Efficacy of desmopressin (Minirin) in the treatment of nocturia: A double-blind placebo-controlled study in women

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OBJECTIVE: The purpose of this study was to investigate the efficacy and safety of oral desmopressin in the treatment of nocturia in women.

STUDY DESIGN: Women aged 18 years or older with nocturia (≥2 voids per night with a nocturia index score >1) received desmopressin (0.1 mg, 0.2 mg, or 0.4 mg) during a 3-week dose-titration period. After a 1-week washout period, patients who responded in this period received desmopressin or placebo in a double-blind fashion for 3 weeks.

RESULTS: In double-blind phase, 144 patients were randomly assigned to groups (desmopressin, n = 72; placebo, n = 72). For desmopressin, 33 (46%) patients had a 50% or greater reduction in nocturnal voids against baseline levels compared with 5 (7%) patients receiving placebo ($P < .0001$). The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis, and ratios of nocturnal per 24 hours and nocturnal per daytime urine volumes changed significantly in favor of desmopressin versus placebo ($P < .0001$). In the dose-titration phase headache (22%), nausea (8%), and hyponatremia (6%) were reported. Two deaths occurred, although neither could be directly associated with the study drug.

CONCLUSION: Oral desmopressin is an effective and well-tolerated treatment for nocturia in women. (Am J Obstet Gynecol 2003;189:1106-13.)

Key words: Arginine vasopressin, desmopressin, nocturia, nocturnal polyuria

Nocturia, defined as waking to void during the night,[1] is one of the most troublesome lower urinary tract symptom (LUTS).[2,3] The incidence of nocturia increases with age[4,5] and has been shown to rise from 30% to 60% in a population with a mean age of 49 years to 60% to 90% in a population aged 60 to 80 years.[5-7] Nocturia is underdiagnosed, despite the fact that it can have profound implications for patients, particularly with respect to quality of life, sleep patterns, and even increased mortality.[8]

There are three main pathophysiologic categories for nocturia: nocturnal polyuria, low nocturnal bladder capacity or a combination of nocturnal polyuria, and low functional bladder capacity. Overproduction of urine at night (nocturnal polyuria) seems to be one of the main causes of nocturia[9,10] presumably because of decreased secretion of antidiuretic hormone (arginine vasopressin [AVP]).[2,9] The fall in AVP secretion is age related, which helps to explain why the ratio of nocturnal to daytime urine production increases with age.[2]

There are several approaches to the treatment of nocturia, including behavioral modification, such as fluid restriction, anticholinergic therapy, hormone replacement therapy, and diuretics.[11] Fluid restriction is rarely effective at reducing nocturnal polyuria because interstitial fluid is redistributed on achieving a recumbent position.[12] Diuretics have demonstrated reduction in nocturia; however, carefully timed administration is required because they exacerbate nocturia if taken before bedtime. Anticholinergic therapy is directed toward the treatment of nocturia where the underlying cause is related to bladder dysfunction.

Desmopressin acetate (Minirin, Ferring Pharmaceuticals, A/S, Copenhagen, Denmark) is a synthetic analog of AVP proven to be efficacious in polyuric conditions, such as nocturnal enuresis[13] and diabetes insipidus,[14] where it has been used successfully for the last 30 years. By mimicking the action of AVP, desmopressin decreases urine production and increases urine osmolality. Several investigators have studied the rationale for treating nocturia with desmopressin. Asplund et al[15,16] have demonstrated significant decreases in nocturnal diuresis and subsequent improvements in sleep. Desmopressin has also been shown to cause a significant

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Table I. Patient characteristics and demographics in the intent-to-treat and safety population

