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Effect of Transdermal Testosterone and Oral Progesterone on Drug-Induced QT Interval Lengthening in Older Men: A Randomized, Double-Blind, Placebo-Controlled Crossover-Design Study

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While female sex is a risk factor for torsades de pointes,[1] 29-44% of drug-induced cases occur in men.[2,3] Older age is also a risk factor.[1] Preclinical studies have shown that testosterone and progesterone protect against drug-induced prolongation of ventricular repolarization, early afterdepolarizations and arrhythmias.[4] Oral progesterone shortens QT intervals and attenuates drug-induced QT lengthening in young women.[5] We hypothesized that transdermal testosterone and oral progesterone attenuate drug-induced QT interval lengthening in older men.

This prospective, randomized, double-blind, placebo-controlled three-way crossover-design study was approved by the Indiana University IRB and conducted from July 2015 – October 2017 (ClinicalTrial.gov Identifier:). Exclusion criteria: history of prostate or breast cancer; benign prostatic hyperplasia; weight <60 or >135 kg; potassium <3.6 mEq/L; magnesium <1.8 mg/dL; hematocrit <26%; hepatic transaminases >3x ULN; baseline Bazett's-corrected QTc >450 ms; heart failure (LVEF <40%); family/personal history of long QT syndrome, arrhythmias or sudden cardiac death; permanently paced ventricular rhythm; taking QT-prolonging drugs or strong CYP3A inhibitors. Subjects provided written informed consent.

Men ≥ 65 years of age received, for 7 days, in randomized order: a) Transdermal testosterone 100mg (1% Androgel®) every morning and 2 placebo capsules every evening,

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Data sharing: Study materials and summary data are available at ClinicalTrials.gov and can be accessed at https://clinicaltrials.gov/ct2/show/NCT02513940?term=Tisdale&rank=2

DISCLOSURES

The authors report no relevant financial, personal or professional relationships with other people or organizations.

b) Oral progesterone 400mg (2×200mg capsules, Teva Pharmaceuticals) every evening and placebo transdermal gel every morning, or c) Placebo transdermal gel every morning and 2 placebo capsules every evening.

On the morning after the 7th day, subjects received a 10-minute intravenous infusion of the QT-lengthening drug ibutilide (0.003 mg/kg). Three 12-lead ECGs were obtained ~ 1 minute apart at baseline (pre-ibutilide), end-of-infusion, and at 5, 10, 15, 20, 30, and 45 minutes and 1, 2, 4, 6, and 8 hours post-infusion. Lead II QT intervals were measured by one investigator (blinded to treatment phases) using computerized high-resolution electronic calipers and the tangent method. QT and RR intervals were averaged over 3 consecutive complexes. QT intervals were Fridericia (QT_F)- and Framingham (QT_{Fram})-corrected. Linear mixed effects modeling was performed, where treatment arms and time periods were fixed effects and the subjects were random effects. When overall p values were significant, pairwise comparisons were performed. Serum concentration data were log-transformed.

Seventy-seven subjects were screened; 16 declined and 39 met ≥1 exclusion criterion. Twenty-two subjects consented; 8 subsequently met ≥1 exclusion criterion. Fourteen subjects were enrolled and completed all study phases. Mean age: 73±6 years (65-86); 13 white, 1 black. Mean weight: 90±16 kg; mean ibutilide dose: 0.27±0.05 mg. There was no significant difference in median (IQR) maximum serum ibutilide concentration between the testosterone, progesterone and placebo phases [955 (679, 1921) vs 1135 (632, 1526) vs 885 (646, 1430) pg/mL, p=0.82]. Median serum testosterone concentration was higher during the testosterone phase [678 (430,1017) vs 258 (227, 276) vs 272 (219,335) ng/dL, p<0.001]. Median serum progesterone concentration was higher during the progesterone phase [18.9 (15.3,23.7) vs 0.45 (0.30,0.60) vs 0.40 (0.30,0.60) ng/mL, p<0.001].

Median pre-ibutilide heart rates (HRs) during testosterone, progesterone and placebo phases were 57 (54, 67) vs 60 (53, 65) vs 58 (55, 66) bpm (p=0.99). HRs were similar, and not significantly different across treatment phases, at the end-of-infusion and one-hour post-infusion. Post-ibutilide QT_F and QT_{Fram} during testosterone, progesterone and placebo phases are presented in Figure 1, panels A&B. Pre-ibutilide QT_F and QT_{Fram} were not significantly different between the testosterone, progesterone or placebo phases (QT_F: 393±19 vs 399±16 vs 399±13 ms, p=0.09; QT_{Fram}: 392±19 vs 397±12 vs 397±18 ms, p=0.22). Maximum post-ibutilide QT_F and QT_{Fram} intervals were lowest during the testosterone phase (Figure 1, panels C&D). There was no significant difference in maximum QT_F or QT_{Fram} between progesterone and placebo.

