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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—We 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 (21-40 years) 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 minutes, after which QT intervals were recorded and blood samples collected for 12 hours. Prior to the treatment phases, subjects underwent ECG monitoring for 12 hours to calculate individualized heart rate-corrected QT intervals (QT_cI).

Results—Fifteen subjects completed all study phases. Maximum serum ibutilide concentrations in the progesterone and placebo phases were similar (1247±770 vs 1172±709 pg/mL, p=0.43). Serum progesterone concentrations were higher during the progesterone phase (16.2±11.0 vs 1.2±1.0 ng/mL, p<0.0001), while serum estradiol concentrations in the two phases were similar (89.3±62.8 vs 71.8±31.7 pg/mL, p=0.36). Pre-ibutilide lead II QT_cI was significantly lower in the

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progesterone phase (412±15 vs 419±14 ms, p=0.04). Maximum ibutilide-associated QT_cI (443±17 vs 458±19 ms, p=0.003), maximum percent increase in QT_cI from pretreatment 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 (497±13 vs 510±16 ms-hr, 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.

Keywords

QT interval; Torsades de pointes; Electrocardiography; Hormonal therapy; Preventive

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 Unites States (2). TdP can be catastrophic, often degenerating into ventricular fibrillation causing sudden cardiac arrest (3). The risk for TdP increases as the heart rate-corrected QT (QT_c) interval increases (4,5), particularly exceeding 500 ms (6,7). Consequently, QT_c interval prolongation is used commonly as a marker of increased risk of TdP.

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 men (11), a difference which becomes apparent only after puberty (12), suggesting that sex hormones may be responsible. Post-pubertal differences in QT_c intervals may be partially due to reduction in QT_c intervals in males 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, premenopausal female volunteers age 21-40 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,

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; unwillingness to use non-hormonal 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 three phases: a pre-randomization phase to determine each subject's individual QT interval heart rate-correction, and the randomized, double-blind progesterone and placebo phases. Prior to inclusion, all subjects underwent a screening physical examination and blood was obtained for determination of serum potassium, magnesium, creatinine, transaminases, hemoglobin, and hematocrit. 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 24-60 hours after menses onset), when serum estradiol and progesterone concentrations are at their lowest, to minimize the effects of endogenous sex hormones (18).

During the pre-randomization phase, subjects underwent a 12-hour stay in the ICRC. Each subject underwent three 12-lead ECGs (Marquette Mac 5500, GE Healthcare Bio-Sciences, Pittsburgh, PA) one minute apart, at 0, 15 & 30 minutes, and 1, 2, 4, 6, 8 & 12 hours. 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 $\beta \cdot RR^{\alpha}$ (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. Following 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, PA) 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 were delivered to the ICRC by IDS personnel; investigators, study subjects, and ICRC personnel were blinded to treatment assignments during data collection and analysis. The minimum desired washout period was 28 days; after 28 days, we initiated dosing 7 days prior to 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-hour stay. Each subject underwent another urine HCG test to assure absence of pregnancy. Three ECGs, one minute 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 ECG monitor (Heal Force model PC 80B, Heal Force Bio-Meditech, Shanghai, China) and one 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, NJ).

Subjects then received a single intravenous dose of ibutilide 0.003 mg/kg diluted in 20 mL normal saline and infused over 10 minutes (18). Three 12-lead ECGs were obtained one minute apart immediately at the end of infusion and at 5, 10, 15, 20, 30, 45 minutes and 1, 2, 4, 6, 8 & 12 hours post-infusion. Pre-ibutilide ECGs were initiated between 7:00 am and 9:00 am, and ibutilide was administered immediately following baseline ECGs. 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, NJ) at the same times as ECGs were obtained. Subjects underwent continuous ECG monitoring for 6 hours post-ibutilide. Subjects were discharged after the 12-hour ECG and blood sample, providing 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 one investigator (HJ) who was blinded to subjects' assigned groups. QT intervals were measured using the MUSE automated system (GE Healthcare Bio-Sciences, Pittsburgh, PA) using electronic calipers. QT and RR intervals were averaged over ≥ 5 consecutive beats and the average of three 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 in the text, in Appendix Table 1, and in Appendix 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) Maximum QT_cI and QT_F intervals following ibutilide administration, 3) Maximum ibutilide-induced % change in QT_cI and QT_F intervals, and 4) Area under the QT_cI and QT_F interval-time curves from 0-1 hour following ibutilide administration.

