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Cardiovascular Safety and Overall Tolerability of Solifenacin in Routine Clinical Use

A 12-Week, Open-Label, Post-Marketing Surveillance Study

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Abstract

Background: Muscarinic receptor antagonists are the standard of care for patients with overactive bladder (OAB). However, they can increase heart rate, and this can be disadvantageous in patients with coronary heart disease (CHD) or congestive heart failure (CHF). Comedications frequently used in the treatment of cardiovascular disease can further increase the risk for elevation of heart rate.

Objective: As such high-risk patients have not been well represented in most randomized trials of muscarinic receptor antagonists, we investigated whether the muscarinic receptor antagonist solifenacin alters heart rate or has other cardiovascular adverse effects during routine use in OAB patients. The study evaluated these effects both in the overall group and in pre-defined risk groups. The overall tolerability and safety of solifenacin were also explored.

Methods: This open-label, post-marketing surveillance study was specifically designed to evaluate the cardiovascular safety of solifenacin 5–10 mg once daily during a 12-week treatment course without specific inclusion or exclusion criteria but with systematic documentation of heart rate-relevant co-morbidities and comedications. The study was conducted in 4450 patients with OAB under the care of office-based urologists. The primary outcome measurement was heart rate. Secondary outcome measures were blood pressure and overall adverse events, which were systematically recorded before, during (after 1 week) and at study end; in many cases, an ECG was also conducted.

Results: CHD, previous myocardial infarction or CHF were reported by 11.9%, 1.6% and 7.0% of patients, respectively, and >60% were receiving at least one comedication. An ECG was conducted prior to solifenacin treatment in 915 patients and revealed abnormalities in 17.3%. At study end, 72.4% and 19.1% of patients were taking solifenacin 5 mg and 10 mg, respectively. No clinically relevant alterations in mean heart rate (75.2 ± 8.2 beats/min pre-treatment vs 74.5 ± 7.6 beats/min at study end) or mean blood pressure (137/82 mmHg pre-treatment vs 134/81 mmHg at study end) were observed. In the subgroup of

patients who underwent ECG both before and during treatment, no increase in the prevalence of pathological findings was noted. Adverse effects were rare (affecting 4.8% of patients), and treatment discontinuations due to adverse effects occurred in only 1.4% of patients. Among various possible cofactors, only age >80 years and the presence of comedications significantly affected adverse event incidence.

Conclusion: In real-life conditions, i.e. with inclusion of large numbers of patients with cardiovascular co-morbidities and taking comedications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure.

Background

Overactive bladder syndrome (OAB) is defined by the presence of urgency, with or without incontinence, usually accompanied by frequency and nocturia.[1] Epidemiological studies have shown OAB to be present in about 16% of the general population aged ≥40 years.[2,3] Muscarinic acetylcholine receptor antagonists are the primary form of treatment for OAB patients.[4,5] A classical adverse effect of muscarinic receptor antagonists is an increase in heart rate, and representatives of this class such as atropine are explicitly used to increase heart beat in bradycardic patients. This adverse effect is mediated by the muscarinic M_2 receptor subtype.[6] Heart rate elevations may potentially create a problem because the prevalence of OAB increases with advancing age,[2,3] as do potential co-morbidities in which elevations of heart rate may put patients at risk, such as coronary heart disease (CHD) or congestive heart failure (CHF).

The most frequently observed adverse effects associated with muscarinic receptor antagonists administered for treatment of OAB in placebo-controlled studies are dry mouth, constipation and blurred vision.[4,5] Surprisingly, elevations of heart rate have not typically been reported as major adverse effects of muscarinic receptor antagonists in OAB studies. However, such results may be false negative since many studies, such as phase III registration trials, often excluded patients with major co-morbidities and/or because those studies were not specifically designed to assess the cardiovascular tolerability of the muscarinic receptor antagonists.

Solifenacin is a muscarinic receptor antagonist recently introduced as a treatment for OAB.[7-9] At the molecular level, solifenacin differs from other muscarinic receptor antagonists used in the treatment of OAB such as tolterodine in that it has a moderate selectivity for M_3 relative to M_2 receptors.[10] In light of the above considerations, a study was designed to investigate the cardiovascular safety of solifenacin in routine clinical use, i.e. under conditions in which patients with a potentially increased risk had not been excluded. The primary question of this study was whether solifenacin, as used in the routine treatment of OAB, increases heart rate, particularly in patients at risk because of co-morbidities and/or concomitant medication use. Because of the inter-relatedness of heart rate and blood pressure, possible drug effects on the latter were also explored. The overall tolerability and safety of solifenacin in routine use were also evaluated.

