The Combined Use of Ibutilide as an Active Control With Intensive Electrocardiographic Sampling and Signal Averaging as a Sensitive Method to Assess the Effects of Tadalafil on the Human QT Interval

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OBJECTIVES
This study was designed to evaluate effects of tadalafil, a phosphodiesterase-5 inhibitor used for the treatment of erectile dysfunction (ED), on the QT interval.

BACKGROUND
Cardiovascular disease is common in men with ED. Men with cardiovascular disease and ED may have decreased cardiac repolarization reserve.

METHODS
Effects of tadalafil (100 mg by mouth), ibutilide (0.002 mg/kg intravenously), and placebo on the QT interval in healthy men were compared (placebo and tadalafil [n = 90], with a subset [n = 61] receiving all treatments; mean age 30 years, range 18 to 53 years). Electrocardiographic sampling was done for two days before treatment and on treatment days. The QT was corrected for RR interval with five correction methods, including an individual correction (QTcI). Plasma concentrations of tadalafil were measured to evaluate concentration-QT effect relationships.

RESULTS
At the time corresponding to maximum plasma concentration of tadalafil, the mean difference in the change in QTcI between tadalafil and placebo was 2.8 ms; tadalafil was equivalent to placebo (a priori, upper limit of 90% confidence interval <10 ms [actual = 4.4 ms]; post hoc, upper limit of 95% confidence interval <5 ms [actual = 4.8]). The active control, ibutilide, significantly increased QTcI by 6.9 and 8.9 ms compared with tadalafil and placebo, respectively. Similar statistical results were obtained with four additional QT correction methods. No subject had a QTcI ≥450 ms or an increase in QTcI ≥30 ms with any treatment.

CONCLUSIONS
Based on the a priori statistical test of equivalence, placebo and high-dose tadalafil produced equivalent effects on the QT interval. This study reliably discerned 5- to 10-ms changes in corrected QT in the ibutilide active control group. (J Am Coll Cardiol 2005;46:678–87)

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Tadalafil, a phosphodiesterase-5 (PDE5) inhibitor, is an effective treatment for erectile dysfunction (ED) (1). The prevalence of heart disease is high among men with ED (2,3). Patients with heart disease may have reduced cardiac repolarization reserve (4) and be at increased risk for arrhythmia when taking medications that prolong ventricular repolarization. Because many patients treated for ED will have heart disease, the effects of tadalafil on ventricular repolarization were evaluated.

Although there is an association between increases in the QT interval and potentially lethal ventricular arrhythmias (e.g., Torsades de Pointes) (4,5), there is debate concerning what constitutes a clinically relevant increase in the QT interval (5,6). The cardiovascular adverse events reported after regulatory approval of terfenadine and cisapride (6–9) have contributed to ongoing efforts at national (U.S. Food and Drug Administration) and international (Committee for Proprietary Medicinal Products and International Committee on Harmonization) levels to develop standards for clinical trials designed to demonstrate an “absence of significant effect” on ventricular repolarization during new
The study had three primary objectives: 1) to test that tadalafil is equivalent to placebo with respect to changes in the QT interval corrected using a subject-specific individual correction (QTcI) (12,17); and to test that, 2) placebo and 3) tadalafil produce significantly smaller increases in the QTcI compared to the active control ibutilide (when ibutilide increases QTcI by 5 to 10 ms). Study design: treatments. Subjects were assigned by random allocation to receive one of two sequences of treatment: either a two-way crossover (placebo, tadalafil) or a three-way crossover (placebo, tadalafil, ibutilide) (Fig. 1). The number of subjects assigned to each sequence of treatments (placebo-tadalafil = 32; placebo-tadalafil-ibutilide = 67)
was sufficient to achieve the total number of subjects treated with both drugs for the three statistical drug pair comparisons specified by the prospective statistical analysis plan (total completed: placebo vs. tadalafil = 90; tadalafil vs. ibutilide = 62; placebo vs. ibutilide = 61) (see “Sample size” section and Fig. 1). The order of treatment administration within the two treatment sequences was also randomized. Each treatment was administered on a separate day and there was a washout period of at least 12 days between each treatment.

