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COMBINATION TREATMENT WITH PROPIVERINE HYDROCHLORIDE PLUS DOXAZOSIN CONTROLLED RELEASE GASTROINTESTINAL THERAPEUTIC SYSTEM FORMULATION FOR OVERACTIVE BLADDER AND COEXISTING BENIGN PROSTATIC OBSTRUCTION: A PROSPECTIVE, RANDOMIZED, CONTROLLED MULTICENTER STUDY

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ABSTRACT

Purpose: We evaluated the efficacy and safety of a therapeutic modality involving propiverine combined with doxazosin in patients with overactive bladder (OAB) and benign prostatic obstruction.

Materials and Methods: Men 50 years or older with OAB symptoms and urodynamically proven bladder outlet obstruction (Abrams-Griffith score greater than 20) were randomized (1:2) into 2 groups, namely group 1—doxazosin controlled release gastrointestinal therapeutic system formulation (4 mg once daily) only and group 2—propiverine hydrochloride (20 mg once daily) plus doxazosin controlled release gastrointestinal therapeutic system formulation for an 8-week treatment regimen.

Results: A total of 211 men, including 69 in group 1 and 142 in group 2, were treated and 198 (93.8%) completed the 8 weeks of treatment. Significant improvements were noted in each group after treatment in urinary frequency, maximum flow rate, average micturition volume and International Prostate Symptom Score. Compared with group 1 improvement rates with regard to urinary frequency (23.5% vs 14.3%, $p = 0.004$), average micturition volume (32.3% vs 19.2%, $p = 0.004$), and storage (41.3% vs 32.6%, $p = 0.029$) and urgency ($p = 0.019$) International Prostate Symptom Score symptoms were more significant in group 2. Post-void residual urine was found to be significantly increased only in group 2 but this was not accompanied by urinary retention. Patient satisfaction rates were found to be significantly higher in group 2 than in group 1 ($p = 0.002$). Overall adverse event rates were higher in group 2 ($p = 0.002$), although discontinuation rates and discontinuation rates due to adverse events were not different between the 2 groups.

Conclusions: This study reveals that combination therapy consisting of α1-adrenoceptor antagonists with antimuscarinics represents an effective and relatively safe treatment modality in select patients with OAB coexisting with benign prostatic obstruction.

KEY WORDS: prostate; prostatic hyperplasia; bladder, neurogenic; cholinergic antagonists

Lower urinary tract symptoms (LUTS) are quite common in elderly men and benign prostatic obstruction (BPO) represents a common cause of LUTS.[1] Storage symptoms including urgency with or without urge incontinence, usually associated with frequency and nocturia, are characterized as overactive bladder (OAB).[2] The prevalence of OAB increases significantly with age, which is similar to the natural history associated with BPO.[3] Therefore, a substantial proportion of men with LUTS show a combination of storage and voiding symptoms, which suggests the possibility of coexisting BPO and detrusor overactivity (DO). OAB occurs in approximately 50% to 75% of men with BPO.[4–6] α1-Adrenoceptor antagonists remain the most widely used pharmacological agents for BPO. Patients with OAB without BPO tend to be treated with antimuscarinics. Recent studies showed the safety of antimuscarinics in terms of post-void residual urine (PVR) and acute urinary retention in cases of BPO.[7,8] Therefore, it would be logical to expect that combination therapy with an α1-blocker and an antimuscarinic agent in patients with OAB/BPO would significantly alleviate symptoms and induce serious improvements in quality of life. We evaluated the efficacy and safety of propiverine hydrochloride treatment combined with doxazosin controlled release gastrointestinal therapeutic system formulation (GITS) in patients with OAB/BPO.

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MATERIALS AND METHODS

Patients. Men 50 to 80 years old with a history of OAB of 6 months or greater and urodynamically proven bladder outlet obstruction (BOO), that is an Abrams-Griffith (AG) score of 20 or greater, were eligible for screening and study enrollment. Subjects were required to have at least 1 episode of urgency daily and an average frequency of greater than 8 times per 24 hours while keeping a 3-day voiding diary.

Subjects with neurogenic disease, any medical conditions that contraindicate antimuscarinics, significant renal or hepatic disease, bladder cancer and prostate cancer were excluded from the study. Also, patients who had received any medical therapy for BPO or any antimuscarinics during the previous 3 months before randomization, those who had undergone bladder or prostate surgery, or those with baseline PVR that exceeded 30% of maximum cystometric capacity were excluded from study.

