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Validation of the Differential Cardiovascular Effects of the Antimuscarinic Agents Darifenacin and Tolterodine in a Randomized, Placebo-Controlled, 3-Way Crossover Study

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ABSTRACT

INTRODUCTION: Previous studies have demonstrated that antimuscarinics used for the treatment of overactive bladder (OAB), such as tolterodine and darifenacin, exert differential effects on heart rate (HR) and HR variability (HRV). OAB is a chronic symptomatic condition of high prevalence in older patients with cardiovascular (CV) comorbidities. Physicians prescribing these medications should take into consideration their specific effects on the parasympathetic control of the heart.

OBJECTIVE: The primary objective was to detect if there was a difference between tolterodine and darifenacin in change from baseline in mean HR over 24 hours during once-daily administration of these compounds in healthy participants. The protocol was designed to confirm results from a previous study.

METHODS: This was a 3-way crossover, placebo-controlled, double-blind study in healthy participants of similar age to OAB patients (≥ 50 years). Participants were randomized to one of 6 possible treatment sequences and consecutively received once-daily tolterodine 4 mg, darifenacin 15 mg, and matched placebo for at least 7 days in separate treatment periods. Electrocardiogram monitoring (Holter) for 24 hours was used to assess changes in mean HR and HRV between treatment arms.

RESULTS: Tolterodine but not darifenacin significantly increased mean HR over 24 hours compared with darifenacin (2.24 beats per minute [bpm], $P = .0004$) and placebo (1.84 bpm, $P = .0037$). In contrast, darifenacin did not significantly alter HR compared with placebo (–0.40, $P = .5219$). Overall, HRV over 24 hours decreased with tolterodine but not with darifenacin or placebo.

CONCLUSIONS: Tolterodine increased HR and reduced HRV compared with darifenacin and placebo in healthy participants aged ≥ 50 years. Because increased HR and decreased HRV are associated with increased CV risk and patients with OAB often have CV comorbidities, careful selection of antimuscarinic treatment for OAB patients may be warranted.

KEYWORDS: Antimuscarinic; Cardiovascular effects; M_3 selectivity

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original study

Differential Effects of Darifenacin and Tolterodine on Cardiovascular Parameters

INTRODUCTION

The antimuscarinic drugs darifenacin and tolterodine are widely used in the treatment of overactive bladder (OAB), a common and chronic condition. The primary symptoms of OAB are urinary urgency with or without urge incontinence (usually in conjunction with increased urinary frequency and nocturia) and are associated with advancing age [1,2]. In a recent study, it was shown that these drugs had different effects on heart rate (HR) in healthy participants of age comparable to a typical OAB population [3]. Tolterodine increased mean 24-hour HR significantly compared with darifenacin (1.8 beats per minute [bpm]) or placebo (1.4 bpm) and increased the proportion of participants with an average increase in HR of ≥ 5 bpm. In contrast, darifenacin did not increase mean HR compared with placebo [3]. Furthermore, tolterodine reduced 24-hour HR variability (HRV) compared with either darifenacin or placebo, which did not differ significantly from each other [3].

Although increases of 2 to 5 bpm in mean HR may appear small, this change represents an average increase over 24 hours in healthy individuals and is similar to the difference in HR observed between physically trained and untrained (unfit) adults [4,5]. A number of studies have shown a close association of elevated resting HR with serious cardiovascular (CV) events and mortality [6–8]. Therefore, prolonged HR elevation poses a great risk, even with relatively small numeric changes [7,9–11]. Additionally sustained increases in HR over time may intensify risk [7].

Furthermore, a decrease in HRV is indicative of adverse changes in parasympathetic /sympathetic balance. In a large community-based population from the Framingham Heart Study, a decrease in HRV (as measured by the standard deviation [SD] of all normal–normal intervals [SDNN]) of 1 SD over 2 hours was associated with a 41% increase in risk of cardiac events, even after adjusting for mean HR and clinical variables [12]. The combination of changes in HR and HRV measurements, therefore, can provide a very powerful tool to identify CV risk.

In the previous study, tolterodine produced significant reductions in SDNN index compared with darifenacin in healthy volunteers [3]. The importance of these findings may have even greater significance in OAB patients, in whom a preexisting state of autonomic imbalance along with CV comorbidities and elevated resting HR may be common [13–17]. Because OAB may require long-term therapy, prolonged exposure to an agent that potentially increases HR, even by small amounts, should be an important consideration when selecting treatment for these patients. The observation that tolterodine but not darifenacin increased HR in a previous study warrants further investigation to demonstrate whether the results and trends detected can be reproduced. Here the authors report the results of a second study, designed to confirm the differential CV effects of these two commonly prescribed antimuscarinics. Hence, the primary objective of this study was to determine whether or not there was a difference between once-daily darifenacin and tolterodine in mean HR over 24 hours in healthy participants over 50 years of age. Secondary outcome measures included mean hourly HR, HRV, and pulse rate.

METHODS

Study Design

This was a prospective, 3-way crossover, randomized, placebo-controlled, double-blind, double-dummy, multicenter study of healthy participants ≥ 50 years of age. Eligible participants were randomly assigned in equal proportions to one of 6 possible treatment sequences (Figure 1), using a computer-generated randomization list. The study investigator identified the appropriate study treatment for each participant using randomization numbers and visit numbers on the label of the study drug. All study personnel and participants were blinded to the identity of the drug throughout the study. Blinding was maintained using a double-dummy technique with matched placebos for darifenacin 15 mg tablets and tolterodine extended-release (ER) 4 mg capsules; treatment compliance was assessed by pill counts and individual reporting.

The study (ClinicalTrials.gov identifier NCT00703703) was conducted in 18 centers across the US between May 2008 and October 2008 in compliance with Good Clinical Practice guidelines, applicable local regulations, and ethical principles laid down in the Declaration of Helsinki, following approval of the protocol by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board. Participants each provided written informed consent.

