design is presented in **Figure 1**. After the pre-randomization phase, subjects were randomized in double-blind fashion to receive oral progesterone 400 mg (2 × 200 mg capsules, Teva Pharmaceuticals, North Wales, Pennsylvania) or matching placebo orally once daily at bedtime for 7 days. Matching placebo was prepared by the IU Health Investigational Drug Service (IDS). Randomization was performed by the IDS using a computerized random number generator and recorded on the IDS randomization log. Participants were assigned to progesterone or placebo in each phase by IDS personnel. Progesterone or matching placebo was delivered to the ICRC by IDS personnel; investigators, study subjects, and ICRC personnel were blinded to treatment assignments during data collection and analysis. The minimal desired washout period was 28 days; after 28 days, we initiated dosing 7 days before the next menstrual cycle, resulting in a total washout period of 49 days.

On the morning after the last dose of oral progesterone or placebo, subjects presented to the ICRC for an approximately 13-h stay. Each subject underwent another urine HCG test to ensure absence of pregnancy. Three ECGs, 1 min apart, were obtained for baseline measurements. If the urine HCG test was negative and the Bazett's corrected QT interval was <450 ms, subjects were placed on a continuous electrocardiographic monitor (Heal Force model PC 80B, Heal Force Bio-Meditech, Shanghai, China), and 1 peripheral indwelling intravenous catheter was inserted into each arm. Blood (4.5 ml) for determination of serum estradiol and progesterone concentrations was collected in gold-top serum separator tubes (Vacutainer, Becton Dickinson, Franklin Lakes, New Jersey).

Subjects then received a single intravenous dose of ibutilide 0.003 mg/kg diluted in 20 ml normal saline and infused over 10 min (18). Three 12-lead ECGs were obtained 1 min apart immediately at the end of infusion and at 5, 10, 15, 20, 30, and 45 min and 1, 2, 4, 6, 8, and 12 h post-infusion. Pre-ibutilide ECGs were initiated between 7:00 AM and 9:00 AM, and ibutilide was administered immediately after baseline ECGs were obtained. ECGs were completed between 7:00 PM and 9:00 PM. These times correspond to the same times of day as those during which ECGs were obtained for determination of individualized QT interval corrections. Blood (10 ml) for determination of serum ibutilide concentrations was obtained from the indwelling catheter in the arm contralateral to that into which ibutilide was infused and collected in red-top tubes (Vacutainer, Becton Dickinson, Franklin Lakes, New Jersey) at the same times that ECGs were obtained. Subjects underwent continuous electrocardiographic monitoring for 6 h post-ibutilide administration. Subjects were discharged after the 12-h ECG and blood sample provided that their Bazett's corrected $QT_c$ interval was <450 ms.

**QT INTERVAL MEASUREMENTS.** QT intervals were measured from leads II, $V_1$, and $V_5$ by 1 investigator (H.J.) who was blinded to the subjects' assigned groups. QT intervals were measured using the MUSE automated system (GE Healthcare Bio-Sciences) using electronic calipers. QT and RR intervals were averaged over ≥5 consecutive beats and the average

**FIGURE 2**   Recruitment and Enrollment for Randomized, Crossover, Placebo-Controlled Study of Influence of Oral Progesterone on Drug-Induced QT$_c$ Interval Lengthening



liquid chromatography with mass spectrometry detection. Additional detail regarding this assay is provided in the Online Appendix, Online Table 1, and Online Figures 1 and 2.
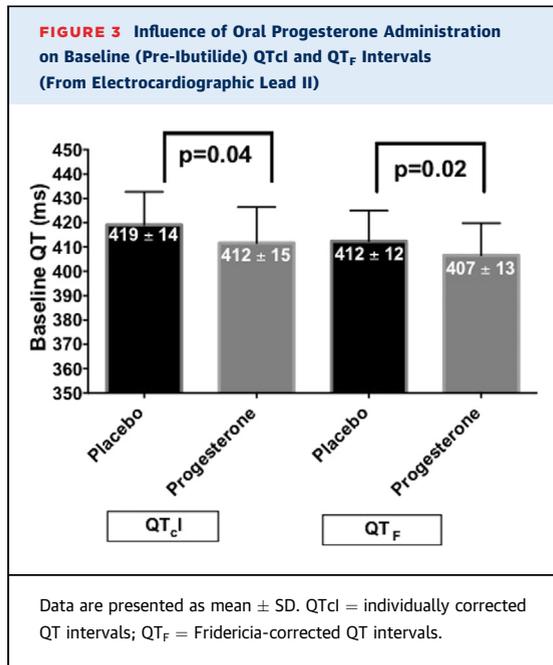
**STUDY OUTCOME MEASURES.** Outcome measures compared in the progesterone and placebo phases were: 1) baseline (pre-ibutilide) QT$_c$I and QT$_F$ intervals; 2) maximal QT$_c$I and QT$_F$ intervals after ibutilide administration; 3) maximal ibutilide-induced percentage change from baseline in QT$_c$I and QT$_F$ intervals; and 4) area under the QT$_c$I and QT$_F$ interval time curves from 0 to 1 h after ibutilide administration.

