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Progesterone Pretreatment Reduces the Incidence of Drug-Induced Torsades de Pointes in AV Node-Ablated Isolated Perfused Rabbit Hearts

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Abstract

INTRODUCTION—Higher progesterone concentrations are protective against drug-induced prolongation of ventricular repolarization. We tested the hypothesis that pretreatment with progesterone reduces the incidence of drug-induced torsades de pointes (TdP).

METHODS AND RESULTS—Female New Zealand white rabbits (2.5–3.2 kg) underwent ovariectomy and were randomized to undergo implantation with subcutaneous 21-day sustained release pellets containing progesterone 50 mg (n=22) or placebo (n=23). After 20 days, hearts were excised, mounted, and perfused with modified Krebs-Henseleit solution. The atrioventricular (AV) node was destroyed manually. Following a 15-minute equilibration period, hearts were perfused with dofetilide 100 nM for 30 minutes, during which the electrocardiogram was recorded continuously. Incidences of spontaneous TdP, other ventricular arrhythmias and mean QTc intervals were compared. Median serum progesterone concentrations were higher in progesterone versus placebo-treated rabbits [3.8 (range, 2.8–5.1) vs 0.7 (0.4–1.7) ng/mL, $p<0.0001$]. Median serum estradiol concentrations were similar [58 (22–72) versus 53 (34–62) pg/mL, $p=0.79$]. The incidence of TdP was lower in hearts from progesterone-treated rabbits (27% vs 61%, $p=0.049$). The incidences of bigeminy (36% vs 74%, $p=0.03$) and trigeminy (18% vs 57%, $p=0.01$) were also lower in hearts from progesterone-treated rabbits. There was no significant difference between groups in incidence of couplets (59% vs 74%, $p=0.54$) or monomorphic ventricular tachycardia

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(14% vs 30%, $p=0.28$). Maximum QTc interval and short term beat-to-beat QT interval variability during dofetilide perfusion were significantly shorter in hearts from progesterone-treated rabbits.

CONCLUSIONS—Pretreatment with progesterone reduces the incidence of drug-induced TdP, bigeminy and trigeminy in isolated, perfused AV node-ablated rabbit hearts.

Keywords

Torsades de pointes; ventricular arrhythmias; QT interval; progesterone; isolated perfused heart; dofetilide; rabbit; beat-to-beat variability

Introduction

Torsades de pointes (TdP) is a polymorphic ventricular tachycardia associated with prolongation of the heart rate-corrected QT (QTc) interval.^{1,2} TdP can be catastrophic, often degenerating into ventricular fibrillation resulting in sudden cardiac death.³ More than 150 medications available in the United States may cause QTc interval prolongation and TdP.⁴

Female sex is an independent risk factor for TdP in patients with acquired or congenital long QT syndrome (LQTS).^{5–8} QTc intervals are longer in women than in men,⁹ a difference that becomes apparent after puberty,¹⁰ suggesting that sex hormones may be responsible. Post-pubertal differences in QTc intervals may be partially caused by a shortening of QTc intervals in males as a result of testosterone and dihydrotestosterone production.⁹ However, female sex hormones also may modulate the QTc interval and risk of TdP in women. Some studies have reported that hormone replacement therapy with estrogen results in QTc interval lengthening.^{11,12} Conversely, some evidence suggests that progesterone may be protective against lengthening of ventricular repolarization.¹³

Progesterone is a testosterone precursor¹⁴ and has a similar androgenic structure.¹⁵ Higher serum progesterone concentrations are associated with shorter QTc intervals¹⁶ and may exert protective effects against lengthening of ventricular repolarization.¹⁷ Preclinical data suggest that exogenous progesterone administration may protect against drug-induced prolongation of ventricular repolarization^{18–20} and ventricular early afterdepolarizations.²⁰ Exogenous progesterone administration was shown to reduce the incidence of spontaneous arrhythmias in a transgenic rabbit model of long QT syndrome.²¹

In a proof-of-concept study, we reported that administration of oral progesterone significantly shortens baseline (prior to administration of a QTc interval-prolonging drug) QTc intervals and attenuates drug-induced QTc interval lengthening in healthy premenopausal women during the menses phase of the menstrual cycle.²² These results suggest that administration of progesterone as a therapeutic agent has the potential to reduce the risk of drug-induced arrhythmias, including TdP. However, the influence of exogenous progesterone administration on susceptibility to drug-induced arrhythmias remains unknown.