Characteristic	*ITT population*		*Total patients exposed (safety population)*
	Desmopressin	*Placebo*	
No. of patients	72	70	224
Age (y)			
Mean (SD)	52.4 (14.7)	58.7 (12.4)	57.1 (13.4)
Median	54.6	59.2	58.1
Minimum-maximum	20.6-79.4	21.2-88.7	20.6-88.7
Ethnic origin			
Black (No. [%])		3 (4)	6 (3)
White (No. [%])	70 (97)	64 (91)	211 (3)
Hispanic (No. [%])	2 (3)	1 (1)	3 (1)
Asian (No. [%])		2 (3)	4 (2)
BMI (kg/m/m)			
Mean (SD)	26.8 (5.1)	26.8 (4.9)	27.4 (5.3)
Median	25.5	25.6	26.4
Minimum-maximum	18.4-38.8	17.4-40.3	16.2-42.4
Nocturnal volume (mL)			
Mean (SD)	782 (259)	762 (247)	798 (296)
Median	739	745	760
Minimum-maximum	269-1472	333-1443	229-1816
24-h urine volume per body weight (mL/kg)			
Mean (SD)	26.5 (7.1)	26.4 (7.7)	26.3 (8.0)
Median	26.0	26.6	25.9
Minimum-maximum	12.5-43.1	12.6-40.5	6.1-53.1
Functional bladder capacity (mL)			
Mean (SD)	421 (147)	418 (127)	426 (151)
Median	400	400	400
Minimum-maximum	160-900	130-750	100-1040
Nocturnal voids			
Mean (SD)	2.92 (0.75)	2.91 (0.87)	2.98 (0.91)
Median	2.83	2.71	2.75
Minimum-maximum	1.43-5.00	1.50-4.86	1.29-6.80

decrease in nocturnal urinary volumes[17] and nocturnal incontinence in geriatric patients.[18]

This phase III study (NOCT-3-A) compared the efficacy and safety of desmopressin with placebo in the treatment of nocturia in women.

Patients and methods

Women aged 18 years or older complaining of nocturia were invited to participate in this randomized, double-blind, placebo-controlled, multinational study. Ethical and regulatory approval was obtained from the Independent Ethics Committee/Institutional Review Board at each site before recruitment began.

The study was undertaken in three phases: screening (1 week), dose titration (up to 3 weeks plus 1-week washout), and randomized double-blind treatment (3 weeks). During the screening period (June 16, 1999, to April 11, 2000) urine volume, fluid intake, and frequency of micturition were recorded in patient-held diaries. After screening, diary entries were used to confirm the diagnosis of nocturia and to identify and exclude women with diabetes insipidus, polydipsia, or abnormal fluid intake. Diaries were used throughout the study to record the characteristics shown in Table I.

Reasons for exclusion included shift work, pregnancy or planned pregnancy, signs or symptoms of vaginitis or urethritis, clinically significant abnormal urine or blood values, serum sodium levels below normal range, and certain preexisting conditions (eg, patients with diabetes insipidus, multiple sclerosis, or polydipsia [40 mL/kg per 24 hours]). Patients with overt lower urinary tract dysfunctions (eg, low bladder capacity, consistent residual volume, urge incontinence) were also excluded, as were patients receiving diuretics, tricyclic antidepressants, indomethacin, carbamazepine, or chlorpromamide. Antihypertensives were permitted providing that no dose adjustments occurred in the previous 3 months and patients were receiving long-term treatment. Other medications considered necessary by the investigator were also permitted and the details of all concomitant medications were recorded.

Women who fulfilled the primary inclusion criteria and who had an average of two or more voids per night during screening with a nocturia index score more than 1[19] (defined as the mean nocturnal volume divided by largest voided volume [LVV]) passed on to the dose titration. In the dose-titration phase, all women were administered desmopressin 0.1 mg orally at bedtime during the first