For the purpose of analysis (i.e., comparison of tadalafil vs. placebo), the data from subjects receiving only placebo and tadalafil were combined with the placebo and tadalafil data from subjects receiving all three treatments (analysis included all subjects who received placebo and tadalafil) (Fig. 1). Those subjects receiving all three treatments were included in the ibutilide versus placebo and ibutilide versus tadalafil comparative analyses because these subjects received ibutilide and placebo as well as ibutilide and tadalafil.

A single oral dose of tadalafil 100 mg and placebo was studied. For tadalafil, 100 mg is five times the maximum approved dose (i.e., 20 mg given a maximum of once daily). The dose of ibutilide (0.002 mg/kg intravenously over 10 min) produced an increase in QTcB in the desired range (5 to 10 ms) and was selected on the basis of an open-label study of ibutilide and placebo in a separate cohort of subjects (for real-time patient management, QTcB was used to analyze changes in the QT interval). The ibutilide infusion was stopped if the QTcB interval increased by ≥12 ms on two consecutive ECG readings or by ≥30 ms on one ECG reading (13 of 67 ibutilide infusions were stopped early on the basis of these criteria).

Personnel were blinded to placebo and tadalafil treatments but were not blinded to ibutilide. Treatments were administered at either 8 or 10 AM and were administered at the same time of day across treatments for each subject.

**Study design: ECG recording and assessment.** All studies were performed in clinical-pharmacology inpatient settings. For 2 days before placebo or tadalafil dosing (Fig. 2), baseline ECGs were recorded at 0, 3, 4, 6, 9, 12, and 24 h. On tadalafil or placebo treatment days, ECGs were recorded before dose and at 3, 4, 6, and 24 h after dose. Blood samples were obtained after recording ECGs to measure plasma concentrations of tadalafil and tadalafil methylcatechohol glucuronide (metabolite has no PDE5 inhibitor activity).

For each time point (indicated by an X in Fig. 2), the QT was calculated as the mean of 10 ECGs. Averaging the values from 10 ECGs optimized signal-to-noise ratio and reduced beat-to-beat variations in the QT measurement as determined in our pilot open-label study used to select the dose of ibutilide. The selection of 10 ECGs for the purpose of signal averaging was based on the premise that the largest number of ECGs that could be practically obtained and contribute to such signal averaging would provide the most accurate signal. The “maximum effect” of ibutilide on QT was calculated as the mean of 10 ECGs at the end of ibutilide infusion (Fig. 2). If the ibutilide infusion was

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**Figure 1.** Subject disposition. Subjects were assigned by random allocation to receive one of two sequences of treatment, either a two-way crossover (placebo, tadalafil) or a three-way crossover (placebo, tadalafil, ibutilide). The number of subjects assigned to each sequence of treatments (placebo-tadalafil, n = 32; placebo-tadalafil-ibutilide, n = 67) was sufficient to achieve the total number of subjects treated with both drugs for the three statistical drug pair comparisons specified by the prospective statistical analysis plan (total receiving: placebo vs. tadalafil = 90; tadalafil vs. ibutilide = 62; placebo vs. ibutilide = 61). Reasons for discontinuation are listed in the Results section. One subject received treatment with ibutilide and two treatments with placebo (rather than treatment with tadalafil and placebo). This subject was included in the intent-to-treat ibutilide-placebo, tadalafil-placebo, and tadalafil-ibutilide comparative analyses. *Not included in any of the comparative analyses because subjects did not receive at least two treatments.
stopped early, the ECGs recorded in the 10 min following
the termination of the infusion were used to calculate
ibutilide-induced changes in the QT interval.

Electrocardiograms were collected electronically on
MAC5000 machines (GE Medical, Waukesha, Wiscon-
sin), sent to a central interpretive site (Cardioanalytics,
Plymouth, United Kingdom), and overread by one of three
technicians and one cardiologist (blinded to all treatments).
The QT interval was measured using median complexes
derived from the full 10 s of recording for each of the 12
leads (using the Marquette Universal System for Electro-
cardiography [MUSE] and the 12SL algorithm). The 12
median waveforms were then superimposed and aligned
using a template correction technique (CardioAnalytics).
The QT interval was measured onscreen using 12SL-
generated markers on the superimposed median waveform
complexes from the earliest deflection of the Q-wave to the
latest termination of the T-wave across all 12 ECG leads.
The earliest Q-wave deflection and the latest T-wave
termination could come from separate leads. The QT was
manually remeasured with onscreen calipers to confirm the
accuracy of the 12SL measurement. If the manual remea-
Surement was within 5 ms of the 12SL measurement, the
12SL measurement was deemed accurate (if >5 ms the
manual measurement was used).