**DATA ANALYSIS.** Area under the QT$_c$I and QT$_F$ interval time curves were calculated using the linear trapezoidal rule. Maximal serum ibutilide concentration was determined by visual inspection of serum concentration data.

**SAMPLE SIZE AND STATISTICAL ANALYSIS.** A sample size of 16 subjects was determined to be sufficient to detect a difference in maximal QT$_c$I of 12 ms (19% reduction), assuming a QT$_c$I prolongation of 63 $\pm$ 13 ms associated with ibutilide in the placebo group and a power of 0.80 (18). Analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). Normality of outcome measures data was determined using the Kolmogorov-Smirnov test. Comparisons of the outcome measures during progesterone and placebo phases were performed using paired Student's *t* tests. Differences in adverse event proportions were analyzed using the Fisher exact test. Potential treatment period interactions were tested by comparing the mean within-individual differences for the progesterone-placebo sequence versus those in the placebo-progesterone sequence for each outcome measure using Student *t* tests for paired samples. All comparisons were performed using a 2-sided α level of 0.05.

## RESULTS

**SUBJECTS.** Nineteen subjects were enrolled (Figure 2). Four subjects were excluded from the outcome measures analysis because they did not complete all treatment phases (n = 3) or were determined to have been nonadherent to study medications after completion of all study phases (n = 1). Therefore, 15 subjects composed the final sample size for analysis of outcome measures. For analysis of adverse effects, 16 subjects received progesterone and 17 subjects received placebo; 15 subjects received ibutilide during the progesterone phase and 17

of 3 QT intervals at each time point for each lead was determined. Only clearly discernible QT intervals were measured. Determination of the QT$_c$I for each subject was performed as described. QT intervals were also corrected using the Fridericia method (QT$_F$) (25).

**DETERMINATION OF SERUM HORMONE AND IBUTILIDE CONCENTRATIONS.** Serum estradiol and progesterone concentrations were determined in the IU Health pathology laboratory using chemiluminescence immunoassays (26,27). Serum ibutilide concentrations were determined in the IU clinical pharmacology analytical core laboratory using reverse-phase high-performance

**FIGURE 3** Influence of Oral Progesterone Administration on Baseline (Pre-Ibutilide) QTcI and QT$_F$ Intervals (From Electrocardiographic Lead II)

Data are presented as mean ± SD. QTcI = individually corrected QT intervals; QT$_F$ = Fridericia-corrected QT intervals.



**FIGURE 4** Individually Corrected QT Interval (QTcI) and QT$_F$ Intervals During and After a 10-Min Infusion of Ibutilide 0.003 mg/kg (From Electrocardiographic Lead II) During Progesterone and Placebo Phases

**(A)** Individually corrected QT Interval (QTcI) and **(B)** Q3 QTF intervals. Data presented as mean ± SEM. Abbreviations as in **Figure 3**.

subjects received ibutilide during the placebo phase. The subjects' mean age was 29 ± 5 years. Nine subjects were white, 5 were black, and 1 was of Middle Eastern descent. Mean weight was 83 ± 20 kg, and the mean ibutilide dose was 0.24 ± 0.06 mg.

**SERUM IBUTILIDE AND HORMONE CONCENTRATIONS.** There was no significant difference between the progesterone and placebo phases in maximal serum ibutilide (1,247 ± 770 pg/ml vs. 1,172 ± 709 pg/ml; p = 0.43) or serum estradiol concentration (89.3 ± 62.8 pg/ml vs. 71.8 ± 31.7 pg/ml; p = 0.36). Serum progesterone concentrations were significantly higher during the progesterone phase (16.2 ± 11.0 ng/ml vs. 1.2 ± 1.0 ng/ml; p < 0.0001), as was the serum progesterone/estradiol concentration ratio (205 ± 40 vs. 18 ± 16; p = 0.001).