Data Analysis

Area under the QT_cI and QT_F interval-time curves were calculated using the linear trapezoidal rule. Maximum serum ibutilide concentration was determined via 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 maximum QT_cI of 12 ms (19% reduction), assuming a QT_cI prolongation of 63±13 ms associated with ibutilide in the placebo group and a power of 0.80 (18). Analyses were performed using SAS 9.2 (SAS, 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's 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 t-tests for paired samples. All comparisons were performed utilizing a two-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, n=15 subjects comprise the final sample size for analysis of outcome measures. For analysis of adverse effects, n=16 received progesterone and n=17 received placebo; n=15 received ibutilide during the progesterone phase, n=17 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 maximum serum ibutilide (1247±770 vs 1172±709 pg/mL, p=0.43) or serum estradiol concentration (89.3±62.8 vs 71.8±31.7 pg/mL, p=0.36). Serum progesterone concentrations were significantly higher during the progesterone phase (16.2±11.0 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 minimum heart rate between the pre-randomization (development of QTcI) phase and on ibutilide administration days in the placebo and progesterone phases (60±7 vs 60±9 vs 61±9 bpm, respectively, p=0.58). There was no significant difference in maximum heart rate between the pre-randomization phase and

ibutilide administration days in the placebo and progesterone phases (78±8 vs 79±9 vs 80±11 bpm, respectively, p=0.70). There was no significant difference in average heart rate between the pre-randomization phase and on ibutilide administration days in the placebo and progesterone phases (68±7 vs 68±8 vs 70±9 bpm, respectively, p=0.51). Heart rates in the three study phases are presented in Appendix Figure 3.

Baseline (Pre-Ibutilide) QT_cI and QT_F Intervals

Baseline (pre-ibutilide) QT_cI and QT_F intervals in ECG 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 from ECG leads V_1 and V_5 (Appendix Figures 4 and 5).

QT_cI and QT_F Intervals Following Ibutilide Administration

Lead II QT_cI and QT_F intervals prior to and during the first hour following ibutilide administration in the progesterone and placebo groups are presented in Figure 4. Similar results were demonstrated in leads V_1 and V_5 (Appendix Figures 6 and 7). The maximum lead II QT_cI and QT_F following ibutilide administration during the progesterone and placebo phases are presented in Figure 5. Maximum 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 (Appendix Figures 8 and 9).

Maximum % Change from Baseline in QT_cI and QT_F Intervals Following Ibutilide Administration

Maximum ibutilide-associated % change in lead II QT_cI and QT_F intervals from baseline values is presented in Figure 6. There were significantly smaller ibutilide-associated % 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 (Appendix Figures 10 and 11).

Area Under the QT_cI and QT_F Interval Versus Time (0-1 hour) Following Ibutilide Administration

Area under the lead II QT_cI interval versus time (0-1.17 hours, 1 hour after completion of ibutilide infusion) curve was significantly lower during the progesterone phase compared with the placebo phase (497±13 vs 510±16 ms hr, p=0.002). Similarly, area under the lead II QT_F interval versus time (0-1.17 hours) curve after ibutilide administration was significantly lower during the progesterone phase compared with the placebo phase (499±17 vs 506±15 ms hr, p=0.013). Similar results were demonstrated with leads V_1 and V_5 (Appendix Table 2).