Participants

The study population consisted of generally healthy men and women (age ≥ 50 years) with documented normal heart rhythm at screening and a body mass index of 18.5 to 35 kg/m^2. Exclusion criteria included known or suspected allergy to tolterodine and/or darifenacin or their components, irregular day and night activity patterns (eg, night-shift workers), significant medical problems known to affect HR, or history of any malignancy within the past 5 years. Use of medications with a potential to affect HR were prohibited throughout the study, including calcium channel blockers, angiotensin receptor blockers, ß-blockers, or thyroid hormone. Administration

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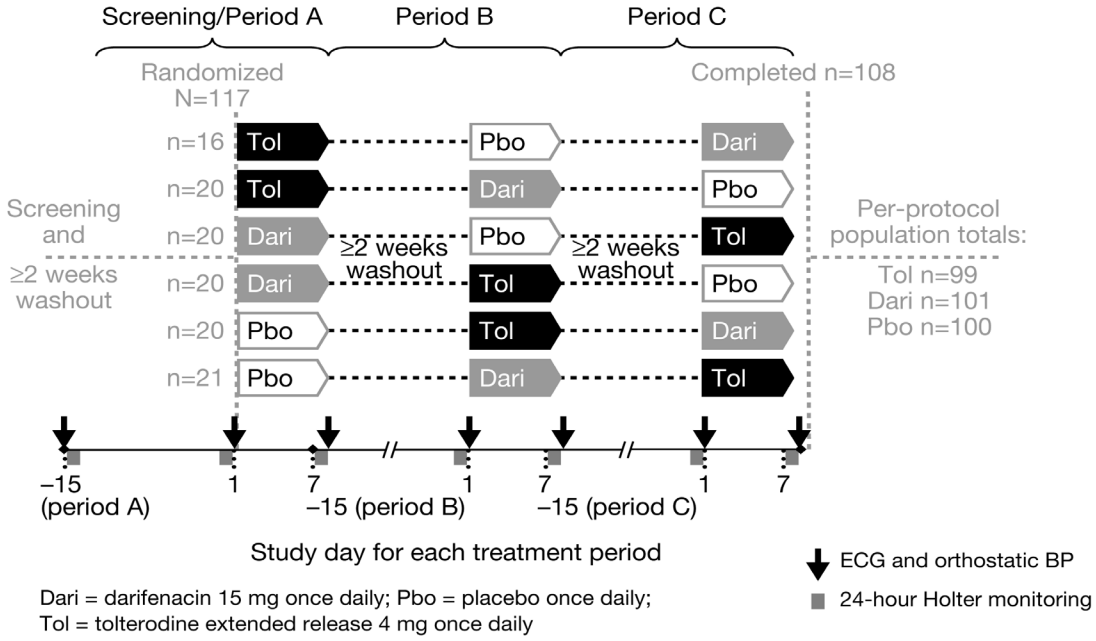
Figure 1. Study Design Overview and Participant Groups. doi: 10.3834/uij.1944-5784.2009.08.07f1



of medications with known anticholinergic side effects was prohibited throughout the study and within 4 weeks prior to study entry. Use of cholinergic agonists and cholinesterase inhibitors or medications with potential for pharmacokinetic interaction with the study drugs or P-glycoprotein was not permitted during the study or within 2 weeks of study entry.

Treatment and Assessments

Eligible participants received tolterodine ER 4 mg, darifenacin 15 mg, and placebo once daily for at least 7 days in 3 periods, each preceded by a 14-day washout period, to ensure a negligible risk of carryover effects between the treatment periods. Participants underwent 24-hour Holter monitoring and a 12-lead electrocardiogram (ECG) after each washout to establish baseline values for the subsequent treatment period, thus providing 3 separate baselines. At steady state of each treatment period the following were assessed: 24-hour Holter monitoring (starting on Day 7), 12-lead ECG, sitting and orthostatic blood pressure, and pulse assessments (on Day 8). Tolerability and safety were monitored throughout the study based on adverse events (AEs; categorized for relationship to treatment), serious AEs (SAEs), treatment discontinuations, abnormal findings from ECG results, vital signs, and laboratory parameters recorded at each study visit.