Patients and Methods

Study Design and Treatment

In an open-label, observational study, 1316 office-based urologists in Germany systematically documented their observations on case report forms in up to five consecutive patients diagnosed with OAB. All office-based urologists in Germany were approached informally concerning participation in the study, and approximately 50% agreed to take part.

Patient Selection and Treatment

There were no specific inclusion and exclusion criteria for patients other than a minimum age of 18 years and the recommendations relating to use of solifenacin included in the Summary of Product Characteristics. Consistent with regulations in Germany, patient consent for participation in the study was neither required nor obtained because patients did not receive medication for study purposes. At the time the study was performed, German regulations did not recommend ethical committee approval for purely observational studies such as this one. Participating physicians were asked to systematically record their observations on patients receiving solifenacin (Vesicare®[1]) [Astellas, Tokyo, Japan], based upon their medical judgment. According to the package insert, the recommended solifenacin doses were 5 and 10 mg once daily. The planned duration of treatment was 12 weeks.

Patient Evaluation

Visits were scheduled at the time of the initial prescription and after approximately 1 and 12 weeks. At the initial visit, a medical history, including existing cardiovascular risk factors, concomitant diseases and current medication, was recorded. This information was used to stratify the population for all further analyses. Moreover, the urologists were asked to measure sitting blood pressure at least twice, with at least 5 minutes between measurements, and to record heart rate. If an ECG had been performed, the ECG-derived heart rate and any abnormalities were also documented. Results of urinalysis, if performed, were also recorded. At each subsequent visit, heart rate, blood pressure and, if performed, results of ECG and urinalysis were documented. The present analysis is based upon the first vital sign measurements; however, blood pressure readings at the second and, if applicable, third measurement yielded very similar results. Moreover, heart rates measured during blood pressure reading and, where available, ECG-derived values showed good correlation ($r^2 = 0.621$). The starting dose of solifenacin was recorded at the first visit, and alterations thereof were documented at subsequent visits. Monitoring of adverse events was based on spontaneous reporting. At the last visit, the patient was asked to separately rate the tolerability of treatment as 'very good', 'good', 'moderate' or 'poor'.

Statistical Analysis

Data handling was performed by Medidata (Konstanz, Germany), a contract research organization. In some cases, reported percentages do not add up to 100% because of missing data. Descriptive statistical analysis (mean ± SD) and multiple regression analysis using the logit link function were performed using the SAS program package (version 8.2) [SAS Institute Inc., Cary, NC, USA].

Results

Patient Characteristics

Patient enrolment commenced in September 2004, and the last patient completed the study in November 2005. A total of 4450 patients were recruited, of whom 83.5% were female. Mean patient age, weight and height were 63.6 ± 13.1 years, 75.5 ± 12.3 kg, and 167 ± 7 cm, respectively. Ethnicity was not recorded in this study, but the vast majority of OAB patients in Germany are Caucasian. Before entering the study, OAB had been present in patients for 2.9 ± 3.7 years (median 1.5 years, range: newly diagnosed to 34.6 years). Accordingly, about 70% of patients had previously received at least one form of non-pharmacological OAB treatment (including 51% absorbent products, 41% pelvic floor exercises, 22% bladder training). About 70% of patients had previously received at least one form of drug treatment (including 28% herbal drugs, 23% oxybutynin, 20% trospium chloride, 13% tolterodine and 12% topical estrogens). Based upon the case record forms provided by the physicians and relying on the individual physician's judgment rather than using defined criteria, the following concomitant diseases related to the cardiovascular system were present:

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Demographics of patients with and without concomitant disease

