

Effectiveness of combined high-dosed trospium and solifenacin depending on severity of OAB symptoms in elderly men and women under cyclic therapy

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Article history

Submitted: Nov. 10, 2013

Accepted: Jan. 15, 2014

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Material and methods 313 patients, 196 women and 117 men over 65 (average age 68.6) were included in this study. All patients underwent urodynamic examination before enrollment and after the study was completed. For clinical evaluation of LUT state ICIQ-SF questionnaires and bladder diaries were used. Patients with moderate (A, n = 155) and severe (B, n = 158) symptoms of OAB. Each group was divided into subgroups in which patients received Trospium 60 mg/day and Solifenacin 20 mg/day during two cycles – 1.5 and 1 month with one month interval (A1 and B1); subgroups in which second cycle was substituted with placebo (A2, B2), and control groups (A3, B3).

Results In groups with moderate symptoms of OAB ratio of patients demonstrated decrease of frequency of EI ≥ 1.5 a day remained at the level of 45-60% during all observation period. In subgroups with severe symptoms of OAB percentage of such patients was 55.3% for the subgroup which received two cycle therapy, and decreased to 26% in the subgroup which underwent 1 cycle therapy.

Urodynamic indices for state of LUT correlated with clinical indicators ($r = 0.57-0.71$ at $p \leq 0.05$).

Conclusions Short single cycle of high-dosed Solifenacin and Trospium in elderly patients with moderate symptoms of OAB enables to maintain long therapeutic effect with acceptable level of side effects. This treatment algorithm applied in two cycle course is an effective and safe method for management of severe symptoms of OAB in elderly patients without increased risk of side effects.

Key Words: overactive bladder ◊ elderly ◊ antimuscarinic

INTRODUCTION

The prevalence of overactive bladder (OAB) symptoms in older age is very high, as evaluated by specialists [1, 2, 3]. This high prevalence is associated with improved diagnostic methods, earlier detection of pathologies, general ageing of population, active raising of awareness among older adults about necessity to consult with specialist if symptoms of lower urinary tract disorders occur, and introduction of effective and safe drugs which can significantly improve quality of their lives [4, 5, 6]. OAB symptoms include frequent urination, urgency, nocturia, and episodes of incontinence (EI). In spite

of reports on successful use of antagonists of b β -adrenoreceptors and other drugs [7]; antimuscarinics, such as Trospium, Solifenacin, Darifenacin, remain drug of choice for management of OAB in elderly men and women. Clinical trials showed that these drugs significantly improve symptoms of OAB, including severe symptoms [8, 9, 10]. The severity of OAB symptoms significantly varies amongst patients. To date, several studies have been performed in order to increase the effectiveness of management of OAB with varying severity using different doses of well-known antimuscarinics [11, 12]. Nevertheless, the issue concerning reactions of patients with various symptoms of OAB to different treatment algorithms

requires further research. Its solution will avoid excessive drug administration when possible, and ultimately result in a decreased risk of adverse effects. The frequency of EI per day or per week is used, among other indicators, for the evaluation of clinical effectiveness of management of OAB symptoms [12]. Importance of this indicator of the state of the lower urinary tract (LUT) is confirmed by its high level of correlation with subjective patient-reported outcomes, such as the Patient's Perception of Bladder Condition (PPBC), health related quality of life (HRQoL), parameters of urodynamic state, and other clinical symptoms. In several studies, a value of EI >21/week or EI >3/day is used for determining severity of OAB symptoms based on comparison of this parameter with other clinical and urodynamic indices [13, 14]. In our work we were guided by these data and considered them proven and persuasive. In the previous study we demonstrated the effectiveness and safety of management of OAB in elderly men and women with combined high-dose antimuscarinics [15]. This study follows the previous one; its aim is to determine an optimal algorithm of drug management of OAB in elderly men and women with varying severities of symptoms and to assess the necessity of cyclic treatment according to the proposed algorithm in order to maintain a long term positive therapeutic effect.

MATERIAL AND METHODS

The study was performed from June 1, 2010 to June 30, 2012 using principles of randomization, blind random assignment method, and placebo control. 313 patients, 196 women and 117 men over 65 (aver-

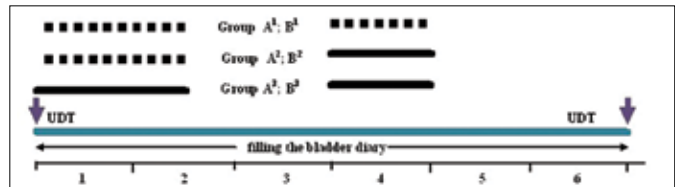


Figure 1. Algorithm of examination and treatment of elderly patients with varying baseline symptom severity.

