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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

James E. Tisdale, PharmD,[a,b] Heather A. Jaynes, MSN,[a] Brian R. Overholser, PharmD,[a,b] Kevin M. Sowinski, PharmD,[a,b] David A. Flockhart, MD, PhD,[b] Richard J. Kovacs, MD[c]

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)

From the [a]Department of Pharmacy Practice, College of Pharmacy, Purdue University, Indianapolis, Indiana; [b]Division of Clinical Pharmacology, Department of Medicine, School of Medicine, Indiana University, Indianapolis, Indiana; and the [c]Krannert Institute of Cardiology, Department of Medicine, School of Medicine, Indiana University, Indianapolis, Indiana. This work was supported by a grant from the American Heart Association Midwest Affiliate (12GRNT12060187). This investigation was also supported by the Clinical Research Center within the Indiana Clinical and Translational Sciences Institute NIH/NCRR grant number UL1TR001108. In addition, this investigation was conducted in a facility constructed with support from Research Facilities Improvement Program grant number C06 RR020128-01 from the National Center for Research Resources, National Institutes of Health. Dr. Overholser was supported in part by National Institutes of Health grant K08 HL095655. Analytical work was performed

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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).

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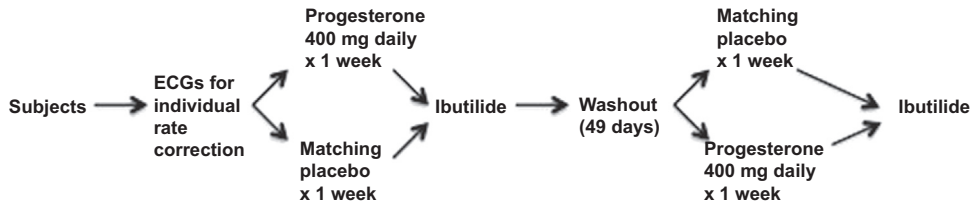
FIGURE 1 Study Design



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, β is the regression coefficient, and α is the slope.

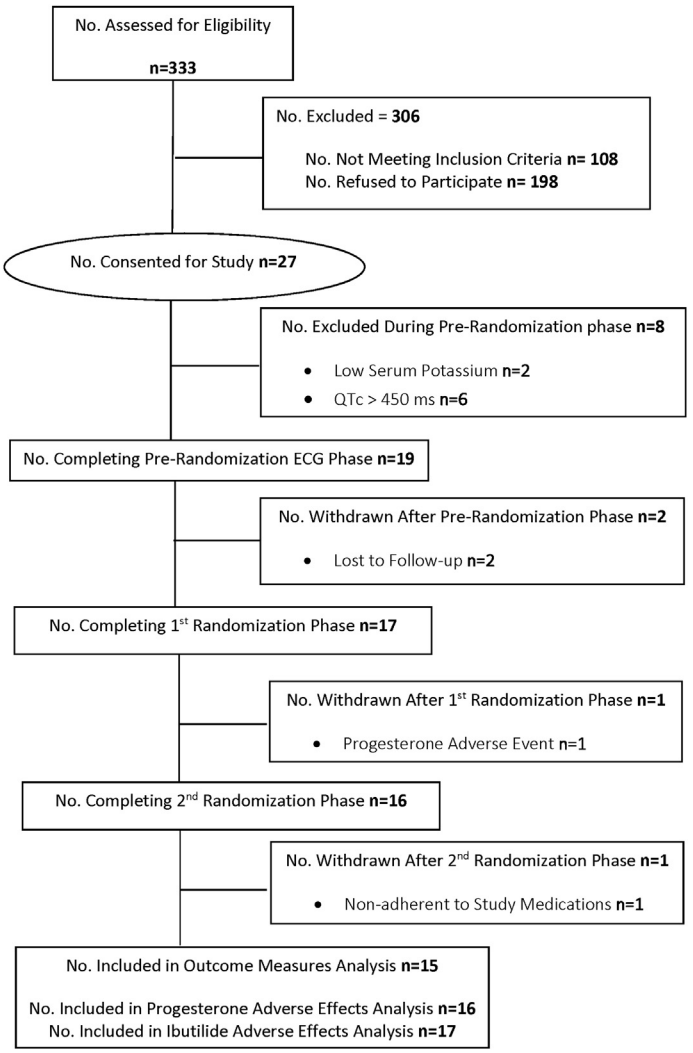
The study design is presented in **Figure 1**. After the pre-randomization phase, subjects were randomized in double-blind fashion to receive oral progesterone 400 mg (2 × 200 mg capsules, Teva Pharmaceuticals, North Wales, Pennsylvania) or matching placebo orally once daily at bedtime for 7 days. Matching 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