Demographic	None	CHD/MI	CHF	Diabetes mellitus
No. of patients	1438	556	313	785
Females (%)	88.4	75.7	83.7	81.3
Age (y) [mean ± SD]	55.9 ± 13.0	72.7 ± 9.7	76.5 ± 9.1	68.5 ± 10.3
Weight (kg) [mean ± SD]	72.9 ± 11.3	75.9 ± 12.6	75.4 ± 13.6	79.2 ± 12.6
Height (cm) [mean ± SD]	168 ± 7	167 ± 8	165 ± 7	167 ± 7
BMI (kg/m^2) [mean ± SD]	25.8 ± 3.7	27.4 ± 3.8	27.7 ± 4.5	28.4 ± 4.2
Concurrent medication (%)	4.2	94.8	96.2	92.9
Final solifenacin dose, 5/10 mg (%)	76.1/15.2	69.8/21.2	67.1/21.4	69.2/23.3

BMI = body mass index; **CHD** = coronary heart disease; **CHF** = congestive heart failure; **MI** = myocardial infarction.

hypertension (41.7%), CHD (11.9%), previous myocardial infarction (1.6%), CHF (7.0%), diabetes mellitus (17.6%), other metabolic disorders (19.5%) and 'other cardiovascular diseases' (5.3%). An ECG had been performed before treatment in 915 patients (20.6%) and had shown abnormalities in 158 cases, of which 41 were judged to be clinically relevant. Among concomitant diseases not related to the cardiovascular system, asthma (3.3%) and 'other concomitant disease' (22.8%) were documented; only 32.3% of patients were not reported to have any concomitant disease. At least one concurrent medications were being taken by 60.8% of patients.

The mean duration of treatment was 13 weeks (interquartile range 12–14 weeks). The study was completed as planned by 4146 patients (93.2%). Discontinuation because of insufficient therapeutic effect was reported in 68 patients (1.5%) and because of adverse events in 62 patients (1.4%). Loss to follow-up was recorded in 68 patients (1.5%).

Solifenacin Dose

The once daily starting dose of solifenacin was 5 mg in 93.4% of patients and 10 mg in 6.1%. At the first and second follow-up visits, the dose was adjusted in 14.5% and 5.8% of patients, respectively. Thus, at the final visit, 3220 patients were taking 5 mg, 851 patients were taking 10 mg, and 17 patients were taking various other dosages (discontinuation or missing data for 362 patients). Interestingly, patients with co-morbidities and/or comedications were more likely to be titrated to the 10-mg dose than those without (table I and table II).

Safety and Tolerability

Treatment-emergent adverse events were reported in 215 patients (4.8%), of which 13 were classified as serious. This included four deaths, none of which was classified as probably or possibly related to treatment (one 85-year-old patient dying from CHF, one 85-year-old patient dying from colon cancer, one 82-year-old patient with CHF, hypertension and renal failure [cause of death not documented], and one 85-year-old patient with hypertension [cause of death not documented]). Only one serious adverse event (generalized oedema, fatigue and flickering vision) was classified as probably treatment-related and one (acute abdominal pain with coprostatis leading to hospitalization) as possibly treatment-related; both patients recovered fully.

A total of 282 non-serious treatment-emergent adverse events were reported in 202 patients (4.5%). Among these, the following were described in ≥0.2% of patients: leukocyturia (48, 1.1%), dry mouth (31, 0.7%), haematuria (26, 0.6%), constipation (20, 0.4%), proteinuria (17, 0.4%), urinary tract infection (15, 0.3%), nausea (14, 0.3%), nitrate present in urine (13, 0.3%), bacteriuria (9, 0.2%), glycosuria (7, 0.2%). Adverse events related to the cardiovascular system were present in <0.2% of patients. At the final visit, the tolerability of solifenacin treatment was rated as very good, good, moderate and poor by 53%, 41%, 3% and 1% of patients, respectively.

A further safety analysis compared patients without concomitant diseases with the (partially overlapping) subgroups of patients with CHD (including all patients with a history of myocardial infarction),

Table II. Demographics of patients taking tachycardic, bradycardic or no concurrent medications at baseline

Demographic	None	Tachycardic	Bradycardic
No. of patients	1513	522	780
Females (%)	86.8	79.9	82.4
Age (y) [mean ± SD]	57.4 ± 13.3	71.7 ± 10.2	68.9 ± 10.5
Weight (kg) [mean ± SD]	73.5 ± 11.6	76.4 ± 12.7	77.3 ± 12.4
Height (cm) [mean ± SD]	168 ± 7	167 ± 7	167 ± 7
BMI (kg/m^2) [mean ± SD]	26.1 ± 3.8	27.6 ± 4.0	27.8 ± 4.1
Concomitant CHD (%)	1.5	46.6	31.0
Concomitant MI (%)	0.1	5.6	4.6
Concomitant CHF (%)	0.7	19.9	17.6
Concomitant diabetes mellitus (%)	3.2	34.9	27.3
Final solifenacin dose, 5/10 mg (%)	73.9/17.3	69.2/21.6	70.6/21.7

BMI = body mass index; **CHD** = coronary heart disease; **CHF** = congestive heart failure; **MI** = myocardial infarction.

