ORIGINAL ARTICLE
Urology

JKMS

DOI: 10.3346/jkms.2010.25.12.1792 • J Korean Med Sci 2010; 25: 1792-1797

Desmopressin is an Effective Treatment for Mixed Nocturia with Nocturnal Polyuria and Decreased Nocturnal Bladder Capacity

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Received: 21 April 2010
Accepted: 22 July 2010

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To investigate the efficacy and safety of desmopressin in patients with mixed nocturia, Patients aged ≥18 yr with mixed nocturia (≥2 voids/night and a nocturnal polyuria index [NPi] >33% and a nocturnal bladder capacity index [NBCi] >1) were recruited. The optimum dose of oral desmopressin was determined during a 3-week dose-titration period and the determined dose was maintained for 4 weeks. The efficacy was assessed by the frequency-volume charts and the sleep questionnaire. The primary endpoint was the proportion of patients with a 50% or greater reduction in the number of nocturnal voids (NV) compared with baseline. Among 103 patients enrolled, 94 (79 men and 15 women) were included in the analysis. The proportion of patients with a 50% or greater reduction in NV was 68 (72%). The mean number of NV decreased significantly (3.20 to 1.34) and the mean nocturnal urine volume, nocturia index, NPi, and NBCi decreased significantly. The mean duration of sleep until the first NV was prolonged from 118.4±44.1 to 220.3±90.7 min (P<0.001). The overall impression of patients about their quality of sleep improved. Adverse events occurred in 6 patients, including one asymptomatic hyponatremia. Desmopressin is an effective and well-tolerated treatment for mixed nocturia.

Key Words: Urinary Bladder; Deamino Arginine Vasopressin; Hyponatremia; Nocturia; Nocturnal Polyuria

INTRODUCTION

Nocturia is defined as waking one or more times to void during the period between going to bed with the intention of sleeping and waking with the intention of arising (1, 2). Recent multinational population-based, cross-sectional survey (EPIC) of adults aged ≥18 yr using 2002 International Continence Society (ICS) definitions showed overall prevalence of any lower urinary tract symptoms (LUTS) was 62.5% in men and 66.6% in women and nocturia (≥2 times/night) was the most commonly reported storage symptom for both men (20.9%) and women (24.0%) (3). Similarly, the epidemiological data in adult Korean aged 40-89 yr national community showed that of 2005 subjects interviewed, 33.5% reported voiding once per night and 48.2% twice or more per night and in addition, the impact of nocturia on daily life was reported by 14.6% of subjects (4). Nocturia is associated with sleep disruption and consequently impairs the quality of life (QOL) and potentially increases mortality (5, 6).

Although this condition should be evaluated and treated, it has only recently been recognized as a clinical entity in its own right, rather than just one of the features of LUTS. Relatively few patients with nocturia seek medical care because of a lack of awareness or misconceptions about nocturia. Furthermore, there is a general lack of knowledge about treatment options for nocturia (4, 7, 8). Because the pathophysiology of nocturia is multifactorial and complex, it is important to adopt a systematic approach to identify the possible causal factors of nocturia and to treat them accordingly. Patients with nocturia can be categorized as having one of the following three disorders: (1) nocturnal polyuria (NP) in which the voided urine volume during the hours of sleep exceeds 33% of the 24-hr output (2), decreased nocturnal bladder capacity (NBC), which results in a nocturnal urinary volume greater than the maximum voided volume (MVV), (3) or mixed nocturia, a combination of the pre-

pISSN 1011-8934
eISSN 1598-6357

ceding two categories (9, 10). In one retrospective study of 194 patients with nocturia, 13 (7%) had pure NP, 111 (57%) had diminished NBC, and 70 (36%) had a combination of the two (9, 11).