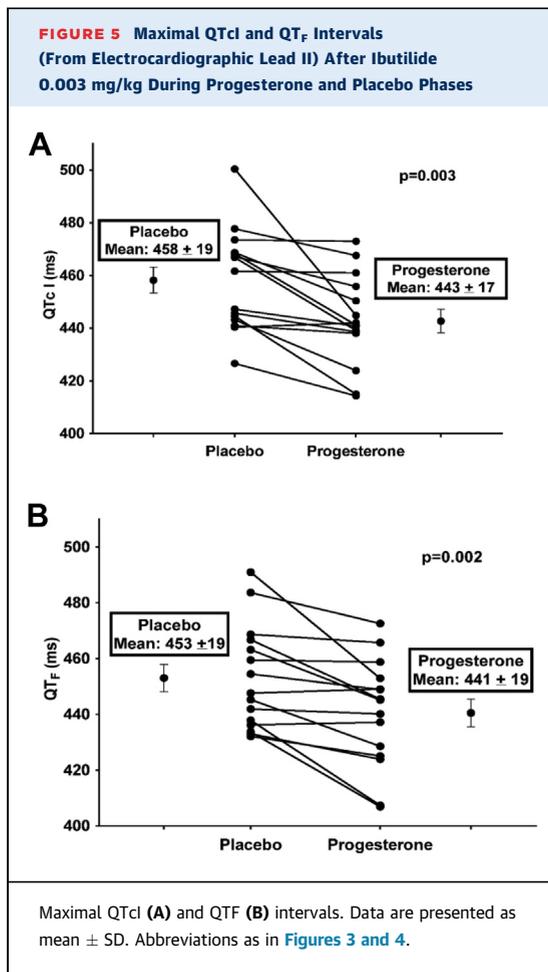**INDIVIDUALIZED QT INTERVAL HEART RATE CORRECTION: HEART RATES.** There was no significant difference in minimal heart rate between the pre-randomization (development of QTcI) phase and the ibutilide administration days in the placebo and progesterone phases (60 ± 7 beats/min vs. 60 ± 9 beats/min vs. 61 ± 9 beats/min, respectively; p = 0.58). There was no significant difference in maximal heart rate between the pre-randomization phase and the ibutilide administration days in the placebo and progesterone phases (78 ± 8 beats/min vs. 79 ± 9 beats/min vs. 80 ± 11 beats/min, respectively; p = 0.70). There was no significant difference in average heart rate between the pre-randomization
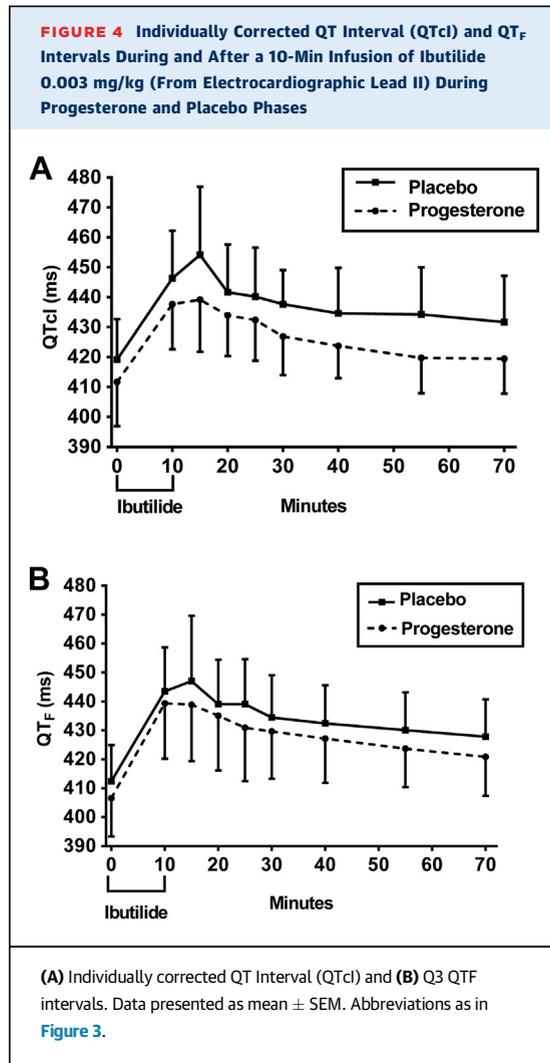
phase and the ibutilide administration days in the placebo and progesterone phases (68 ± 7 beats/min vs. 68 ± 8 beats/min vs. 70 ± 9 beats/min, respectively; p = 0.51). Heart rates in the 3 study phases are presented in Online Figure 3.

