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ORIGINAL ARTICLE

The effect of tolterodine 4 and 8 mg on the heart rate variability in healthy subjects

Maya Schiffers · Peter Sauermann · Brigitte Schurch · Ulrich Mehnert

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Abstract
Purpose To investigate the potential effect of tolterodine on the human heart rate variability (HRV). Oral antimuscarinic treatment for overactive bladder might significantly alter HRV, which is an important predictor for cardiac and all-cause mortality. Yet, little information exists regarding the influence of oral antimuscarinics on the HRV.
Methods Healthy female volunteers were randomly assigned to either placebo, tolterodine extended release (ER) 4 or 8 mg. Before and 4 h post treatment, a 10 min electrocardiogram (ECG) was recorded in supine position. Frequency domain and time domain analysis of both ECG measurements resulted in very low frequency (VLF), low frequency (LF), and high frequency (HF) data, the root mean square of differences of successive NN (= normal to normal, i.e. interval between two R-peaks) intervals (RMSSD), and the standard deviation of the NN intervals (SDNN).
Results Thirty subjects (mean age: 23.7 ± 2.3 years) were investigated. Placebo caused no significant HRV changes. Tolterodine 4 mg significantly increased heart rate (HR) and significantly decreased VLF. Tolterodine 8 mg significantly decreased HF, VLF, RMSSD and SDNN and significantly increased HR and LF/HF ratio. The changes observed with 4 mg were not significantly different versus placebo, but 8 mg significantly increased LF/HF as compared to placebo.
Conclusions A single dose of 8 mg tolterodine ER, but not 4 mg seems to reduce resting HRV versus placebo in young healthy subjects. This might be particular relevant for patients with pre-existing cardiac conditions on daily overactive bladder drug treatment and should be further investigated in larger trials.

Keywords Tolterodine · Heart rate variability · Adverse drug event · Antimuscarinic agents · Overactive bladder

M. Schiffers · B. Schurch · U. Mehnert (✉)
Neuro-Urology, Spinal Cord Injury Center,
University of Zurich, Balgrist University Hospital,
Forchstrasse 340, 8008 Zurich, Switzerland
e-mail: ulrich.mehnert@paralab.balgrist.ch

P. Sauermann
Department of Urology, University Hospital Zurich,
Zurich, Switzerland

Introduction

Overactive bladder (OAB) is quite common with an overall prevalence range from 10 to 17% [1–3] with the incidence of OAB increasing with age [4, 5].

The first line drug therapy for OAB is oral antimuscarinic treatment which is usually administered on a daily basis for several months or years [6].

Heart rate (HR) elevations are a well known adverse effect of this class of drugs [7–9] and like OAB, the incidence of cardiovascular diseases increases with age [10]. In addition, a recent study showed that the prevalence of cardiovascular comorbidities is significantly higher in patients with than without OAB and that previous exposure to medications with antimuscarinic effects was also higher in patients with OAB [11].

Elevations in HR increase cardiac oxygen demand and concomitantly decrease cardiac oxygen supply due to shortening of the diastole [9]. This might be of little relevance for a healthy heart, but patients with cardiac comorbidities or impaired cardiac autonomic regulation

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might be at risk for cardiovascular events [9, 11]. A recent cohort study showed that elevated resting HR (rHR) is an independent predictor for myocardial infarction or coronary death [12].

Another important HR-related indicator of cardiac autonomic function and predictor of cardiac mortality and of all-cause mortality is the heart rate variability (HRV) [13, 14].

However, very little information exists on the effect of oral antimuscarinic drugs used in daily OAB treatment on the human HRV. It was therefore our aim to investigate the effect of the widely used antimuscarinic drug tolterodine extended release (ER) on the human HRV.

Subjects and methods

Following approval of the local ethics committee, healthy female volunteers were recruited. Written informed consent of all subjects was obtained prior to inclusion.

A 10 min baseline electrocardiogram (ECG) was recorded in all subjects. Afterwards, subjects received either placebo, tolterodine ER 4 mg (Tol4) or 8 mg (Tol8). Placebo and tolterodine capsules (provided by the pharmacy of the University Hospital Zurich), were packed individually for each subject into neutral drug containers. The sequence of the containers was randomized using a standard scientific randomizer (http://www.randomizer.org/form.htm) and documented on a blinding protocol, which was not known by subjects and investigators. Subjects received their drug container in the same sequence as they were included into the study, i.e., subject 1 received container 1, subject 2 received container 2, etc.