Desmopressin is a synthetic analogue of arginine vasopressin (AVP), but desmopressin has a more potent antidiuretic effect than AVP. Desmopressin has been shown to be an effective treatment for nocturia with NP by decreasing night-time urine production (12-16). However, a patient with a significantly decreased nocturnal bladder capacity index (NBCi) >2 may have bladder outlet obstruction, detrusor overactivity (DO), sensory urgency, and/or primary bladder disorders such as infection, or malignancy (16). Specific treatment of the underlying urological condition would therefore be expected to have a mitigating effect on decreased NBC as a component of nocturia. Although clinicians usually treat nocturia patients with decreased NBC based on their personal experience and use anticholinergic and hypnotic agents as well as desmopressin, these treatments have not been studied extensively clinically. In the present study, we investigated the safety and efficacy of oral desmopressin for the treatment of mixed nocturia in patients with both NP and a decreased NBC.

MATERIALS AND METHODS

Patients aged ≥18 yr with mixed nocturia (≥2 voids/night, nocturnal polyuria index [NPi] >33% and NBCi >1) were enrolled in this open label, prospective, seven-center study. The formula for calculating NPi is simply nocturnal urine volume (NUV) divided by 24-hr urine volume, and NBCi, more complicated formula that addresses voids at night in patients with decreased NBC, is defined as the difference between the predicted number of nightly voids (PNV) and the actual number of nightly voids (ANV). PNV is derived by calculating (NUV/MVV) and subtracting 1 (17). The following exclusion criteria were used: nocturia due to other defined causes of increased urinary frequency, primary polydipsia (>40 mL/kg/24 h), neurogenic bladder dysfunction, urge incontinence, continued post-voiding residual urine >150 mL, serum sodium levels <135 mM/L, uncontrolled hypertension, congestive heart failure, use of diuretics, and actual or planned pregnancy. The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. The study protocol received ethical committee approval at each study site and written informed consent was obtained from all patients before recruitment into the study.

The study included the following periods: screening (1-week), dose titration (1-3 weeks), and treatment (4 weeks) (Fig. 1). The patients that fulfilled the primary inclusion criteria entered the dose titration phase. During an open-label dose-titration period of up to 3 weeks, the patients' optimum oral desmopressin dose (0.1, 0.2, or 0.4 mg) was determined as the dose that decreased the number of nocturnal voids by ≥50% or decreased NUV by ≥20% without hyponatremia. If the patients did not meet the above criteria during the dose titration period, they received the maximum tolerable dose instead of the optimum dose. In addition, if the patients complained the adverse effects in spite of good responses to desmopressin during the dose titration period, they received the just lower dose instead of the optimum dose. Then, eligible patients were treated with the determined optimum desmopressin dose for 4 weeks. All patients kept 3-day frequency-volume charts (FVC), recorded bedtime and sleep disruption, and answered a sleep questionnaire at baseline and after treatment. The sleep questionnaire included items about the duration of sleep until the first nocturnal void, the frequency of >5 hr of undisturbed sleep, and the patient's overall impression about his/her quality of sleep expressed as feeling fresh in the morning or feeling tired in the morning. Clinical and laboratory assessments including body weight, blood and urine analysis, serum sodium monitoring, and adverse event reports were recorded at baseline and after 4 weeks of treatment. The patients with serum sodium levels <125 mM/L, symptomatic hyponatremia, or intolerable adverse effects were withdrawn from the study.

The efficacy assessments were based on data from the patients' FVC and answers to the sleep questionnaire after the 4-week treatment period. The primary efficacy endpoint was the proportion of patients with a 50% or greater reduction in the mean number of nocturnal voids compared with baseline levels after the 4-week treatment phase. Secondary endpoints included changes in the mean number of nocturnal voids, changes in the mean duration of the period from bedtime to the first nocturnal void (first sleep interval), and the proportion of patients that felt they