Study design. This multicenter, randomized, double-blind study was performed at 9 centers. The procedures of this study complied with the guidelines provided by the Declaration of Helsinki, revised Edinburgh, 2000 and were in accordance with the International Conference on Harmonization of Guidelines for Good Clinical Practice. The appropriate institutional review board at each participating center reviewed and approved the protocol and consent forms.

Eligible patients recorded 3-day voiding diary, International Prostatic Symptom Score (I-PSS) and bother score. PVR was measured by ultrasonography and urodynamic studies were performed according to International Continence Society standards.[9] All patients who were eligible based on voiding diaries were randomized to 1 of 2 treatment groups using an unequal allocation randomization ratio (1:2) for group —doxazosin GITS (4 mg once daily) only and group 2—propiverine hydrochloride (20 mg once daily) plus doxazosin GITS. The medication period was 8 weeks.

Efficacy assessments. After randomization and the start of the 8-week treatment period patients were evaluated for efficacy after 8 weeks of treatment according to the voiding diary, I-PSS and bother score. The primary efficacy end point was the change from baseline in the mean number of voids per 24 hours at 8 weeks. The secondary efficacy end point was the change from baseline in mean voided volume per void, I-PSS, bother score and patient satisfaction with treatment. Voiding diaries were completed prior to each followup visit. I-PSS was analyzed in terms of total score, storage symptoms score (sum of items 2, 4 and 7), voiding symptoms score (sum of items 1, 3, 5 and 6) and urgency (item 4). Each patient completed a global satisfaction questionnaire after 8 weeks of treatment. Patient satisfaction with treatment was rated as very satisfied, satisfied, somewhat satisfied or unsatisfied.

Safety and tolerability assessments. Safety assessments at weeks 4 and 8 included maximum flow rate (Qmax) on uroflowmetry, PVR assessment, vital signs, physical examination and the recording of adverse events. If PVR increased and exceeded 50% of voided urine volume, the patient was withdrawn from the study. Tolerability was evaluated according to adverse event reports and withdrawal rates with special attention given to the reporting of clinically significant voiding difficulties.

Statistical analysis. At 5% significance with 80% power 204 patients (68:136) were required to detect a 1.0 difference between the 2 groups in the change from baseline at 8 weeks in daytime and the nighttime frequency (SD 2.39 and 1.16, respectively). At an expected withdrawal rate of 10% 228 patients (76:152) were required to enroll in this study. All primary and secondary efficacy and safety assessments were performed using the intent to treat patient sample. Differences in continuous variables between the 2 groups was tested with the t or Mann-Whitney test according to normality. Distributions of categorical variable were compared between the 2 groups with the chi-square or Fisher exact test. Changes in ordinal variables was analyzed using GEE.

RESULTS

A total of 228 men were randomized into the study, including 76 in group 1 and 152 in group 2. Mean patient age ± SD was 65.9 ± 7.85 years. A total of 17 patients withdraw consent and 211 were treated, including 69 in group 1 and 142 in group 2 (fig. 1). Demographic data and clinical characteristics were comparable in the 2 treatment groups ($p > 0.05$, table 1). Of the 211 treated patients 198 (93.8%) completed the 8 weeks of treatment, including 67 (97.1%) in group 1 and 131(92.2%) in group 2. Efficacy analysis included all randomized patients who had received at least 1 dose of study drug and who had efficacy data available from baseline and from at least 1 on treatment visit, including 69 in group 1 and 142 in group 2.

Efficacy. Significant improvement in the mean number of voids per 24 hours, daytime frequency, nocturia, mean voided volume and functional bladder capacity was noted in each group after treatment (table 2). Compared with group 1 changes from baseline in daytime frequency, total voiding frequency and mean voided volume were significantly more pronounced in group 2 (fig. 2). Compared with the change observed in group 1 there was a statistically significant decrease in the number of voids per 24 hours in group 2 (14.3%