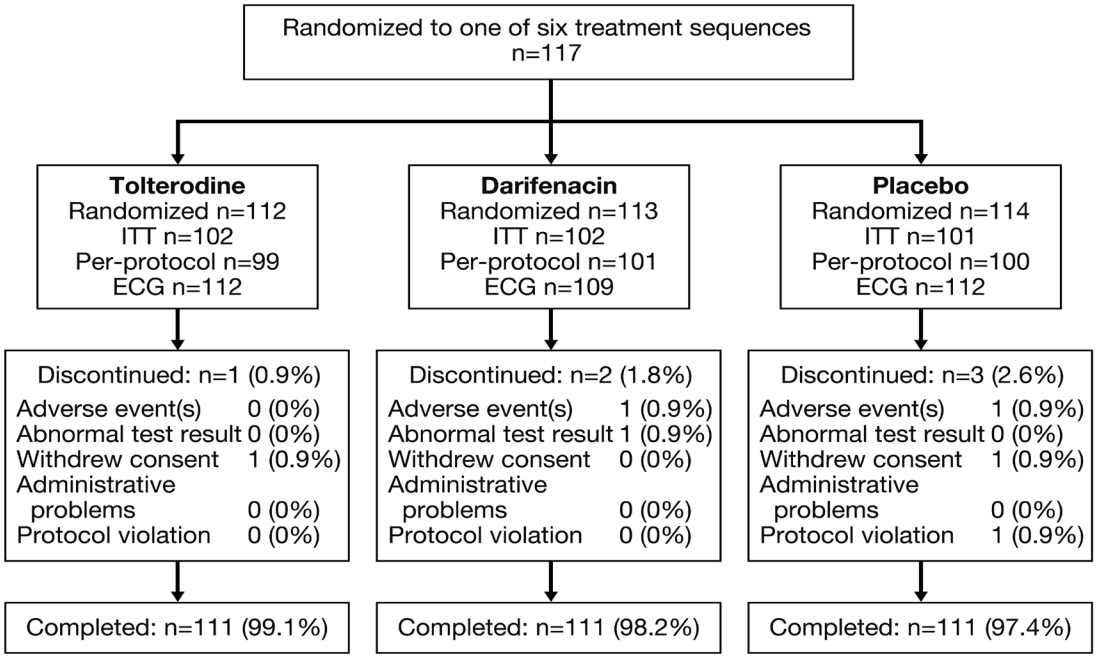
Statistical Analysis

Using a one-sample two-sided paired *t* test at a two-sided significance level of 5%, and assuming an expected difference of 2 bpm in mean HR over 24 hours (a standard deviation of 5.1 bpm and 90% power), it was found that a total of 71 per protocol (PP) participants were required for the study. If it is assumed that about 25% of the randomized participants would be excluded from the PP population, then approximately 96 participants needed to be randomized.

The primary population for analysis of all primary and secondary CV endpoints was the PP population, defined as: all treated participants who completed at least 2 study periods, who were treated for at least 6 complete days in each study period, and who had no major protocol deviations. This population was selected for analyses of the CV endpoints because 7 days of treatment exposure were required to ensure steady-state conditions for the active treatments. Analyses of the primary endpoint and HRV endpoints were also carried out in the intent-to-treat (ITT) population (randomized participants with baseline and post-baseline assessment within the same treatment period).

The primary outcome measure was change from baseline in mean 24-hour HR after 7-day exposure to tolterodine, darifenacin, or placebo. The primary analysis compared the

Figure 2. **Participant disposition and flow**. Randomized n is the total number of participants who started that treatment period. Discontinued n is the number of participants who discontinued during that treatment period. In addition, 3 participants discontinued *after* completed treatment periods: 1 participant after tolterodine treatment due to protocol violation, and 2 participants after placebo treatment due to adverse event(s) and withdrawn consent, respectively. Abbreviations: ECG, electrocardiogram; ITT, intent-to-treat population. doi: 10.3834/uij.1944-5784.2009.08.07f2



difference between treatment groups in the primary outcome, using an analysis of covariance (ANCOVA) model which included the effects of treatment, sequence, study period, and baseline mean HR over 24 hours as fixed effects and participants within sequences as random effect.

The overall treatment, period, and sequence effects were tested at 5% level of significance using a generalized *F* test that was generated using the procedure PROC MIXED, which is part of the SAS software (SAS Institute, Cary, NC). A *t* test with two-sided alternative was performed at 5% level of significance to assess differences in change from baseline to Day 7 in mean HR between the treatments using the least-squares means estimate from the full model. As a supportive analysis, pairwise response data were used to statistically compare the percentage of participants with mean 24-hour HR increases of ≥ 5 or ≥ 10 bpm between tolterodine vs darifenacin, tolterodine vs placebo, and darifenacin vs placebo. These statistical comparisons were made using exact McNemar's test at a two-sided significance level of 5%.

Secondary outcome measures were treatment differences in the change from baseline after 7 days of treatment for the following CV parameters after exposure to tolterodine or darifenacin, compared with placebo: mean hourly HR; mean HR at the time of anticipated maximum plasma concentration (T_{max}) of each drug; minimum and maximum HR over 24 hours; HRV over 24 hours; orthostatic blood pressure; pulse rate. Analyses of most of these secondary endpoints were conducted using ANCOVA models similar to the one described for the primary analysis variable. As was done for the primary analysis variable, fitted models were used for pairwise comparison of the 3 treatments. All tests were two-sided at 5% significance level.

Another secondary CV outcome measure that was analyzed was HRV over 24 hours. Median treatment differences with associated 95% confidence intervals and Wilcoxon signed-rank test-based *P* values were derived for the following pre-specified HRV parameters: standard deviation (SD) of all normal–normal intervals (SDNN), the mean of the SD of all the normal–normal intervals for all 5-minute segments (SDNN index), and the square root of the mean squared differences between adjacent

normal–normal intervals (R-MSSD) [18]. It has been proposed that the SDNN index and R-MSSD correlate better with parasympathetic tone than the SDNN [19].

AEs were summarized by treatment for the safety population, which included all participants who received at least 1 dose of study drug and had any post-baseline safety assessments.