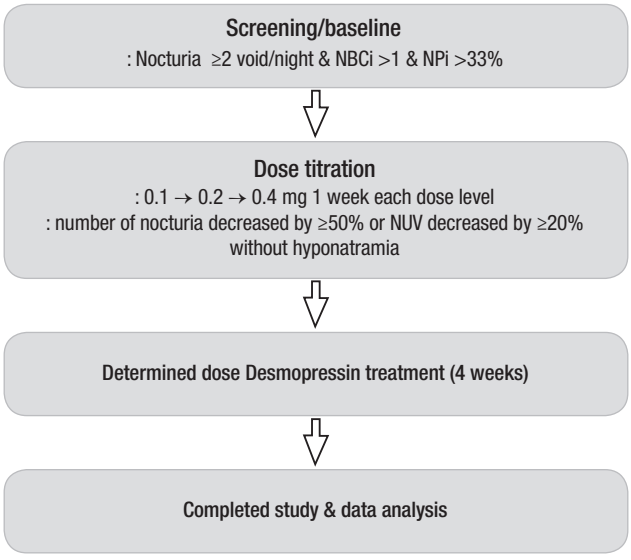

Fig. 1. The study design and treatment schedule.
NBCi, nocturnal bladder capacity index; NPi, nocturnal polyuria index; NUV, nocturnal urine volume.

had a good sleep experience. The safety of oral desmopressin was evaluated based on the collected adverse events, body weight gain, and laboratory data with an emphasis on serum sodium levels. The significance of the results obtained was tested with a paired t-test or Wilcoxon's Signed Rank test according to the normality of the data. Binary variables such as the quality of sleep were analyzed using Generalized Estimating Equations (GEE) (P value <0.001). A P value of <0.05 was considered statistically significant and the statistical software package SPSS version 17.0 was used for data management and analysis.

Ethnics statement

The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. The study protocol, patient information and informed consent forms were reviewed and approved by independent review board at each study and all patients were informed of the nature and purpose of the study (IRB No. 2004-04-05 at Samsung Medical Center). Desmopressin was supplied by Ferring Korea Inc. in 2005. This study was registered as a clinical tral: ClinicalTrials.gov ID: NCT00902655.

RESULTS

Among 103 patients enrolled in the dose-titration phase, 9 (8.7%) withdrew due to informed consent withdrawal (n=3) and protocol violation (n=6) during the dose-titration period (Fig. 2). A total of 94 patients received the optimal desmopressin dose, and 90 (95.7%) patients completed the study. Four patients withdrew due to neck stiffness (n=1) or loss to follow-up (n=3). The study population included 79 men (84%) and 15 women (16%) with a median age of 64.2 yr (39–86 yr); their baseline characteristics are summarized in Table 1.

The efficacy analysis included 94 patients that received at least one dose of the study drug during the dose-titration period, had baseline data before the study, and at least one post-baseline efficacy measurement. During the 4 weeks of active treatment, 44% (n=41) of patients received 0.1 mg oral desmopressin, 33% (n=31) received 0.2 mg of desmopressin, and 23% (n=22) received 0.4 mg of desmopressin. Overall patient compliance was high; 84 (89.7%) patients took ≥80% of the prescribed medication during the treatment period.

The mean number of nocturnal voids/night was reduced in at least 50% compared with baseline levels. In 72% of the patients (n=68) (95% CI, 0.63-0.81) (P<0.001), the mean number of nocturnal voids decreased significantly from 3.20 to 1.34 after the 4-week treatment with oral desmopressin (Table 1). Furthermore, the total number of voids/24 hr decreased significantly after treatment (11.18 vs 9.15, P<0.001); however, the number of mean daytime voids before and after treatment was not significantly different (7.97 vs 7.82, P=0.38). Moreover, the factors associated with nocturnal urine production including the mean NUV, NPi, and nocturnal diuresis all decreased significantly after desmopressin treatment. Oral desmopressin treatment was also associated with improved nocturnal bladder capacity as evidenced by decreases in both the nocturia index (Ni) and NBCi (both P<0.001). The mean duration of sleep until the first nocturnal void increased from 118.4±44.1 to 220.3±90.7 min (P< 0.001) (Fig. 3A), and 17 (18%) patients had more than 5 hr of undisturbed initial sleep per night after treatment compared to none at baseline (Fig. 3B). The overall impression of patients about their quality of sleep was improved quality; the number of patients who reported a good night of sleep increased significantly from 19.8% to 78.7% after desmopressin treatment for 4 weeks (P<0.001) (Fig. 3C).

