Transdermal Testosterone Administration Attenuates Drug-Induced Lengthening of Early and Late Repolarization in Older Men

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QT Interval: ECG representation of ventricular depolarization and repolarization

J-Tpeak and Tpeak-Tend: ECG representation of early vs late ventricular repolarization

Sex Differences in Ventricular Repolarization

- **GAP IN KNOWLEDGE:** The effects of progesterone and testosterone on early and late ventricular repolarization associated with attenuation of drug-induced QT-interval lengthening are still unknown.
- **HYPOTHESIS:** Transdermal testosterone and oral progesterone attenuate drug-induced lengthening of both the J-Tpeakc interval (early repolarization) and Tpeak-Tend interval (late repolarization) in older men.

Female sex is a risk factor for drug-induced QT prolongation, however 29-46% of reported cases of TdP have occurred in men.

Older age is a risk factor for drug-induced QT prolongation due to declining testosterone concentrations in men.

Administration of transdermal testosterone attenuates drug-induced QT lengthening in men ≥65 years.

Oral progesterone attenuates drug-induced QT interval lengthening in young women during the menses phase.

Randomized, Double-Blind, Placebo-Controlled Crossover-Design Study

Men ≥ 65 yrs (n=14)

Screening Visit/Baseline ECGs

Randomization

Crossover

Placebo gel qam & Progesterone 400 mg qhs x 7 days

Testosterone gel 1% (100 mg) qam & placebo capsules qhs x 7 days

Placebo gel qam & placebo capsules qhs daily x 7 days

ICRC Visit

1) Baseline ECGs and blood draw
2) Infusion of sub-therapeutic dose QT prolonging drug Ibutilide (0.003 mg/kg)
3) Collection of ibutilide samples and ECGs (0-8 hr)

Washout (minimum 13 days)
Study Methods

- ECG intervals were determined manually from lead II
  - Computerized electronic caliper (EP Calipers 1.6)
  - Investigator (E.T.M.) blinded to the subjects’ assigned groups

- ECG interval heart rate corrections
  - \( J-T_{\text{peakc}} = J-T_{\text{peak}} / (RR)^{0.58} \)

- Primary Outcome Measures
  - Baseline \( J-T_{\text{peakc}} \) and \( T_{\text{peak}}-T_{\text{end}} \) intervals
  - Maximum \( J-T_{\text{peakc}} \) and \( T_{\text{peak}}-T_{\text{end}} \) intervals
  - Area under the effect (\( J-T_{\text{peakc}} \) and \( T_{\text{peak}}-T_{\text{end}} \) intervals)-time curves for 1.17 and 8.17 hours during and after ibutilide infusion (AUEC\(_0-1.17\) and AUEC\(_0-8.17\))

- Statistical analyses (SPSS Inc, Chicago, IL)
  - Repeated-measures ANOVA with Bonferroni post-hoc test
  - Data are presented as means, SD in table and SEM in figures
Subject Recruitment

Assessed for eligibility (n=77)
- Excluded (n=55)
  - Taking QT interval-prolonging medication (n=2)
  - Atrial fibrillation (n=20)
  - Current use of testosterone (n=4)
  - HFrEF (n=4)
  - Dialysis (n=1)
  - < 65 years of age (n=2)
  - Prostate cancer (n=3)
  - Treatment for BPH (n=3)
  - Declined to participate (n=16)

Consented to participate (n=22)

Randomized (n=14)
- Excluded (n=8)
  - QTc interval > 450 ms: n=5
  - Atrial fibrillation: n=1
  - Paced ventricular rhythm: n=1
  - Treatment for BPH: n=1

Assessed for Outcome Measures (n=14)
## Serum Hormone and Ibutilide Concentrations During Testosterone, Progesterone and Placebo Phases

<table>
<thead>
<tr>
<th></th>
<th>Testosterone</th>
<th>Progesterone</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum testosterone concentration (ng/dL)</td>
<td>904 ± 789*</td>
<td>261 ± 44</td>
<td>267 ± 77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum progesterone concentration (ng/mL)</td>
<td>0.5 ± 0.2</td>
<td>20.9 ± 11.5§</td>
<td>0.4 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum peak ibutilide concentration at end of infusion (ng/mL)</td>
<td>1236 ± 762</td>
<td>1144 ± 587</td>
<td>1121 ± 600</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Bonferroni-adjusted P-value < 0.05
*Testosterone vs Placebo, §Progesterone vs Placebo
Results – Early Repolarization

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<tbody>
<tr>
<td>Baseline J-Tpeakc (ms)</td>
<td>216 ± 23*</td>
<td>226 ± 28</td>
<td>227 ± 21</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximum J-Tpeakc (ms)</td>
<td>233 ± 22*</td>
<td>246 ± 29</td>
<td>249 ± 24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum % change in J-Tpeakc from baseline (%)</td>
<td>8.2 ± 4.8</td>
<td>9.3 ± 5.1</td>
<td>8.6 ± 4.1</td>
<td>0.70</td>
</tr>
<tr>
<td>AUEC₀-1.17hr J-Tpeakc (ms·hr)</td>
<td>262 ± 25*</td>
<td>273 ± 32</td>
<td>277 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUEC₀-8.17hr J-Tpeakc (ms·hr)</td>
<td>1797 ± 176*</td>
<td>1881 ± 207</td>
<td>1915 ± 191</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bonferroni-adjusted P-value < 0.05: * Testosterone vs. Placebo
Results – Late Repolarization

<table>
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<tr>
<td>Baseline Tpeak-Tend (ms)</td>
<td>70 ± 8</td>
<td>75 ± 13</td>
<td>73 ± 11</td>
<td>0.16</td>
</tr>
<tr>
<td>Maximum Tpeak-Tend (ms)</td>
<td>80 ± 12*</td>
<td>89 ± 18</td>
<td>87 ± 15</td>
<td>0.008</td>
</tr>
<tr>
<td>Maximum % Change Tpeak-Tend from Baseline (%)</td>
<td>14.5 ± 10.1</td>
<td>18.2 ± 9.1</td>
<td>18.0 ± 11.4</td>
<td>0.52</td>
</tr>
<tr>
<td>AUEC&lt;sub&gt;0-1.17hr&lt;/sub&gt; Tpeak-Tend (ms·hr)</td>
<td>86 ± 13*</td>
<td>92 ± 15</td>
<td>93 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>AUEC&lt;sub&gt;0-8.17hr&lt;/sub&gt; Tpeak-Tend (ms·hr)</td>
<td>583 ± 79*</td>
<td>628 ± 95</td>
<td>626 ± 85</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Bonferroni-adjusted P-value < 0.05: * Testosterone vs. Placebo
Conclusion & Clinical Implications

- Transdermal testosterone attenuates drug-induced lengthening of both early and late ventricular repolarization.
- Oral progesterone does not attenuate drug-induced lengthening of early or late ventricular repolarization.
- Transdermal testosterone may be effective for attenuating QT interval lengthening associated with drugs that prolong early repolarization, late repolarization, or both.