11

Rovner E[1], Nørgaard J P[2], Raymond K[2], Juul K[2]
1. *Medical University of South Carolina,* ***2.*** *Ferring Pharmaceuticals Kay Fiskers Plads 11 Copenhagen S, Denmark*

LOW DOSE DESMOPRESSIN AND TOLTERODINE FOR NOCTURIA IN FEMALE PATIENTS WITH OVERACTIVE BLADDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Hypothesis / aims of study
Overactive bladder (OAB) is characterized by urgency, with or without urge urinary incontinence, usually with frequency and nocturia. This adversely affects day-time activities, and sleep. Therefore, there is an emergent need to control both day- and night-time symptoms in these patients. Tolterodine, an antimuscarinic agent, reduces symptoms of OAB such as the urge to void and urinary frequency, and may therefore control the day-time symptoms but has not been shown to reduce nocturia in a statistically significant manner. It has also been reported that urological conditions such as OAB frequently coexist with nocturnal polyuria (NP), especially with increasing age. Desmopressin, a synthetic analogue of arginine vasopressin, reduces urine production leading to a decreased amount of urine in the bladder during the night, and may improve the nocturia associated with OAB. Hence, a combination of the two may be beneficial in patients with OAB and nocturia. The present study aimed to evaluate the efficacy and safety of low dose oral desmopressin combined with tolterodine in female patients with OAB and nocturia. In addition, the efficacy in a subgroup of patients with NP, defined as ≥33% of total daily urine volume at baseline, was evaluated.

Study design, materials and methods
This was a double-blind, randomized, parallel-group study. A total of 106 patients (using an estimated sample size of 50 per group), ≥18 years of age, who had OAB with nocturia for ≥6 months prior to trial entry (≥2 nocturnal voids each night during screening) were randomized to receive either desmopressin 25 µg combined with tolterodine 4 mg (combination therapy, n=49) or tolterodine 4 mg only (tolterodine monotherapy, n=57) for a three month period. Excluded were patients with >20 day-time voids in one day, >10 nocturnal voids in one night, and those with conditions that might contribute to symptoms of OAB, and those with hyponatremia. The full analysis set (FAS) comprised of all 97 patients (combination therapy, n=45; monotherapy, n=52). Per protocol (PP, n=89) analysis set comprised of FAS except those with major protocol violations (combination therapy, n=41; monotherapy, n=48). The primary endpoint was to compare the change from baseline in mean number of nocturnal voids during 3 months of treatment between the two treatment groups. Also, the change from baseline in the mean nocturnal volume, and the change from baseline in nocturia-related quality of life (QoL) was compared between the two treatment groups. An electronic diary (eDiary) was used to document voiding behavior, and daily impact of nocturia, and impact on sleep to evaluate the QoL. The change in the mean number of nocturnal voids from baseline was analyzed with a longitudinal analysis of the three months of treatment. Similar analysis was repeated for the subgroup of evaluable patients with NP (n=25 and n=22 in combination and monotherapy, respectively in FAS; n=21 and n=20 in combination and monotherapy, respectively in PP analysis set). Safety of this combination therapy was also evaluated.

Results
The mean age of the patients was 53.4 years, mean BMI 30.4 kg/m^2, with a mean number of nocturnal voids of 3.24 and mean day-time voids of 9.9. The change from baseline in the mean number of nocturnal voids during 3 months of treatment was numerically greater in the combination therapy group versus tolterodine monotherapy group, and did not reach statistical significance in FAS. However, the difference reached statistical significance in the PP analysis set. The reduction in the mean nocturnal volume during 3 months treatment was also significantly greater in the combination therapy group versus tolterodine monotherapy group in PP analysis set though it did not reach statistical significance in FAS. The change in the mean time to first nocturnal void was not different between the two treatment groups. The key results are summarized in Table 1.

Table 1. Mean Number of Nocturnal Voids and Mean Volume of Nocturnal Voids in Study Population

	Full Analysis Set	**Per Protocol Analysis set**
Treatment Contrast for the Change in Mean Number of Nocturnal Voids, voids	-0.34	-0.41
p-value	0.112	0.049
Treatment Contrast for the Change in Mean Volume of Nocturnal Voids, mL	-64.16	-76.57
p-value	0.103	0.046

The analysis in the NP subgroup is presented below. Overall results showed that the combination therapy significantly improved the mean number of nocturnal voids, the mean volume of nocturnal voids, and the mean time to first nocturnal void (Table 2). In the subgroup of patients with NP, there was a consistently greater improvement in QoL with combination therapy versus tolterodine monotherapy for all QoL tools reaching statistical significance for daily impact of nocturia total scores (p=0.031).

Table 2. Mean Number of Nocturnal Voids, Mean Volume of Nocturnal Voids, and Mean Time to First Nocturnal Void in the NP Subgroup

	Full Analysis Set	**Per Protocol Analysis set**
Treatment Contrast for the Change in Mean Number of Nocturnal Voids, voids	-0.62	-0.80
p-value	0.064	0.017
Treatment Contrast for the Change in Mean Time to First Nocturnal Void, min	65.11	67.06
p-value	0.045	0.052

Treatment Contrast for the Change in Mean Volume of Nocturnal Voids, mL	-166.0	-182.4
p-value	0.034	0.018

The safety profile of the two treatment groups remained comparable, and no difference between the two treatments was seen on day-time lower urinary tract symptoms, as expected. There were no deaths or serious adverse events. There was one case of clinically significant hyponatremia leading to treatment discontinuation; the event resolved on a subsequent follow-up.

Interpretation of results

The combination therapy demonstrated clinical benefits that exceeded that of antimuscarinic monotherapy on nocturia in the subgroup of patients with NP. The combination therapy did not reach significance compared to antimuscarinic monotherapy in patients where nocturia was <33% of total daily urine volume. This indicates that especially the subset of population with NP may benefit from the combination therapy. This seems plausible since desmopressin, being an antidiuretic agent, reduces the urine production leading to a decreased amount of urine stored in the bladder during the night. This is supported by a significant reduction in mean nocturnal volume in the combination therapy group versus tolterodine monotherapy group. The improvement in QoL was in-line with the improvement in nocturia.

Concluding message

Overall, the results showed that low dose desmopressin can be safely combined with tolterodine for treating nocturia in females with OAB, and an additional clinical benefit can be expected for OAB patients with NP. However, these findings need to be confirmed by further prospective studies in patients with OAB and NP.

Disclosures

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2. Medical University of South CAroline, Institutional Review Board for Human Research, Charleston, South Carolina, US
3. NorthShore University HealthSystem, Institutional Review Board, Evanston, IL, US
4. Quorum Institutional Review Board, Lower Gwynedd, PA, US **Helsinki:** Yes **Informed Consent:** Yes