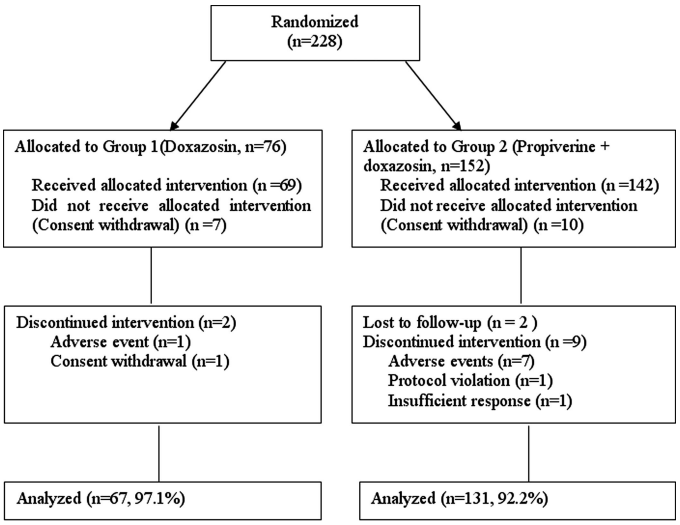

FIG. 1. Subject progress through randomized trial phases

TABLE 1. *Baseline patient characteristics in each treatment group*

	Group 1	Group 2
No. pts	69	142
Mean age ± SD	65.8 ± 8.5	66.1 ± 7.5
Mean prostate specific antigen ± SD (ng/ml)	2.2 ± 3.0	1.8 ± 2.2
Mean detrusor pressure at max flow ± SD (cm H_2O)	59.0 ± 21.2	56.2 ± 22.0
Mean max detrusor pressure ± SD (cm H_2O)	66.3 ± 21.4	65.3 ± 24.6
Mean max cystometric capacity ± SD (ml)	324.4 ± 114.4	339.9 ± 111.5
No. DO (%):		
Present	28 (40.6)	45 (31.7)
Absent	41 (59.4)	97 (68.3)
Mean PVR ± SD (ml)	30.8 ± 31.0	28.8 ± 31.2
AG score:		
Mean ± SD	41.5 ± 17.4	39.3 ± 19.9
No. 20–40 (%)	36 (52.2)	87 (61.3)
No. 40–60 (%)	23 (33.3)	39 (27.5)
No. greater than 60 (%)	10 (14.5)	16 (11.3)
Mean I-PSS ± SD	20.6 ± 7.2	22.0 ± 7.3
No. prostate enlargement (%):*		
Mild	28 (40.6)	62 (43.7)
Moderate	36 (52.2)	70 (49.3)
Severe	5 (7.2)	10 (7.0)

* Estimated by digital rectal palpation.

TABLE 2. *Voiding diary and uroflowmetry parameters at baseline and 8 weeks after treatment*

	Mean Group 1 ± SD		Mean Group 2 ± SD		p Value
	Baseline	Wk 8	Baseline	Wk 8*	
No. pts	69		142		
Daytime frequency	8.5 ± 2.1	7.6 ± 1.7*	8.8 ± 3.2	6.9 ± 2.3	0.004
Nocturia	2.2 ± 1.2	1.6 ± 0.9*	2.2 ± 1.2	1.5 ± 1.0	0.110
Total voiding frequency	10.7 ± 2.9	9.1 ± 2.2*	11.0 ± 3.7	8.4 ± 2.7	0.002
Mean voided vol (ml)	164.3 ± 51.7	195.5 ± 72.7*	169.6 ± 57.1	224.4 ± 94.7	0.004
Functional bladder capacity (ml)	281.1 ± 99.4	320.8 ± 132.7*	294.6 ± 105.3	342.6 ± 127.5	0.155
Qmax (ml/sec)	10.5 ± 4.2	12.2 ± 7.2*	10.4 ± 4.3	11.4 ± 5.1	0.139
PVR (ml)	30.8 ± 31.0	26.1 ± 29.6	28.8 ± 31.2	49.6 ± 69.2	0.002

* Vs baseline $p < 0.05$.

vs 23.5%, p = 0.004). Also, the increase in mean voided volume per void was higher in group 2 than in group 1 (32.3% vs 19.2%, p = 0.004).