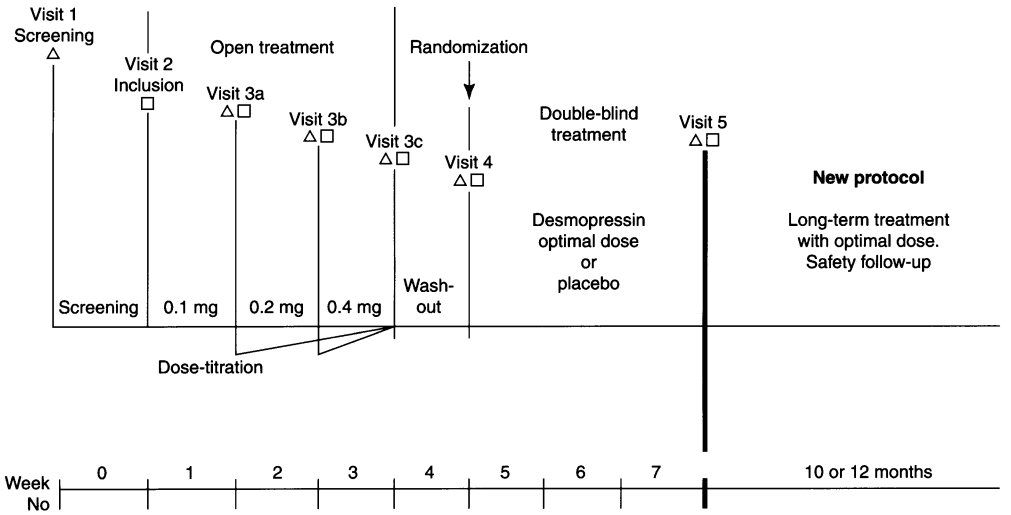

Fig 1. Study design and treatment schedule. *Open triangles*, Serum sodium measurements taken; *open squares*, adverse events recorded.

week. Patients with zero nocturnal voids at this dose were considered to have had a full treatment response and 0.1 mg was selected as their optimal dose for the double-blind period. Patients, who did not show a full treatment response after 1 week, received 0.2 mg during week 2. If a full response was not achieved with the 0.2 mg dose, the dose was increased to 0.4 mg (2×0.2 mg) during week 3. Patients who experienced adverse reactions considered related to treatment during the dose-titration period were allocated to the best tolerated dose that showed greatest treatment response, even if this was not a full response. Patients who did not show a sufficient response during dose-titration period (ie, $< 20\%$ reduction in nocturnal diuresis) and patients who failed to return to 78% or greater of baseline nocturnal diuresis values after the 1-week washout period were excluded. The criteria for choosing less than 20% reduction in nocturnal diuresis were based on an earlier observation in elderly patients with spontaneous variation in nocturnal diuresis, whereas the value of 78% was based on data from Asplund et al relating to the natural intrapatient variation in nocturnal urine volume. These cutoff values ensured that the study population consisted of patients in whom the diuresis component was the key pathogenic factor.

Eligible patients were randomly assigned to receive either their optimum desmopressin dose or placebo. Ferring Pharmaceuticals A/S generated the randomization lists and treatments were stratified by dose and center. Blinding was maintained by administering identical-looking tablets and labeling by using a preprinted treatment number from the randomization list. The study duration ranged from 6 weeks for those achieving optimal response at the lowest dose to 8 weeks for those requiring 3 weeks' dose titration. An overview of this study and the schedule of evaluations are outlined in Fig 1.

Serum sodium was monitored once at screening, potentially three times during dose titration, once during washout, and a final measurement at the end of the double-blind period. Patients were withdrawn during the study if any of the following applied: serum sodium less than125 mmol/L or symptomatic hyponatremia, experience of an intolerable adverse event, protocol deviation, failure to cooperate, or a condition developed that jeopardized the welfare of the patient and pregnancy. Symptomatic hyponatremia was defined as serum sodium below the normal range considered clinically relevant with one or more of the following symptoms: headache, nausea, vomiting, dizziness, muscle cramps, lethargy, restlessness, disorientation, and/or depressed reflexes. Patients could also be withdrawn at the discretion of the investigator or at the request of the patient.