of 3 QT intervals at each time point for each lead was determined. Only clearly discernible QT intervals were measured. Determination of the QT_cI 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 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_cI and QT_F intervals; 2) maximal QT_cI and QT_F intervals after ibutilide administration; 3) maximal ibutilide-induced percentage change from baseline in QT_cI and QT_F intervals; and 4) area under the QT_cI and QT_F interval time curves from 0 to 1 h after ibutilide administration.

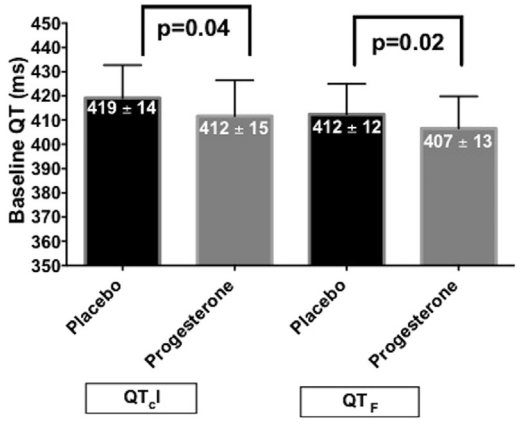
DATA ANALYSIS. Area under the QT_cI and QT_F interval time curves were calculated using the linear trapezoidal rule. Maximal serum ibutilide concentration was determined by visual inspection of serum concentration data.

SAMPLE SIZE AND STATISTICAL ANALYSIS. A sample size of 16 subjects was determined to be sufficient to detect a difference in maximal QT_cI of 12 ms (19% reduction), assuming a QT_cI 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

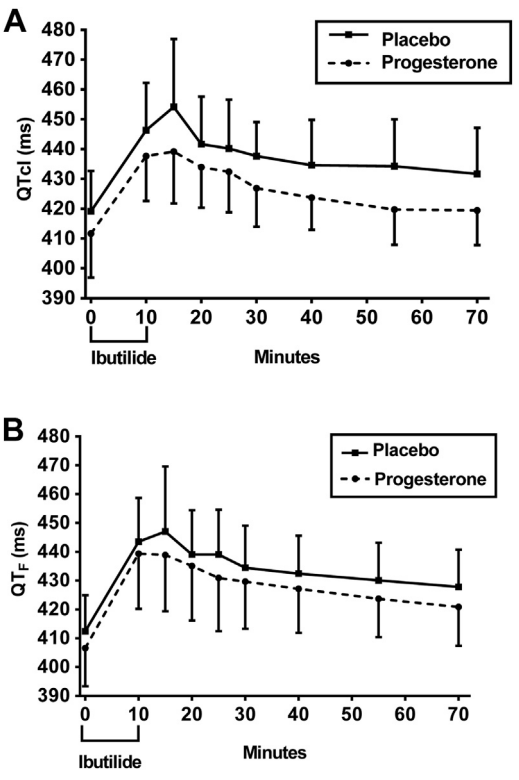
SUBJECTS. Nineteen subjects were enrolled (Figure 2). Four subjects were excluded from the outcome measures analysis because they did not complete all treatment phases (n = 3) or were determined to have been nonadherent to study medications after completion of all study phases (n = 1). Therefore, 15 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

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.

