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Which antimuscarinic agents used in the treatment of overactive bladder increase heart rate? a prospective randomized clinical trial

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Abstract

Purpose To compare the heart rate increase side effect of different antimuscarinic drugs used in overactive bladder (OAB).

Methods Overall 341 patients were consecutively randomized to take seven different antimuscarinic drugs between January 2014 and June 2016 at three institutions, and 250 patients who completed the follow-up visits were accepted into this study. Ninety-one patients who never came to visits were excluded. Drugs were classified into two groups as selective (darifenacin hydrobromide, solifenacin succinate and oxybutynin hydrochloride) and non-selective (fesoterodine fumarate, tolterodine tartrate, trospium chloride and propiverine hydrochloride) antimuscarinic drugs. The cardiac pulse rates and the blood pressures were recorded during the baseline, first visit (1 week) and second visit (1 month). Data were compared for drugs and two groups (selective versus non-selective) by using ANOVA test.

Results Baseline characteristics were similar among the patients using different antimuscarinic drugs. Statistically significant increase in heart rate occurred in patients treated with non-selective antimuscarinic drugs compared to those treated with selective drugs ($p < 0.001$), and this increase was especially evident in patients treated with trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride ($p < 0.001$, 0.003, 0.011 and 0.37, respectively). There was no statistical difference for the other side effects.

Conclusions Our results showed that heart rate significantly increased in OAB patients treated with non-selective antimuscarinic drugs. Trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride seem to have the most unfavorable properties with regard to increased heart rate side effect when compared to the other antimuscarinic drugs (darifenacin hydrobromide, solifenacin succinate and oxybutynin hydrochloride).

Keywords Antimuscarinics · Cardiovascular system side effects · Muscarinic receptor selectivity · Overactive bladder

Introduction

Overactive bladder (OAB) syndrome is characterized by the symptom combination of urinary urgency, urgency incontinence, frequency and nocturia in the absence of local bladder pathologies [1]. The most commonly cited studies report the prevalence of OAB as one in six while a more recent study found this prevalence in Iranian women to be higher than the prevalences in these studies [2–4]. The treatment strategy of OAB varies from behavioral therapy to percutaneous tibial nerve stimulation, but if behavioral therapy fails the first line treatment of OAB is with antimuscarinic drugs which block the most frequent muscarinic (M_3) receptors located on the detrusor muscle [5, 6].

Pharmacodynamic properties of antimuscarinic agents are different regarding their interactions with muscarinic receptors [7]. It has been shown that trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride do not possess selectivity for muscarinic receptors while darifenacin hydrobromide, oxybutynin hydrochloride and solifenacin succinate show some selectivity for M_3 over M_2/M_4/M_5 receptors [7]. Antimuscarinic agents other than

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blocking M_3 receptors in detrusor muscle also block the other muscarinic receptors such as M_1, M2, M_4 and M_5 in other organs which explain their important cardiovascular and central nervous system side effects. Muscarinic type 2 receptors other than being located on detrusor muscle are also present in heart, and the blockage of these receptors results in an increase in heart rate [8]. It has been demonstrated that prolonged increase in heart rate might result in increased mortality in the long term [9–11].

Although antimuscarinic agents are accepted to be an efficacious treatment of OAB syndrome, the side effect of heart rate increase has not been evaluated sufficiently in the trials of antimuscarinic treatment of OAB [12–14]. Hence, this study aims to compare and focus on heart rate increase side effect of different antimuscarinic agents available on the market which may result in increased mortality and morbidity in OAB patients using these agents for a long period of time.

Materials and methods

The present study protocol was reviewed and approved by the Institutional Review Board of Istanbul University-Cerrahpasa Cerrahpasa School of Medicine (IRB:671/2014). After institutional approval, we conducted an open-label, prospective, multi-center, randomized and controlled follow-up study for the patients who would start antimuscarinic drugs for OAB to determine and compare especially the heart rate increase side effect of these drugs. Overall 341 patients randomized between January 2014 and June 2016 at three institutions and 250 patients who completed the follow-up visits were included. Ninety-one patients who never came to follow-up visits were excluded from the study.