**BASELINE (PRE-IBUTILIDE) QTcI AND QT$_F$ INTERVALS.** Baseline (pre-ibutilide) QTcI and QT$_F$ intervals in electrocardiographic lead II were significantly lower during the progesterone phase than during the placebo phase (**Figure 3**), indicating that oral progesterone administration affected ventricular repolarization in the absence of a QT-lengthening drug. Similar results were demonstrated with electrocardiographic leads V$_1$ and V$_5$ (Online Figures 4 and 5).

**QTcI AND QT$_F$ INTERVALS AFTER IBUTILIDE ADMINISTRATION.** Lead II QTcI and QT$_F$ intervals before and during the first hour after ibutilide

**FIGURE 5** Maximal QTcI and $QT_F$ Intervals (From Electrocardiographic Lead II) After Ibutilide 0.003 mg/kg During Progesterone and Placebo Phases

Maximal QTcI **(A)** and QTF **(B)** intervals. Data are presented as mean ± SD. Abbreviations as in **Figures 3 and 4**.

administration in the progesterone and placebo groups are presented in **Figure 4**. Similar results were demonstrated in leads $V_1$ and $V_5$ (Online Figures 6 and 7). The maximal lead II $QT_cI$ and $QT_F$ after ibutilide administration during the progesterone and placebo phases are presented in **Figure 5**. Maximal $QT_cI$ and $QT_F$ intervals were significantly lower during the progesterone phase than during the placebo phase. Similar results were demonstrated in leads $V_1$ and $V_5$ (Online Figures 8 and 9).

**MAXIMAL PERCENTAGE CHANGE FROM BASELINE IN $QT_cI$ AND $QT_F$ INTERVALS AFTER IBUTILIDE ADMINISTRATION.** Maximal ibutilide-associated percentage change in lead II $QT_cI$ and $QT_F$ intervals from baseline values is presented in **Figure 6**. There were significantly smaller ibutilide-associated percentage changes in $QT_cI$ and $QT_F$ intervals in the progesterone phase compared with the placebo phase. Similar results were shown in leads $V_1$ and $V_5$ (Online Figures 10 and 11).

**AREA UNDER THE $QT_cI$ AND $QT_F$ INTERVAL VERSUS TIME (0 TO 1 H) AFTER IBUTILIDE ADMINISTRATION.** Area under the lead II $QT_cI$ interval versus time (0 to 1.17 h, 1 h after completion of ibutilide infusion) curve was significantly lower during the progesterone phase compared with the placebo phase (497 ± 13 ms·h vs. 510 ± 16 ms·h; p = 0.002). Similarly, area under the lead II $QT_F$ interval versus time (0 to 1.17 h) curve after ibutilide administration was significantly lower during the progesterone phase compared with the placebo phase (499 ± 17 ms·h vs. 506 ± 15 ms·h; p = 0.013). Similar results were demonstrated with leads $V_1$ and $V_5$ (Online Table 2).

**ADVERSE EFFECTS ASSOCIATED WITH PROGESTERONE.** Progesterone-associated adverse effects were generally mild, including fatigue/general malaise (progesterone, 6 of 16 [38%] vs. placebo, 1 of 17 [6%]; p = 0.04), headache (2 of 16 [13%] vs. 1 of 17 [6%]; p = 0.60), mood changes (2 of 16 [13%] vs. 0; p = 0.23), breast tenderness (2 of 16 [13%] vs. 0; p = 0.23], hypotension (1 of 16 [6%] vs. 0; p = 0.48), and vertigo (1 of 16 [6%] vs. 0; p = 0.48). The subject who experienced vertigo and hypotension during progesterone therapy withdrew from the study as a result.

**ADVERSE EFFECTS ASSOCIATED WITH IBUTILIDE.** There were no differences between the progesterone and placebo phases in ibutilide-associated adverse effects, which included bradycardia (heart rate <60 beats/min; progesterone phase, 3 of 15 [20%] vs. placebo phase, 2 of 17 [12%]; p = 0.65) and burning at the infusion site (1 of 15 [7%] vs. 1 of 17 [6%]); p > 0.99]. In 1 subject (during the placebo phase), Bazett's corrected QT interval was transiently prolonged to >500 ms.