The primary efficacy end point was the proportion of women with a 50% or greater reduction in the mean number of nocturnal voids after treatment compared with baseline levels. Secondary end points included changes in the mean number of nocturnal voids, duration of the sleep period until the first nocturnal void, nocturnal diuresis, ratios of nocturnal/24 hours and nocturnal/daytime urine volumes. Further, impact on quality of life and the safety of desmopressin treatment were investigated by using an abbreviated version of the Bristol female lower urinary tract symptom (BFLUTS) questionnaire,[20] which was completed during screening and at the end of the study.

Reported adverse events and laboratory measurements (in particular serum sodium monitoring) were assessed for the evaluation of treatment safety.

Statistical analyses were performed by the Biometrics Department at Ferring Pharmaceuticals A/S with SAS version 8.0 software (Windows). All randomly assigned patients who took at least one dose of study medication and produced relevant follow-up data, defined as at least one valid night in the double-blind treatment period, were included in the intent-to-treat (ITT) population. The per protocol (PP) population comprised a subset of the ITT population who fulfilled all inclusion criteria, did not meet any of the exclusion criteria, received 80% or more of the study medication during the double-blind period, and did not violate the protocol at any time. The safety population comprised all patients taking at least one dose of study medication. For the primary end point, the analysis was based on the ITT population (primary analysis) as well as the PP population (secondary analysis). The analyses of all the secondary end points were based on the ITT population.

The primary end point was tested by using a Cochran-Mantel-Haenszel (CMH) test controlling for country. Breslow-Day and Zelen's tests were used to assess the homogeneity of country-specific odds ratios (ORs). The common OR, if homogeneity was indicated, was presented with approximate 95% CI. Results of secondary end points were presented by using 95% CI and *P*-values that were based on the two-sample *t* test, with $P \leq .05$ deemed significant. Analysis of the BFLUTS questionnaire was based on frequency counts of individual questions.

The sample size calculation was based on the assumption that 30% of the patients treated with desmopressin would respond to treatment (defined as ≥50% reduction in the mean number of nocturnal voids), whereas a placebo response would be observed in 7% or less of the patients. These figures (30% and 7%) are based on an evaluation of phase II clinical studies.[16,21] A sample of 55 patients per treatment group was needed to allow for the detection of 23% units (30% vs 7%) difference calculated with a power of 90% and $\alpha = .05$, two sided. If 30% of patients dropped out during dose titration and 10% during the double-blind period, 174 patients needed to be enrolled in the dose-titration period.

Results

Patient demography and baseline characteristics were similar for the desmopressin and placebo groups in the ITT population, although the mean age was significant higher in the placebo group than in the desmopressin group (58.7 vs 52.4 years) (Table I).

A total of 391 women were screened for entry at 27 centers in Denmark (5), Sweden (5), The Netherlands (8), the United Kingdom (5), and the United States (4). The major reason for screening failure was fewer than two voids per night (approximately 50%). The safety population, defined as patients receiving at least one dose of study medication, comprised 224 patients with a mean age of 57 years. During the dose-titration period, 33 were excluded on the basis of failing to return to baseline diuresis and 8 because of lack of response. The remaining 39 were excluded for other reasons, including adverse events (n = 22) and failure to comply (n = 3). At the end of the washout period, 144 (64%) women returned to 78% or greater of their nocturnal diuresis compared with baseline and were subsequently randomly assigned into the double-blind treatment period where they received either desmopressin (n = 72) at their optimum dose or placebo (n = 72). In total, 141 of 144 (98%) patients completed the study. The withdrawals were in the placebo group: one because of adverse events (angina pectoris and atrial flutter) and the remaining two withdrawals because of a lack of efficacy. Patient disposition is summarized in Fig 2.