Total I-PSS, I-PSS subscales and bother score decreased significantly after treatment in each group (table 3). Improvement in voiding symptoms was similar in the 2 groups but the improvement in storage symptoms was significantly higher in group 2 than in group 1 (41.3% vs 32.6%, p = 0.029). As measured by I-PSS item 4, urgency severity decreased more significantly in group 2 than in group 1 (p = 0.019, table 3 and fig. 3). Patient global satisfaction with treatment was evaluated in 198 patients who completed the 8 weeks of treatment. Scores regarding patient satisfaction with treatment were significantly higher in group 2 than in group 1 (p = 0.014, fig. 4). The odds of a patient reporting a benefit were 2.34 times higher in patients receiving propiverine and doxazosin than in those receiving doxazosin alone (95% CI 1.21 to 4.52).

Safety and tolerability. Qmax increased in each groups and changes from baseline were not statistically different between the 2 groups (table 2). PVR increased significantly in group 2 after treatment but not in group 1. Statistically significant increases in PVR in group 2 (20.7 ml) were not accompanied by urinary retention

Two patients (2.9%) in group 1 and 11 (7.8%) in group 2 discontinued treatment before study completion (fig. 1). Nine and 4 of the 13 patients who elected to discontinue made this decision for reasons related and unrelated to study treatment, respectively. Discontinuation due to adverse events occurred in 1 group 1 patient (1.5%) and in 7 group 2 patients (4.9%) (fig. 1). Discontinuation rates and discontinuation rates due to adverse events were similar between the 2 groups (p = 0.2291 and 0.278, respectively). Adverse events resulting in discontinuation in group 2 were dry mouth in 4 patients, increased PVR in 2 and constipation in 1. In group 2 PVR increased above 50% of voided urine volume after medication in 2 patients (150 and 180 ml, respectively), who were withdrawn from the study.

The overall incidence of adverse events was 18.9% in group 1 and 42.7% in group 2, which was significantly higher in group 2 ($p < 0.05$). Of adverse events 85% were of mild severity. The majority of adverse events in group 2 were anticholinergic related effects (table 4). Dry mouth was the most common side effect. Acute urinary retention was not reported in any treatment group. No patient reported serious adverse events.

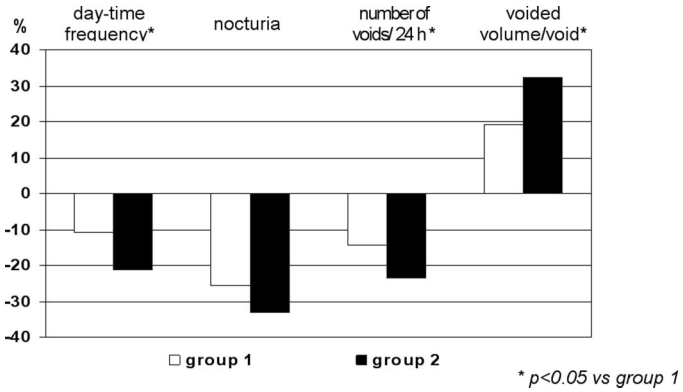

FIG. 2. Change from baseline to end point in mean daytime frequency, nocturia, number of voids per 24 hours (*h*) and voided volume. Values are adjusted for baseline as covariate. White bars represent group 1. Black bars represent group 2.

DISCUSSION

α1-Adrenoceptor antagonists relieve not only voiding symptoms, but also storage symptoms in BPO.[10] However, the therapeutic effect with regard to OAB symptoms is limited. According to the report of Lee et al[11] only a third of men undergoing treatment for BPO combined with OAB were helped by doxazosin alone but three-fourths found a combination of tolterodine and doxazosin to be effective therapy. The first therapeutic benefit of combining anticholinergic (propiverine) with α1-adrenoceptor antagonists (tamsulosin) compared with α1-adrenoceptor antagonists alone was reported by Saito et al.[12] More favorable improvement rates of daytime frequency, urinary incontinence and urgency resulted in the combination group. However, in the study of Saito et al BOO was only assumed and not defined by pressure flow studies. Athanasopoulos et al studied 50 men with LUTS, and urodynamically confirmed BOO and DO. [8] They reported statistically significant improvements in quality of life scores but only in the combination group.