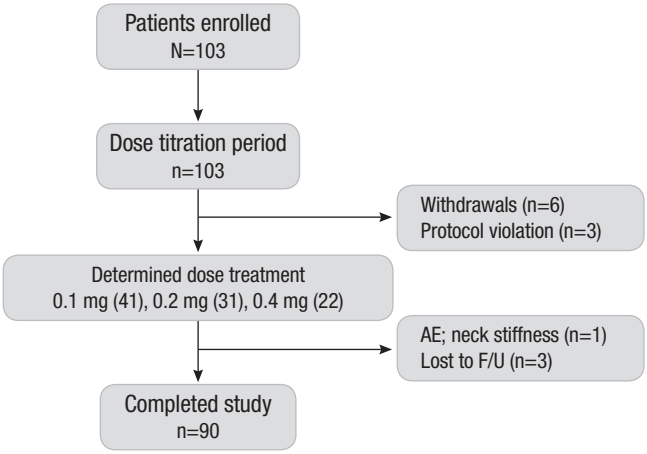

Fig. 2. Disposition of patients.
AE, adverse event; F/U, follow-up.

Table 1. The baseline characteristics and comparison of secondary endpoints after 4-week desmopressin treatment (n=94)

Variable (Mean±SD)	Baseline	Treatment	% change	P value
No. of nocturia	3.20±1.01	1.34±0.76	-57.9	<0.001
No. of daytime frequency	7.97±2.52	7.82±2.47	-0.04	0.38
No. of 24-hr frequency	11.18±2.83	9.15±2.72	-17	<0.001
Nocturnal urine volume (mL)	725.2±256.1	409.2±199.2	-41.7	<0.001
Nocturnal diuresis (mL/min)	1.57±0.53	0.92±0.43	-39.9	<0.001
Nocturnal polyuria index	43.49±9.0	29.55±9.8	-31.3	<0.001
Nocturnal index	2.57±0.60	1.57±0.58	-38.9	<0.001
Nocturnal Bladder Capacity index	1.62±0.72	0.73±0.48	-54.9	<0.001