In these experiments, we tested the hypothesis that pretreatment with progesterone reduces the incidence of drug-induced TdP and other ventricular arrhythmias in an AV-node ablated isolated perfused rabbit heart model.

Methods

Animal model and preparation

This prospective, randomized, placebo-controlled study was approved by the Institutional Animal Care and Use Committee at Indiana University (IU), and the study conformed to the National Institute of Health's Guide for the Care and Use of Laboratory Animals. The study was conducted in 45 female New Zealand white rabbits (Charles River Laboratories, Wilmington, AM, USA), each weighing 2.5–3.2 kg (mean = 2.9 ± 0.5 kg). Rabbits were housed individually, and received food and water daily. The Laboratory Animal Resource Center veterinary staff checked the rabbits daily to assess their health and to change pan liners. The rabbits were provided time in a play pen for additional exercise at least once weekly, and rabbit banks were changed/sanitized weekly.

The animals were anesthetized with 2% isoflurane and oxygen and underwent ovariectomy under sterile survival surgery conditions. Immediately following ovariectomy, the mid-to-upper back was shaved and a small incision was made. All rabbits were implanted with two 21-day sustained release pellets (Innovative research of America, Sarasota, FL, USA); one group was implanted with one progesterone 50 mg pellet ($n=22$), while the other group was implanted with one placebo pellet ($n=23$). A progesterone dose of 50 mg was utilized to achieve a desired serum progesterone concentration of 3–4 ng/mL.² Following pellet implantation, the rabbits were allowed to recover from surgery. During the subsequent 20-day stay in the IU Laboratory Animal Resources Center, rabbits were fed Rabbit Diet 2030 (Harlan Teklad, Madison, WI, USA) which is a fixed formula pellet diet consisting of a minimum of 2.5% fat and a maximum of 16% crude fiber. The diet was supplemented with greens including lettuce, spinach and kale, and fruits such as apples and cherries.

Isolated Perfused Heart Experiments

Twenty days following pellet implantation, animals were anesthetized with sodium pentobarbital (50 mg/kg) administered into an ear vein (progesterone, $n=11$, placebo, $n=10$) or inhaled isoflurane 2% and oxygen (progesterone, $n=11$, placebo, $n=13$). In a subset of rabbits studied, a venous blood sample (10 mL) was collected from an ear vein into a gold top serum separator tube (Vacutainer, BD, Franklin Lakes, NJ, USA) for determination of serum progesterone and estradiol concentrations. Serum was harvested and frozen at -80°C until analyzed. Serum progesterone and estradiol concentrations were determined in the IU Clinical Pathology Laboratory using electrochemiluminescent immunoassays.^{23,24}

The diaphragm was accessed and the thorax opened with a bilateral incision, exposing the heart, which was rapidly excised and mounted on a Langendorff isolated perfused heart apparatus (IH-SR 5, Harvard Apparatus, Inc., Holliston, MA), and immersed in a tissue bath filled with a modified Krebs-Henseleit solution, which consisted of: NaCl 118.5 mM, KCl 3.5 mM, MgSO_4 1.2 mM, NaHCO_3 25.0 mM, KH_2PO_4 1.2 mM, CaCl_2 1.8 mM and glucose 11.0 mM. All reagents were obtained from Sigma Chemical Co. (St. Louis, MO, USA). The perfusate was equilibrated to $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using a temperature control system (Thermostatic Circulator E103, Harvard Apparatus, Holliston, MA) and infused with 95%

O₂ and 5% CO₂, at pH 7.4. The perfusate was maintained at an aortic pressure of 70–90 mm Hg throughout the study period.