**POTENTIAL TREATMENT PERIOD INTERACTIONS.** There were no significant treatment period interactions for any of the study outcome measures.

## DISCUSSION

This is the first study to investigate the effect of oral progesterone administration on drug-induced QT interval lengthening in humans. In this initial proof of concept study, we found that oral progesterone 400 mg administered daily for 1 week significantly reduced nondrug-associated $QT_cI$ and $QT_F$ intervals during the menses phase in young healthy women. In addition, oral progesterone attenuated the $QT_cI$ and $QT_F$ interval response to low-dose ibutilide. These findings suggest that oral progesterone could be

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effective for reducing the risk of drug-induced $QT_c$ interval prolongation in patients requiring therapy with $QT_c$ interval-prolonging drugs and provide support for further investigation of the effect of oral progesterone in targeted populations requiring $QT_c$ interval-prolonging drug therapy.

Previous studies have suggested that progesterone may be protective against lengthening of ventricular repolarization and/or drug-induced arrhythmias. In studies in which hormone replacement therapy with estrogen alone prolonged the $QT_c$ interval, regimens that included progesterone did not (13,14,28,29). In women with congenital LQTS, the risk of TdP is low during pregnancy but increases immediately post-partum, when serum progesterone concentrations abruptly decline (30). The $QT_c$ interval is significantly shorter during the luteal phase of the menstrual cycle, when serum progesterone concentrations are highest, compared with the follicular phase (17). In healthy volunteers, drug-induced $QT_c$ interval lengthening is greatest during the menses and ovulation phases and least during the luteal phase. There was a significant inverse correlation between serum progesterone concentrations and degree of ibutilide-associated QT interval lengthening (18). Progesterone shortens the ventricular action potential duration in guinea pig ventricular myocytes, effects that were reversed by mifepristone, a progesterone receptor inhibitor (20). Progesterone and dihydrotestosterone protected against sudden cardiac death in a transgenic rabbit model of LQTS type 2, whereas estradiol promoted sudden cardiac death (23).

Potential mechanisms by which progesterone exerts protective effects against lengthening of ventricular repolarization and ventricular arrhythmias have been investigated. Nakamura et al. (20) reported that progesterone enhances the slow component of the delayed rectifier current and inhibits L-type $Ca^{2+}$ currents under cyclic adenosine monophosphate-stimulated conditions in isolated guinea pig myocytes. These effects were found to be mediated by nitric oxide release through nongenomic activation of endothelial nitric oxide synthase (21). Odening et al. (23) found that progesterone decreases the density of L-type $Ca^{2+}$ currents in rabbit cardiomyocytes and increases expression of sarcoplasmic reticulum calcium adenosine triphosphatase 2a, which may contribute to increasing sarcoplasmic reticulum $Ca^{2+}$ uptake, thus shortening $Ca^{2+}$ transient duration (23). Whether the effects of oral progesterone on attenuation of drug-induced $QT_c$ interval lengthening are maintained during longer-term progesterone therapy or whether there is compensatory lengthening of the



FIGURE 6   Maximal Percentage Change From Baseline in QTcI and $QT_F$ Intervals (From Electrocardiographic Lead II) After Ibutilide 0.003 mg/kg During Progesterone and Placebo Phases