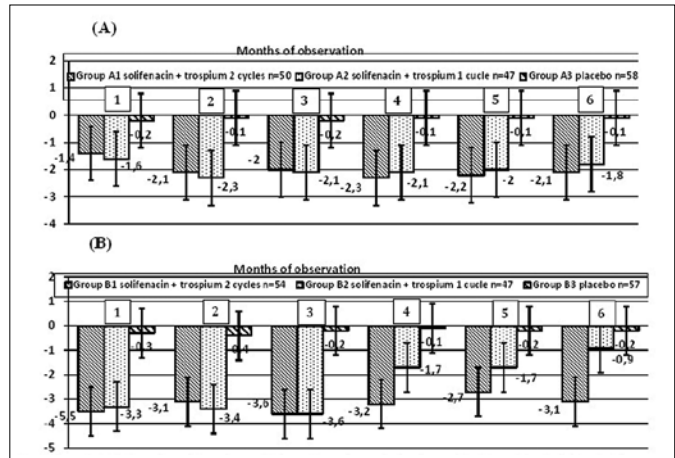


Figure 2. Impact of solifenacin and trospium on urinary incontinence episodes per day over time in patients with OAB according to baseline symptom severity.

age age 68.6) were included in this study (Table 1). In accordance with research protocol, the main criteria for exclusion included intolerance of antimuscarinic drugs, any pathological conditions in which antimuscarinics are contraindicated, and presence of organic damage of the

Table 1. Baseline Characteristics of patients (n = 313; 298)

Characteristics	Group taking solifenacin 60 mg + trospium 40 mg – 2 cycles		Group taking solifenacin 60 mg + trospium 40 mg – 1 cycle and placebo – 1 cycle		Group taking placebo	
	Moderate* Group A1	Severe** Group A2	Moderate Group B1	Severe Group B2	Moderate Group A3	Severe Group B3
Number of patients	50	47	54	47	58	57
Mean age in years	69.8 (7.8)	67.0 (11.4)	71.3 (6.9)	69.1 (5.9)	69.7 (7.9)	67.8 (13.7)
Median incontinence episodes/day, n	2.6 (0.9)	4.7 (0.4)	2.8 (0.6)	5.4 (1.2)	2.8 (0.4)	5.3 (0.9)
Median urgency episodes/day, n	3.0 (1.1)	5.1 (1.3)	3.5 (0.5)	5.5 (0.9)	3.4 (1.2)	6.1 (0.8)
Median number of urination/day, n	8.9 (1.9)	11.7 (1.9)	9.7 (2.6)	12.4 (4.1)	9.1 (1.1)	12.3 (2.8)
Median volume voided/once, ml	145.8 (13.5)	129.8 (17.9)	157.8 (9.0)	107.8 (17.6)	155.8 (21.9)	125.9 (13.3)

*Patients with moderate OAB baseline symptoms (≤ 3 incontinence episodes per day), **Patients with severe OAB baseline symptoms (≥ 3 incontinence episodes per day)

central nervous system. Patients were distributed into groups and research was performed in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki [16, 17]. All patients in the groups demonstrated clinically and urodynamically proven OAB dysfunction. Clinical profiles of patients are shown in tables No. 1, 2. All patients underwent urodynamic examination before enrollment and after the study was completed (in 6 months) results of reflex volume, bladder capacity, detrusor compliance, and post-void residual volume were recorded. The urodynamic state of the lower urinary tract was evaluated using the "Relief-01" (DALPRIBOR, Vladivostok, Russia) system with a double catheter microtip (Apexmed International B.V., Netherlands) [18, 19]. For the clinical evaluation of urinary dysfunction we used an ICIQ-SF questionnaire recommended by ICS and bladder diaries in which frequency of urinations, incontinence events per day, amount of urine while urinating, and number of urgencies were recorded. Additionally, patients were asked to note any signs of unwellness in their diaries (without limited lists of side effects) [20, 21, 22].

The frequency of incontinence events was used as a measure of severity. In case of $EI \leq 3$ per day, severity of symptoms was considered to be moderate, in case of $EI \geq 3$ per day severity of symptoms was considered to be significant [12]. In accordance with severity criteria, patients were distributed into two main groups: patients with moderate (A, $n = 155$) and severe (B, $n = 158$) symptoms of OAB. The groups were then further divided into subgroups depending on their treatment algorithm. Patients from groups A¹ and B¹ ($n = 50$; 54) received Trospium 60 mg/day and Solifenacin 20 mg/day for 6 weeks and again for 4 weeks following a 6 week-interval; for a total of 2 cycles. Patients from subgroups A² and B² ($n = 47$; 47) received the same treatment as the previous groups during the first cycle and during the second cycle – placebo. Patients in subgroups A³ and B³ ($n = 58$; 57) received placebo during both cycles (Figure 1).