In our study doxazosin also resulted in improvements in voiding frequency and average micturition volume, and it decreased urgency severity but changes in symptoms and patient satisfaction rates were more prominent in the combination group. The odds of a patient reporting a benefit of therapy were 2.34 times greater in those receiving propiverine and doxazosin compared with those receiving doxazosin only. This difference in patient satisfaction rates may be attributable to the difference in the quantity and quality of symptom improvement. 1) The improvement in daytime frequency and the number of voids per 24 hours was more prominent in the combination treatment group. The improvement rate with regard to nocturia was similar in the 2 groups. This discrepancy in terms of daytime and nighttime improvement may have been due to the multifarious etiology of nocturia.[13] 2) Combination therapy significantly improved storage symptoms and urgency to a greater degree than doxazosin monotherapy but did not result in the attenuation of voiding symptoms. Using the validated International Continence Society questionnaire for older men it was shown that storage symptoms tend to be more bothersome than voiding symptoms.[14,15] Urgency, the central symptom of OAB, is bothersome to patients and, therefore, any effective OAB treatment must ameliorate this symptom.[16] Combination treatments improved these bothersome storage symp-

TABLE 3. *I-PSS and bother score at baseline and 8 weeks after treatment*

Items		Mean Group 1 ± SD		Mean Group 2 ± SD		p Value
		Baseline	Wk 8*	Baseline	Wk 8*	
No. pts		69		142		
Total I-PSS		20.6 ± 7.2	13.3 ± 6.4	22.0 ± 7.3	14.6 ± 6.9	0.598
Storage symptoms	2 + 4 + 7	8.9 ± 3.2	6.0 ± 3.0	9.2 ± 3.1	5.4 ± 3.0	0.029
Voiding symptoms	1 + 3 + 5 + 6	11.8 ± 5.4	7.3 ± 4.2	12.8 ± 5.2	9.1 ± 4.8	0.513
Urgency	4	2.5 ± 1.7	1.8 ± 1.5	2.8 ± 1.7	1.6 ± 1.4	0.019
Bother score		4.4 ± 0.9	3.2 ± 1.4	4.3 ± 0.9	3.0 ± 1.2	0.622

* Vs baseline p <0.0001.

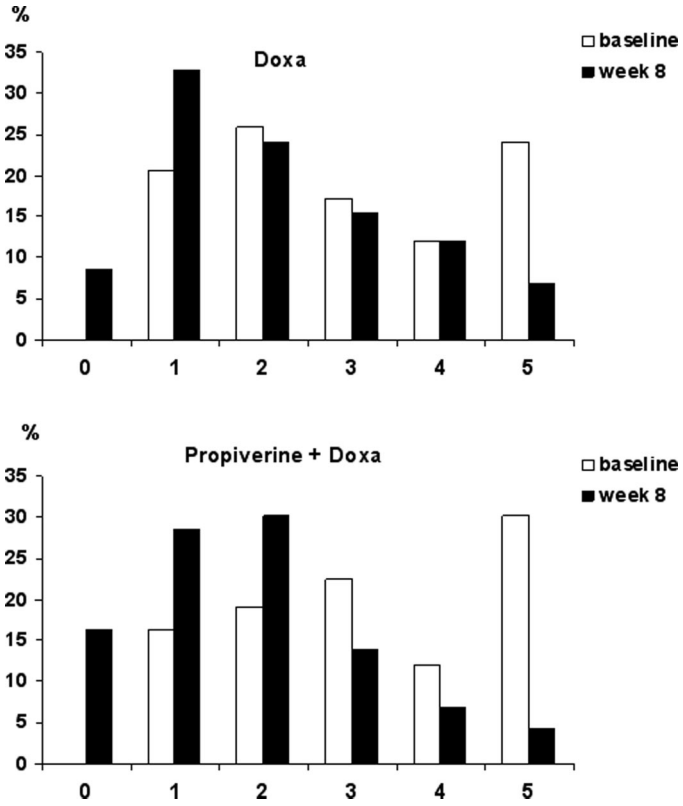

FIG. 3. Urgency severity measured by I-PSS item 4 at baseline and after 8 weeks of treatment with doxazosin (*Doxa*) or propiverine and doxazosin.

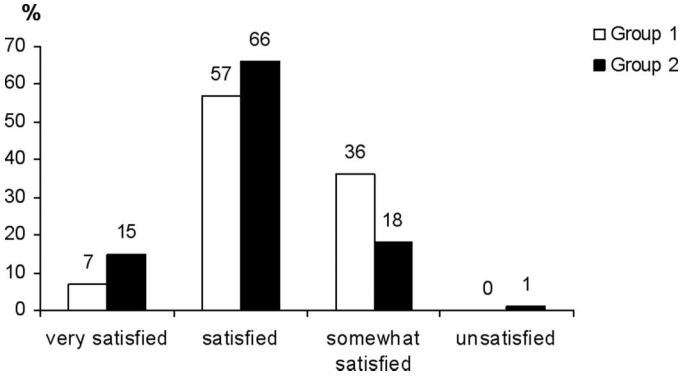

FIG. 4. Differences in patient global satisfaction with treatment between 2 groups.

toms more effectively than monotherapy, which may well be the cause of the higher satisfaction rate.