Patients with OAB who were decided to be treated with antimuscarinic drug monotherapy were informed about the study, and the ones with heart rate between 60 and 90, aged over 18, with body-mass index between 18.5 and 35 kg/m^2 included to our study. Patients with a pacemaker, bladder cancer or hematuria by unknown etiology, allergy to antimuscarinic drugs, abnormal kidney or liver functions, insufficient mental and physical capacities to conduct the study and major contraindications of antimuscarinic drug usage such as high amount of residual urine, myasthenia gravis, ulcerative colitis, toxic megacolon, narrow angle glaucoma were excluded from the study. Pregnant and breast feeding women were also excluded. For the randomization process, seven groups of antimuscarinic drugs were constituted (Table 1), and the patients were systematically and consecutively randomized into these seven groups to use these drugs. Randomization process was conducted by an experienced urodynamic nurse. The urodynamic nurse randomized the patient into one out of seven drug arms without having any clinical and demographic data about the patient. The physician who determined the blood pressure and the heart rate was unaware of the antimuscarinic drug which was given to the patient.

Table 1 Doses and the using types of the drugs

1. Darifenacin hydrobromide	7.5 mg 1 × 1	Unrelated to meals
2. Solifenacin succinate	5 mg 1 × 1	Unrelated to meals
3. Trospium chloride	30 mg at mornings, 15 mg at nights	Before meals
4. Fesoterodine fumarate	4 mg 1 × 1	Unrelated to meals
5. Tolterodine tartrate	4 mg 1 × 1	Unrelated to meals
6. Propiverine hydrochloride	15 mg 2 × 1	Unrelated to meals
7. Oxybutynin hydrochloride	5 mg 3 × 1	Unrelated to meals

The calculation of sample number was performed by Gpower v. 3.1.2; assigning the statistical power as 0.8, the alpha as 0.05 and the group size as 7 and the effect size as 0.25, it was planned to accept 32 patients for each antimuscarinic drug to study.

The storage symptoms of the patients were recorded on their patient files. The symptom scores were evaluated and noted by patients according to translated form of OAB evaluation form (OAB-v8) in the screening visits [15]. Thereafter, all patients rested for 10 min in a quiet room without being allowed to do any work such as having phone call et cetera under a nurse supervision and the cardiac pulse rates were measured from both index finger via pulse oximetry device (BTM-1060, Shenzhen Aeon Technology Co., Ltd. P.R.C.), and the mean value of these two measurements were taken into consideration. The blood pressures of the patients were also measured when they were still at the sitting position from their both arms and the higher values were noted and the follow-up measurements were taken from the same side. After the patients stand up and keep still for 3 min, the orthostatic blood pressures were also measured and noted.

After the baseline evaluation patients received the first and second visits on the first week and first month, respectively, the treatment outcomes and side effects of the treatment were evaluated. The cardiac pulse rates and the blood pressures were also measured in these visits as described above.

Drugs were classified into two groups as selective (darifenacin hydrobromide, solifenacin succinate and oxybutynin hydrochloride) and non-selective (fesoterodine fumarate, tolterodine tartrate, trospium chloride and propiverine hydrochloride). Solifenacin succinate and oxybutynin hydrochloride were included into selective group for statistical analysis since it has moderate selectivity for M3 receptor over M2 subtype. Statistical analysis was performed using commercial software (SPSS version 16.0, SPSS, Chicago IL, USA). All measurements are expressed as the mean ± two

standard deviations. Statistical significance was accepted at $p < 0.05$. Data collected during visits were compared for every single drug and also for two groups classified as selective versus non-selective by using ANOVA test.