Adverse Effects Associated with Progesterone

Progesterone-associated adverse effects were generally mild, including fatigue/general malaise [progesterone 6/16 (38%) vs placebo 1/17 (6%), p=0.04], headache [2/16 (13%) vs 1/17 (6%), p = 0.60], mood changes [2/16 (13%) vs 0, p=0.23], breast tenderness [2/16 (13%) vs 0, p=0.23], hypotension [1/16 (6%) vs 0, p=0.48], and vertigo 1/16 (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 bpm; progesterone phase 3/15 (20%) vs placebo phase 2/17 (12%), p=0.65] and burning at the infusion site [1/15 (7%) vs 1/17 (6%), p>0.99]. In one subject (during the placebo phase), Bazett's-corrected QT interval 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 one week significantly reduced non-drug 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 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 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 (I_{Ks}) and inhibits L-type Ca^{2+} currents ($I_{Ca,L}$) 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 $I_{Ca,L}$ in rabbit cardiomyocytes and increases expression of sarcoplasmic reticulum calcium ATPase2a, which may contribute to increasing sarcoplasmic reticular 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, non-drug-associated QT_cI and QT_F intervals. This was an important contributor to the overall effect of progesterone-associated reduction in maximum 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 following 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 % change in maximum ibutilide-associated QT_cI and QT_F interval from pretreatment 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 than 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 via inhibition of the rapid component of the delayed rectifier potassium current (35), as well through activation of a slow inward sodium current (36). Ibutilide was an appropriate probe drug for this investigation since 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 based on 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 60-90 minutes of ibutilide administration. There was no significant difference in maximum serum ibutilide concentration between the progesterone and placebo phases; therefore, differences in QT_cI and QT_F intervals in the two phases were not attributable to differences in serum ibutilide concentration.

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 those in 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 Fridericia heart rate correction for QT interval, and the QT_F 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

bpm	Beats per minute
ECG	Electrocardiogram

HCG	Human chorionic gonadotropin
ICRC	Indiana Clinical Research Center
IDS	Investigational Drug Service
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
IU	Indiana University

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Perspectives

Competency in Medical Knowledge: Torsades de pointes 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. Torsades de pointes 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.

