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IMIDAFENACIN REDUCES NIGHT TIME URINE PRODUCTION AS WELL AS INCREASES BLADDER CAPACITY IN BPH PATIENTS WITH NOCTURIA AND OAB. RESULTS FROM PROSPECTIVE RANDOMIZED CONTROLLED TRIAL, GOOD-NIGHT STUDY

Hypothesis / aims of study

Nocturia is a common lower urinary tract symptom that deteriorates quality of Life. It is caused by nocturnal polyuria, reduced bladder capacity, or a combination of the two. Our previous study showed that the efficacy and safety of combination therapy with imidafenacin (IM) plus alpha-blocker as second-line therapy after failed alpha-blocker therapy for men with nocturia [1]. IM is the newest anticholinergic in Japan; its superiority to placebo and noninferiority to propiverine have been demonstrated in placebo- and propiverine-controlled clinical studies, and it was marketed in Japan in 2007. We further investigate the effects of IM on nocturnal polyuria and low bladder capacity.

Study design, materials and methods

Stratified analyses were conducted on data from patients in a randomized, controlled trial of IM, GOOD-NIGHT study, in Japan. A total of 152 patients aged 50 years or older with persisting nocturia who have been treated unsuccessfully with alpha-blocker for more than 4 weeks were randomly assigned to receive 8 weeks treatment with alpha-blocker alone (group 1), alpha-blocker plus IM (group2a; 0.1 mg twice daily or group.2b; 0.1 mg nightly). A total of 130 subjects (46 in group 1, 43 in group 2a, and 41 in group 2b) were assessed efficacy at 8 weeks. The relative contributions of night time urine production and bladder capacity were determined by analysis of the three-day voiding diary. The primary end points were improvements in night time frequency and N-QOL score. The changes from baseline in nocturnal urine volume and post void residual volume, and hours of undisturbed sleep (HUS) were also assessed as secondary efficacy measures. Nocturnal polyuria was defined as the nocturnal polyuria index (NPi) more than 33% of 24hours' urine volume and low bladder capacity was defined as the nocturnal bladder capacity index (NBCi) more than 1.3 [2]. NBCi, derived from the voiding diary, is a quantitative method of comparing nocturnal bladder capacity with 24-hr bladder capacity (maximum voided volume) [2]. Higher NBCi means lower bladder capacity. For statistical analysis, Wilcoxon signed-rank test, ANOVA, and Fisher's exact test were used, and p value <0.05 was considered statistically significant.

Results

Seventy eight percent of patients have nocturnal polyuria and 38% of patients have low bladder capacity. In the subgroup analysis of nocturnal polyuria (Fig.1), compared with baseline, group 2a and 2b patients experienced significantly decreased nocturia episodes by 0.62 episodes (p=0.0006) and 0.48 episode (p=0.0094) respectively, while group1 did not change. N-QOL and HUS were also significantly improved from baseline, and group2a significantly improved compared with group1. Furthermore, the nocturnal urine volume was reduced in group 2a (-58.89mL; p=0.1562) and group 2b (-98.04mL; p=0.0089), while group1 did not change (+4.05mL; p_0.8928). In the subgroup analysis of low bladder capacity (Fig.2), compared with baseline, group 2a and group 2b patients experienced significantly decreased nocturia episodes by 0.89 episodes (p=0.0002) and 0.69 episode (p=0.0207) respectively, while group1 did not change. N-QOL was also significantly improved from baseline in group2b (p=0.0087). HUS was significantly increased in group 2a (p=0.0412) but not in group1. NBCi was significantly changed in group2a and group2b (p=0.0012, 0.0162, respectively), while group1 did not change. Residual urine volume was not changed in this study period.

Interpretation of results

Standard therapies for nocturia, including alpha blockers, 5-alpha reductase inhibitors and anticholinergics have shown statistically significant improvements in nocturnal voiding episodes in several clinical trials. Clinically significant results, however, have not been achieved with most studies showing a reduction of a half a void or less per night. Alternative therapeutic options for this bothersome condition are needed.