RESULTS

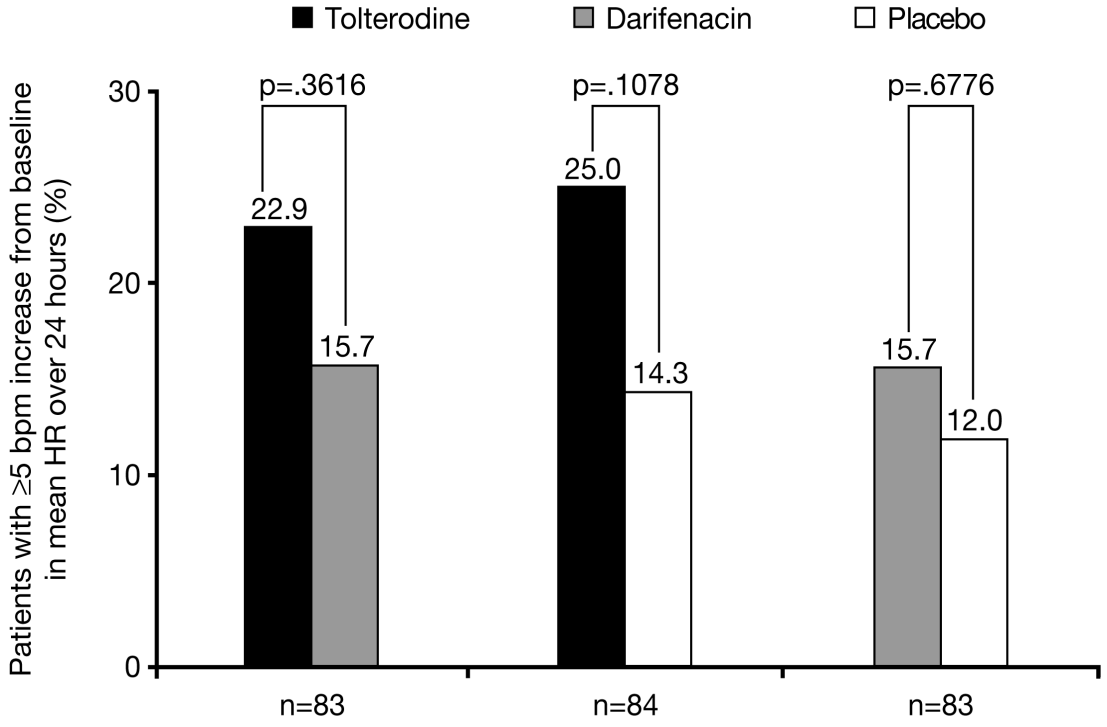
Participants

A total of 117 participants (50-86 years) were randomized to the 6 treatment groups (Figure 1) and 111 completed treatment with darifenacin, tolterodine, and placebo, respectively. Overall, 108 patients completed all 3 study periods (Figure 2). Most participants were less than 65 years of age (97/117, 82.9%), female (74/117, 63.2%) and Caucasian (103/117, 88.0%). Baseline (collected at the start of each phase) HR and blood pressure data were comparable and are summarized by treatment in Table 1.

CV Effects in the PP Population

The mean change from baseline in HR over 24 hours at steady state was significantly higher for tolterodine compared with darifenacin and compared with placebo, whereas there was no statistically significant difference between darifenacin and placebo (Table 2). The treatment difference in adjusted mean change from baseline was an increase of 2.24 bpm (P = .0004) for tolterodine vs darifenacin and 1.84 bpm (P = .0037) for tolterodine vs placebo. The proportion of participants with an increase in mean 24-hour HR of ≥ 5 bpm with one therapy was not significantly greater after exposure to tolterodine compared with darifenacin or placebo (Figure 3). Although not statistically significant, 5 participants had an increase in mean 24-hour HR of ≥ 10 bpm with tolterodine, compared with none during darifenacin treatment. In patients that had an increase in HR with either of the 2 pairs of therapies under consideration, the percentage of patients with an HR increase of ≥ 5 bpm was 15.7 vs 22.9 for tolterodine with darifenacin, respectively. For the comparison of tolterodine with placebo, the percentage was 25.0 vs 14.3. In contrast, for the comparison of darifenacin with placebo, the percentage was 15.7 vs 12.0.

Figure 3. Pairwise analysis of the proportion of participants with ≥ 5 bpm increase from baseline in mean HR over 24 hours at the end of each study period for the per-protocol population. Abbreviations: bpm, beats per minute; HR, heart rate. doi: 10.3834/uij.1944-5784.2009.08.07f3



p values based on McNemar's test

Table 1. Baseline Cardiovascular Characteristics. doi: 10.3834/uij.1944-5784.2009.08.07t1

Parameter	Per-protocol population[a]		
	Tolterodine (n = 99)	Darifenacin (n = 101)	Placebo (n = 100)
Mean HR over 24 hours (bpm)			
n	95	98	95
Mean ± SD	76.53 ± 8.84	76.15 ± 8.44	76.05 ± 8.42
Minimum, maximum	55.0, 96.0	51.0, 101.0	51.0, 96.0
Minimum HR over 24 hours (bpm)			
n	95	98	95
Mean ± SD	51.22 ± 6.93	50.56 ± 7.26	50.67 ± 7.85
Minimum, maximum	37.0, 74.0	27.0, 76.0	27.0, 72.0
Maximum HR over 24 hours (bpm)			
n	95	98	95
Mean ± SD	122.98 ± 12.29	123.11 ± 12.71	124.23 ± 14.53
Minimum, maximum	93.0, 147.0	86.0, 158.0	93.0, 178.0
Systolic BP (mmHg)[b]			
n	99	101	98
Sitting, mean ± SD	119.26 ± 10.97	119.96 ± 9.85	118.18 ± 11.63
Standing, mean ± SD	118.99 ± 12.06	120.02 ± 10.65	118.07 ± 11.21
Diastolic BP (mmHg)[b]			
n	99	101	98
Sitting, mean ± SD	75.8 ± 6.32	75.43 ± 6.21	75.13 ± 6.16
Standing, mean ± SD	77.6 ± 6.53	78.0 ± 6.42	76.94 ± 6.79
Pulso (bpm)[b]			
n	99	101	98
Sitting, mean ± SD	68.35 ± 9.33	68.43 ± 9.26	67.13 ± 8.33
Standing, mean ± SD	73.01 ± 9.42	72.82 ± 9.72	71.76 ± 9.31
HRV (msec)			
n	95	98	95
SDNN, mean ± SD	122.37 ± 30.91	122.06 ± 30.85	125.08 ± 29.98
SDNN index, mean ± SD	51.15 ± 16.31	50.97 ± 14.32	52.45 ± 14.62
R-MSSD, mean ± SD	30.76 ± 18.28	29.13 ± 15.72	31.95 ± 17.76

Abbreviations: BP, blood pressure; bpm, beats per minute; HR, heart rate; R-MSSD, square root of the mean squared differences between adjacent normal-normal intervals; SD, standard deviation; SDNN, standard deviation of all the normal-normal intervals; SDNN index, the mean of the standard deviation of all the normal-normal intervals for all 5-minute segments of the recording intervals.