Results

Complete data were available on 250 patients. Of the 250 patients, the mean age and OABSS (overactive bladder symptom score) of the patients were 51.21 ± 14.04 and 23.60 ± 7.97, respectively. Stress urinary incontinence was noted in 6 of 175 female patients. With regard to overall patient satisfaction, 77.6% of 250 patients were satisfied, while remaining 22.4% were dissatisfied with the treatment. The percentage of patients with heart rate of ≥ 80 beat per minute before treatment was 47.6%.

Baseline mean heart rate was 79.8 ± 11.2 beats per minute. Mean systolic/diastolic pressures in sitting and standing setting were 122.4/77.4 and 121/75.3 mmHg, respectively. Table 2 presents data on baseline variables for patients in our cohort.

Baseline age, height, weight and BMI were similar among the patients using different antimuscarinic drugs. In addition, there were no statistical differences in terms of heart rate, systolic/diastolic pressures in sitting and standing setting of the patients among the groups before treatment ($p > 0.05$) (Table 3).

The heart rates of the patients during baseline, first and second visits are shown in Tables 4 and 5 and Figs. 1, 2. Remarkable increase in heart rate occurred in patients treated with non-selective antimuscarinic drugs ($p = 0.0016$), and this increase was especially evident in patients treated with trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride ($p = 0.001$, 0.003, 0.011 and 0,037, respectively). While an increase in approximately 9–10 beats per minute was determined at first and second visits in trospium chloride group ($p = 0.001$), this increase was found to be 6–5 beats per minute in tolterodine tartrate group ($p = 0.003$) 4–6 beats per minute in fesoterodine fumarate group ($p = 0.011$) and 3–4 beats per minute in propiverine hydrochloride group ($p = 0.037$). There were no statistically significant difference in terms of systolic/diastolic pressures in sitting and standing setting of the patients for all type of antimuscarinic drugs ($p > 0.05$).

There was no statistical difference for the other side effects of antimuscarinic drugs used in this cohort ($p > 0.05$) (Table 6).

Table 2 Baseline characteristics of patients

		No. of patients
Number of centers		
1. Center		96
2. Center		121
3. Center		33
Gender (female/male)		175/75
Mean age ± SD (years)	51.2 ± 14	
Mean height ± SD (cm)	162.9 ± 9.6	
Mean weight ± SD (kg)	77.2 ± 13.6	
Mean body mass index ± SD (weight (kg)/height $(m)^2$)	29.2 ± 5.2	
Mean overactive symptom score (OABSS) ± SD	23.6 ± 7.9	
Distribution of antimuscarinic drugs		
1. Fesoterodine 4 mg		32
2. Tolterodine 4 mg SR		41
3. Trospium chloride 30 mg		41
4. Solifenacin 5 mg		36
5. Oxybutynin hydrochloride 5 mg		30
6. Darifenacin 7.5 mg		37
7. Propiverine 15 mg		33
Mean heart rate ± SD (beats/minute)	79.8 ± 11.2	
Mean systolic blood pressure ± SD (sitting) (mmHg)	122.5 ± 21.7	
Mean diastolic blood pressure ± SD (sitting) (mmHg)	77.5 ± 35.7	
Mean systolic blood pressure ± SD (standing) (mmHg)	121 ± 23.6	
Mean diastolic blood pressure ± SD (standing) (mmHg)	75.3 ± 13.1	

Table 3 Baseline characteristics of patients according to the antimuscarinic drugs