The RR interval was determined from the MUSE/12SL-
calculated HR, and the accuracy was verified by manual
measurement. To verify the MUSE/12SL-generated HR, if
the rhythm appeared regular, the technician initially mea-
sured one RR interval, and if the rhythm appeared irregular,
the technician initially measured multiple RR intervals.
This interpretation of the rhythm regularity was a subjective
interpretation on the part of the technician. This initial
assessment was intended to provide only a first evaluation of
the accuracy of MUSE/12SL-generated HR. If this initial
assessment resulted in a HR value that differed from the
MUSE/12SL by ±5 beats/min, the technician would mea-
sure all RR intervals in the 10-s ECG recording to calculate
the HR. Of the 34,630 ECGs in the data set, a total of 6
ECGs (0.017%) required manual HR correction.

The QT was corrected for RR interval by fitting a linear
model to all baseline (drug-free) data and using the slope to
construct a subject-specific (individual) QT correction for-
mula (QTcI) (12,17).

Sample size. Sample size was based on an intrasubject
variability of 8.7 ms for uncorrected QT interval based on
review of Phase I studies supporting tadalafil registration.
Ninety subjects provided 99% power to declare equiva-
ience between tadalafil and placebo with respect to mean
change in QTcI when equivalence required the upper
limit of the two-sided 90% confidence interval (CI) for
the difference to be <10 ms (a priori definition of
equivalence) and 98% power for the difference to be <5
ms. The power was 97% when equivalence required the
upper limit of the two-sided 95% CI for the difference to
be <5 ms (post-hoc definition of equivalence, more
stringent than the a priori definition).

To demonstrate the superiority of tadalafil and placebo
to ibutilide with respect to mean change in the QTcI, 60
subjects provided 99% power to detect a mean difference
of 10 ms between treatments with a two-sided significance
level of 5%, and 87% power to detect a mean difference
of 5 ms with a two-sided significance level of 5%. The a priori
definition of significant difference was based on a two-sided
significance level of 5% (two-sided 95% confidence interval).

Figure 2. Study design and times of electrocardiogram (ECG) recording. At each time point indicated by an X, a 12-lead ECG was recorded for ≥10 s
at 1-min intervals for 10 min (total of 10 ECGs recorded at each time point). For ibutilide treatment days (bottom panel), at each time point indicated
by a filled circle, a single 12-lead ECG was recorded for ≥10 s. Administration of oral tadalafil and placebo was double blind and administration of
intravenous ibutilide was unblinded. × = 10 ECGs obtained at 1-min intervals; ● = single ECG.
Analysis of primary outcomes. TADALAFIL VERSUS PLACEBO AT T<sub>MAXH</sub>. For tadalafil and placebo, the change in QT<sub>cI</sub> was calculated as the change from before dose to T<sub>max</sub>h (time of maximum concentration of tadalafil for each subject) in two steps: first on baseline days and then on treatment days (baseline represented the average of two days of measurements). The change measured on baseline days was subtracted from the change on treatment days to give the change in QT<sub>cI</sub> due to treatment alone (this method corrected for any diurnal variation in QT<sub>cI</sub>) (18). The difference in QT<sub>cI</sub> was then calculated as (change after tadalafil) − (change after placebo).

TADALAFIL AND PLACEBO VERSUS IBUTILIDE AT T<sub>MAXH</sub>. Tadalafil and placebo were compared with ibutilide on the basis of the change from before dose to T<sub>max</sub>h for tadalafil and placebo and the change from before dose to maximum effect for ibutilide.

Analysis of secondary outcomes. The changes in QT<sub>cI</sub> at 3, 4, 6, and 24 h post-tadalafil were compared with placebo using the analysis described earlier for tadalafil minus placebo at T<sub>max</sub>h.

Additional analyses. Four additional QT correction methods were applied: Bazett’s (QT<sub>cB</sub>) (16), Fridericia’s (QT<sub>cF</sub>) (19), a nonlinear “population-based” formula ([QT/RR<sup>0.14</sup>]) (QT<sub>cP</sub>) (20), and a “model-based” formula that computed the difference in change in absolute QT between treatments with RR included as a covariate (QT<sub>cM</sub>) (21).