It is a common perception that the use of an antimuscarinic agent in men with BPO can induce acute urinary retention due to the inhibitory effects of antimuscarinics on bladder

TABLE 4. *Treatment related side effects*

	No. Group 1 (%)	No. Group 2 (%)
Pts	69	142
Dry mouth	4 (5.8)	26 (18.3)*
Constipation	0	3 (2.1)
Dizziness	0 (2.6)	8 (5.6)
Indigestion	1 (1.5)	5 (3.5)
Difficult voiding	1 (1.5)	4 (2.8)
Blurred vision	1 (1.5)	2 (1.4)
Significant PVR	0	2 (1.4)

* Vs group 1 p <0.05.

contraction. As a result, these drugs tend not to be used in men with BPO. The rationale for the use of antimuscarinics in patients with BPO is based on the mechanism of action of antimuscarinics. The classic view is that antimuscarinics function by blocking muscarinic receptors on the detrusor muscle and this blocking activity in turn decreases bladder contractile ability. However, recent research revealed a new mechanism of action for antimuscarinic agents with regard to OAB.[17] During the storage phase acetylcholine may be released from neuronal and nonneuronal sources, and then directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium as well as in the detrusor. This mechanism may be deeply relevant to the pathophysiology of OAB and it may also represent a possible target for antimuscarinic drugs. Furthermore, most antimuscarinic drugs function as competitive antagonists. Therefore, when there is a massive release of acetylcholine during micturition, the effects of antimuscarinics decrease. From a theoretical point of view unless antimuscarinic doses are extremely high these drugs should not impair bladder contractility and, therefore, they should not lead to decreases in voiding pressure and flow rate. Few groups have formally assessed the safety of antimuscarinics in men with BPO. Abrams reported the safety of 2 mg tolterodine twice daily on urodynamic parameters in a group of men with urodynamically proven BPO and DO.[7] Tolterodine induced an increase in PVR compared with placebo (25 vs 0 ml) but this was hardly a substantial clinical change. Our results also revealed that propiverine was not associated with any urinary safety concerns. We used 20 mg propiverine, a relatively low dose used in European countries, which ensured to some degree the safety and tolerability of this study. In chronic obstruction morphological, biochemical and functional changes together with detrusor denervation make it reasonable to assume that blockage of a damaged bladder with antimuscarinic agents can lead to drug induced detrusor decompensation. To date the effects of antimuscarinics have been studied primarily in patients with OAB without BPO. Further research is necessary to determine the optimal dose of antimuscarinics in patients with BPO. It is probable that a lower dose of antimuscarinics can be used safely in patients with OAB and BPO with the same efficacy.

If antimuscarinics are prescribed for LUTS associated with BPO, different results are to be expected depending on BOO grade. We evaluated the efficacy of the treatment according

to BOO grade. Therapeutic efficacy in the groups with regard to the AG numbers 20 to 40, 41 to 60 and greater than 60 were found to be similar. However, 3 of the 16 patients with severe obstruction patients (AG greater than 60) on combination treatment discontinued treatments due to significant PVR (greater than 50% of voided urine volume). Of course, this was not urinary retention and the patients did not complain of voiding difficulty but we discontinued the study due to concerns for patient safety. In patients with severe BOO on antimuscarinics it is necessary to watch carefully for increases in PVR.

CONCLUSIONS

We compared propiverine with doxazosin against doxazosin alone in patients with OAB and BPO. Compared with doxazosin monotherapy improvement rates with regard to urinary frequency, average micturition volume, I-PSS storage and urgency symptoms, and patient satisfaction with treatment were more significant for combination treatment. Propiverine did not affect the urinary flow rate and no acute urinary retention was observed. This study reveals that combination therapy with α1-adrenoceptor antagonists and antimuscarinic agents represents an effective and relatively safe treatment modality in select patients with OAB and BPO.

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