	Fesoterodine	Tolterodine	Trospium chloride	Solifenacin	Oxybutynin	Darifenacin	Propiverine	*p*
No. of patients	32	41	41	36	30	37	33	
Gender								
Female	28	26	33	26	18	15	21	0.09
Male	4	15	8	10	12	15	12	
Mean age ± SD (years)	50.6 ± 12.7	48.7 ± 15.4	52.9 ± 13.9	51.7 ± 12.9	51.4 ± 15.4	50.9 ± 13.1	51.3 ± 15.4	0.906
Mean height ± SD (cm)	160.4 ± 8.6	164.9 ± 9.1	162.1 ± 9.7	161.8 ± 9.5	164.5 ± 11.8	162.8 ± 8.4	163.2 ± 10.0	0.480
Mean weight ± SD (kg)	74.6 ± 13.6	76.0 ± 16.2	79.9 ± 11.3	77.2 ± 11.2	78.3 ± 14.1	76.0 ± 12.0	78.3 ± 15.9	0.714
Mean body mass index ± SD	29.1 ± 5.9	27.9 ± 6.0	30.6 ± 4.4	29.7 ± 5.1	29.1 ± 5.7	28.5 ± 4.4	29.3 ± 5.0	0.424
Mean heart rate ± SD (beats/minute)	79 ± 10.0	79.2 ± 13.1	77.9 ± 8.8	81.1 ± 14.4	78.1 ± 11.0	81.9 ± 11.8	81.0 ± 8.9	0.679
Mean systolic blood pressure ± SD (sitting) (mmHg)	121.5 ± 26.2	121.2 ± 19.5	124.7 ± 24.9	121.1 ± 21.8	127.3 ± 19.6	116.2 ± 19.3	126.7 ± 23.5	0.360
Mean diastolic blood pressure ± SD (sitting) (mmHg)	72.5 ± 12.7	74.8 ± 10.9	76.7 ± 14.9	74.5 ± 12.6	78.6 ± 13.0	87.1 ± 12.3	77.6 ± 12.9	0.701
Mean systolic blood pressure ± SD (standing) (mmHg)	120.6 ± 23.5	120.1 ± 20.7	13.0 ± 32.5	120.4 ± 20.0	124.4 ± 21.8	115.9 ± 19.6	123.5 ± 24.9	0.805
Mean diastolic blood pressure ± SD (standing) (mmHg)	72.1 ± 12.3	74.3 ± 11.4	78 ± 15.2	75.9 ± 13.6	78.2 ± 13.6	73.3 ± 12.0	75.1 ± 13.2	0.419

Table 4 Mean ± SD heart rates of the patients using selective and non-selective antimuscarinic agents in baseline, first and last visits

	Non-selective		Selective		*p*
	Mean	SD	Mean	SD	
Baseline	79.2	10.4	80.4	12.7	0.420
First visit (1st week)	84.9	11.4	80.8	12.7	0.007
Second visit (1st month)	86.2	12.1	80.4	12.8	0.0016

Discussion

Pharmacodynamic properties of antimuscarinic agents are different regarding their interactions with muscarinic receptors [7]. It has been shown that trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride do not possess selectivity for muscarinic receptors and are known as non-selective antimuscarinics agents. Darifenacin hydrobromide, oxybutynin hydrochloride and solifenacin succinate show some selectivity for M_3 over M_2/M_4/M_5 receptors [7]. Antimuscarinic agents in the treatment of OAB syndrome are usually intended to be used for a long period of time, and theoretically antimuscarinic agents having some selectivity for M_3 over M_2 receptors should be vitally superior to non-selective antimuscarinics in terms of increased heart rate side effect which has been determined to result in increased mortality in long-term existence. In this study, seven different antimuscarinic drugs were evaluated in terms of the side effects of cardiovascular system; we found that remarkable increase in heart rate occurred in patients treated with non-selective antimuscarinic drugs compared to those treated with selective drugs ($p = 0.0016$). Furthermore, trospium chloride and tolterodine tartrate had the most unfavorable properties regarding the increase in the heart rate

Table 5 Mean ± SD heart rates of the patients using each antimuscarinic agent in baseline, first and last visits

	Baseline		First visit (1st week)		Heart beat increases from baseline	Second visit (1st month)		Heart beat increases from baseline	
	Mean	SD	Mean	SD		Mean	SD		
Fesoterodine	79.1	9.7	83.5	12.5	4.4	85	11.6	5.9	0.011
Tolterodine	79.4	13.3	85.4	12.3	6	84.6	14.1	5.2	0.003
Trospium	78.4	9.3	87.8	11.2	9.4	88.1	11.3	9.7	0.001
Solifenacin	81.3	14.7	82.7	14.6	1.4	83.8	12.7	2.5	0.427
Oxybutynin	77.1	11.3	75.5	11.2	−1.6	75	11.4	−2.1	0.530
Darifenacin	80.7	12.6	81.2	11.6	0.5	79.8	12.5	−0.9	0.746
Propiverine	82.7	9.1	85.8	11.4	3.1	86.9	11.5	4.2	0.037