Although Tol8 is not the officially approved dose for OAB treatment, we included Tol8 into the protocol, to observe a potential dose-dependent effect on the HRV, which might be especially relevant for patients with neurogenic detrusor overactivity (NDO), who frequently use higher doses of antimuscarinics to achieve an acceptable effect on the DO.

Following 4 h-post dosing, a second 10 min ECG was recorded. A telephone follow-up was performed 2–3 days after the investigation to check for any side-effects.

Both, pre- and post-dosing ECG measurements were performed after 30–35 min of rest, with subjects in supine position. The ECGs were analyzed using frequency domain and time domain analysis as described in detail previously [15, 16]. Briefly, the following steps were performed for the frequency domain analysis: (1) extraction of the middle 5 min section of each 10 min ECG measurement, (2) detection of R-waves in ECG lead II, (3) calculation of RR-intervals and generation of discrete event series (DES), (4) calculation of power spectra from the DES, (5) calculation of the integral of very low frequency (VLF, 0.003–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) ranges. From the LF and HF values, the LF/HF ratio was calculated. The sum of all frequency ranges resulted in the 5-min total power (TP).

For the time domain analysis, the mean rHR, the standard deviation of all NN intervals (SDNN, NN = normal to normal, i.e., interval between two R-peaks), and the root mean square of the sum of the squares of differences between adjacent NN intervals (RMSSD) were calculated.

All analyzing processes were performed using the scientific software Soleasy® (ALEA Solutions GmbH, Zurich, Switzerland).

For comparison of the outcome parameters within the same group, the Wilcoxon Signed Ranks test was used. An α of 0.05 was considered as statistically significant.

The Kruskal–Wallis test and subsequently the Mann–Whitney test were used for statistical analysis between the three groups either pre- or post-treatment. Due to multiple comparisons when using the Mann–Whitney test, α had to be adjusted to 0.025.

All tests were calculated using SPSS® 14.0 (SPSS®, Inc., Chicago, IL, USA).

Non-parametric statistical tests were applied, as group sizes are rather small and a Gaussian distribution of the data is not given.

Results

Thirty healthy female subjects (mean age: 23.7 ± 2.3 years, mean BMI: 20.5 ± 1.7 kg m^{-2}) were included and equally randomized among the three groups.

Only minor side-effects were reported in single cases from all groups 4 h post-dosing or at the follow-up interview. In detail, tiredness was reported from four subjects (3 placebo, 1 Tol8), headache from six subjects (2 placebo, 1 Tol4, 3 Tol8), nausea from two subjects (1 placebo, 1 Tol8), dry mouth from two subjects (1 placebo, 1 Tol4), and the feeling of increased pressure behind the eye from one subject in the Tol8 group.

All side-effects were reported as self-limited (12–24 h) and mild to moderate in intensity.

The median values and interquartile ranges of the pre- and post-treatment HRV parameters of each group are summarized in Table 1. No significant differences were detected between the three groups pre-dosing (rHR: $p = 0.225$, TP: $p = 0.170$, VLF: $p = 0.225$, LF: $p = 0.18$, HF: $p = 0.254$, LF/HF: $p = 0.647$, RMSSD: $p = 0.151$, SDNN: $p = 0.263$).

In the placebo group no significant changes between the pre- and post-dosing HRV parameters were observed (Table 1).

Table 1 Summary of the HRV parameters analyzed from the ECG recordings of all subjects, ordered by group and pre- and post-treatment period