The relationships between changes in QT<sub>cI</sub> and plasma concentrations of tadalafil and tadalafil methylcatechol glucuronide (sum of free and bound concentration) were also analyzed. Treatment-emergent adverse events were reported and were collected based on spontaneous complaints and open-ended questioning.

Statistical methods. A mixed-model analysis of variance was used to analyze differences between treatments with respect to changes in QT<sub>cI</sub> with terms for treatment (fixed effect), subject (random effect), time (fixed effect), subject by treatment (random effect), subject by time (random effect), and treatment by time (fixed effect) (22). SAS 8.2 software (SAS Institute, Cary, North Carolina) was used for all statistical analyses and the mixed models were fit using the MIXED procedure. The relationships between changes in QT<sub>cI</sub> and plasma concentrations were analyzed by estimating the slope of a linear regression model and computing the p value.

RESULTS

Subject demographics. Demographics were comparable among the intent-to-treat population (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Tadalafil (n = 93)</th>
<th>Placebo (n = 91)</th>
<th>Ibutilide (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean ± SD)</td>
<td>30 ± 8.8</td>
<td>30 ± 8.7</td>
<td>31 ± 8.5</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;, mean ± SD)</td>
<td>24.7 ± 2.7</td>
<td>24.7 ± 2.7</td>
<td>24.5 ± 2.7</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88 (95%)</td>
<td>86 (95%)</td>
<td>61 (91%)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
<td>6 (9%)</td>
</tr>
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<td>Tobacco use, n (%)</td>
<td>23 (25%)</td>
<td>23 (25%)</td>
<td>18 (27%)</td>
</tr>
<tr>
<td>Alcohol use, n (%)</td>
<td>68 (73%)</td>
<td>68 (75%)</td>
<td>50 (75%)</td>
</tr>
</tbody>
</table>

A total of 99 subjects entered the study. The n values represent the intent-to-treat population that received the indicated treatment (subjects were randomized to receive two or all three treatments). Tobacco use = 1 to 5 cigarettes/day or 3 to 25 g tobacco/week; Alcohol use = 1 to 24 U/week (1 U = 1.5 oz 80 proof equivalent).

by an adverse event (fractured ankle, considered unrelated to study treatment), and five failed to continue to meet inclusion criteria (low serum calcium [n = 2], first-degree atrioventricular block [n = 1], positive drug of abuse screen [n = 1], and QT<sub>c</sub> could not be read accurately owing to the presence of U waves [n = 1]). Subjects that discontinued but received one treatment included tadalafil (n = 2), placebo (n = 1), and ibutilide (n = 5); one subject discontinued after receiving two treatments (tadalafil and ibutilide) (Fig. 1). Additionally, one subject received treatment with ibutilide and two treatments with placebo (rather than treatment with tadalafil and placebo). This subject was included in the intent-to-treat ibutilide-placebo, tadalafil-placebo, and tadalafil-ibutilide comparative analyses.

Effects of tadalafil, placebo, and ibutilide. The top half of Table 2 shows the baseline mean HR, absolute QT, and QT<sub>cI</sub> measured before treatment with placebo and tadalafil. Over a 24-h period (average of 2 days), baseline HR varied by 4.6 beats/min, absolute QT interval by 9.9 ms, and QT<sub>cI</sub> by 3.7 ms. The bottom half of Table 2 shows the effect of tadalafil, placebo, and ibutilide on the mean HR, QT, and QT<sub>cI</sub>. The mean differences between treatments at T<sub>max</sub>h are shown in the top half of Table 3. For tadalafil minus placebo, the mean difference in the change in QT<sub>cI</sub> was 2.8 ms. The effect of tadalafil was statistically equivalent to placebo (both a priori upper 90% CI of 4.4 ms and more stringent post-hoc upper 95% CI of 4.8 ms did not exceed either the a priori 10 ms or more stringent post hoc 5-ms limits for declaring equivalence). The mean difference for ibutilide minus placebo was 8.9 ms and for ibutilide minus tadalafil was 6.9 ms (significantly different; 95% CIs did not contain 0). Because the mean difference between ibutilide and placebo was significant and <10 ms, this study had the sensitivity to identify as significant small differences between treatments in the change in QT<sub>cI</sub>.