[a]Data from baselines of the per-protocol participants prior to each study period; [b]Mean of 2 measurements

Further post hoc categorical analyses by increases of single bpm (from ≥ 1 bpm to ≥ 10 bpm) confirmed that more participants had an increase in HR on tolterodine compared with darifenacin and placebo across the increments ≥ 1 to ≥ 3 bpm (Figure 4), while similar numbers of participants on darifenacin compared with placebo had increases in HR across all increments. Conversely, a significantly greater proportion of participants receiving darifenacin had a decrease in HR of ≥ 1 to ≥ 3 bpm compared with those receiving tolterodine ($P < .02$; Figure 4). However, there was no statistically significant difference between darifenacin and placebo in the number of participants with decreases in HR of each 1 bpm increment.

Consistent with the findings for mean 24-hour HR, mean HR values recorded over consecutive 1-hour intervals were significantly higher with tolterodine than darifenacin and/or placebo at most hourly intervals from 5-17 hours post-dose (Figure 5). This time period followed immediately after

Table 2. Change from Baseline in Key Heart Rate Parameters at the End of Each Study Period. doi: 10.3834/uij.1944-5784.2009.08.07t2

Parameter and treatment (A vs B)	Change from baseline for each treatment, adjusted mean		Treatment difference	95% Confidence Interval	*P*
	A	B	A - B		
Mean HR over 24 hours (bpm)					
Tolterodine vs darifenacin: PP	1.98	–0.26	2.24	1.02, 3.47	.0004
ITT	1.84	–0.24	2.07	0.91, 3.24	.0006
Tolterodine vs placebo: PP	1.98	0.14	1.84	0.61, 3.08	.0037
ITT	1.84	0.07	1.77	0.61, 2.93	.0030
Darifenacin vs placebo: PP	–0.26	0.14	–0.40	–1.63, 0.83	.5219
ITT	–0.24	0.07	–0.30	–1.47, 0.86	.6090
Minimum HR over 24 hours (bpm)					
Tolterodine vs darifenacin: PP	0.35	0.10	0.25	-0.77, 1.26	.6303
Tolterodine vs placebo: PP	0.35	–0.08	0.43	–0.59, 1.46	.4019
Darifenacin vs placebo: PP	0.10	–0.08	0.19	–0.83, 1.21	.7180
Maximum HR over 24 hours (bpm)					
Tolterodine vs darifenacin: PP	1.28	0.15	1.13	–1.41, 3.66	.3814
Tolterodine vs placebo: PP	1.28	0.55	0.72	–1.82, 3.27	.5760
Darifenacin vs placebo: PP	0.15	0.55	–0.40	–2.95, 2.14	.7548
HR at anticipated T_{max}[a] (bpm)					
Tolterodine vs darifenacin: PP	1.60	–0.16	1.76	–0.69, 4.22	.1567
Tolterodine vs placebo: PP	1.82	–0.30	2.12	–0.24, 4.48	.0776
Darifenacin vs placebo: PP	–0.09	–1.98	1.89	–0.60, 4.37	.1360

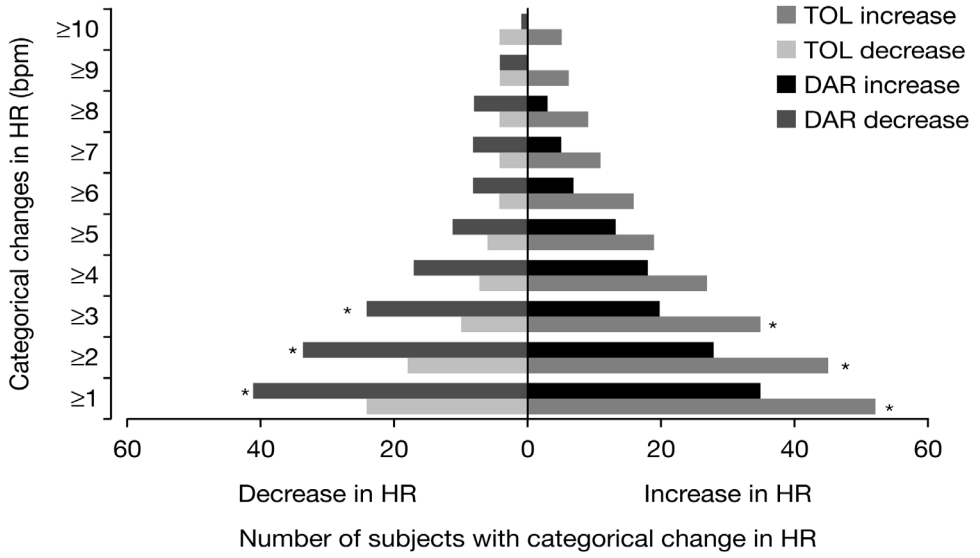
Abbreviations: bpm, beats per minute; PP, per-protocol population; ITT, intent-to-treat population.

Data analysis using analysis of covariance with treatment, period and participant fitted as main effects, and baseline fitted as a covariate, excluding participants with missing data.

Based on PP participants: tolterodine n=99, darifenacin n=101, placebo n=100; and ITT participants: tolterodine n=102, darifenacin n=102, placebo n=101.

[a]Mean HR at 6-8 hours post-dose for darifenacin, and 3-5 hours post-dose for tolterodine, and corresponding time for placebo.

Figure 4. **Pairwise comparison of categories of HR increase by single bpm increments (from ≥ 1 bpm to ≥ 10) during individual treatment (per-protocol population).** Abbreviations: bpm, beats per minute; DAR, darifenacin; HR, heart rate; TOL, tolterodine. doi: 10.3834/uij.1944-5784.2009.08.07f4



*p<.05 for comparison between DAR and TOL

the anticipated time of maximum serum concentration of tolterodine (4 hours), based on the pharmacokinetic data from the US prescribing information for this product [20]. For the comparison of tolterodine with placebo, statistically significant differences were detected in most hourly intervals from 5-12 hours post-dose. Minimum and maximum HRs over 24 hours were comparable between the 3 treatments (Table 2).

Measurements of HRV over 24 hours after 7 days' exposure showed a reduction with tolterodine but not darifenacin or placebo. Tolterodine was associated with significant reduction in SDNN index (P = .0087) and R-MSSD (P = .0011) compared with darifenacin and also in R-MSSD (P = .0219) when compared with placebo. Estimated median treatment differences are shown in Table 3. HRV did not differ between darifenacin and placebo using any of the 3 measures.