Initial data was collected using the Excel program of standard package Microsoft-XP (Microsoft-Rus, Vladivostok, Russia) and analyzed with the statistical analysis program SAS JMP Statistical Discovery 8.0.2 (SAS Institute, Cary, NC, USA). The Wilcoxon test was used to compare results in each treatment group before and after examination; the Kruskal-Wallis rank test was used for control of equality of medians from different groups. One-way analysis of variance (ANOVAs) with Tukey-Kramer honestly significant difference was used to compare effects in the three groups. Standard deviation P values of < 0.05 were considered statistically significant.

RESULTS

Improvement of incontinence events in patients with moderate symptoms in the course of treatment is shown in Figure 2A. Steady decrease of incontinence events in subgroups A¹ and A², both in subgroups which underwent two-cycle therapy and in the subgroup with one cycle treatment, was observed. Improvement continued for up to 6 months; a significant difference between subgroups was not found (-2.2 ; -1.8 $p \geq 0.05$). In the group of patients who received placebo, improvement of the indicator was insignificant. In the groups of patients with severe symptoms of OAB (Figure 2B) improvements of the indicator differed as follows: decrease of EI was steady only for the group in which patients underwent two cycle therapy (B¹); in group B² improvements significantly slowed by 4th month and by 6th month it was statistically equivalent to the group in which patients received placebo (B¹ = $-3.1(0.4)$; B² = $-0.9(0.2)$; $p \leq 0.05$). Changes in urinary urgency for patients with moderate symptoms (Figure 3A) also did not depend on number of cycles of the therapy. In subgroups A¹ and

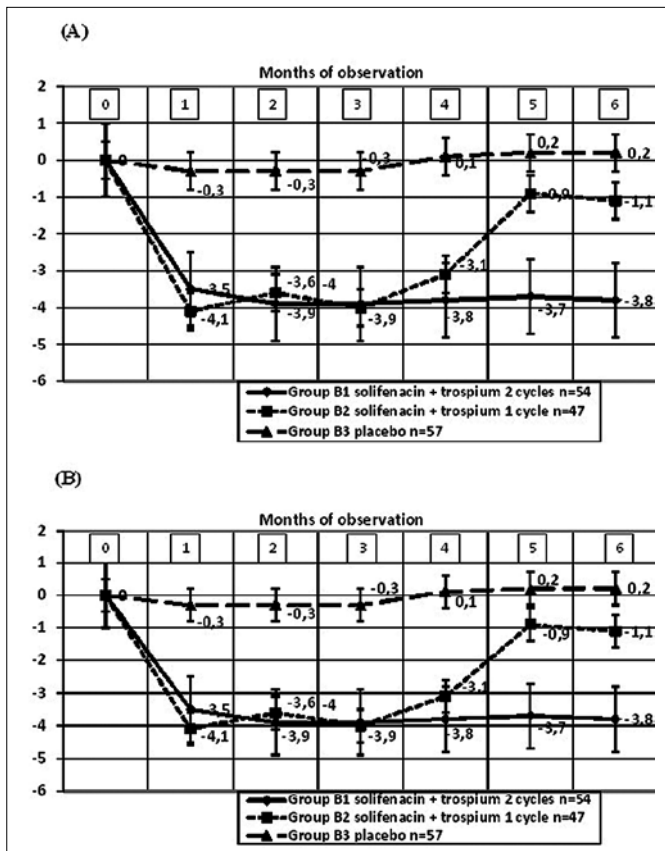


Figure 3. Effectiveness of solifenacin and trospium on urinary urgency episodes per day over time in patients with OAB according to baseline symptom severity.

A² decrease was steady until completion of the therapy [-2.7 (1.0); -2.3 (0.8); $p \geq 0.05$]; in placebo group (A³) it remained at the minimal level during all period of records. In subgroups with severe symptoms of OAB results were different. In subgroup B¹ values of the indicator changed insignificantly, in subgroup B² urinary urgency increased dramatically by the 5th month of observation [(-0.9 (0.7))]. In subgroup B³ values remained within statistical error.

The analysis of number of patients, who demonstrated decrease of incontinence events to ≥ 1.5 per day, allowed us to find the following regularity (Figure 4A,B). In groups with moderate severity of OAB symptoms, the ratio of such patients remained at the level of 45–60% during the entire observation period. In subgroup B¹ (two cycle therapy), the percentage of patients who demonstrated significant decrease of EI was 55.3% at the 6th month and did not change significantly during the examination period. In the subgroup with one-cycle therapy, by the end of examination the amount of such patients did not exceed 26%.