Transdermal testosterone decreased the area under the QT interval effect curves (AUEC) one-hour post-ibutilide ($AUEC_{0\text{-}1.17}$, accounting for the 10-minute infusion) compared to progesterone and placebo (QT_F: 471±24 vs 480±24 vs 483±18 ms•hr; overall p=0.0003, p≤0.002, testosterone vs placebo and testosterone vs progesterone; QT_{Fram}: 469±23 vs 477±25 vs 482±17 ms•hr, overall p=0.0005; p≤0.007 testosterone vs placebo and testosterone vs progesterone). Progesterone did not significantly affect QT_F or QT_{Fram} $AUEC_{0\text{-}1.17}$ vs placebo.

Transdermal testosterone also attenuated the $AUEC_{0\text{-}8.17}$, indicating a more prolonged effect (QT_F: 3255±173 vs 3304±145 vs 3335±142 ms•hr; overall p=0.001, p≤0.02, testosterone vs placebo and testosterone vs progesterone; QT_{Fram}: 3234±160 vs 3289±146 vs 3328±130 ms•hr, overall p<0.0001; p≤0.003 testosterone vs placebo and testosterone vs progesterone). Progesterone did not significantly influence QT_F $AUEC_{0\text{-}8.17}$ versus placebo (p=0.10). However, the difference between progesterone and placebo on QT_{Fram} $AUEC_{0\text{-}8.17}$ was significant (p=0.03). Adverse effects included fatigue (progesterone, n=1) and mild rash (transdermal placebo, n=1).

In conclusion, despite a small sample, our results suggest that transdermal testosterone attenuates drug-induced QT lengthening in older men. We cannot rule out an effect of oral progesterone on attenuation of drug-induced QT lengthening. These findings support larger studies investigating the efficacy, safety and feasibility of transdermal testosterone and oral progesterone for attenuating drug-induced QT interval lengthening in older men with risk factors who require therapy with QT-prolonging drugs.

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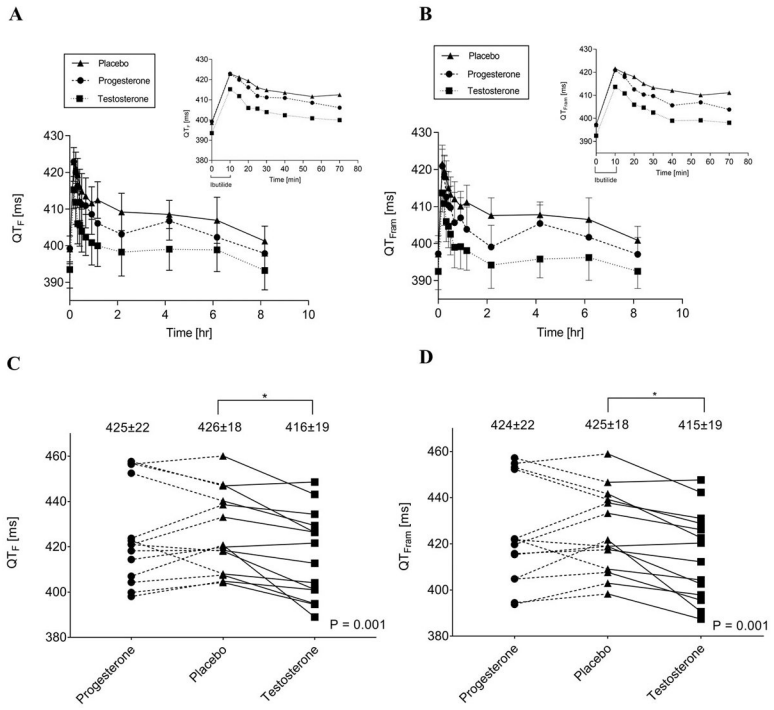

Figure 1.

Effect of transdermal testosterone and oral progesterone on drug-induced QT interval lengthening.

Panel A. Mean QT_F intervals during and for 8 hours (± SEM) and 1 hour (inset) after a 10-minute infusion of ibutilide 0.003 mg/kg in testosterone, progesterone and placebo phases, Panel B. Mean QT_{Fram} intervals during and for 8 hours (± SEM) and 1 hour (inset) after a 10-minute infusion of ibutilide 0.003 mg/kg in testosterone, progesterone and placebo phases. Panel C. Lead II maximum QT_F interval after ibutilide 0.003 mg/kg during progesterone, placebo and testosterone phases (mean ± SD), and Panel D. Lead II maximum QT_{Fram} interval after ibutilide 0.003 mg/kg during progesterone, placebo and testosterone phases (mean ± SD).

QT_F = Fridericia-corrected QT interval; QT_{Fram} = Framingham-corrected QT interval; SD = Standard deviation; SEM = Standard error of the mean

* $p<0.002$, testosterone vs placebo and testosterone vs progesterone

■ Testosterone

● Progesterone

▲ Placebo