CHF and diabetes (table I). Patients with concomitant disease were slightly more likely to be male, were on average 13 (diabetes) to 20 (CHF) years older and had a higher body weight and body mass index (BMI) than patients without concomitant disease. Concurrent medication use was rare in patients without concomitant disease but present in most patients with concomitant disease. Interestingly, patients with concomitant disease were less likely to receive 5 mg and more likely to receive 10 mg as the final solifenacin dose.

These data demonstrated that co-morbidity was linked to sex, age, BMI and comedication. Therefore, we explored whether any of these variables might identify patients at increased risk for adverse events using a multiple regression model (table III). In this analysis, only age and the presence of comedication were statistically associated with adverse events. While the odds ratio (OR) for comedication was 1.8 (95% CI 1.2, 2.6), among all age subgroups only those aged >80 years had a statistically significant increase in their likelihood to experience adverse events (OR 3.9 [95% CI 1.3, 11.5]).

In the overall population, solifenacin treatment did not increase heart rate (75.2 ± 8.2 pre-treatment vs 74.5 ± 7.6 beats/min at study end) or blood pressure (137 ± 15/82 ± 7 mmHg pre-treatment vs 134 ± 13/81 ± 8 mmHg at study end). More importantly, the mean intra-individual alteration in heart rate was −0.8 ± 6.3 beats/min (median 0, inter-

Table III. Multiple regression analysis of the presence of treatment-emergent adverse events and possible explanatory factors. Odds ratios and p-values are relative to the respective reference group, i.e. female sex, age ≤40 years and absence of comedication or the various co-morbidities

Explanatory variable	Odds ratio (95% CI)	p-Value
Male sex	0.840 (0.559, 1.265)	0.4042
Age (y)	NA	0.0019
41–50	1.144 (0.363, 3.608)	0.8180
51–60	1.773 (0.614, 5.119)	0.2900
61–70	1.941 (0.682, 5.524)	0.2137
71–80	1.816 (0.627, 5.262)	0.2715
>80	3.902 (1.327, 11.472)	0.0133
BMI (kg/m^2)	NA	0.9052
Comedication present	1.768 (1.219, 2.564)	0.0027
CHD/MI present	0.997 (0.667, 1.491)	0.9892
CHF present	1.243 (0.774, 1.997)	0.3684
Diabetes mellitus present	1.083 (0.762, 1.541)	0.6557

BMI = body mass index; **CHD** = coronary heart disease; **CHF** = congestive heart failure; **MI** = myocardial infarction; **NA** = not applicable.