	Placebo		Tol 4 mg		Tol 8 mg	
	Pre	Post	Pre	Post	Pre	Post
rHR (bpm)	68.8 (60.2–74.2)	74.7 (62.7–80.5)	59.9 (51.7–67.9)	67.6 (61.2–73.7)	62.6 (58.0–72.6)	72.9 (70.4–78.8)
Sig.	p = 0.185		p = 0.047		p = 0.005	
TP (ms^2)	42.9 (39.6–60.9)	36.5 (34.0–54.0)	62.7 (48.1–81.9)	46.9 (40.0–73.7)	54.9 (38.9–83.2)	41.1 (34.2–42.1)
Sig.	p = 0.093		p = 0.074		p = 0.005	
VLF (ms^2)	42.4 (36.9–54.7)	35.6 (32.9–51.3)	57.7 (43.7–76.9)	44.2 (38.7–58.9)	53.0 (37.7–62.0)	39.5 (33.8–41.0)
Sig.	p = 0.169		p = 0.047		p = 0.005	
LF (ms^2)	1.1 (0.3–1.3)	0.7 (0.4–0.9)	1.5 (0.9–3.8)	1.2 (0.6–2.2)	0.7 (0.5–1.4)	1.0 (0.5–1.3)
Sig.	p = 0.285		p = 0.799		p = 0.646	
HF (ms^2)	0.8 (0.3–2.5)	0.6 (0.3–1.6)	2.4 (1.5–5.2)	1.7 (0.5–2.4)	1.1 (0.6–5.1)	0.3 (0.1–0.6)
Sig.	0.139		p = 0.114		p = 0.028	
LF/HF	1.1 (0.6–1.4)	1.0 (0.8–1.9)[#]	0.7 (0.4–1.1)	1.3 (0.7–2.0)	0.9 (0.2–1.6)	2.9 (2.4–4.6)[#]
Sig.	p = 0.508		p = 0.093		p = 0.007	
RMSSD (ms)	47.5 (32.2–76.9)	42.5 (28.8–76.3)	102.88 (55.6–125.5)	69.2 (31.9–92.4)	75.5 (36.7–120.9)	33.1 (16.2–44.6)
Sig.	p = 0.386		p = 0.114		p = 0.009	
SDNN (ms)	62.6 (37.0–74.6)	45.4 (39.0–71.0)	83.2 (61.7–119.0)	67.0 (44.7–85.0)	63.1 (59.2–114.1)	43.2 (37.4–56.9)
Sig.	p = 0.241		p = 0.169		p = 0.005	

Presented are median (interquartile range) values

rHR resting heart rate, *TP* 5 min total power, *VLF* very low frequency, *LF* low frequency, *HF* high frequency, *LF/HF* low frequency/high frequency ratio, *RMSSD* root mean square of the sum of the squares of differences between adjacent RR intervals, *SDNN* standard deviation of all RR intervals. *Sig.* significant difference between pre- and post-treatment within each group (Wilcoxon Signed Ranks test)

[#] p = 0.01 (Mann–Whitney test), difference between placebo and tolterodine 8 mg group post treatment for LF/HF. All other parameters showed neither pre- nor post-treatment any significant difference between groups

Tol4 significantly increased rHR and significantly decreased VLF (Table 1). The other parameters within this group did not show any significant changes between pre- and post-dosing (Table 1).

Tol8 significantly increased rHR and LF/HF ratio and significantly decreased TP, HF, VLF, RMSSD and SDNN (Table 1). For the LF parameter, no significant difference was found within the Tol8 group.

In the comparison between all groups post-dosing, Tol8 significantly increased the LF/HF ratio versus placebo (p = 0.01) (Fig. 1). No further significant differences were found between groups post-dosing (rHR: p = 0.348, TP: p = 0.206, VLF: p = 0.305, LF: p = 0.287, HF: p = 0.095, RMSSD: p = 0.175, SDNN: p = 0.192).