Analysis of urodynamic data before and after therapy made it possible to confirm tendencies of the dynamics of various clinical symptoms. In groups with moderate OAB symptoms (A¹, A²) parameters such as reflex volume, bladder capacity, and detrusor compliance were significantly high in comparison with starting levels (Table 2). Increase of level of post-void residual volume was insignificant. In groups with severe symptoms, parameters were different: in subgroup B² only volume index demonstrated significant difference; on the contrary, in subgroup B¹ all urodynamic indices were different from initial with $p \leq 0.001$.

During the period of the study, 15 (4.8%) people stopped their treatment. Among them 9 patients stopped due to development of side effects (6 – dry mouth, 1 – headaches, 1 – rash and itching, 1 – diarrhea). Three patients stopped their treatment

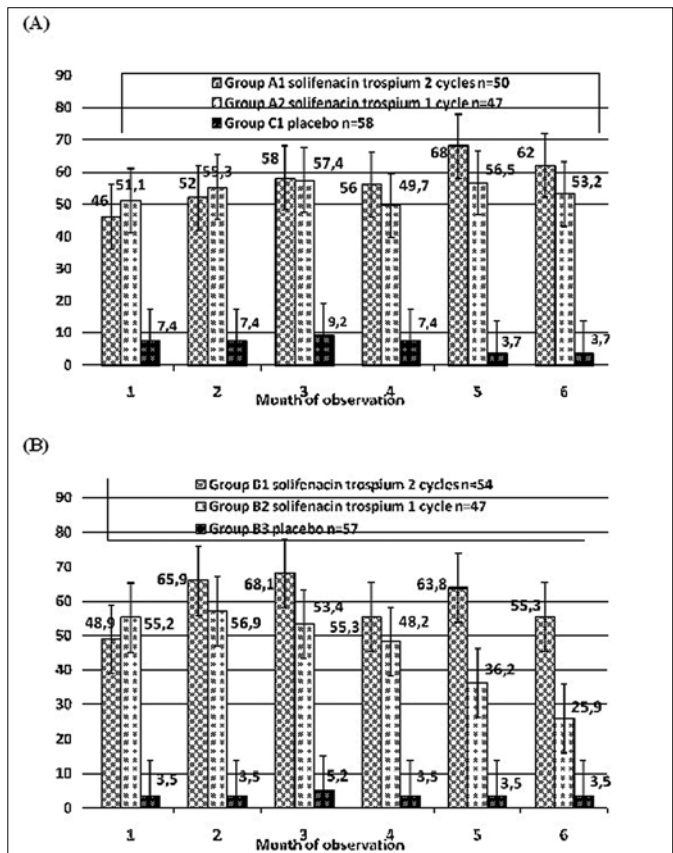


Figure 4. Ratio of patient overtime a reduction over 1.5 incontinence episodes per day according to baseline symptom severity.

because they did not experience any satisfactory results (at 2nd, 4th and 5th weeks of first cycle). In 2 cases treatment was discontinued due to circumstances not related to the treatment. One patient died of acute heart failure (not in the period of administration of the drugs).

37 (11.8%) patients reported side effects, but their severity was moderate, therefore it was not the rea-

Table 2. Result of urodynamic (n = 313; 298)

Form of control		Indicators of urodynamics (\pm SD)							
Parameters of the LUT	Post-void residual (ml)		Reflex volume (ml)		Bladder capacity (ml)		Detrusor compliance (ml/cm H ₂ O)		
	Before treat	After treat	Before treat	After treat	Before treat	After treat	Before treat	After treat	
Ttime of study	Before treat	After treat	Before treat	After treat	Before treat	After treat	Before treat	After treat	
Group A1 (n=50)	18.7 (7.4)	34.1 (5.7) *	164.6 (26.3)	275.3 (45.3)**	217.6 (24.6)	317.7 (35.6)**	24.3 (3.3)	36.3 (5.4)*	
Group A2 (n=47)	15.8 (12.2)	23.7 (4.9)	173.5 (41.5)	212.3 (35.9)	201.3 (37.7)	247.9 (26.8)	20.8 (1.5)	25.6 (2.4)	
Group A3 (n=58)	22.3 (4.8)	21.9 (9.2)	148.2 (37.8)	153.6 (44.2)	188.4 (47.4)	211.7 (34.3)	23.9 (11.6)	25.7 (4.9)	
Group B1 (n=54)	18.5 (4.7)	31.7 (5.8)*	121.4 (30.5)	285.7 (64.2)**	155.6 (47.8)	277.4 (35.6)**	15.8 (2.5)	33.5 (6.3)**	
Group B2 (n=47)	21.2 (4.6)	29.2 (9.4)	141.2 (15.8)	186.2 (14.5)*	178.4 (47.4)	201.7 (34.3)	17.7 (4.4)	23.5 (4.6)	
Group B3 (n=57)	22.6 (6.6)	19.1 (6.2)	136.6 (32.5)	115.6 (36.3)	159.5 (34.6)	145.4 (44.3)	17.3 (2.3)	16.4 (4.6)	