The mean differences in the changes in QT<sub>cI</sub> for tadalafil minus placebo from 3 to 24 h post-dosing ranged from 1.1 to 3.5 ms (bottom half of Table 3). The effects of tadalafil were statistically equivalent to placebo at all time points (upper 90% and 95% CIs <10 ms).

Means showed the mean difference between treatments in
the change in QT interval at $T_{\text{max},h}$ using five correction methods. The results with our a priori statistical tests resulted in identical conclusions (i.e., tadalafil is equivalent to placebo, and ibutilide evoked significantly greater increases in the corrected QT interval compared with placebo or tadalafil), regardless of the QT correction method employed. The HR increased slightly after tadalafil and ibutilide compared with placebo and decreased after ibutilide compared with tadalafil (Table 3, top). Because Bazett's method inadequately corrects for changes in HR (23), the mean treatment differences using Bazett's correction were overestimated for the tadalafil-placebo and ibutilide-placebo comparisons and were underestimated for the ibutilide-tadalafil comparison (Table 4).

Categorical change results. No subject had a QTcI interval $\geq 450$ ms or an increase in the QTcI interval from baseline of $\geq 30$ ms with placebo, tadalafil, or ibutilide treatment.

Mean change in QTcI versus tadalafil plasma concentration. There was no significant relationship between changes in the QTcI interval and plasma concentration of tadalafil (slope = 0.001; $p = 0.488$) (Fig. 3A) or its metabolite (slope = $-0.003$; $p = 0.090$) (Fig. 3B).

Safety. The treatment-emergent adverse events in $\geq 5\%$ of subjects when taking tadalafil 100 mg (n = 93) were headache (76%), back pain (23%), nasal congestion (22%), myalgia (19%), flushing (16%), pain in limb (13%), dizzi-ness (11%), arthralgia (10%), spontaneous penile erection (10%), nausea (9%), and eye pain (5%). Headache was reported by 12% of subjects when taking placebo (n = 91). The adverse events reported for tadalafil 100 mg are consistent with those expected after administration of a PDE5 inhibitor (e.g., effects due to mild vasodilation) at a dose five-fold greater than the maximum therapeutic dose.

Post-hoc analyses. The 95% CI for the 2.8-ms mean difference in the change in QTcI at $T_{\text{max},h}$ for tadalafil minus placebo was 0.9 to 4.8 ms (Table 3, top). Tadalafil was statistically equivalent to placebo based on our a priori equivalence test (upper limit of 90% CI $< 10$ ms) as well as based on the upper limit of 95% CI $< 5$ ms (post hoc). However, 2.8 ms represents a significant difference using a conventional inferential test (95% CI did not contain zero). A 2.8-ms increase in QTcI is below the threshold of 10 ms recognized as likely to impart some arrhythmic risk as well as below the 5-ms change often observed with placebo (12,13) and believed to be without meaningful risk.

One subject, randomly selected to receive all three treatments, inadvertently received placebo during the tadalafil period. The inferential conclusions did not change when the data were reanalyzed after excluding this subject.

**DISCUSSION**

Tadalafil was equivalent to placebo with respect to effects on ventricular repolarization as assessed by the QTc interval. Additionally, the effect of tadalafil on QTc was significantly

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**Table 2.** HR, QT, and QTcI at Baseline and After Treatment.

<table>
<thead>
<tr>
<th></th>
<th>0-h</th>
<th>1-h</th>
<th>2-h</th>
<th>3-h</th>
<th>4-h</th>
<th>6-h</th>
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<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>63.5</td>
<td>389.3</td>
<td>389.0</td>
<td>390.0</td>
<td>392.5</td>
<td>392.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>64.4</td>
<td>389.0</td>
<td>389.3</td>
<td>390.3</td>
<td>392.9</td>
<td>392.9</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>65.8</td>
<td>392.0</td>
<td>392.2</td>
<td>393.2</td>
<td>393.2</td>
<td>393.2</td>
</tr>
</tbody>
</table>