(A) QTcI and (B) QTF intervals. Data are presented as mean ± SD. Abbreviations as in Figures 3 to 5.
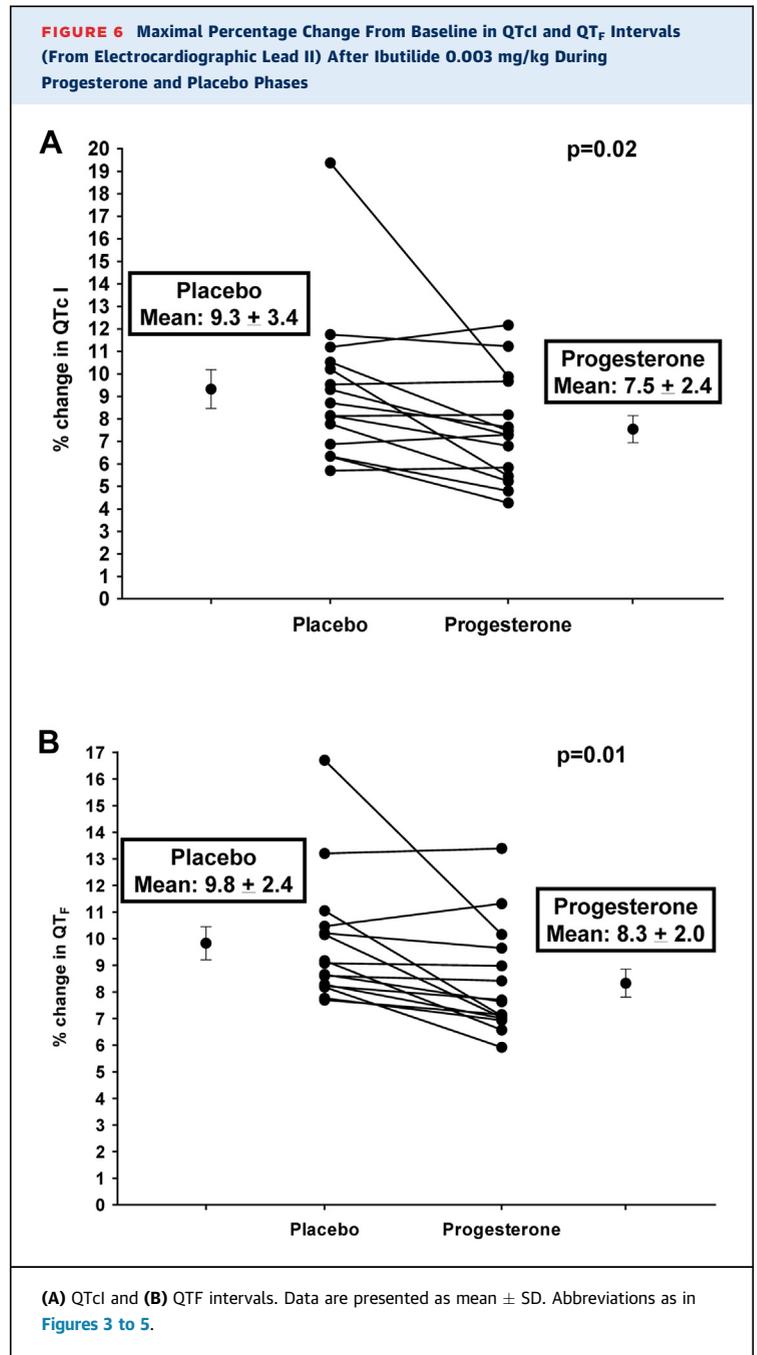
$QT_c$ interval after longer-term progesterone exposure requires additional study.

We selected a progesterone dose of 400 mg daily, as this dose is used commonly for management of polycystic ovary syndrome (31) and for prevention of preterm birth (32). Oral progesterone 400 mg once daily led to a significant reduction in baseline nondrug-associated QTcI and $QT_F$ intervals. This was an important contributor to the overall effect of

progesterone-associated reduction in maximal ibutilide-associated $QT_cI$ and $QT_F$ intervals and areas under the $QT_cI$ interval and $QT_F$ interval versus time curves during the first hour after ibutilide administration. However, the effects of progesterone were not solely attributable to a reduction in baseline QT intervals. Oral progesterone also exerted a protective effect against ibutilide-associated $QT_cI$ and $QT_F$ interval lengthening, as manifested by a reduction in percentage change in maximal ibutilide-associated $QT_cI$ and $QT_F$ interval from pre-treatment values.

Progesterone 400 mg once daily was associated with adverse effects, most of which were mild. Additional study is necessary to determine whether a lower dose of oral progesterone resulting in proportionately lower serum concentrations is effective for attenuation of drug-induced $QT_c$ interval lengthening. The long-term incidence of adverse effects associated with oral progesterone 400 mg daily has not been well studied. The incidence of adverse effects associated with oral progesterone 300 mg daily for 12 weeks was not significantly different from that associated with placebo (33). Oral progesterone 400 mg daily administered for 18 weeks was associated with no reported adverse effects in pregnant women (34). The incidence of adverse effects associated with longer-term administration of oral progesterone 400 mg daily requires further study.