A volume-conducted electrocardiogram (ECG) using eight flexible unipolar electrodes (Harvard Apparatus Inc., Holliston, MA) was recorded via immersion of the heart in the modified Krebs-Henseleit solution. Signals from a simulated Einthoven configuration were amplified using an ECG amplifier (filter settings 0.1–300 Hz) (Hugo Saks Elektronik Harvard Apparatus D79232, March-Hugstetten, Germany). The atrioventricular (AV) node was destroyed manually using forceps to achieve AV dissociation and slow the intrinsic heart rate. AV dissociation was considered successful when the P wave was dissociated from the QRS complex on real-time continuous ECG recordings. Following AV node ablation, hearts were not paced and were allowed to beat at their own intrinsic spontaneous rate, in order to avoid the occurrence of electrical pacing-induced arrhythmias.²⁵ Hearts were allowed to equilibrate and stabilize for 15 minutes prior to initiation of the experimental protocol, during which baseline ECGs were recorded continuously. The investigators were blinded to treatment assignment (progesterone or placebo pellets) during the conduct of the experiments.

Study Protocol

Following the 15-minute equilibration and stabilization period, hearts were perfused for 30 minutes with modified Krebs-Henseleit solution containing dofetilide 100 nM. Dofetilide was selected as the probe drug for prolonging ventricular repolarization as it has been shown to inhibit the rapid component of the delayed rectifier current (I_{Kr}).²⁶ ECGs were recorded continuously during dofetilide infusion.

Electrocardiographic Measurements

Data were acquired and recorded using the HSE-IsoHeart W Data acquisition system (Hugo Sachs Elektronik-Harvard Apparatus, March-Hugstetten, Germany). For analysis of QT interval, 5 beats from the continuous ECG recordings within the last 60 seconds of the 15-minute equilibration/stabilization period and 5 beats at each designated time point during dofetilide perfusion were chosen for analysis and averaged. Investigators performing the arrhythmia analysis and QT interval measurements were blinded to treatment groups. QT intervals were measured from the Q wave to the end of the T wave using electronic calipers at the end of the equilibration period and at 1, 2, 5, 7, 10, 15, 20 and 30 minutes after initiation of perfusion with dofetilide. If the QT interval was not measurable due to the presence of an arrhythmia, the results were not included for analysis. QT interval measurements were not analyzed beyond the time of the first sustained ventricular arrhythmia due to the effect of arrhythmias on ventricular repolarization.

QT intervals were corrected to remove the influence of heart rate during idioventricular escape rhythm following AV block.²⁷ QT intervals and corresponding RR intervals were derived from all hearts included in this study in sinus rhythm at baseline, prior to AV node ablation. In sinus rhythm, linear regression revealed a positive correlation between QT and RR intervals ($QT_{\text{Sinus}} = 0.335RR + 109.6$, $R=0.77$, $p<0.05$). Following destruction of the AV node, in idioventricular escape rhythm, the QT vs RR correlation was no longer significant

($QT_{AV-block} = 0.091RR + 202.3$, $R=0.008$, $p=0.79$). However, as there was a difference between the slope of the regression line during sinus rhythm vs idioventricular rhythm, the equations were rearranged to calculate the rate-corrected QT interval in sinus rhythm at an RR interval of 300 ms (corresponding to a ventricular rate of 200 bpm) using the formula $QTc-Sinus = QT_{Sinus} - 0.335(RR-300)$ and in idioventricular escape rhythm ($QTc-AV$) at an RR interval of 500 (corresponding to a ventricular rate of 120 bpm) using the formula $QTc-AV = QT_{AV-block} - 0.09(RR-500)$. With these equations, plotting $QTcSinus$ and $QTc-AV$ against the corresponding RR interval yields a regression line with a slope of 0, indicating the removal of the influence of heart rate.²⁷