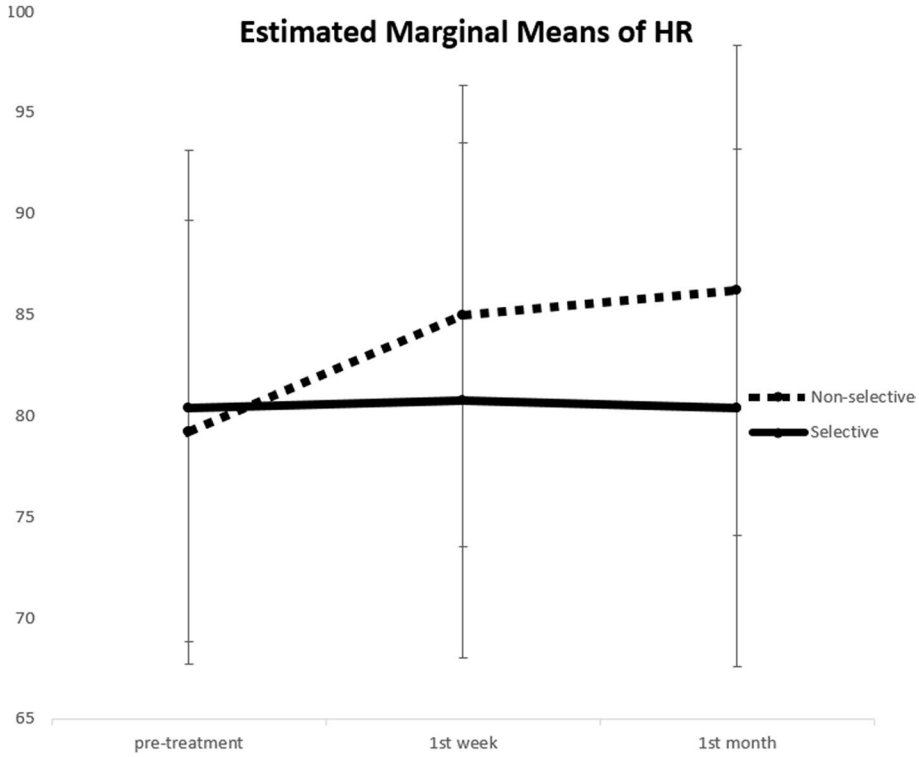

Fig. 1 Changing pattern of heart rate per minute with treatment for selective versus non-selective antimuscarinic drugs