A significant increase in the pulse rate change when rising from the sitting to the standing position was observed with tolterodine when compared with darifenacin. In contrast, there was a significant reduction in pulse (change from sitting to first standing and change from sitting to mean standing) with darifenacin vs placebo (Table 4).

There were no differences in orthostatic or sitting diastolic and systolic blood pressure measurements between treatment groups.

Results of ITT Population Analysis

The ITT and PP populations were comparable among analyzed measures of mean HR over 24 hours and HRV parameters (Table 2 and Table 3) confirming the relevance of the PP analysis.

Tolerability and Safety

AEs were reported by 23 participants when taking tolterodine (20.5%), 35 taking darifenacin (31.0%), and 21 taking placebo (18.4%). AEs reported by > 5% of participants were those commonly reported with all antimuscarinics, ie, constipation (0% tolterodine, 5.3% darifenacin, 1.8% placebo) and dry mouth (5.4%, 13.3%, 0.9%, respectively).

There was 1 SAE, a hypersensitivity reaction, reported during darifenacin treatment. A 54-year-old African-American male with a history of gonorrhea and taking nutritional supplements developed shortness of breath, tightness in the chest, nausea, fatigue, and diarrhea after 2 doses of darifenacin treatment and was hospitalized. His ECG was normal upon admission. Study medication was discontinued and the participant was reported as completely recovered after 2 days. The investigator suspected a relationship with the study medication. Two additional participants experienced AEs while receiving placebo that led to discontinuation from the study: 1 participant experienced moderate dizziness and 1 participant experienced a mild

Table 3. Pairwise Analysis of Change from Baseline in Heart Rate Variability at the End of the Study Periods. doi: 10.3834/uij.1944-5784.2009.08.07t3

Parameter	Estimated Median Difference	95% Confidence Interval	*P*
SDNN			
Tolterodine vs darifenacin: PP	–4.0	–9.0, 2.0	.2789
ITT	–4.0	–9.0, 2.0	.2553
Tolterodine vs placebo: PP	–2.5	–9.0, 9.0	.7723
ITT	–3.0	–11.0, 4.0	.2931
Darifenacin vs placebo: PP	–1.0	–11.0, 7.0	.8152
ITT	–1.0	–8.0, 7.0	.6620
SDNN Index			
Tolterodine vs darifenacin: PP	–2.0	–5.0, 0.0	.0087
ITT	–1.0	–5.0, 0.0	.0220
Tolterodine vs placebo: PP	–2.5	–4.0, 0.0	.0686
ITT	–3.0	–4.0, 0.0	.0672
Darifenacin vs placebo: PP	0.0	–2.0, 3.0	.7787
ITT	–1.0	–3.0, 2.0	.9431
R-MSSD			
Tolterodine vs darifenacin: PP	–4.0	–6.0, –1.0	.0011
ITT	–3.0	–6.0, –1.0	.0054
Tolterodine vs placebo: PP	–3.5	–6.0, –2.0	.0219
ITT	–3.5	–6.0, –2.0	.0356
Darifenacin vs placebo: PP	1.0	–2.0, 2.0	.6195
ITT	0.0	–2.0, 2.0	.8258

Abbreviations: ITT, intent-to-treat population; PP, per-protocol population.

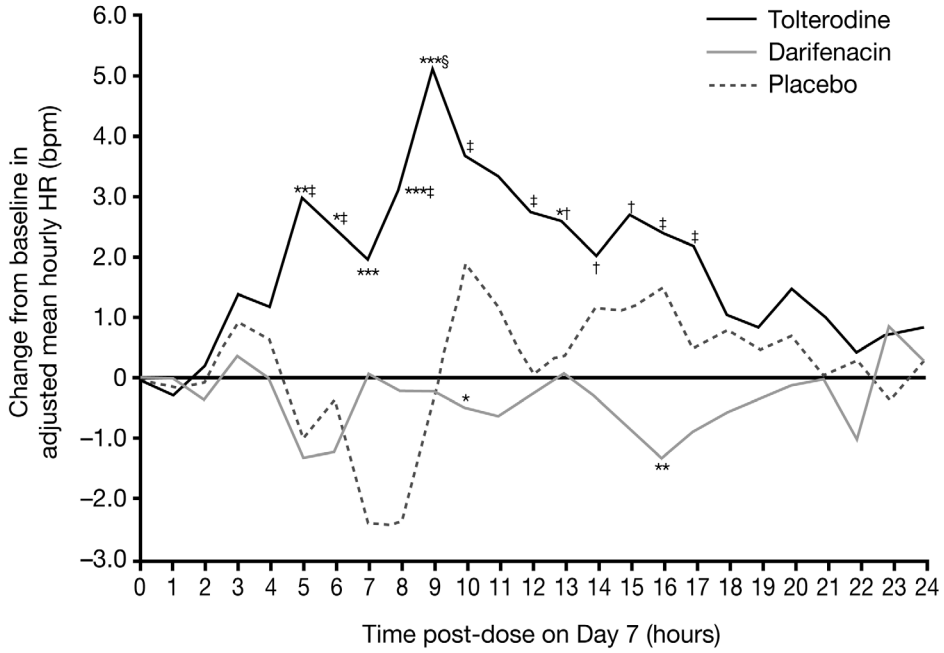
P value is from Wilcoxon signed-rank test; 95% confidence interval for median difference.

Based on PP participants: tolterodine n=92, darifenacin n=93, placebo n=90; and ITT participants: tolterodine n=102, darifenacin n=102, placebo n=101.

episode of unsustained ventricular tachycardia. The investigator suspected that the 1 SAE and 2 AEs leading to discontinuation from the study were treatment-related. There were no clinically significant findings in hematology, biochemistry, or urinalysis and there were no obvious trends among treatments. There were no deaths during the study.