In addition to determining $QTc-AV$, we also calculated short-term beat-to-beat QT interval variability ($QT-STV$), a parameter of proarrhythmic risk.²⁸ A series of 30 QT and RR intervals were measured 5 minutes prior to the initiation of dofetilide perfusion and again at 5 minutes following the initiation of dofetilide perfusion. If there was a sustained arrhythmia during the first 5 minutes of dofetilide perfusion, then the 30-beat measurement was initiated at 30 seconds prior to the first arrhythmia. If there was a premature ventricular complex (PVC) during the 30 complex measurement period, then this complex and the subsequent complex were disregarded, and additional consecutive QT intervals were measured to account for the disregarded beats. $QT-STV$ was calculated using the following formula: $QT-STV = \sum |D_{n+1} - D_n| / (30 \times \sqrt{2})$, where D represents the duration of the QT intervals.

Outcomes Measures

Primary outcome measure:

1. Incidence of spontaneous TdP during the 30-minute dofetilide perfusion. TdP was defined as a polymorphic ventricular tachycardia with 4 consecutive complexes displaying clear twisting of the QRS complex around the isoelectric axis observed in at least one ECG lead²⁷

Secondary outcome measures:

1. Incidence of other spontaneous ventricular arrhythmias during the 30-minute dofetilide perfusion. Ventricular premature complexes, couplets, bigeminy, trigeminy, and monomorphic ventricular tachycardia were defined using accepted definitions.^{29,30} Ventricular arrhythmia burden was defined as the total number of complexes of any arrhythmia (premature ventricular complexes, bigeminy, trigeminy, couplets, monomorphic ventricular tachycardia, TdP).
2. QTc intervals at baseline and during the 30-minute dofetilide perfusion, and maximum QTc interval during the 30-minute dofetilide perfusion. Maximum QTc interval was defined as the maximum QTc interval at any of the measured time points, but prior to the first occurrence of a sustained arrhythmia.
3. $QT-STV$ at baseline (5 minutes prior to initiation of dofetilide perfusion) and 5 minutes following the initiation of dofetilide perfusion.

Data Analysis

Statistical analyses were performed using Statistical Analysis Software (SAS 9.4, Cary, NC, USA). The incidences of arrhythmias in the two groups were compared using the Chi-square or Fisher's Exact test, as appropriate. For all continuous data, differences between groups were compared using Student's unpaired t-test if the assumption of normality was met and a Wilcoxon rank-sum test for non-normally distributed data. Normality of data was determined using the Kolmogorov-Smirnov test. For QTc interval changes over time, groups were compared using repeated measures analysis of variance (ANOVA). Where statistically significant differences were found, *post-hoc* testing was performed to determine between-group differences using Tukey's Honest Significant Difference (HSD) test. For all comparisons, α was set at 0.05.

Results

Serum Hormone Concentrations

Serum progesterone and estradiol concentrations and progesterone:estradiol ratios in a subset of the rabbits prior to heart excision are presented in Table 1. Serum progesterone concentrations were significantly higher in progesterone-treated rabbits than in those treated with placebo, and were similar to those occurring in women during the ovulation phase of the menstrual cycle.¹⁵ Serum estradiol concentrations in the two groups were not significantly different. The ratio of serum progesterone: estradiol concentrations was significantly higher in progesterone-treated rabbits versus those in the placebo group.

Influence of Progesterone on Incidence of Dofetilide-Induced TdP and other Ventricular Arrhythmias

The incidence of dofetilide-induced TdP was significantly lower in hearts from rabbits treated with progesterone compared to that in hearts from placebo-treated rabbits (Figure 1). Compared to placebo, progesterone pre-treatment significantly reduced the relative risk (RR) of dofetilide-induced spontaneous TdP (0.45, 95% CI 0.21–0.95). An example of spontaneous TdP occurring during dofetilide perfusion in a heart pretreated with placebo is provided in Figure 2.