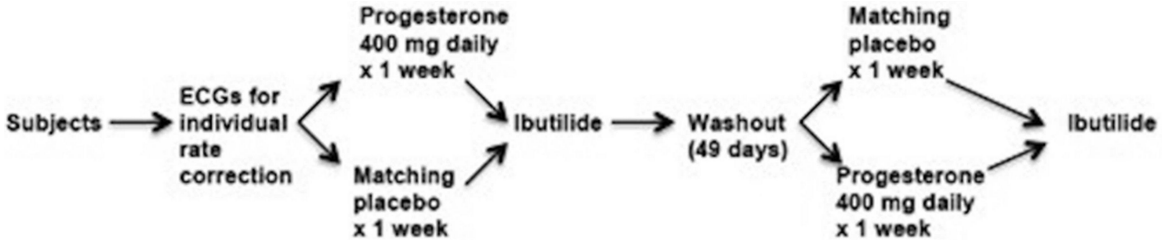


Figure 1.
Study Design

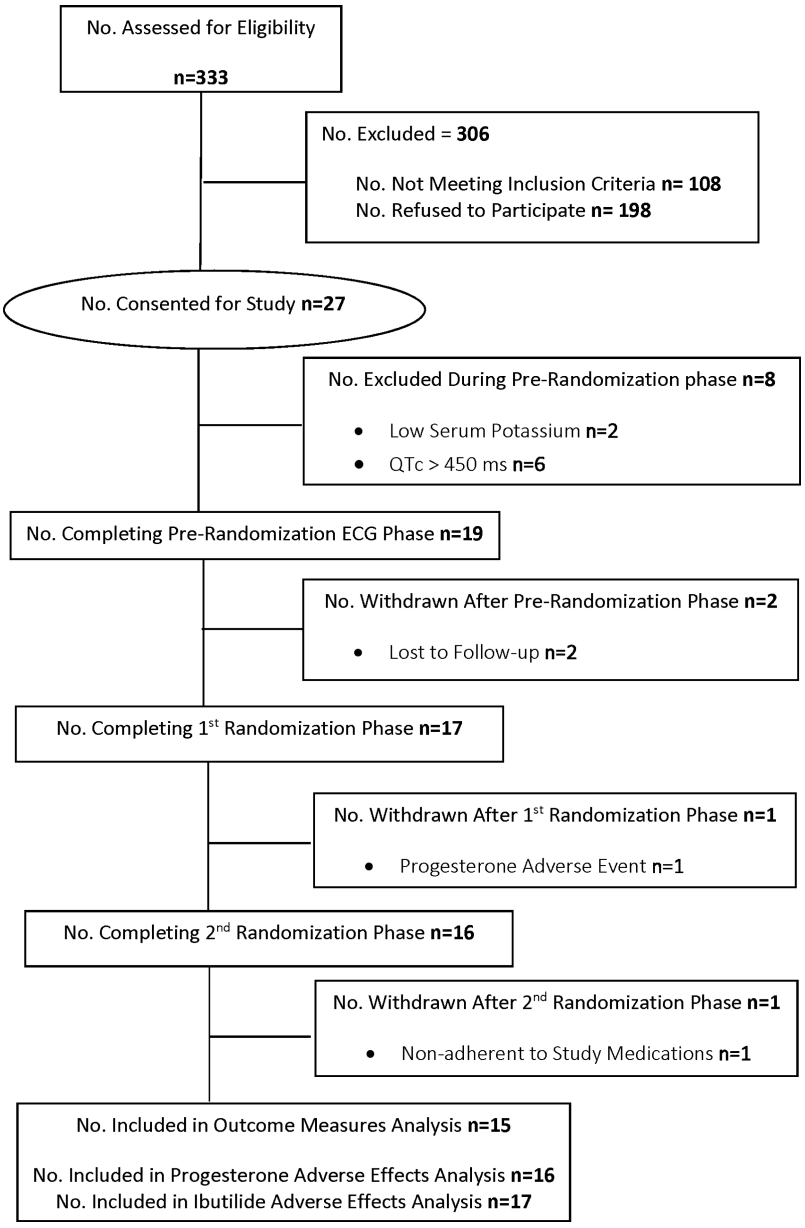


Figure 2.

Recruitment and Enrollment for Randomized, Crossover Placebo-Controlled Study of Influence of Oral Progesterone on Drug-Induced QT_c Interval Lengthening

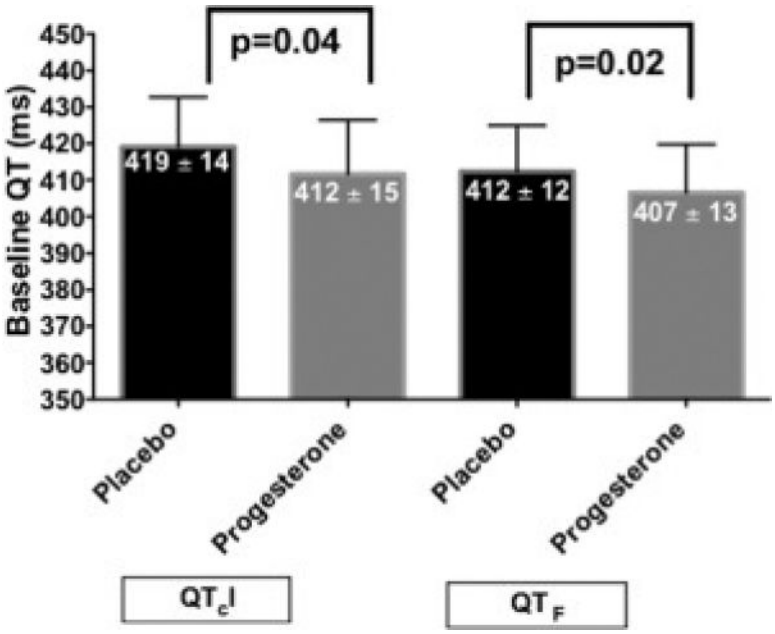


Figure 3.

Influence of Oral Progesterone Administration on Baseline (Pre-Ibutilide) QTcI and QT_F Intervals (from ECG lead II)