DOI: 10.3346/jkms.2010.25.12.1792

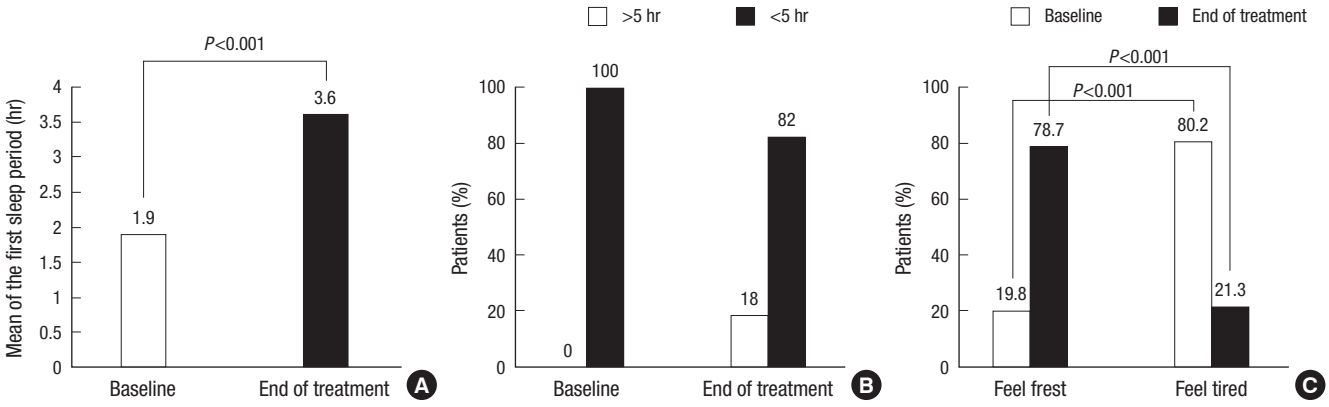

Fig. 3. The effect of desmopressin on the quality of sleep. (**A**) The duration of the first sleep period. (**B**) The proportion of more than 5 hr of undisturbed initial sleep per night. (**C**) The overall patient impression about his/her quality of sleep.

No significant serum sodium changes (141.8 to 141.5 mM/L, P=0.41) or changes in serum creatine (P=0.85), potassium (P=0.68), or body weight (P=0.43) were observed in the safety analysis compared with baseline. One 74-yr-old man treated with 0.1 mg desmopressin for 4 weeks showed significant hyponatremia (132.4 mM/L), but was asymptomatic. Although adverse events occurred in a total of 6 (6.4%) patients treated with a desmopressin dose of 0.2 mg, the symptoms were generally mild (headache [3], facial edema [1], anorexia [1]). One patient withdrew from the study because of neck stiffness.

DISCUSSION

Nocturia can be a symptom of several medical disorders other than lower urinary tract abnormalities, and is also a condition in its own right. Therefore, it is important that urologists identify the precise type and causes of nocturia to treat it effectively. For example, in one study, the type of nocturia was classified into three groups based on the voiding diaries and the results of urodynamic study (UDS): Pure NP in which the voided urine volume during the hours of sleep is more than 35% of the 24-hr urine volume, DO defined as existing uninhibited contraction on filling cystometrogram, and mixed (NP with DO). They reported that the proportion of NP, DO and mixed type were 50.0%, 7.9%, and 17.1% respectively (18). In general, nocturia can be categorized into three types: NP, decreased NBC, mixed nocturia with a combination of NP and decreased NBC, or global polyuria which refers to urine overproduction over a 24-hr period (19). Pharmacological options that could be considered include the cautious use of loop diuretics in the afternoon, anti-muscarinics for decreased NBC, and desmopressin for nocturia caused by NP. Because the number of patients with mixed nocturia has been underestimated and few results about the effect of desmopressin on mixed nocturia have been reported, we analyzed the clinical effects of oral desmopressin on patients with mixed nocturia by evaluating the improvements in both NP and NBC.

The results of our study showed that treatment with desmopressin for 4 weeks resulted in a significant improvement in the parameters associated with NP including NUV (41.7% reduction), NPi (31.3% reduction), and nocturnal diuresis (39.9% reduction). NP is believed to be responsible for at least 50–65% of nocturia cases (9, 20). The hormone AVP is normally released into the circulation following the diurnal pattern linked to the wake–sleep cycle, and decreases urine production by promoting osmotic re-absorption of solute-free water in the collecting tubules (21). Oral desmopressin, is effective against NP because it compensates for loss of circadian rhythm-related ADH secretion and furthermore, it causes slight changes in drinking habits. In one randomized, double-blind, placebo-controlled study for men ≥18 yr with verified nocturia and Ni >1, the decrease in the mean number of nocturnal voids (from 3.0 to 1.7), mean nocturnal diuresis (from 1.5 to 0.9 mL/min), and mean ratio of night/24-hr urine volume (23%) were significantly different between the desmopressin and placebo groups (all P<0.001) (15). Rembratt et al. (22) also found in a short-term study that desmopressin treatment reduced the mean number of nocturnal voids and there was a reduction of ≥20% in nocturnal diuresis in 58 patients (82%) and of ≥50% in 31 (44%). The effects of desmopressin on the NP component of nocturia in patients with mixed nocturia in the present study are similar to those reported in previous studies which inclusion criteria were not limited to mixed nocturia.