In addition, the incidence of bigeminy and trigeminy were significantly lower in progesterone-treated rabbits (Figure 1), corresponding to relative risks of 0.49 (0.27–0.90) and 0.32 (0.12–0.84), respectively. The incidence of couplets, monomorphic ventricular tachycardia, and any ventricular ectopy was not significantly different between the two groups (Figure 1). However, the overall ventricular arrhythmia burden was significantly lower in progesterone-treated rabbits compared with that in the placebo group (Figure 3).

Influence of Progesterone on Dofetilide-Induced QTc Interval Lengthening

Baseline (pre-dofetilide) QTc intervals in the two groups were not significantly different (Figure 4a). However, mean maximum QTc interval during dofetilide perfusion was significantly shorter in hearts from progesterone-treated rabbits than in those from placebo-treated animals (Figure 4b). QTc intervals during the entire 30-minute dofetilide perfusion in hearts from progesterone and placebo-treated rabbits are presented in Figure 5; over the

course of the 20-minute dofetilide perfusion period, QTc intervals were significantly shorter in hearts from progesterone-treated rabbits.

Influence of Progesterone on Dofetilide-Associated Changes in QT-STV

There was no significant difference between hearts from rabbits pretreated with progesterone vs placebo in mean ($\pm$ SD) baseline (pre-dofetilide perfusion) QT-STV (10.2 ± 3.2 vs 9.4 ± 2.5 ms, $p=0.80$). However, QT-STV was significantly lower in hearts from rabbits pretreated with progesterone (22.0 ± 5.8 vs 27.5 ± 6.3 , $p=0.004$). QT-STV was significantly larger in hearts that developed TdP during dofetilide perfusion compared with hearts that did not develop dofetilide-induced TdP (32.8 ± 6.8 vs 21.4 ± 6.2 , $p<0.0001$).

Discussion

In these investigations, progesterone pretreatment significantly reduced the incidence of drug-induced TdP in isolated perfused AV-blocked hearts from ovariectomized female rabbits. In addition, progesterone pretreatment reduced the incidence of drug-induced bigeminy and trigeminy, and decreased the overall burden of ventricular arrhythmias. Progesterone pretreatment also significantly attenuated dofetilide-induced QTc interval lengthening.

Evidence from preclinical and human studies suggests that progesterone may shorten ventricular repolarization. Progesterone has been shown to rapidly shorten action potential duration in isolated guinea pig ventricular myocytes.¹⁸ Progesterone was also shown to shorten action potential duration in right ventricular papillary muscle from female rabbits, and reduced the incidence of dofetilide-induced early afterdepolarizations.²⁰ In a study of 11 healthy women between the ages of 18–32 years, QT intervals were found to be shorter during the luteal phase of the menstrual cycle, when serum progesterone concentrations are highest, compared to those during the follicular phase.¹⁶ Fridericia-corrected QT intervals (QT_F) were found to be significantly shorter in women with congenital adrenal hyperplasia, in which progesterone overexpression occurs, than in healthy female controls.³¹ QT_F intervals were inversely correlated with serum progesterone concentrations and the ratio of serum progesterone:estradiol concentrations.³¹

In addition to shortening ventricular repolarization, evidence suggests progesterone may protect against drug-induced lengthening of ventricular repolarization. Rodriguez et al¹⁷ reported that ibutilide-induced lengthening of the QTc interval was greatest during the menses and ovulation phases of the cycle in young healthy women, and significantly less pronounced during the luteal phase. Serum progesterone concentration and the ratio of serum progesterone:estradiol concentrations were significantly inversely correlated with ibutilide-associated lengthening of the QTc interval.¹⁷ In our present study, serum progesterone concentrations were achieved that are similar to those that are achieved in premenopausal women during the ovulation phase of the menstrual cycle, and found that these progesterone concentrations were sufficient to reduce the incidence of drug-induced TdP. However, the rabbits in our study underwent ovariectomy, to remove the potential confounding influence of estradiol. Therefore, serum concentration ratios of progesterone:estradiol were substantially higher in our rabbits compared to the female

