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THE EFFECT OF DESMOPRESSIN IN THE TREATMENT OF MIXED NOCTURIA HAVING NOCTURNAL POLYURIA AND LOW NOCTURNAL BLADDER CAPACITY

Hypothesis / aims of study

Nocturia, one of the most common lower urinary tract symptoms, is a frequent complaint of patients in urologic department. The patient with nocturia may be categorized as having one of these three: nocturnal polyuria, low nocturnal bladder capacity (NBC), or mixed nocturia (a combination of the preceding two categories) (1). Thirty-six percent of the nocturia patients were found to have a combination of nocturnal polyuria and low NBC (1).

Specific treatment of these patients should be directed at both disorders. It was well known that desmopressin acetate, a synthetic analogue of AVP, is effective against nocturnal polyuria by decreasing night-time urine production. However to our knowledge, we don't have any results about the effect of desmopressin on mixed nocturia. The purpose of this study was to investigate the efficacy and safety of oral desmopressin in mixed nocturia.

Study design, materials and methods

This open label, prospective, multi-center study was designed to evaluate the efficacy and safety of oral desmopressin in patients with mixed nocturia. Patients aged 18 years or older with nocturia (≥2 nocturnal voids/night with nocturnal polyuria index>33% and NBC index>1) were recruited. The main exclusion criteria was diabetes insipidus, primary polydipsia (>40 mL/kg/24 h), neurogenic bladder dysfunction, urge incontinence, continued postvoiding residual urine more than 150ml, serum sodium levels below the normal range (<135mmol). Written informed consent was obtained before any study procedures were commenced. Patients who fulfilled the primary inclusion passed on to the dose titration. During a 3-week dose-titration period, optimum desmopressin dose (0.1mg, 0.2mg, 0.4mg) was determined with the dose which number of nocturia decreased by ≥50% and nocturnal urine volume decreased by ≥20% without hyponatremia, and then treatment continued for 4weeks with determined dosage. If the patients did not meet above criteria, maximum tolerable dose was determined. All the patients recorded frequency-volume charts, sleep questionnaire before and after treatment. Sleep questionnaire includes duration of sleep period until first void, >5 hours undisturbed sleep, and overall impression about quality of sleep; feel fresh in the morning or feel tired in the morning. Patients were withdrawn during the study if any of the following applied: serum sodium of <125 mmol/L or symptomatic hyponatraemia; experience of an intolerable adverse event. The efficacy assessments were based on data in the patients' diaries and endpoints were derived after the 4-week treatment period. The primary efficacy endpoint was change in mean number of nocturia episodes and the proportion of patients with a 50% or greater reduction in the mean number of nocturnal voids after treatment compared with baseline. Safety was evaluated from reported adverse events and laboratory data, with emphasis on serum sodium levels. All results variables were tested with the Paired T-test or Wilcoxon's Signed Rank test according to the normality. Binary variables(quality of sleep) were analysed by using GEE(Generalized Estimating Equations).

Results

A total of 103 patients were enrolled for dose-titration. During the dose-titration period,

9 were excluded on the basis of informed consent withdrawal (3) and protocol violation (6). In treatment phase, 94 patients were treated and 90 completed the study. Four patients withdrew; 1 because of adverse events (neck stiffness), 3 because of lost to follow up. The efficacy analysis included all patients who received at least one dose of the study drug, had a baseline and at least one post-baseline efficacy measurement (94 patients). The study population comprised 79 men (84%) and 15 women (16%), with a median (range) age of 64.2 (39–86) years. During the 4weeks of active treatment, 41 received 0.1mg desmopressin, 31 received 0.2mg, 22 received 0.4mg, as determined by their optimal response in the dose-titration study. After treatment mean number of nocturnal voids was significantly decreased (3.20 to 1.34) and the proportion of patients had a 50% or greater reduction in nocturnal voids against baseline levels was 68 (72%). The mean nocturnal urine volume, nocturia index, nocturnal polyuria index, and NBC index were decreased significantly ($p<0.0001$) after treatment (Table). Diurnal voiding frequency was not changed significantly. For the quality of sleep, the mean duration of sleep until the first nocturnal void was prolonged by 118.4±44.1 to 220.3±90.7min ($p<0.0001$), and 17(18%) patients had more than 5 hours of undisturbed initial sleep period per night after treatment newly compared with none(0%) at the baseline. Overall impression of patients about quality of sleep was also improved, that is, the incidence of the patients who got a feeling of good sleep increased significantly from 19.7% to 78.7%($p<0.0001$). Adverse events occurred in 6(6.38%) patients. All adverse events were mild but one patient withdrew because of neck stiffness. Hyponatremia was reported in only one case but asymptomatic.

Interpretation of results

This open label, multi center study during 4weeks showed reduction in nocturia, nocturnal urine volume, NI, NPI and NBCI in mixed nocturia patients. Overall impression of patients about quality of sleep was also improved. Adverse events were minimal except one, neck stiffness. Oral desmopressin has shown to be an effective and well tolerated treatment for patients with mixed nocturia.

Concluding message

Desmopressin can be recommended as a primary efficacious treatment in patients with mixed nocturia.

Variable	Baseline	Ttreatment	% change	p-value
No. of nocturia	3.20 ± 1.01	1.34±0.76	-57.9	<0.0001*
No. of daytime frequency	7.97±2.52	7.82±2.47	-0.04	0.37772*
No. of 24-hour frequency	11.18±2.83	9.15±2.72	-17	<0.0001**
Nocturnal urine volume(ml)	725.2±256.1	409.2±199.2	-41.7	<0.0001*
Nocturnal diuresis (ml/min)	1.57±0.53	0.92±0.43	-39.9	<0.0001 **
Nocturnal polyuria index(NPI)	43.49±9.0	29.55±9.8	-31.3	<0.0001**
Nocturnal index(NI)	2.57±0.60	1.57±0.58	-38.9	<0.0001**
Nocturnal bladder capacity index(NBCI)	1.62±0.72	0.73±0.48	-54.9	<0.0001*
Serum sodium (mg/dl)	141.76±2.39	141.48±2.42		0.41342*

*: Wilcoxon signed rank test, **: paired t-test

Reference:
1) Neurourol Urodyn 1997; 16:401

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CLINICAL TRIAL REGISTRATION:

This clinical trial has not yet been registered in a public clinical trials registry.

HUMAN SUBJECTS: This study was approved by the Samsung Medical Center and followed the Declaration of Helsinki Informed consent was obtained from the patients.