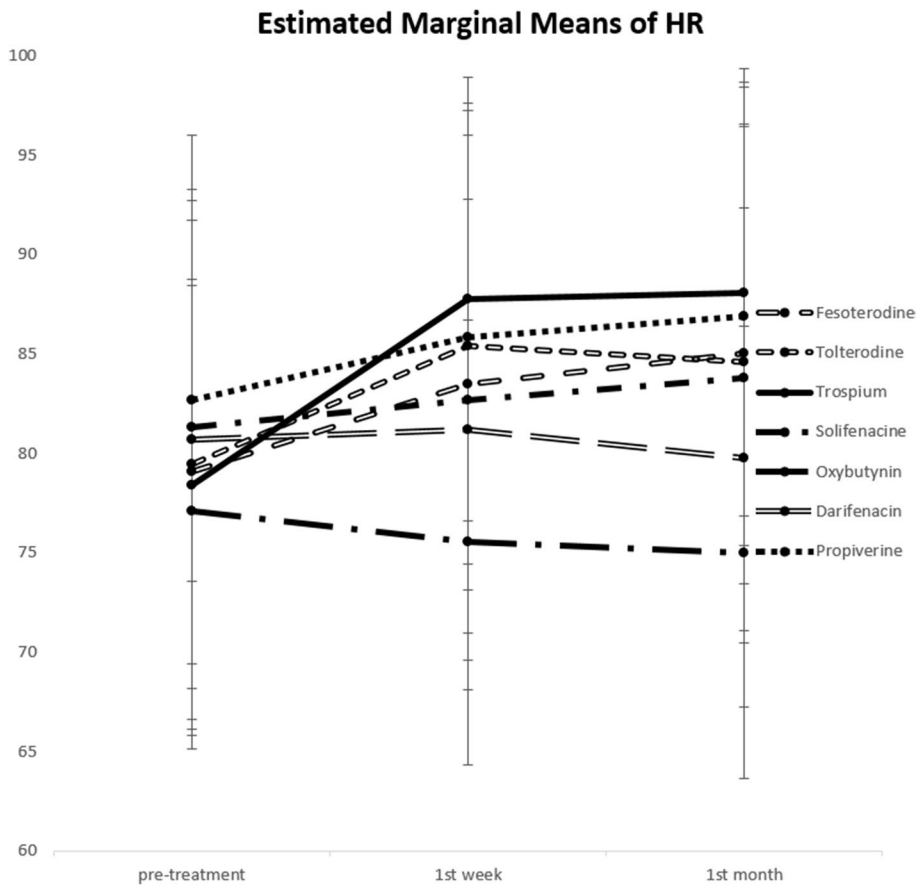

Fig. 2 Changing pattern of heart rate per minute with treatment for each single antimuscarinic drug

Table 6 Other adverse effects of the antimuscarinic drugs occurring in our cohort

	Fesoterodine	Tolterodine	Trospium	Solifenacin	Oxybutynin	Darifenacin	Propiverine	*p*
No. of patients	25	33	34	31	21	28	23	
Dry mouth	13 (52.0)	20 (60.6)	23 (67.6)	15 (48.3)	17 (81.0)	15 (57.7)	13 (56.5)	0.304
Blurred vision	3 (12.0)	3(9.1)	11 (32.4)	6 (19.4)	3 (14.3)	2 (7.7)	4 (17.4)	0.143
Flushing	6 (24.0)	3 (9.1)	2 (5.9)	5 (16.7)	1 (4.8)	0	1 (4.3)	0.055
Dry skin	1 (4.0)	2 (6.1)	2 (5.9)	4 (12.9)	4 (19.0)	3 (11.5)	1 (4.3)	0.494
Tachycardia	3 (12.0)	2 (6.1)	7 (20.6)	8 (25.8)	3 (14.3)	1 (3.8)	1 (4.3)	0.094
Urinary retention	4 (16.0)	7 (21.2)	4 (11.8)	1 (3.2)	6 (28.6)	5 (19.2)	3 (13.0)	0.260
Constipation	4 (16.0)	7 (21.2)	7 (20.6)	5 (16.1)	5 (23.8)	8 (34.6)	7 (30.4)	0.551
Fever	3 (12.0)	1 (3.0)	4 (11.8)	2 (6.5)	3 (14.3)	1 (3.8)	3 (13.0)	0.470
Confusion/hallucination	0	0	2 (5.9)	0	1 (4.8)	0	1 (4.3)	0.390
Skin eruption	0	3 (9.1)	0	0	0	0	0	0.023

($p = 0.001$ and 0.003, respectively). It was demonstrated that the prolonged existence of increased heart rate might result in increased mortality [9–11]. Taking these findings into consideration, the results of this study seem to be crucially important when planning the rationale antimuscarinic treatment of OAB.

It was shown that 39% of OAB patients had heart rates of ≥ 80 beat per minute before treatment [16]. Similarly in our study, 47.6% of the patients had heart rates ≥ 80 beat per minute before treatment.