Values represent means from the intent-to-treat population. Baseline HR, QT, and QTcI are the mean of 10 electrocardiograms obtained at 1-min intervals and averaged over 2 days of baseline recordings. Treatment HR, QT, and QTcI are the mean of 10 ECGs obtained at 1-min intervals. Baseline (ranges) — HR (57.6 to 67.8 beats/min), QT (313 to 390 ms), QTcI (390 to 430 ms). Treatment (ranges) — HR (57.0 to 67.0 beats/min), QT (313 to 390 ms), QTcI (390 to 430 ms). "0 h" was the time immediately before the treatment administration on treatment days; $T_{\text{max},h}$ was the specific hour (of hours 3, 4, or 6) at which the tadalafil concentration was highest for each subject on the actual day of treatment. Ninety placebo-treated subjects also received tadalafil, thus for the $T_{\text{max},h}$ time points n = 93. Placebo and ibutilide groups were reanalyzed after excluding this subject. The HR, QT, and QTcI results are given throughout the period of Tadalafil, with the HR, QT, and QTcI in the third column. The treatment comparisons used the terms "significant", "not significant", and "equivocal" to describe the results of the statistical tests. 

HR = heart rate; QT = QT interval; QTcI = individual corrected QT.
Table 3. Mean Differences Between Treatments in Change in QTc, HR, and QTcI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ΔQTc (ms)</th>
<th>ΔQT (ms)</th>
<th>ΔHR (beats/min)</th>
<th>QTc (CIs)</th>
<th>QT (CIs)</th>
<th>HR (CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadalafil minus placebo (n = 90)</td>
<td>T_maxh</td>
<td>2.8</td>
<td>3.1 (1.2, 4.4)</td>
<td>(−5.5, 0.7)</td>
<td>(1.7, 4.5)</td>
<td></td>
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<tr>
<td>Ibutilde minus placebo (n = 61)</td>
<td>T_maxh</td>
<td>8.9</td>
<td>5.7 (6.5, 11.2)</td>
<td>(1.3, 10.1)</td>
<td>(0.2, 3.5)</td>
<td></td>
</tr>
<tr>
<td>Ibutilde minus tadalafil (n = 62)</td>
<td>T_maxh</td>
<td>6.9</td>
<td>10.9 (4.6, 9.2)</td>
<td>(6.4, 15.4)</td>
<td>(−4.1, −0.5)</td>
<td></td>
</tr>
<tr>
<td>Tadalafil minus placebo (n = 90)</td>
<td>3-h</td>
<td>3.3</td>
<td>3.5 (1.7, 4.9)</td>
<td>(−6.3, 0.1)</td>
<td>(2.0, 4.9)</td>
<td></td>
</tr>
<tr>
<td>Tadalafil minus placebo (n = 90)</td>
<td>4-h</td>
<td>3.1</td>
<td>2.1 (1.4, 5.2)</td>
<td>(−6.9, 0.8)</td>
<td>(1.7, 5.2)</td>
<td></td>
</tr>
<tr>
<td>Tadalafil minus placebo (n = 90)</td>
<td>6-h</td>
<td>3.5</td>
<td>3.0 (1.9, 5.2)</td>
<td>(−3.4, 3.0)</td>
<td>(1.5, 4.4)</td>
<td></td>
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<tr>
<td>Tadalafil minus placebo (n = 90)</td>
<td>24-h</td>
<td>1.1</td>
<td>5.7 (−0.6, 2.7)</td>
<td>(−11.3, −4.9)</td>
<td>(4.2, 7.1)</td>
<td></td>
</tr>
</tbody>
</table>

Changes (Δ) represent mean differences for the comparisons indicated in the first column. The 90% and 95% confidence intervals (CIs) are shown for the mean differences (tadalafil minus placebo) and the 95% CIs are shown for the ibutilide comparisons. T_maxh was the specific hour (of hours 3, 4, or 6) at which the tadalafil plasma concentration was highest for each subject on the actual day of treatment.

Abbreviations as in Table 2.

Table 4. Mean Difference Between Treatments in the Change in QTc Measured at T_maxh Using Five QT Correction Methods