SD – standard deviation, * <0.05 , ** <0.001 ; “Before treat” – amounts taken at onset of study and considered baseline,

“After treat” – 6 months from the start of the study

son for stopping treatment. In 19 cases this symptom was dry mouth, in 5 – rash and skin itching, in 6 – nausea, in 4 – diarrhea, in 2 – headache, and in 1 – transient colour vision disorder. One patient suffered acute urinary retention, which disappeared during one day.

DISCUSSION

It is well known that approximately 30% of patients do not benefit from antimuscarinics administered at standard dosage [23, 24, 25]. In previous studies it was concluded that an increase of doses of antimuscarinic drugs of 1.5–2 times is well tolerated; without a rise, in most cases, of the quantity and strength of side effects [26, 27].

In our previous study we concluded that combination of high-dosed Trosipium and Solifenacin in elderly patients enables the decrease of OAB symptoms significantly with an acceptable level of side effects and absence of complications [15].

In this study we tried to determine effectiveness of one and two cycle therapy, with these high-dosed antimuscarinics, in elderly patients with different severity of OAB symptoms. It was established that a one-cycle, 1.5-month long treatment in elderly patients with moderate OAB resulted in significantly different symptom parameters of OAB from that of initial levels at the beginning of the study to those at the 6th month after treatment. In patients with severe symptoms of OAB, the total level of markers returns to the initial level by the 4th–5th month of observation. At two-cycle treatment, independent of severity of initial symptoms, parameters of state of LUT are significantly different from the initial parameters.

In other words, two-cycle treatment in accordance with proposed regimen provides satisfactory therapeutic effect under any severity of OAB; one-cycle treatment is sufficient for maintaining therapeutic effect for at least 6 months only in patients with moderate symptoms.

It is well known that the M_2 -muscarinic receptors are the predominant receptors in the urinary bladder. M_3 -muscarinic receptors are more efficient but they are represented in a lower amount. Relatively recently, pre-junctional-inhibitory M_2 - or M_4 -muscarinic receptors and M_1 -muscarinic receptors were detected

in the urinary bladder. There are articles stating that the M_2 -muscarinic receptors in urinary bladder of elderly people are the first to undergo involution. From this point of view, Solifenacin, which is a specific competitive inhibitor of mainly M_3 -subtype of receptors, and Trosipium, which has high affinity to all muscarinic receptors, are chosen for management of OAB in elderly men and women. Elderly patients tolerate high doses of these drugs comparatively well and effectiveness of such combinations is high [28–33].

It can be assumed that the high stability of therapeutic effect in patients with moderate symptoms of OAB is ensured by some cumulative effect at influencing “elderly bladder” M_3 receptors, which remained in satisfactory condition, as well as by the synergistic effect of two antimuscarinics with different spectrums. Probably such a reaction of the urinary bladder is also caused by the influence of drugs on specific receptors of urothelial and myogenic afferent pathways and suppression of “afferent noise” at this level [32]. In this case, a second cycle of antimuscarinics strengthens suppression of excessive action of receptors and obtains a significant effect for a comparatively longer period of time in patients with severe symptoms of OAB. Obtained results make it possible to receive satisfactory therapeutic effect in patients with moderate symptoms under a short therapeutic course lasting less than 6 months. We believe that this has important applied meaning given the fact that elderly patients follow prescriptions quite poorly and quickly get tired of long therapeutic courses.

We suppose that further study of bladder reaction, especially in elderly patients with moderate symptoms of OAB, to various doses of combined antimuscarinics, is necessary in order to decrease drug load.

CONCLUSIONS

Short cycle of high-dosed Solifenacin and Trosipium in elderly patients with moderate symptoms of OAB enables to maintain long therapeutic effect with acceptable level of side effects. It has important applied meaning for elderly men and women who are not good at exactly following prescriptions for a long time. Combinations of high-dosed Solifenacin and Trosipium in two-cycle treatment is an effective and safe method for management of severe symptoms of OAB in elderly patients without increased risk of side effects.

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