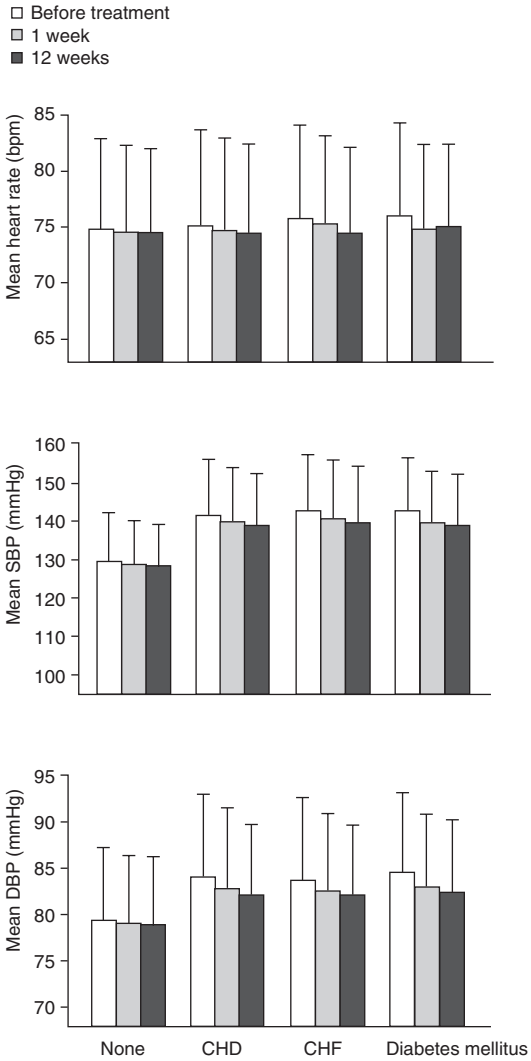

Fig. 1. Effect of co-morbidities on solifenacin treatment-associated alterations in heart rate and systolic (SBP) and diastolic blood pressure (DBP). The T bars represent the standard deviation. **bpm** = beats/min; **CHD** = coronary heart disease; **CHF** = congestive heart failure.

quartile range −4 to 3 beats/min). Similar findings were observed when ECG-derived heart rate was assessed in the subgroup in which an ECG had been preformed (73.4 ± 8.7 pre-treatment vs 72.0 ± 7.7 beats/min at study end). Patients with CHD, CHF or diabetes had higher basal blood pressure and a very slightly higher heart rate than those without concomitant disease (figure 1). However, solifenacin did not increase mean heart rate or blood pressure in patients with concomitant disease (figure 1).

Finally, we explored the role of comedication with known effects on heart rate on the cardiovascular safety of solifenacin. For this purpose, we compared patients taking concurrent medications that could potentially increase heart rate, such as calcium channel antagonists or nitrates, with those taking concurrent medications that could potentially decrease heart rate, such as β-adrenoceptor antagonists or digitalis glycosides (table II). Patients with concurrent medication were more likely to be male than those not taking concurrent medications and were on average about 12–14 years older. While concomitant disease was rare in patients not taking concurrent medications, it was frequently observed in those taking concurrent medication. Patients taking concurrent medication tended to be administered higher doses of solifenacin. Patients taking concurrent medication also had higher basal blood pressure, but solifenacin did not increase heart rate or blood pressure, regardless of whether concomitant medication was potentially brady- or tachycardic or not being taken at all (figure 2).

Discussion

OAB mainly affects elderly patients,[2,3] a group that is also likely to have co-morbidities and to be taking concomitant medications, including some that act on the cardiovascular system. In recent years, OAB has become the most frequent indication for the systemic use of muscarinic receptor antagonists, and such drugs are now the mainstay of medical treatment for OAB.[4,5] The most frequent adverse effects of muscarinic receptor antagonists in the treatment of OAB are dry mouth, constipation and blurred vision.[4,5] While these can be unpleasant and can lead to treatment discontinuation, they are not dangerous, with the possible exception of severe constipation in the elderly. Nevertheless, it is surprising that despite widespread use of muscarinic receptor antagonists in the treatment of OAB, no comprehensive analysis of their cardiovascular tolerability has been presented.

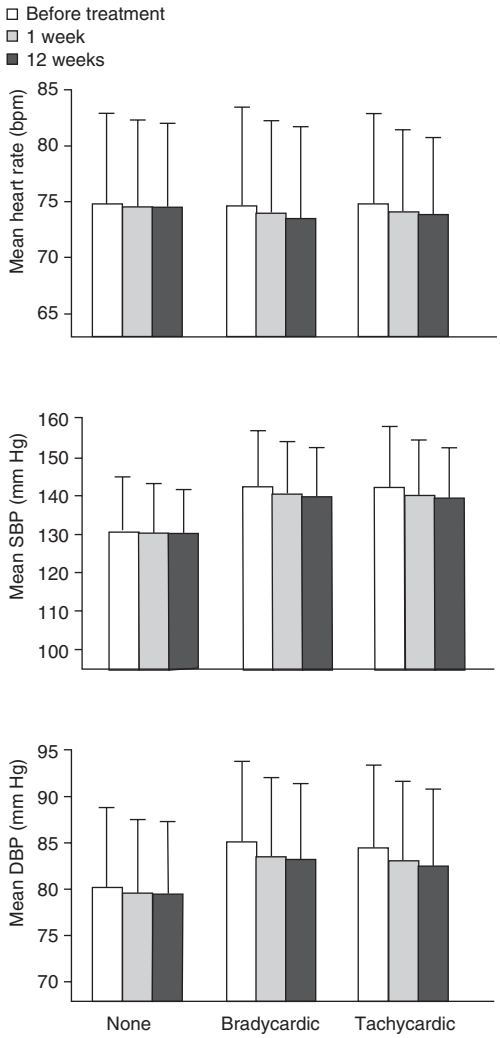

Fig. 2. Effect of comedications (none, bradycardic or tachycardic) on solifenacin treatment-associated alterations in heart rate and systolic (SBP) and diastolic blood pressure (DBP). The T bars represent the standard deviation. **bpm** = beats/min.