<table>
<thead>
<tr>
<th></th>
<th>ΔQTc Tadalafil Minus Placebo</th>
<th>ΔQTc Ibutilde Minus Placebo</th>
<th>ΔQTc Ibutilde Minus Tadalafil</th>
<th>CIs Tadalafil Minus Placebo</th>
<th>CIs Ibutilde Minus Placebo</th>
<th>CIs Ibutilde Minus Tadalafil</th>
</tr>
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<tbody>
<tr>
<td>Individual</td>
<td>2.8</td>
<td>8.9</td>
<td>6.9</td>
<td>(1.2, 4.4)</td>
<td>(6.5, 11.2)</td>
<td>(4.6, 9.2)</td>
</tr>
<tr>
<td>Population</td>
<td>3.5</td>
<td>9.5</td>
<td>7.0</td>
<td>(2.0, 5.1)</td>
<td>(7.2, 11.8)</td>
<td>(4.9, 9.2)</td>
</tr>
<tr>
<td>Bazett</td>
<td>6.6</td>
<td>11.5</td>
<td>5.0</td>
<td>(4.6, 8.7)</td>
<td>(8.8, 14.1)</td>
<td>(2.5, 7.5)</td>
</tr>
<tr>
<td>Fridericia</td>
<td>3.5</td>
<td>9.5</td>
<td>7.1</td>
<td>(1.9, 5.1)</td>
<td>(7.2, 11.8)</td>
<td>(4.9, 9.2)</td>
</tr>
<tr>
<td>Model based</td>
<td>3.3</td>
<td>9.6</td>
<td>6.8</td>
<td>(1.7, 5.0)</td>
<td>(7.3, 12.0)</td>
<td>(4.6, 9.1)</td>
</tr>
</tbody>
</table>

The 90% and 95% confidence intervals (CIs) are shown for the mean differences (tadalafil minus placebo) and the 95% CIs are shown for the ibutilide comparisons. T_maxh was the specific hour at which the tadalafil plasma concentration was highest for each subject on the actual day of treatment.

QTc = corrected QT.

less than that of the active control ibutilide. For ibutilide compared with placebo (i.e., the prospective evaluation of the study’s assay sensitivity), the difference in the change in QTcI of 8.9 ms was significant, with the actual sensitivity of the study (smaller difference that could be found significant) being at least as low as 6.5 ms (lower limit of the 95% CI).

This study employed techniques to increase the sensitivity of detecting any existent signal of QT prolongation. The study is unique in collecting a large number of ECGs (over 34,000) with signal averaging, obtaining intensive baseline ECG sampling, and using intravenous ibutilide as an active control. The combined use of these methodologies was intended to: 1) detect a small change in QTc if such a change was occurring; 2) allow a definitive conclusion that a change in QTc was not occurring within extremely small limits, and thus define an absence of change if such were the case; and 3) include a means to specify the sensitivity of detecting the presence or absence of a change in the QTc interval. Because this study was designed to demonstrate absence of effect (zero difference) within extremely tight margins (5 ms), we believed that substantial measurements would be necessary to overcome beat-to-beat variability and measurement error in the QT interval. Although we included more replicate ECG measurements than necessary for the signal-averaging methodology, at the onset of the study we did not know and had no basis for predicting the number required. The 10 replicate number accomplished the goal and also provided us with the basis for determining the number of ECGs necessary in a signal averaging process to overcome variability and measurement error. On the basis of this study, it is likely that three to six replicate ECGs at each time point would be sufficient for adequate signal averaging.

Concerning the protocol design, one must consider the ethics of conducting a study in which subjects are given an “active control” that is known to delay ventricular repolarization and that may impart some risk. An ideal active control should fulfill several criteria: 1) evoke only small, reliable increases in the QT interval (5 to 10 ms with small standard deviation); 2) produce effects on the QT interval that can be controlled in real time; and 3) have a short pharmacokinetic half-life and pharmacodynamic active period. Although oral medications that prolong the QT interval (e.g., moxifloxacin, sotalol, imipramine) are easy to administer, they may not produce mean QT changes in the desired range, they may result in excessive variability in the
change in QT across subjects, and their effects cannot be terminated quickly (24,25). By choosing low-dose ibutilide as the active control, effects on the QT interval were controlled in real time and began to decline approximately 10 min after stopping the infusion. The dose of ibutilide was below the therapeutic dose, but reliably produced the desired difference from placebo in change in QT across subjects (i.e., 8.9 ms). Furthermore, no subject had a QTcI ≥450 ms or an increase of ≥30 ms from before infusion in response to ibutilide. These results underscore that ibutilide, as used, met the criteria for a desirable and safe active control. Although low-dose ibutilide was not used as an active control, Rodriguez et al. (26) used it to compare the degree of QT interval prolongation between men and women and demonstrated that ibutilide could be used safely, producing only moderate increases in QTcB.