subjects in the ovulation phase in the Rodriguez study;¹⁷ serum estradiol concentrations are at their highest during the ovulation phase. Estradiol may prolong the QT interval, and may, to some degree, counteract the protective effects of progesterone. This likely explains why ovulation-phase serum progesterone concentrations in our study were protective against drug-induced TdP, whereas in premenopausal women, progesterone concentrations and serum progesterone:estradiol ratios in the luteal phase may be required for optimal protection against drug-induced QT interval lengthening.

Additional data support the concept that progesterone may be protective against drug-induced QT interval lengthening. We previously published the results of a prospective, double-blind placebo-controlled crossover study in which young healthy premenopausal women were randomized to receive oral progesterone 400 mg orally once daily or placebo for one week during the menses phase of the menstrual cycle.²² Oral progesterone significantly shortened baseline (pre-ibutilide) QT intervals, and significantly attenuated QT interval lengthening induced by a subtherapeutic dose of intravenous ibutilide. In addition, women taking the progestin oral contraceptive levonorgestrol were reported to have a significantly smaller increase in QT intervals provoked by sotalol than women taking drospirenone, which has antiandrogenic properties.³²

While previous evidence indicates that progesterone shortens ventricular repolarization and attenuates drug-induced lengthening of ventricular repolarization, there is less evidence regarding whether progesterone reduces the risk of ventricular arrhythmias. In patients with the congenital long QT syndrome, the risk of TdP is low during pregnancy, when serum progesterone concentrations are high, and increases markedly postpartum, when serum progesterone concentrations abruptly decline.³³ In a transgenic rabbit model of long QT syndrome, exogenous progesterone administration reduced the incidence of spontaneous ventricular arrhythmias including premature ventricular contractions, bigeminy, couplets, triplets, and polymorphic ventricular tachycardia.²¹ However, while these studies provide evidence that progesterone may reduce the risk of arrhythmias in the long QT syndrome, the influence of exogenous progesterone administration on drug-induced arrhythmias remains unknown. In our present work, we have demonstrated that pretreatment with progesterone significantly reduces the incidence of drug-induced arrhythmias including TdP, bigeminy, trigeminy, and overall ventricular ectopy burden.

Short-term beat-to-beat variability of QT intervals (QT-STV) quantifies the heterogeneity of the QT interval from one cycle to the next.³⁴ Increased QT-STV has been associated with an increased risk of drug-induced TdP.^{35–37} An increase in QT-STV may enhance the likelihood of triggered activity, including early afterdepolarizations (EADs), which may provoke TdP.³⁷ In our study, QT-STV was significantly longer in hearts from rabbits that developed dofetilide-induced TdP compared to those that did not. Further, QT-STV was significantly shorter in hearts pretreated with progesterone compared to those pretreated with placebo, suggesting that progesterone may protect against triggered activity that may provoke TdP. Future studies should include analysis of the influence of progesterone on QT-STV and associated triggered activity, including EADs and associated TdP.

In addition to provoking TdP, dofetilide has been shown to induce monomorphic ventricular tachycardia in animals studies and in humans.^{38,39} In this present study, the incidence of monomorphic ventricular tachycardia was not significantly lower in hearts from rabbits pretreated with progesterone compared to those pretreated with placebo. It is possible that this could be owing to differences in mechanisms associated with drug-induced monomorphic ventricular tachycardia versus TdP. However, this could also be due to our study being underpowered to detect significant differences between the groups in monomorphic ventricular tachycardia, as the ventricular tachycardia event rate was substantially lower than that of TdP.