Therefore, the present study was designed to investigate the safety and tolerability of a recently introduced representative of this class, solifenacin. Our analysis has focused on subgroups of patients putatively at risk, i.e. the elderly and those with comorbidities and/or taking comedications. Moreover, we have specifically focused on the cardiovascular safety of solifenacin in such subgroups. For this purpose, we designed a large, open-label observational study as recommended by the German regulatory authorities. This design has the obvious limitation that it does not include a control group and hence does not allow for conclusions of whether observed effects can indeed be attributed to study medication. However, the present data provide a realistic impression of what physicians and patients can expect during routine use of a drug. More importantly, by design, such observational studies do not include specific inclusion and exclusion criteria and, therefore, also provide a more realistic impression of the composition of the patient population receiving a given drug in routine care. In other words, such observational studies have low internal but high external validity.[11] Finally, observational studies of this type can more easily recruit large patient numbers which are required to maintain statistical power when evaluating multiple, potentially related explanatory variables for a given parameter. These advantages and disadvantages need to be considered in the subsequent discussion of our findings.

In the present study, the overall tolerability of solifenacin was rated as very good or good by about 95% of patients, and treatment-emergent adverse events were recorded in <5% of patients. Adverse events reported in ≥0.2% of patients included dry mouth and constipation, which have also been the most frequently reported adverse events in randomized controlled studies of solifenacin, where they occurred at much higher frequencies than in placebo groups.[7-9] A similar pattern has been observed in an observational study of tolterodine for treatment of OAB.[12] Surprisingly, abnormal urinalysis indicators such as leukocyturia, haematuria, proteinuria, nitrate or bacteria present in urine were also reported in ≥0.2% of patients in the current study but were not noted in an observational study of tolterodine.[12] The simple explanation for these divergent findings may be that the case record form used in the present study, but not that used in the study of tolterodine,[12] specifically asked whether urinalysis had been performed and, if so, what results had been obtained. Placebo-controlled studies of solifenacin and other muscarinic receptor antagonists show that, relative

to placebo, urinary tract infection is a rare but typical class effect of such drugs.[4,5]

Not unexpectedly, our initial descriptive analysis showed that patients with co-morbidities were slightly more likely to be male, tended to be considerably older, had a greater BMI and were much more likely to be taking comedications. This prompted us to specifically explore the potential role of these factors as indicators of increased risk for adverse events. Our analysis shows that despite the inclusion of large patient numbers and hence the development of great statistical power for evaluating the role of these variables, only age and the presence of comedication were associated with an increased OR for experiencing an adverse event. When specific age groups were considered, a significantly increased likelihood for adverse events was observed only in patients aged >80 years, which is an age group that is well known to be more susceptible to experiencing adverse events. A more modest increase in the OR of experiencing an adverse event was observed in patients taking comedications. As we recorded treatment-emergent rather than only causally-related adverse events in our study, it remains unclear whether this increase in adverse events was the result of a pharmacodynamic or pharmacokinetic interaction of the comedication with solifenacin, or perhaps attributable to the comedication alone. Irrespective of this consideration, it should be emphasized that given the overall low incidence of adverse events and the moderate increase in their incidence in patients taking comedications, their overall presence even in this group was fairly low. Interestingly, sex, BMI and co-morbidity were not associated with an increased likelihood of adverse events. At least with respect to sex, this has also been observed in a previous observational study of another muscarinic receptor antagonist.[12]