This study provides the new evidence that IM is useful for not only nocturia but also nocturnal polyuria. The most important clinical finding from this analysis may be that IM provided significant nocturia relief for patients with BPH and concomitant OAB, especially those with nocturnal polyuria. It has been reported that nocturnal polyuria shows a high prevalence in men with nocturia resistant to alpha-blocker therapy. Nocturnal urine production has been implied as one of the main determining factors of nocturia in elderly men. It was reported that solifenacin, a long blood half life anticholinergic, is effective for storage symptoms and nocturia, but it is not effective for nocturnal polyuria [3].

It's interesting to note that taking IM 0.1 mg nightly might reduced nocturnal urine volume more than in taking IM 0.1 mg twice daily, while IM 0.1mg twice daily reduced night time frequency and improved N-QOL more than in taking IM 0.1mg nightly. IM has a short blood half-life – 2.9 hours – but receptor binding assay in preclinical research has shown that the duration of receptor binding is longer in the bladder than in other tissue (the salivary glands, colon, heart, and brain etc) and that IM thus has high bladder selectivity. We need further investigation whether taking IM nightly contribute to reduce nocturnal urine volume.

It is noteworthy that there were no clinically or statistically changes in the incidence of acute urinary retention and increased residual urine volume, while taking IM 0.1 mg twice daily dramatically decreased nocturia episodes by 0.89 episodes in the subgroup analysis of low bladder capacity. IM was well tolerated in BPH patients with nocturia and OAB.

Concluding message

This is the first results that IM reduced the nocturnal urine volume in patients with nocturnal polyuria by the prospective randomised trial. Combination therapy with alpha-blocker and 0.1 mg or 0.2 mg of IM is a reasonably safe and effective treatment for nocturia, not only improve low bladder capacity but also relieve nocturnal polyuria.

1. EAU-2012 (Paris) Abstract No.745
2. Neurourology and Urodynamics 30:52-57, 2011
3. Int Urogynecol J 18: 737-741, 2007

Changes from baseline to 8 weeks endpoint in Frequency-volume chart

Fig.1: Patients with Nocturnal Polyuria

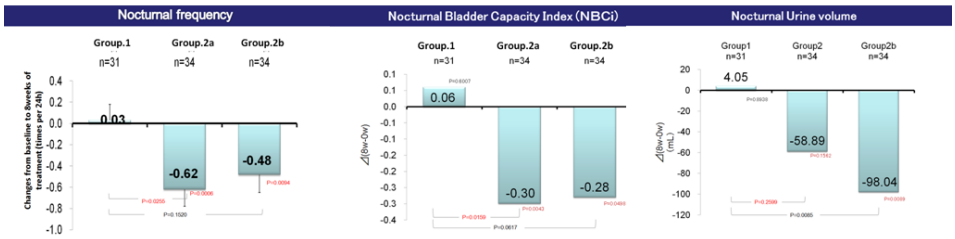
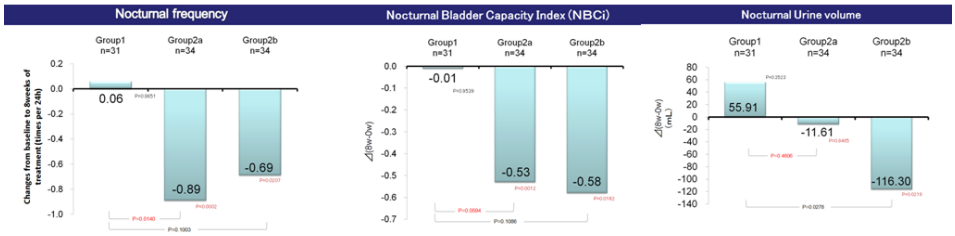


Fig.2: Patients with low bladder capacity



Mean±SEM
Intragroup (baseline vs. 8weeks) : paired t-test
Intergroup (vs. Group.1): unpaired t-test

References

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Disclosures

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