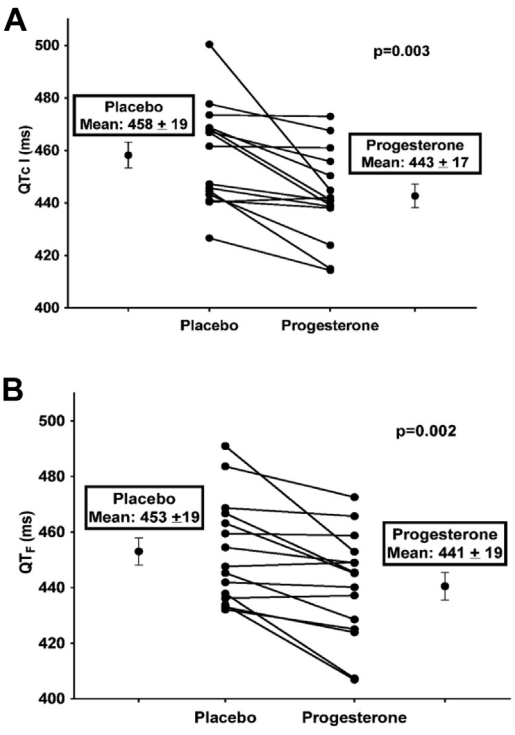
SERUM IBUTILIDE AND HORMONE CONCENTRATIONS. There was no significant difference between the progesterone and placebo phases in maximal serum ibutilide (1,247 ± 770 pg/ml vs. 1,172 ± 709 pg/ml; p = 0.43) or serum estradiol concentration (89.3 ± 62.8 pg/ml vs. 71.8 ± 31.7 pg/ml; p = 0.36). Serum progesterone 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) QT_CI AND QT_F INTERVALS. Baseline (pre-ibutilide) QT_CI 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).

QT_CI AND QT_F INTERVALS AFTER IBUTILIDE ADMINISTRATION. Lead II QT_CI 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

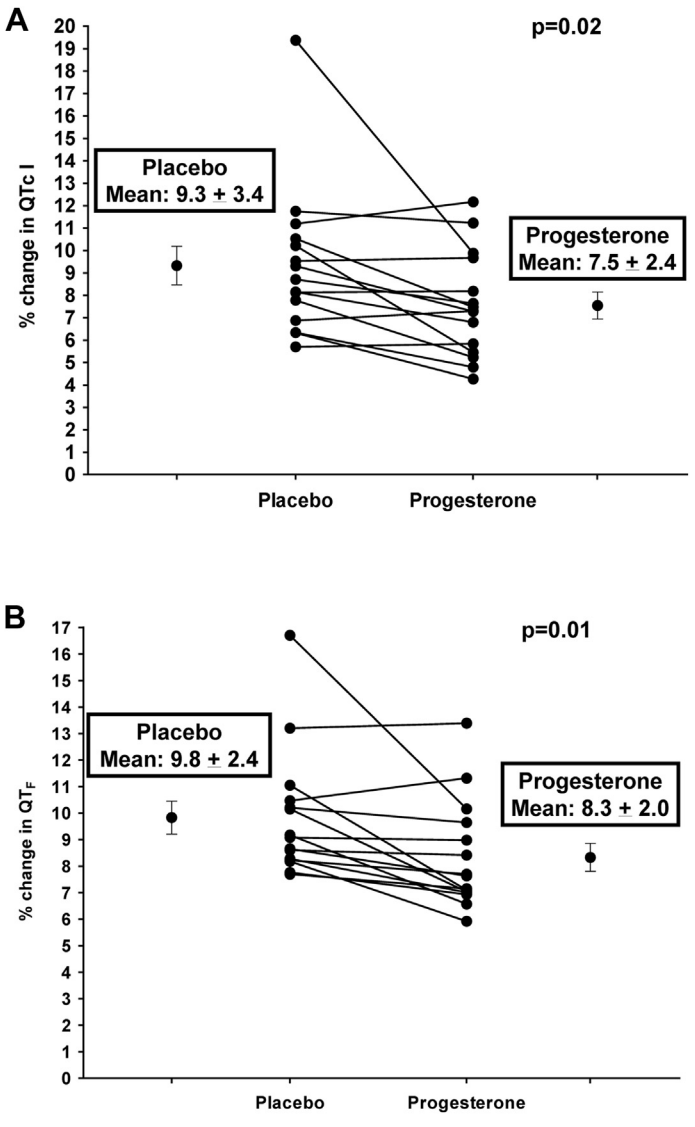
effective for reducing the risk of drug-induced QT_c interval prolongation in patients requiring therapy with QT_c interval-prolonging drugs and provide support for further investigation of the effect of oral progesterone in targeted populations requiring QT_c interval-prolonging drug therapy.

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 postpartum, 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 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 QT_cI and QT_F intervals. This was an important contributor to the overall effect of

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.

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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 ± 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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REPRINT REQUESTS AND CORRESPONDENCE: Dr. James E. Tisdale, College of Pharmacy, Purdue University, 640 Eskenazi Avenue, Indianapolis, Indiana 46202. E-mail: jtisdale@purdue.edu.

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.

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KEY WORDS electrocardiography, hormonal therapy, QT interval, torsades de pointes

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