Mechanisms by which progesterone shortens ventricular repolarization have been investigated. Progesterone has been shown to enhance I_{Ks} current in isolated guinea pig ventricular myocytes.¹⁸ In addition, progesterone inhibits L-type calcium current.¹⁸ These effects are mediated by nongenomic activation of endothelial nitric oxide synthase, resulting in release of nitric oxide.¹⁸ However, progesterone has also been shown to inhibit the rapid component of the delayed rectified potassium current (I_{Kr}) via impaired plasma membrane trafficking of the pore-forming subunit, KCNH2 (HERG),⁴⁰ an effect that should promote lengthening of the QT interval and proarrhythmia, rather than attenuation of QT interval lengthening and protection against proarrhythmia. These apparently contrasting ion channel effects of progesterone are likely concentration-related. Progesterone concentrations required to inhibit I_{Kr} are much higher than those that occur in women under normal physiologic conditions, except during the late stages of pregnancy, when QTc interval tend to increase.⁴⁰ However, other than during the late stages of pregnancy, (ie in all phases of the menstrual cycle), serum progesterone concentrations in women are much lower, such that progesterone's effects on I_{Ks} and L-type calcium current likely predominate. Further investigation is required to determine which mechanisms predominate during progesterone-associated attenuation of drug-induced QTc interval lengthening and reduction in the risk of drug-induced TdP.

Limitations

Due to the need for rapid heart excision following the initiation of anesthesia, blood for determination of serum progesterone concentrations was not obtainable in all rabbits studied. In addition, as discussed above, the sample size may have been too small to detect significant differences between the progesterone and placebo-treated hearts in the incidence of couplets, monomorphic ventricular tachycardia or any ventricular ectopy, though these were not the primary outcome measures of the study.

Conclusions

Pretreatment with progesterone significantly reduces the incidence of drug-induced TdP and other ventricular arrhythmias in an AV-node ablated isolated perfused female rabbit heart model.

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Clinical Implications

Progesterone pretreatment significantly attenuated drug-induced QTc interval lengthening and reduced the incidence of drug-induced TdP, a potentially life-threatening arrhythmia. In view of these findings, oral progesterone could be administered to patients at high risk for QTc interval prolongation and TdP who require therapy with one or more QTc interval-prolonging drugs to reduce the risk of life-threatening drug-induced arrhythmias. This hypothesis requires testing in clinical studies.

Figure 1.
Incidence of Torsades de Pointes and Other Ventricular Arrhythmias During Dofetilide Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

Figure 2.
Spontaneous Torsades de Pointes During Dofetilide Perfusion in an Isolated Perfused Rabbit
Heart Pretreated with Placebo

Figure 3.

Ventricular Arrhythmia Burden During Dofetilide Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

3a. Median (range) Number of Total Ventricular Arrhythmia Complexes During Dofetilide Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

3b. Mean (±SD) Number of Ventricular Arrhythmia Complexes During a 5-Minute Period (from 10–15 Minutes Following Initiation of Perfusion) During Dofetilide Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

SD = Standard deviation

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Figure 4.

Mean (±SD) QTc Intervals Prior to and During Dofetilide Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

4a. Mean (±SD) Baseline (pre-dofetilide) QTc Intervals During Modified Krebs-Henseleit Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

4b. Mean (±SD) Maximum QTc Intervals During Dofetilide Perfusion in Hearts From Progesterone and Placebo-Treated Rabbits

SD = Standard deviation

Figure 5.

Mean (± SEM) QT intervals During the 30-minute Period of Dofetilide Perfusion

----- Progesterone

————— Placebo

Overall p value = 0.04

*Tukey's post-hoc p = 0.04

**Tukey's post-hoc p = 0.008

SEM = Standard error of the mean

Table 1.

Median (Range) Serum Hormone Concentrations in a Subset of Rabbits

Hormone concentration	Progesterone (n=14)	Placebo (n=17)	p
Progesterone (ng/mL)	3.8 (2.8–5.1)	0.7 (0.4–1.7)	<0.0001
Estradiol (pg/mL)	58 (22–72)	53 (34–62)	0.79
Progesterone:estradiol ratio	68 (48–116)	11 (9–24)	<0.0001