ECG evaluations for treated participants with evaluable baseline and post-baseline data (tolterodine n=112; darifenacin n=109; placebo n=112), showed a comparable incidence of newly occurring ECG findings between treatment groups. Newly occurring ECG abnormalities were seen in 10 (8.9%) participants during tolterodine treatment (first degree AV block [n=4]; depressed ST segment [n=1]; flat or inverted T waves [n=3]; sinus bradycardia [n=2]; atrial premature contractions [n=1]). Newly occurring ECG abnormalities were seen in 4 (3.7%) participants during darifenacin treatment (left anterior hemiblock [n=1]; depressed ST segment [n=1]; flat or inverted T waves [n=2]). Finally, newly occurring ECG abnormalities were seen in 10 (8.9%) participants while receiving placebo (first degree AV block [n=1]; left anterior hemiblock [n=2]; depressed ST segment [n=2]; flat or inverted T waves [n=3]; sinus bradycardia [n=1]; ectopic supraventricular rhythm [n=1]). The proportion of participants with newly occurring ECG interval changes was generally comparable between groups and no specific interval change was seen in ≥ 10% of participants during any study treatment. The most commonly reported newly occurring interval change (≥ 5% in any treatment group) was QTcB

Figure 5. **Change from baseline in adjusted mean hourly HR by treatment (per-protocol population).** Similar time profiles were obtained for the intent-to-treat population (data not shown). The results of statistical analysis of treatment differences at each time point using analysis of covariance for the change from baseline in mean hourly HR, adjusted for participant, period, and baseline effects are also shown: $^{\dagger}P < .05$, $^{\ddagger}P < .01$, $^{\S}P \leq .0001$ for comparison with darifenacin; $^{*}P < .05$; $^{**}P < .01$, $^{***}P < .001$ for comparison with placebo. Abbreviations: bpm, beats per minute; HR, heart rate. doi: 10.3834/uij.1944-5784.2009.08.07f5



increase ≥ 30 msec (3.67% darifenacin, 6.25% tolterodine ER, 4.46% placebo). In addition, new PR intervals of > 200 msec and QTcF increases of ≥ 30 msec were seen in slightly higher proportions of participants during tolterodine ER treatment (3.57% tolterodine ER vs ≤ 0.92% for darifenacin and placebo).

DISCUSSION

Long-term follow-up studies have indicated that a higher HR is associated with an increase in all-cause mortality, CV disease, atrial fibrillation, and sudden death in patients with hypertension or known or suspected coronary heart disease, and in survivors of myocardial infarction [10,21–23]. Single-digit increases in average HR over prolonged periods have been associated with marked increases in mortality risk [11,24], even in normal participants [7]. Effects of therapeutic agents on HR may be of particular importance for patients with OAB, because CV comorbidities and elevated resting HR are known to be more common in this patient population [13–17]. In addition, the chronic nature of the condition requires long-term treatment, which is likely to increase the risk for emergence of cardiac effects or exacerbation of preexisting cardiac conditions.

The purpose of this randomized, controlled trial was to validate the findings from a previous study of the effects of tolterodine and darifenacin on HR parameters under steady-state conditions in healthy participants aged 50 years and older [3]. As in the previous study, tolterodine significantly increased mean HR over 24 hours compared with both darifenacin and placebo, while darifenacin did not affect HR compared with placebo. The differences between the effects of these antimuscarinics were statistically significant both in the present and previous studies [3].

Tolterodine caused an increase in mean hourly HR compared with darifenacin over time, with the differences being significantly greater during several of the hourly intervals from 5-17 hours post-dose. In the previous study, statistically significant differences were observed at several time points after only 2 hours post-dose, and tolterodine caused a peak increase in the mean hourly HR that coincided with its expected T_{max} at approximately 4 hours. Despite using doses

Table 4. Pairwise Analysis of the Change from Baseline Pulse (bpm) at the End of Each Study Period (PP). doi: 10.3834/uij.1944-5784.2009.08.07t4

Parameter and treatment (A vs B)	Change from baseline for each treatment, adjusted mean		Treatment difference	95% Confidence Interval	*P*
	A	B	A - B		
Pulse: change from sitting to first standing					
Tolterodine vs darifenacin: PP	–0.39	–1.65	1.26	–0.01, 2.53	.0521
Tolterodine vs placebo: PP	–0.39	0.36	–0.75	–2.03, 0.53	.2487
Darifenacin vs placebo: PP	–1.65	0.36	–2.01	–3.29, –0.74	.0022
Pulse: change from sitting to mean standing[a]					
Tolterodine vs darifenacin: PP	–0.01	–1.60	1.59	0.32, 2.86	.0142
Tolterodine vs placebo: PP	–0.01	–0.24	0.23	–1.05, 1.50	.7245
Darifenacin vs placebo: PP	–1.60	–0.24	–1.36	–2.63, –0.09	.0359

Abbreviations: bpm, beats per minute; PP, per protocol population.

Based on PP participants: tolterodine n=99, darifenacin n=101, placebo n=98.

[a]Change from mean sitting to mean standing is calculated as mean of two standing pulse measurements – mean of two sitting pulse measurements.

and treatment periods identical to the previous study, there was no clear association between peak increases in mean HR and expected drug T_{max} in this study. The magnitude of HR changes was similar to the previous study but was sustained across a longer time period. These results could reflect a slight difference in the composition of the 2 populations regarding their ability to metabolize tolterodine; for example, participants who are poor metabolizers could prolong the time of exposure to maximal concentration and drug effects compared with good metabolizers [25]. However, neither study evaluated pharmacokinetic parameters; therefore, the influence of intrinsic differences between participants cannot be assessed.