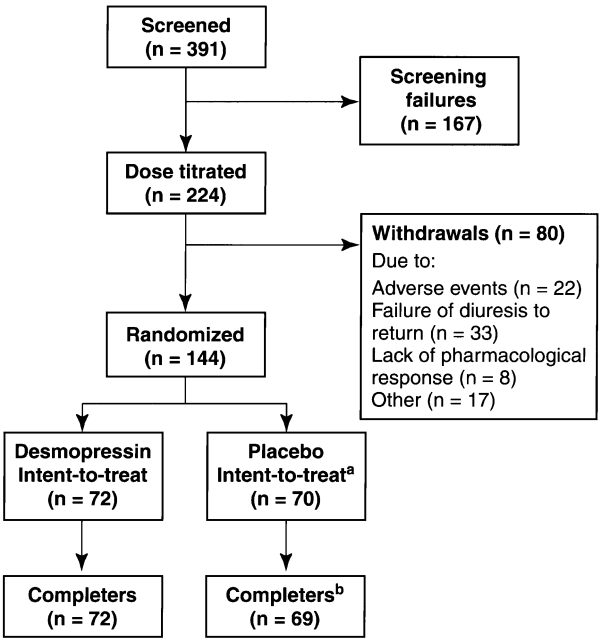

Fig 2. Patient disposition. *a*, Two patients were excluded from the intent-to-treat analysis because efficacy data were not available; *b*, one patient did not complete the study as a result of adverse events.

All patients receiving desmopressin and 68 (94%) receiving placebo took 80% or more of the prescribed medication and were considered compliant. As an indicator of treatment tolerability and acceptability, 83% of patients completing the double-blind treatment period agreed to continue therapy in 10- or 12-month follow-up studies.

In the ITT population, a clinical response (≥50% reduction in the mean number of nocturnal voids) was achieved in 33 (46%) patients receiving desmopressin compared with 5 (7%) receiving placebo (OR = 13.4 [95% CI 4.6-39.2]) ($P < .0001$). These findings were

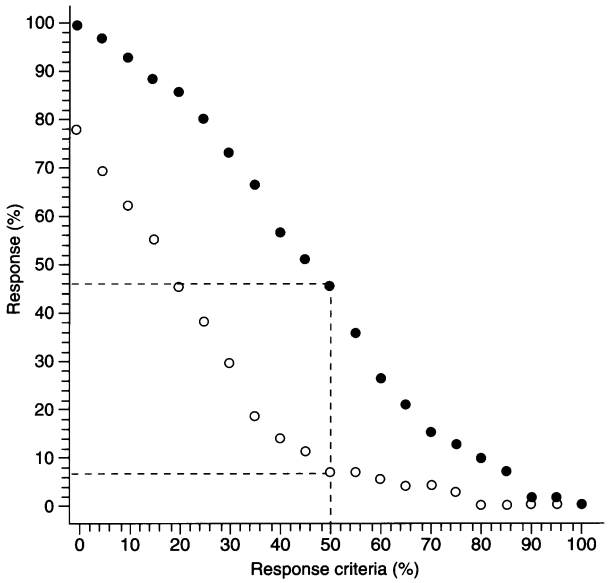

Fig 3. Proportion of patients responding at different definitions of the clinical response. *Dashed line*, Proportion of patients with a ≥50% reduction in nocturnal voids; *open circles*, placebo; *closed circles*, desmopressin.

confirmed in the PP population with 24 (44%) patients receiving desmopressin and 2 (4%) receiving placebo ($P < .0001$) achieving a clinical response with a common OR = 33.2 (95% CI 6.0-183.6). The proportion of patients responding at different definitions of the clinical response is illustrated in Fig 3. Independently of dose, the response rate in the desmopressin group was significantly higher than in the placebo group.

All secondary efficacy end points showed a highly statistically significant difference in favor of desmopressin ($P < .0001$) (Table II). At the end of the double-blind treatment period, the mean number of nocturnal voids was almost halved from 2.9 to 1.6 (−46%) in the desmopressin-treated group compared with 2.9 to 2.4 voids (−17%) in the placebo group. All the desmopressin-treated patients had fewer nocturnal voids by the end of treatment, independent of the number of nocturnal voids at baseline.