Limitations of the study included the following: 1) Inclusion of only healthy men with no known cardiac electrophysiologic risk factors. This population was part of the study design because an active control was administered, it was consistent with regulatory guidelines (9,10), and the objective of the study was to determine if tadalafil had direct effects on ventricular repolarization in the absence of any disease or drug interactions. 2) The study did not include women. Women are more likely than men to develop Torsades de Pointes after receiving drugs that prolong the QT interval (27,28). 3) The threshold for use of manually measured heart rate values of ≥5 beats/min (difference between manually measured and MUSE/12SL measured of ≥5 beats/min) could result in an error in the Bazett-corrected QT interval of over 20 ms in an individual ECG measurement. In this study, six (0.017%) individual ECGs showed such discrepancy between MUSE/12SL and hand measurements (all ECGs were both hand and machine measured). 4) Both the subject and the physician were unblinded to the ibutilide treatment (however, the cardiologist and technicians reading the ECGs were blinded to all treatments). Ideally, the active control should be fully blinded.

The equivalent effect of tadalafil and placebo on the QTcI
indicates that tadalafil conveys no risk for arrhythmia due to prolonged ventricular repolarization in healthy men. Although these results do not definitively prove that changes in ventricular repolarization would not occur in men with ED and/or cardiovascular disease, the data support and extend results from phase II and III tadalafil clinical trials that showed no ECG evidence of QT prolongation in patients with ED from the general population (including men with ED and comorbid cardiovascular disease and/or diabetes mellitus) (29).

Furthermore, pre-clinical studies conducted as part of the normal course of drug development demonstrated that compounds that inhibit PDE5 (i.e., sildenafil citrate, tadalafil, and vardenafil HCl) were not potent blockers of the human ether-a-go-go-related gene (hERG) channel (e.g., the IC50 for tadalafil was 100 μM) (30). Blockade of hERG channels and reduction of the repolarizing current, IKr, can be a signal for drugs that cause Torsades de Pointes; however, this effect is not specific, because many drugs have been shown to reduce IKr yet not evoke Torsades de Pointes (6). To our knowledge there have been no explicit cases of Torsades de Pointes for tadalafil, sildenafil, or vardenafil described in published reports.

Critical to the assessment of ventricular repolarization using the QT interval is selecting an optimal correction method for HR (12,16,17,19–21,23,31–33). As shown in Table 4, the magnitude of calculated changes in the QTc interval varied depending on the correction method applied. Some methods over- or undercorrect when HR changes (16), and many rely on control populations that differ from the study population (16,19,20). Malik et al. (12,17,33) showed that the QT-RR interval relationship varies across individuals and proposed that the optimal correction is individually based. This requires 60 to 100 nontreatment ECGs and distribution of RR values such that a best-fit correction can be computed for each subject (assuming the within-subject QT-RR relationship is constant). This individual-based QT correction was used for our primary analysis; however, some studies have shown that even within individuals the QT-RR relationship can be variable (18,31).

Because there is risk of arrhythmia when using medications that prolong the QT interval, definitive studies are necessary that accurately and reliably measure drug effects on ventricular repolarization. Such studies may become the pre-approval standard for medications from various therapeutic classes, except for medications where prolongation of the QT interval is a desired characteristic (some antiarhythmic medications), medications where the benefits of therapy clearly outweigh subtle increases in QTc, or medications shown to prolong the QTc through routine preapproval trials. Our study provides a method to accurately measure subtle drug-induced increases in the QT interval, if they occur, and allows the conclusion of absence of effect, if such is the case.

In conclusion, this study combined signal averaging for a large number of ECGs, intensive baseline ECG sampling, and the use of ibutilide as an active control to increase the sensitivity of detecting any signal of drug-induced QT interval prolongation. The results showed that the effects of high-dose tadalafil were equivalent to placebo with respect to mean changes in the QT interval. This study or some of its design characteristics may serve to guide future studies evaluating the effects of drugs on ventricular repolarization.

**Acknowledgments**

The authors acknowledge Gregory D. Sides, MD, and Richard W. Peck, MRCP, FFPM, for their advice regarding conduct and analyses of the results of this study; Brian P. Smith, PhD, Huan Lu, MS, and Grant Luo, MS, for data analysis and statistics; Sarah Noordwier and Stacy L. Kaper for clinical coordination; and Dawn M. Rebhun for coordination of ECG handling.

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**REFERENCES**