Ibutilide prolongs the QT interval in a dose-dependent fashion through inhibition of the rapid component of the delayed rectifier potassium current (35) as well as through activation of a slow inward sodium current (36). Ibutilide was an appropriate probe drug for this investigation because serum concentrations peak and decline rapidly after intravenous administration (18). We administered a mean dose of $0.24 \pm 0.06$ mg, 24% of the lowest therapeutic dose (1 mg), and 12% of the highest total therapeutic dose (2 mg). This subtherapeutic dose was selected on the basis of previous investigations in which ibutilide 0.003 mg/kg provoked a modest, but not excessive, lengthening of the $QT_c$ interval in healthy volunteers (18). In our subjects, $QT_cI$ and $QT_F$ intervals generally returned to baseline values within 60 to 90 min of ibutilide administration. There was no significant difference in maximal serum ibutilide concentration between the progesterone and placebo phases; therefore, differences in $QT_cI$ and $QT_F$ intervals in the 2 phases were not attributable to differences in serum ibutilide concentration.

**STUDY LIMITATIONS.** Limitations of this study include the fact that it was conducted in young healthy women during the menses phase, when endogenous serum progesterone and estradiol concentrations are lowest. It remains unknown whether the effects of oral progesterone would be similar if administered during different phases of the menstrual cycle or to postmenopausal women. The range of heart rates in our healthy subjects was relatively narrow during the phase when the heart rate correction factors for the individualized QT interval corrections were determined. However, there were no differences in heart rates during the pre-randomization phase versus the placebo or progesterone phases; therefore, the individualized heart rate corrections were derived using a similar range of heart rates during each phase of the study. In addition, we also report our results using the $QT_F$, and these results mirror those of our QTcI analysis. The period of progesterone administration was relatively short (7 days); the effect of longer periods of progesterone administration on naturally occurring $QT_c$ interval and drug-induced $QT_c$ interval lengthening, as well as the safety of long-term oral progesterone, require further study.

## CONCLUSIONS

Oral progesterone 400 mg daily reduces baseline $QT_cI$ intervals and attenuates drug-induced $QT_cI$ interval lengthening. These findings provide support for additional studies investigating the efficacy, safety, and clinical feasibility of oral progesterone administration for reducing the risk of drug-induced $QT_c$ interval prolongation and TdP in patients with risk factors who require therapy with QT interval-prolonging drugs.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** TdP is a potentially life-threatening polymorphic ventricular tachycardia associated with QT interval prolongation, which may be induced by more than 70 medications available in the Unites States. TdP can be a catastrophic occurrence, as it may degenerate into ventricular fibrillation and cause sudden cardiac arrest. Methods for reducing the risk of drug-induced QT interval prolongation may result in improved medication safety. However, few effective strategies have been developed to reduce the risk of drug-induced $QT_c$ interval prolongation and torsades de pointes.

**TRANSLATIONAL OUTLOOK 1:** Administration of oral progesterone at a dose of 400 mg daily reduces baseline $QT_cI$ intervals and attenuates drug-induced $QT_cI$ interval lengthening during the menses phase of the menstrual cycle in young healthy female subjects.

**TRANSLATIONAL OUTLOOK 2:** These data provide support for additional studies investigating the efficacy, safety, and clinical feasibility of oral progesterone administration for reducing the risk of drug-induced $QT_c$ interval prolongation and TdP in patients with risk factors who require therapy with QT interval–prolonging drugs.

## REFERENCES

**1.** Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 2007;153: 891–9.

**2.** Tisdale JE. Ventricular arrhythmias. In: Tisdale JE, Miller DA, editors. Drug-Induced Diseases. Prevention, Detection and Management. second edition. Bethesda, MD: American Society of Health-System Pharmacists, 2010:485–515.

**3.** Drew BJ, Ackerman MJ, Funk M, et al., American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2010;55:934–47.

**4.** Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136–44.

**5.** Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. N Engl J Med 1998;339: 960–5.

**6.** Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993;269:1532–6.

**7.** De Bruin ML, Langendijk PN, Koopmans RP, Wilde AA, Leufkens HG, Hoes AW. In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging drugs. Br J Clin Pharmacol 2007;63:216–23.

**8.** Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993;270:2590–7.

**9.** Lehmann MH, Hardy S, Archibald D, Quart B, MacNeil DJ. Sex difference in risk of torsade de pointes with d,l-sotalol. Circulation 1996;94: 2535–41.

**10.** Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 1998;97:2237–44.

**11.** Pham TV, Rosen MR. Sex, hormones, and repolarization. Cardiovasc Res 2002;53:740–51.

**12.** Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8:690–5.

**13.** Carnethon MR, Anthony MS, Cascio WE, et al. A prospective evaluation of the risk of QT prolongation with hormone replacement therapy: the atherosclerosis risk in communities study. Ann Epidemiol 2003;13:530–6.