However, the use of desmopressin for the treatment of nocturia with decreased NBC has not been thoroughly evaluated, and a standard treatment protocol aimed at improving the decrease in NBC has not been developed to date. Our results suggest that oral desmopressin improves nocturia by increasing NBC as well as decreasing NUV, which is reflected by improved Ni (38.9% reduction) and NBCi (54.9% reduction). Desmopressin most likely improves NBC as follows. Type E2 neurons in and around the micturition center directly regulate the activity of the bladder, and type E1 and type I neurons modulate the activity of type E2 neurons by excitatory and inhibitory effects (23). Desmopressin suppresses bladder activity by inhibiting type E1 neu-

rons or activating type I neurons. Moreover, ureterovesical flow has been demonstrated to trigger local and general detrusor activity in an unstable bladder by distension of detrusor muscle bundles around the ureteric hiatus detrusor activity in a pig model (24). Based on these findings, desmopressin treatment would improve the decreased NBC seen in mixed nocturia patients by suppressing detrusor activity and inhibiting neuron-associated bladder contraction and the ureterovesical flow rate during sleep.

The mean duration of the time until the first nocturnal void in patients with mixed nocturia was prolonged by desmopressin and the patients' overall impression about their quality of sleep improved due to a decrease in the frequency of nocturnal voids in the present study. Similarly, Van Kerrebroeck et al. showed that the duration of the first sleep period was prolonged by 108 min (placebo group: 41 min, $P<0.001$) and an average of >5 hr of unbroken first sleep period per night was experienced by 27% of desmopressin-treated patients (placebo group: 9%), resulting in a highly significant between-group difference (25). These authors reported that two questions concerning the quality of sleep and tiredness favored desmopressin over the placebo ($P=0.02$). Among the physiological theories associated with nocturnal urine output, sleep is one of the most important factors. Elderly people with frequent awakenings have a larger part of their 24-hr urine output at night than those with fewer awakenings (26). The ability to sleep without waking is more indicative of quality sleep than interrupted longer periods of total sleep time during the night. It seems that not only spontaneous sleep, but also less fragmented sleep with undisturbed sleep duration, and deep stages of sleep with a decreased nocturnal voiding frequency improve after desmopressin treatment as a result of the effects of endogenous in vivo ADH secretion on NU. However, in another study to investigate the effects of long-term oral desmopressin on baseline ADH secretion in elderly patients with nocturia, administration of desmopressin for 1 yr in elderly patients did not affect baseline ADH secretion in spite of significantly decreasing nocturnal urine output and the number of nocturia episodes ($P<0.01$) (27). The practical importance of the increase in endogenous ADH with regard to the treatment of NP requires further investigation.

Finally, the safety analysis of desmopressin in the present study confirmed that adverse events associated with treatment are infrequent and usually mild. Significant hyponatremia occurred in only one case, and this particular patient was asymptomatic. In addition, other side effects such as body weight gain and electrolyte imbalance including sodium abnormalities and decreased renal function did not occur. In a meta-analysis of the risk of hyponatremia in older adults using desmopressin for treatment of nocturia, hyponatremia was found to be a relatively common adverse event with a frequency of 7.6% (28). However, other studies have suggested that desmopressin has antidiuretic activity for one night or less; a daytime pause in treatment may therefore be sufficient to maintain water and electrolyte balance (29, 30). In addition, at least a 10-fold higher-than-recommended dose did not cause changes in the serum sodium concentration.

In conclusion, oral desmopressin treatment results in a significant improvement in the number of mixed nocturia episodes by reducing NUV and increasing NBC. This drug improves the quality of sleep by prolonging the period of sleep until the first void, and is shown to have an acceptable safety profile.

ACKNOWLEDGMENT

Desmopressin was supplied by Ferring Korea Inc. in 2005.

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