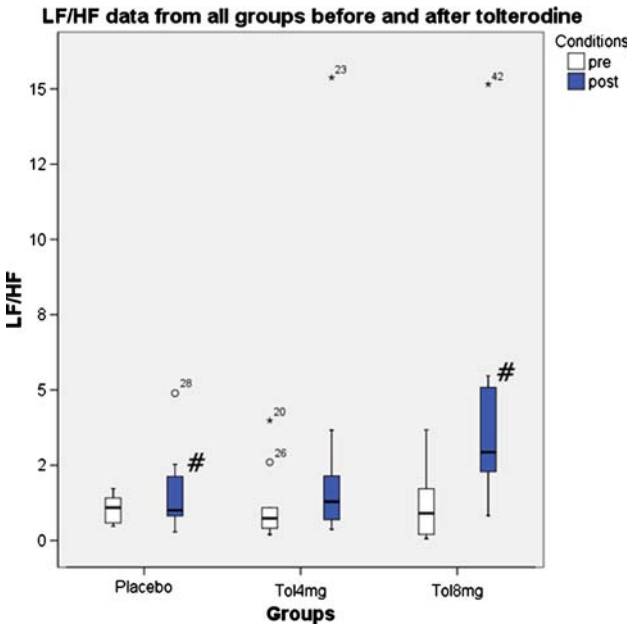

Fig. 1 LF/HF data for each group, sorted by pre (*white boxplots*) and post (*blue boxplots*) treatment period. The boxplots demonstrate minimum, 25% percentile, median, 75% percentile, and maximum. #p = 0.01. Tol tolterodine

Discussion

Tolterodine is not selective for a muscarinic receptor subtype [17] and can therefore cause cardiac side effects via the M_2 receptors on the heart [8, 18].

Besides M2, other muscarinic receptors (M1, M3 and M5) have been localized in the heart [8, 19]. Low-dose

muscarinic antagonists might cause different effects via M1 than M2 (i.e., HR decrease) [19]. However, cholinergically mediated HR regulation is mainly regulated by M2 receptors and the exact functional role of the non-M2 receptors in the heart is rather speculative and needs to be further clarified [7, 8].

Anticholinergic influence on the HRV has been demonstrated in human subjects by Pentillä et al. [20], showing a reduction in HF power of 99% after a single intravenous injection of 10 μg kg^{-1} atropine or glycopyrolate. These results are not surprising as the HF spectrum almost exclusively reflects the parasympathetic input to the heart [15, 21], which is reduced or inhibited after the intravenous anticholinergic application [20]. A similar effect was observed in our study group for Tol8 with a significant decrease in the HF spectrum post-medication.

Another important frequency domain parameter is the LF, which is influenced by both parasympathetic and sympathetic cardiac input [15, 21]. LF did not significantly change in any group and it might be possible that the influence of tolterodine on the parasympathetic system is strong enough to decrease the HF spectrum but does not alter the LF spectrum, as it reflects also sympathetic input.

The parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) are antagonists and cardiac input from both is usually never in a complete equilibrium. Rather, there is a constant variability reflecting the ability of the organism to rapidly adapt the cardiovascular system to changing needs in response to a broad range of internal and external stimuli [22]. A decrease of one antagonist (e.g., PNS) causes a relative increase of the other antagonist (e.g., SNS), which is why the LF/HF ratio, an indicator of sympathovagal balance [15, 21], significantly increased after Tol8.

Whilst the intrinsic heart rate is influenced by both the PNS and SNS, the resting heart rate is mainly dependent on the parasympathetic tone [8], which explains why the rHR is significantly elevated after Tol8 and Tol4, although subjects were in the same recumbent position during the pre- and post-dosing measurements. These rHR findings are in line with the findings from a large randomized controlled study investigating tolterodine and darifenacine in healthy subjects older than 50 years, showing a significantly increased HR after Tol4 [7]. The results of Olshansky et al. [7] show, in contrast to our rHR results, a significant increase in HR after tolterodine dosing versus placebo. This difference might be due to the multiple dose investigation in the Olshansky study as compared to a single dose investigation in our study [7].

The physiological basis of the VLF component is less clear, although earlier studies described that VLF is a more powerful risk predictor in cardiovascular disease than HF or LF [23]. Some authors suggest it may represent the influence of the peripheral vasomotor and renin-angiotensin systems [15].

Regarding the time domain parameters, RMSSD represents a measure of the variability of the interval between successive beats and mainly reflects parasympathetic activity [15, 16, 22]. Therefore, a reduction in RMSSD can be expected after application of antimuscarinic drugs, as observed in the Tol8 group. This result is again in agreement with the findings from Pentillä et al. [20], who demonstrated a RMSSD decrease of 97% after intravenous injection of atropine and glycopyrolate. The SDNN is a more simple but unspecific indicator of the total amount of variability, which likewise decreases in response to anticholinergic influence on the heart, as again demonstrated by the results of the Tol8 group. A reduction of RMSSD or SDNN generally implies a reduction in HRV, which could also be observed in the reduction of the total spectral power in the Tol8 group.