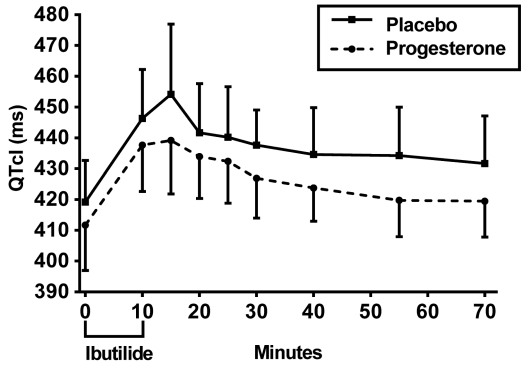
ECG = Electrocardiogram

QTcI = Individually-corrected QT intervals

QT_F = Fridericia-corrected QT intervals

Data are presented as mean ± SD

a



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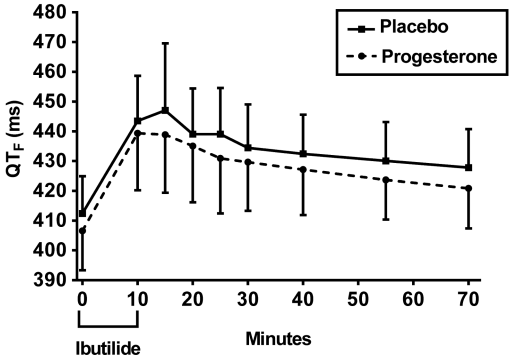


Figure 4.

QTcI (4a) and QT_F (4b) Intervals During and Following a 10-Minute Infusion of Ibutilide 0.003 mg/kg (from ECG lead II) During Progesterone and Placebo Phases

ECG = Electrocardiogram

QTcI = Individually-corrected QT intervals

QT_F = Fridericia-corrected QT intervals

Data presented as mean ± SEM

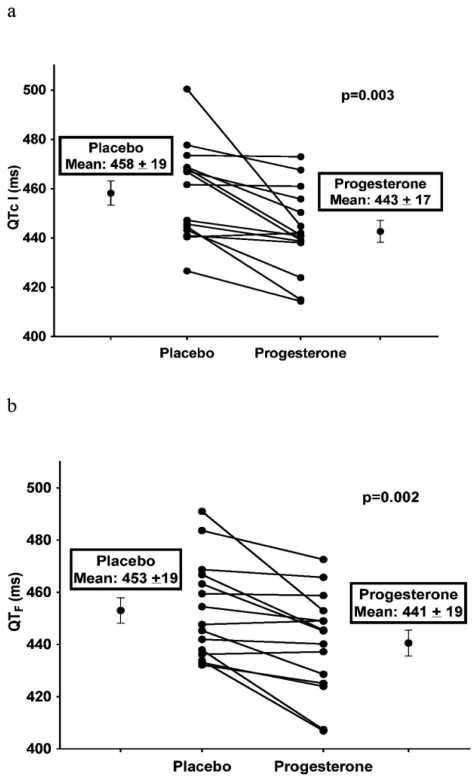


Figure 5.

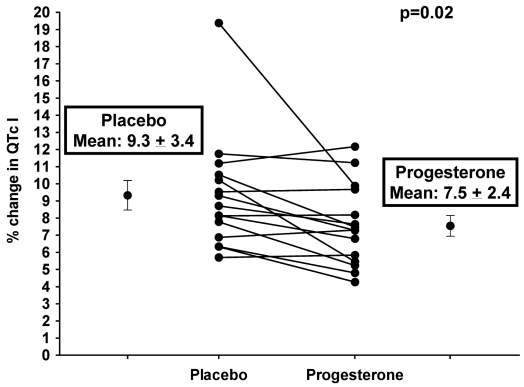
Maximum QTcI (5a) and QT_F (5b) Intervals (from ECG lead II) Following Ibutilide 0.003 mg/kg During Progesterone and Placebo Phases

QTcI = Individually-corrected QT intervals

QT_F = Fridericia-corrected QT intervals

Data are presented as mean ± SD

a



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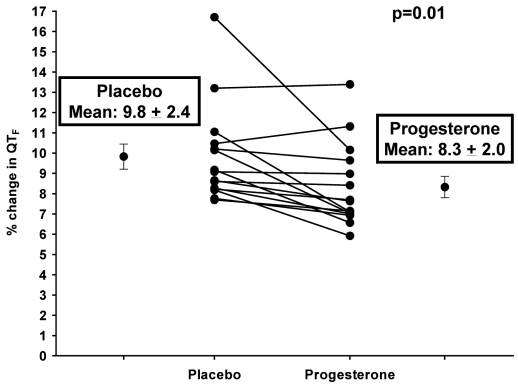

Figure 6.

Maximum % Change from Baseline in QTcI (6a) and QT_F (6b) Intervals (from ECG lead II) Following Ibutilide 0.003 mg/kg During Progesterone and Placebo Phases

QTcI = Individually-corrected QT intervals

QT_F = Fridericia-corrected QT intervals

Data are presented as mean ± SD