Studies investigating the increased heart rate side effect of antimuscarinics are scarce. Two placebo-controlled trials for patients treated with trospium chloride due to OAB showed that the mean increase in heart rate compared with placebo was found to be 3.0 and 4.0 beats per minute, respectively [17, 18]. In the present study, heart rate increased approximately 9–10 beats per minute at 1st and 4th week visits in patients treated with trospium chloride ($p = 0.001$). This increase in heart rate, which may result in increased cardiovascular mortality in the long-term usage of this drug, must be taken into consideration when planning long-term antimuscarinic treatment of OAB. In a previous study, an increase in heart rate during the treatment with trospium chloride was found to be related to dose increment; however, no significant effect on blood pressure was noted at any dose [19]. Consistent with this finding, in our study, trospium chloride treatment in regular dose was not found to be associated with systolic/diastolic blood pressure changes.

Two placebo controlled studies in healthy volunteers comparing the effect of darifenacin hydrobromide and tolterodine tartrate on heart rate demonstrated that darifenacin hydrobromide did not increase the heart rate while tolterodine tartrate significantly increased it [20, 21]. Two other placebo controlled studies with tolterodine tartrate and fesoterodine fumarate at both 4 mg and 8 mg doses showed that these two drugs increased the heart rate significantly compared with placebo [22, 23]. Similar to the findings of the above-mentioned studies, in the present study the heart rate increase was found to be five beats per minute in tolterodine tartrate group, and this increase reached statistical significance ($p = 0.003$). Also in this study it was evident that uptrend of heart rate increase occurred with fesoterodine fumarate and this increase reached statistical significance ($p = 0.011$).

Hence, heart rate increase side effect of tolterodine tartrate and fesoterodine fumarate should also be kept in mind when long-term antimuscarinic treatment of OAB is planned.

A randomized crossover study comparing the safety of oxybutynin hydrochloride and propiverine hydrochloride found a significantly higher heart rate in propiverine hydrochloride treatment group [24]. In the present study, heart rate increase was found to be four beats per minute in propiverine hydrochloride group, and this increase reached statistical significance ($p = 0.037$).

In the present study, it is clearly evident that when classified into two groups as selective and non-selective antimuscarinics, statistically significant increase in heart rate occurred in patients treated with non-selective antimuscarinic drugs ($p = 0.0016$) because of fairly high numbers of patients in each group. These findings are consistent with the findings of several other studies [20, 21, 24–26]. To our knowledge, this is the largest randomized, prospective clinical trial comparing the effect of all available antimuscarinic drugs on heart rate. At this moment, tolterodine tartrate, fesoterodine fumarate, propiverine hydrochloride and trospium chloride (non-selective antimuscarinic drugs) appear to increase heart rate, while darifenacin hydrobromide, oxybutynin hydrochloride and solifenacin succinate (selective antimuscarinic drugs) do not. These findings should have clinical implications when treating OAB patients with antimuscarinics.

Although each single drug group in the present study does not include sufficiently high number of patients for

attempting to draw a more precise conclusion, we believe that our results might help urologists to consider the heart rate increase side effect of antimuscarinics when planning the rationale OAB long-term treatment.

Conclusion

Our results showed that heart rate significantly increased in patients with OAB treated with non-selective antimuscarinic drugs. Trospium chloride, tolterodine tartrate, fesoterodine fumarate and propiverine hydrochloride seem to have the most unfavorable properties with regard to heart rate increase side effect when compared with the other antimuscarinic drugs (darifenacin hydrobromide, solifenacin succinate and oxybutynin hydrochloride). We believe that our results might help urologists to consider the heart rate increase side effect of antimuscarinics when planning the rationale OAB long-term treatment.

Authors' contribution BC contributed to protocol/project development, manuscript writing/editing. BO, MHG helped with protocol/project development, data collection or management, data analysis, manuscript writing/editing. MG, FAT, MD involved in data collection or management.

Compliance with ethical standards

Conflict of interest Authors of this study have no conflict of interest.

Ethical approval This open-label, prospective, multi-center, randomized and controlled follow-up study has institutional approval from Cerrahpasa School of Medicine Ethical Commitee with IRB number of 671/2014.

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