The mean duration of sleep until the first nocturnal void was prolonged by 130 to 272 minutes in the desmopressin group compared with an increase of 37 to 181 minutes in the placebo group. The 93-minute difference between desmopressin and placebo is statistically significant ($P < .0001$). Furthermore, it is a prolongation of the first sleep period. Twenty-four (33%) desmopressin patients had more than 5 hours of undisturbed initial sleep period per night compared with 4 (6%) in the placebo group.

The mean nocturnal diuresis decreased by 0.7 mL/min (from 1.5-0.8 mL/min) in the desmopressin group and by 0.1 mL/min (from 1.44-1.35 mL/min) in the placebo group ($P < .0001$). Regarding the mean ratio of nocturnal/24-hour urine volume, there was a greater reduction in the desmopressin group (13%) compared with placebo (1%) ($P < .0001$). A similar result was observed for the mean ratio of nocturnal/daytime urine volume with a greater reduction in the desmopressin group.

Analysis of the BFLUTS questionnaire demonstrated that at screening, urinary symptoms were similar for the two treatment groups; the most common being nocturia, followed by urinary frequency during the day and night. After the double-blind period, the prevalence of nocturia fell from 97% to 68% in the desmopressin group compared with 100% to 85% in the placebo group. Other urinary symptoms did not differ significantly during treatment (ie, frequency [30% vs 34%] and urgency [67% vs 74%] for desmopressin and placebo, respectively). The potential for an increase in daytime frequency with desmopressin was not evident. Voiding frequency during daytime did not change significantly during treatment. Bothersomeness caused by nocturia was reduced from 97% to 75% in the desmopressin group compared with a reduction from 98% to 84% in the placebo group. The proportion of patients who considered nocturia to be "quite a problem" or "a serious problem" fell from 73% to 21% in the desmopressin group compared with a decrease from 80% to 52% in the placebo group. Statistical improvements in bother of nocturia were shown for treatment with desmopressin compared with placebo ($P = .01$). Thus, patient perception of an improvement in quality of life reflects the improvement in efficacy.

During the dose-titration and washout periods, adverse events were reported by 158 (71%) patients in the safety population (n = 224) (Table III). The most frequently reported adverse events during the dose-titration period were headache (22%), nausea (8%), and hyponatremia (6%). In the double-blind period, the frequency of patients having adverse events was similar for both treatment groups with 26 (36%) versus 25 (35%) in the desmopressin and placebo groups, respectively. In the double-blind period, the most frequent adverse event related to study drug was headache, which was reported in 10% of desmopressin-treated patients and 7% of placebo-treated patients.

The majority of adverse events related to study drug were mild (53%) with moderate and severe events comprising 37% and 10%, respectively. In the double-blind period, treatment-related adverse events were reported in nine (13%) desmopressin patients versus six (8%) placebo patients. The most frequent adverse events occurring in more than 3% of patients, which were related to the study medication, are shown in Table III.

During the study, five (2%) patients had serious adverse events. Four cases were reported during the dose-titration period (a fatal outcome was recorded for two patients and

Table II. Secondary end points

	Desmopressin (mean [SD])			*Placebo (mean [SD])*				
	Baseline	*Treatment*	*% change**	*Baseline*	*Treatment*	*% change**	*Mean†*	*95% CI*
No. of nocturnal voids	2.92 (0.75)	1.61 (0.84)	−46	2.91 (0.87)	2.36 (0.87)	−17	−0.76	[−1.01 to −0.50]‡
Duration of first sleep period (min)	142 (49)	272 (103)	+78	144 (53)	181 (75)	+20	93.73	[64.1 to 123]‡
Nocturnal diuresis (mL/min)	1.51 (0.53)	0.82 (0.36)	−44	1.44 (0.50)	1.35 (0.50)	−6	−0.60	[−0.71 to −0.49]‡
Ratio of nocturnal/24-h urine volume (%)	41.5 (10.6)	28.3 (11.4)	−30	40.7 (10.6)	39.6 (12.4)	+2	−12.4	[−16.4 to −8.37]‡
Ratio of nocturnal/day urine volume	0.84 (0.59)	0.49 (0.48)	−36	0.79 (0.40)	0.77 (0.44)	+9	−0.33	[−0.48 to −0.18]‡

*Mean (or median) of the individual % changes between end of treatment values compared with baseline values.
†Difference between desmopressin and placebo in terms of the absolute change in mean values.
‡$P < .0001$.