As observed in the previous study, darifenacin did not show any consistent effect in the average hourly HR or 24-hour HRV compared with placebo. In both studies, tolterodine consistently increased HR and decreased HRV parameters compared with darifenacin and placebo. There were no significant changes in HR or HRV observed with darifenacin, but an increased propensity for decreases in HR was observed. A significantly greater number of participants receiving darifenacin had decreases in HR of ≥ 1 to ≥ 3 bpm than participants receiving tolterodine. However, the comparison between darifenacin and placebo was not statistically significant. Reductions in HR are known to decrease mortality [7]; however, the clinical relevance of the decreases observed in these studies is not known.

Further observation across the two studies included pulse rate and blood pressure changes. In the first study, neither antimuscarinic affected systolic or diastolic blood pressure with the exception of a small change observed with darifenacin in diastolic blood pressure in the sitting position only–an observation that was not repeated in the second study. In the second study, darifenacin was shown to significantly reduce pulse (from sitting to first standing and from sitting to mean standing) compared with placebo, which may suggest that darifenacin has a beneficial effect on vagal response.

The effect of tolterodine on HR was accompanied by reductions in 2 HRV parameters (SDNN index and R-MSSD) that reflect parasympathetic influences, when compared with darifenacin. The effects on HRV, and in particular R-MSSD, were consistent with blockade of parasympathetic influences over the HR. HRV is a potentially more powerful predictor of sudden cardiac death than HR alone [26]. Indeed, in the Framingham Heart Study, HRV was identified as a highly significant predictor of CV events and mortality in the overall community-based population and in an elderly subset (mean age 72 years) [12,27]. In this subset, HRV was a powerful predictor of CV risk and mortality and a 1 SD decrement was associated with a 70% increase in all-cause mortality (41% increase in the overall population) [12,27]. Therefore, HRV may be even more sensitive in detecting autonomic imbalance than mean HR [12].

In view of the high level of consistency between the results from these 2 studies of antimuscarinic effect on HR in healthy participants, it is likely that similar effects would be observed in patients with OAB. Importantly, the prevalence of preexisting CV diseases in an OAB population has been reported to be 47%, including hypertension in 36% of patients [16]. Elevated resting HR of ≥ 80 bpm was recorded in 39% of patients prior to antimuscarinic therapy [15]. In view of the high average age and prevalence of preexisting CV conditions in the OAB population, the possibility that an antimuscarinic drug may increase HR and reduce HRV is concerning. However, further studies on differential CV effects of antimuscarinics in patients with OAB are warranted.

The reasons for the differential CV effects of tolterodine and darifenacin may be related to their muscarinic receptor selectivity. Darifenacin has shown 59-fold selectivity in binding to the M_3 receptor over the M_2 subtype, while in the same study tolterodine displayed only 3.6-fold selectivity [28]. The higher selectivity of darifenacin for the M_3 receptor, thought to be responsible for detrusor muscle contraction in the bladder, is expected to spare the overwhelming majority of cholinergic M_2 receptors present in the sinus node. In contrast, antimuscarinics with significant M_2 receptor affinity can block the post-junctional effects of cardiac parasympathetic tone, resulting in decreased HRV and increased mean average diurnal HR [17,28,29].

The present study has several strengths. First, the robust 3-way crossover design ensured that study participants served as their own control, reducing the problem of between-group differences and making the study efficient by reducing sample size. Second, the study population was comparable in age and gender to typical OAB patient populations [2,30,31]. Third, rigorous study inclusion and exclusion criteria ensured that intersubject variability was minimized. Fourth, Holter monitoring was used to measure HR during 24 hours. This provided mean diurnal values instead of the spot measurements that are generally used in practice, but which are only reflective of short observation periods. The use of Holter monitoring helped ensure objectivity and safety in the assessment of the HR by detecting all events occurring within the 24-hour period of observation. Some cardiac events could be difficult to detect using routine ECG, due to their often limited duration and irregular occurrence [32].

A potential limitation of the study was the population of generally healthy participants. However, it is reasonable to expect that cardiac treatment effects observed in healthy participants would also occur in OAB patients because these participants were of similar age to the OAB population. Indeed, tolterodine-treated OAB patients showed an increase in pulse rate or mean HR in previous studies [33–35]. In addition, assessing these CV parameters in healthy participants minimizes confounding factors such as CV comorbidities and drug to drug interaction, increasing the ability of this study to discern pharmacological effects of the studied medications.

It remains to be seen whether this differential in pharmacologic effect is also seen with other antimuscarinic agents and whether any effects are related to their muscarinic receptor selectivity profile. Currently, only limited prospectively evaluated HR data are available. These data are mainly from cardiac safety studies evaluating each agent individually. For example, in one such study, 39.1% of participants given 4 mg/day fesoterodine and 76.5% given supratherapeutic doses of 28 mg/day fesoterodine experienced HR increases of > 25% and HR over 100 bpm, compared with 16.9% on placebo [35]. Similarly, the nonselective antimuscarinic drug, trospium, at 20 mg twice daily increased HR in healthy participants by 9.1 bpm [36]. In contrast, studies with oxybutynin or solifenacin, which have demonstrated intermediate selectivity for the M_3 over M_2 receptors [37] have revealed either a small decrease or no change in HR [38,39].

CONCLUSION

The results of the present study substantiate prior evidence that the antimuscarinic drugs darifenacin and tolterodine differ with respect to their effects on HR. Differences are likely related to their muscarinic receptor binding profiles, specifically, their selectivity for M_3 receptors over M_2 receptors. The relatively nonselective muscarinic blocker, tolterodine, significantly increased HR and reduced HRV compared with placebo whereas the more M_3-selective blocker, darifenacin, did not. Based on these data, careful consideration should be given to the selection of the antimuscarinic drug used to treat patients with OAB.

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Conflict of Interest

Brian Olshansky: Paid consultant to sponsor
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José Brum: Employee of sponsor (Procter and Gamble Pharmaceuticals Inc.)
Lidia Mongay: Employee of sponsor (Novartis Pharmaceuticals Corporation)
Mathias Egermark: Employee of sponsor (Novartis Pharma AG)
Yodit Seifu: Employee of sponsor (Novartis Pharmaceuticals Corporation)

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