A reduced HRV has been associated with a poor prognosis of cardiovascular disease, an increased risk of incident myocardial infarction, cardiovascular mortality, and death from other causes in the general population [14]. Previous studies however, linking HRV to cardiovascular outcomes, have looked at basal parameters. Whether drug-induced changes of HRV play a similar role is not fully clear.

Although Tol8 showed a significant effect on nearly all HRV parameters within this group (Table 1), only the increase in LF/HF appeared significantly different in comparison to the placebo group. This is probably due to the high interindividual variability in combination with the quite small group sizes [20]. However, the effect of Tol8 on LF/HF seems strong enough to show significant differences between groups even with these group sizes. This increase in the LF/HF ratio indicates a significant shift in the autonomic balance towards a sympathetic predominance on the heart, which can have unfavorable cardiac effects if this condition were to persist for longer terms. As the 8 mg dose is not approved for OAB treatment and therefore rarely used, those results might be irrelevant for the usual non-neurogenic OAB population. However, patients with NDO usually require higher antimuscarinic doses or a combination of antimuscarinic drugs [24, 25]. The underlying disease in NDO (e.g., spinal cord injury, multiple sclerosis) often causes some degree of autonomic dysfunction that can also affect the heart [26, 27], resulting amongst others in elevated HR [27]. Thus, a high dose antimuscarinic treatment might expose those patients to an increased cardiac risk.

In the Tol4 group, none of the post-treatment HRV values—including rHR—were significantly different compared to the post-treatment values of the placebo group.

However, it cannot be stated that Tol4 does not have any relevant influence on the HRV, as VLF and rHR values are significantly altered post treatment in the 4 mg group.

It has to be considered that only a single dose of tolterodine ER was investigated and a development of tolerance towards antimuscarinic cardiac effects might occur with chronic dosing. Thus, effects observed in a single-dose study might overestimate HR effects during long term treatment, although steady state plasma levels are on average higher than with a single dose [28]. To our knowledge there is no published study specifically investigating changes in heart rate over time in regard to antimuscarinic treatment. However, the results of the study by Olshansky et al. [7] showed a significant increase in HR with tolterodine compared to placebo even after 7 days. Moreover, a study, investigating cardiac risks under respiratory medications, showed that supraventricular tachycardia was associated with long term antimuscarinic treatment rather than with short term treatment [29].

Although significant elevations of HR after Tol4 versus placebo have been demonstrated in a population >50 years of age [7], an extrapolation of our findings to the elderly, more OAB relevant population, has to be regarded cautiously as elderly patients might react differently to antimuscarinic drugs than young subjects due to potential aging related changes in atrial muscarinic receptor density and function [30].

Nevertheless, it is well established that with increasing age, the HRV decreases [16] and the incidence for cardiovascular diseases increases [10]. This might be especially important considering that the incidence of OAB, and subsequently the incidence of antimuscarinic drug treatment, also increase with age [4, 5]. Together, these conditions and the well-established relationships between age, increasing HR, and mortality/morbidity rates can make patients with OAB and concomitant cardiovascular diseases more vulnerable to the cardiac side-effects of antimuscarinics [11].

Adverse events on the heart due to antimuscarinic OAB treatment might remain undiscovered as they are usually not as obvious as the antimuscarinic effect on the salivary glands, causing dry mouth.

We would therefore encourage the implementation of HRV evaluation in future clinical trials with antimuscarinic drugs to gain more insight about possible adverse cardiac effects of these drugs and its clinical relevance in a larger patient population. This investigation of the influence of an oral antimuscarinic drug, used in OAB treatment, on the HRV provides useful first results and a basis for further larger investigations.

Conclusions

Although VLF and rHR are significantly altered after a single dose of Tol4, which might be of prognostic value, it seems not to significantly alter the HRV or rHR versus placebo in healthy young female subjects. A single dose of Tol8, however, seems to reduce HRV and showed a significant reduction in LF/HF as compared to placebo. Although Tol8 is not the recommended and approved dose in OAB treatment, these findings can be relevant for the daily therapy of patients with pre-existing cardiac disorders and patients with NDO, requiring higher antimuscarinic doses, and need to be further investigated by implementing the HRV analysis in larger future clinical trials with antimuscarinic drugs for OAB treatment.

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Conflict of interest statement Brigitte Schurch is a consultant for Pfizer.

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