Unlike dry mouth, constipation and blurred vision, cardiovascular adverse events, specifically tachycardia, have not routinely been reported in placebo-controlled studies of muscarinic receptor antagonists for the treatment of OAB.[4,5] This is surprising because elevations in heart rate are a well established class effect of muscarinic receptor antagonists. They are typically seen upon acute administration of prototypical muscarinic receptor antagonists such as atropine,[6] and such drugs are used in the treatment of bradycardic arrhythmias. Elevations in heart rate increase cardiac oxygen demand due to a higher workload and concomitantly decrease cardiac oxygen supply as a result of selective shortening of diastole, i.e. the part of the cardiac cycle during which the ventricle receives most of its blood supply. While this may be of little relevance in the healthy heart, it can have a damaging effect in an oxygen-starved heart and can potentially lead to myocardial infarction. Patients at risk for such events include those with CHD because they have an impaired cardiac oxygen supply at baseline. Patients with CHF may also be at risk because the failing heart is considered to be an oxygen-starved heart. Finally, autonomic regulation of heart rate may be impaired in diabetic patients because of diabetic polyneuropathy. Vasodilator drugs such as calcium channel antagonists or nitrates can cause reflex tachycardia and, therefore, patients taking such comedications may also be at higher risk for tachycardic effects of muscarinic receptor antagonists than those taking potentially bradycardic comedications (e.g. β-adrenoceptor antagonists and digitalis glycosides) or those not taking any concurrent medications. Therefore, our study was specifically designed to determine whether the muscarinic receptor antagonist solifenacin is more likely to cause tachycardia in such at-risk populations.

Patients in our study had a diagnosis of OAB and the study was accordingly conducted by board-certified urologists. As this is a group of physicians not routinely involved in cardiovascular medicine, we took specific steps to verify the technical quality of the haemodynamic measurements conducted in the study. Firstly, the physicians were asked to take multiple vital sign measurements per visit. Secondly, an ECG was performed in a considerable fraction (20.6%) of patients, and ECG-derived and manually recorded heart rates were in good agreement, indicating that our values are reliable. Our data demonstrated that solifenacin did not increase heart rate or blood pressure in the overall group of patients and

that patients with CHD, CHF or diabetes did not exhibit greater treatment-associated alterations of either parameter than those without such co-morbidities. Moreover, neither potentially bradycardic nor potentially tachycardic comedication was associated with alterations in heart rate or blood pressure during solifenacin treatment.

While, at least in patients with known or suspected coronary artery disease, higher heart rate is associated with greater cardiovascular risk,[13] it remains unclear what extent of resting heart rate elevation will make a drug unsafe. Decreases in heart rate of <5 beats/min apparently do not provide benefit, and it may be that elevations of <5 beats/min do not cause harm,[13] although this remains to be investigated in more detail. While there are no reports on elevations of heart rate exceeding 5 beats/min with administration of muscarinic receptor antagonists in the treatment of OAB, our study appears to be the first to systematically investigate this issue in a large cohort including numerous patients at increased risk. Several explanations can be proposed to account for the fact that solifenacin treatment in OAB patients did not increase heart rate. Firstly, most reports of tachycardia following administration of muscarinic receptor antagonists to humans reflect short-term effects.[14,15] Long-term treatment with muscarinic receptor antagonists,[16,17] similar to tissue denervation,[18] causes upregulation of the receptors and hence may make the heart less susceptible to the tachycardic effects of these drugs. Secondly, in contrast to several other muscarinic receptor antagonists used in the treatment of OAB, solifenacin has a moderate selectivity for M_3 over M_2 muscarinic receptors,[19] i.e. is moderately selective for the main receptor involved in bladder contraction as opposed to the receptor mediating heart rate elevations.[6] Thus, a solifenacin dose adequate to occupy M_3 receptors in the bladder is likely to cause a lesser degree of M_2 receptor occupation in the heart. Finally, it should be considered that the heart rate-elevating effects of muscarinic receptor agonists decline with age,[14] probably because of reduced cardiac expression of these muscarinic receptors.[15]

Conclusion

Our data demonstrate that solifenacin treatment of OAB patients does not increase heart rate, even in patients potentially at risk of this adverse event because of relevant cardiovascular co-morbidities or comedications. Our data confirm that solifenacin is a well tolerated drug in the treatment of OAB. Among several potential risk factors, the presence of concomitant medication use is associated with a moderate increase in treatment-emergent adverse events, but even in this group, adverse events are not frequent. As with any other medication, caution should be exercised when treating the very elderly, i.e. those aged >80 years. While effects on heart rate typically occur in the first weeks after treatment initiation, our findings on the overall tolerability and safety of solifenacin should be extended to evaluation of long-term treatment effects in future studies.

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