**14.** Gökçe M, Karahan B, Yilmaz R, Örem C, Erdöl C, Özdemir S. Long term effects of hormone replacement therapy on heart rate variability, QT interval, QT dispersion and frequencies of arrhythmia. Int J Cardiol 2005;99:373–9.

**15.** Ye L, Su ZJ, Ge RS. Inhibitors of testosterone biosynthetic and metabolic activation enzymes. Molecules 2011;16:9983–10001.

**16.** Guyton AC, Hall JE. Textbook of Medical Physiology. 11th ed. Philadelphia, PA: Saunders, 2006.

**17.** Nakagawa M, Ooie T, Takahashi N, et al. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol 2006;29: 607–13.

**18.** Rodriguez I, Kilborn MJ, Liu X-K, Pezzullo JC, Woosley RL. Drug-induced QT prolongation in women during the menstrual cycle. JAMA 2001; 285:1322–6.

**19.** Tisdale JE, Overholser BR, Wroblewski HA, Sowinski KM. The influence of progesterone alone and in combination with estradiol on ventricular action potential duration and triangulation in response to potassium channel inhibition. J Cardiovasc Electrophysiol 2011;22:325–31.

**20.** Nakamura H, Kurokawa J, Bai CX, et al. Progesterone regulates cardiac repolarization through a nongenomic pathway: an in vitro patch-clamp and computational modeling study. Circulation 2007;116:2913–22.

**21.** Cheng J, Zhang J, Ma X, Su D. Frequency-dependent acceleration of cardiac repolarization by progesterone underlying its cardiac protection against drug-induced proarrhythmic effects in female rabbits. Eur J Pharmacol 2012;689:172–8.

**22.** Cheng J, Su D, Ma X, Li H. Concurrent supplement of estradiol and progesterone reduces the cardiac sensitivity to $_{D,L}$-sotalol-induced arrhythmias in ovariectomized rabbits. J Cardiovasc Pharmacol Ther 2012;17:208–14.

**23.** Odening KE, Choi B-R, Liu GX, et al. Estradiol promotes sudden cardiac death in transgenic long QT type 2 rabbits while progesterone is protective. Heart Rhythm 2012;9:823–32.

**24.** Malik M, Färbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 2002;87:220–8.

**25.** Fridericia LS. Die systolendauer im elektrokardiogramm bei normalen menchen und bei herzkranken. Acta Med Scand 1920;53:469–86.

**26.** Bryant C, Moore J, Curry TE Jr. Determination of serum estradiol levels by radiometric and chemiluminescent techniques. Methods Mol Biol 2009;590:21–32.

**27.** Ren S, Wang X, Lin Z, et al. Development of a high-throughput, indirect antibody immobilization format chemiluminescence immunoassay (CLEIA) for the determination of progesterone in human serum. Luminescence 2008;23:175–81.

**28.** Haseroth K, Seyffart K, Wehling M, Christ M. Effects of progestin-estrogen replacement

therapy on QT-dispersion in postmenopausal women. Int J Cardiol 2000;75:161–5.

**29.** Kadish AH, Greenland P, Limacher MC, Frishman WH, Daugherty SA, Schwartz JB. Estrogen and progestin use and the QT interval in postmenopausal women. Ann Noninvas Electrocardiol 2004;9:366–74.

**30.** Seth R, Moss AJ, McNitt S, et al. Long QT syndrome and pregnancy. J Am Coll Cardiol 2007;49:1092–8.

**31.** Setji TL, Brown AJ. Polycystic ovary syndrome: update on diagnosis and treatment. Am J Med 2014;127:912–9.

**32.** Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev 2013;7:CD004947.

**33.** Hitchcock CL, Prior JC. Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women. Menopause 2012;19:886–93.

**34.** Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. Am J Perinatol 2011;28:377–81.

**35.** Yang T, Snyders DJ, Roden DM. Ibutilide, a methanesulfonanilide antiarrhythmic, is a potent blocker of the rapidly activating delayed rectifier K+ current (IKr) in AT-1 cells. Concentration-, time-, voltage-, and use-dependent effects. Circulation 1995;91:1799–806.

**36.** Lee KS. Ibutilide, a new compound with potent class III antiarrhythmic activity, activates a slow inward Na+ current in guinea pig ventricular cells. J Pharmacol Exp Ther 1992;262:99–108.

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**APPENDIX** For supplemental methods, results, tables, and figures, please see the online version of this article.