Table III. Summary of adverse events

	Dose titration		*Double-blind*			
	Desmopressin		*Desmopressin*		*Placebo*	
	No. (%)	*E*	*No. (%)*	*E*	*No. (%)*	*E*
Patients exposed	224 (100)		72 (100)		72 (100)	
Total adverse events	158 (71)	398	26 (36)	38	25 (35)	50
Serious adverse events	5 (2)	10	0		1 (1)	2
Deaths*	2 (1)	3	0		0	
Adverse events related to study medication	109 (49)	231	9 (13)	10	6 (8)	10
Most frequently reported (>3%) adverse events related to study medication						
Headache	50 (22)	63	7 (10)	8	5 (7)	8
Nausea	17 (8)	18	—	—	1 (1)	1
Hyponatremia	14 (6)	15	—	—	—	—
Abdominal pain	9 (4)	10	—	—	—	—
Dry mouth	9 (4)	9	—	—	—	—
Micturition frequency	8 (4)	9	—	—	—	—
Dizziness	7 (3)	7	—	—	—	—
Fatigue	7 (3)	8	—	—	—	—
Peripheral edema	7 (3)	9	—	—	—	—

N, Number of patients with adverse events; *E*, Number of adverse events.
*One death was unlikely to be study related (patient experienced nighttime respiratory insufficiency but fully recovered after withdrawal and subsequently died). For the other death, the main cause of the fatal outcome was probably related to the patient's underlying disease (late diabetic complications); however, the initial causal relation between the onset of the events (pneumonia and respiratory insufficiency) cannot be excluded or ruled out.

two patients had serious hyponatremia). The fifth case was reported during the double-blind period in the placebo group (angina pectoris and supraventricular tachycardia).

Regarding the two fatalities, it is unlikely that hyponatremia was responsible because the patient's serum sodium levels were within the normal range during both the dose-titration period (143 mmol/L) and at admission to hospital (135 mmol/L). Therefore, the first fatal outcome was deemed unlikely to be related to desmopressin (the patient had respiratory insufficiency during the night and after withdrawal fully recovered from the adverse event); however, the patient subsequently died of unrelated causes. In the second case, the causal relationship between desmopressin and onset of adverse events (pneumonia and respiratory insufficiency) was a temporal association; however, the fatal outcome was mainly caused by the underlying diabetic complications.

A total of 14 (6%) patients recorded hyponatremia as an adverse event, which was considered clinically relevant. In total, 27 (12%) patients recorded serum sodium levels below the normal range during the study. Thirteen of these patients were characterized by serum sodium levels below 130 mmol/L. Eleven of these patients were aged 65 years or older. All cases of hyponatremia occurred during the dose-titration period. A total of 7 patients withdrew because of hyponatremia during the dose-titration

period. There were no reports of serum sodium values below the normal range throughout the double-blind treatment period.

Comment

The rationale behind the study design was to allow the evaluation of desmopressin in a specific population of patients experiencing nocturia associated with the nocturnal polyuria component and establish the optimal dose. One week at each dose was deemed sufficient to enable desmopressin to exert a response and allow an assessment of safety. A 1-week washout period was introduced to ensure no residual desmopressin effect was present before the double-blind treatment period. To ensure that the study population consisted of patients with nocturia resulting from a pathologic diuresis component, it was required that the nocturia index score was more than 1 and patients with symptoms of bladder overactivity were excluded.

The active versus the placebo population were fairly comparable, although the mean age was significant higher in the placebo group. However, this finding did not result in differences in any of the key parameters investigated.

The results from this study demonstrate that desmopressin can offer relief to women who have nocturia. For the primary endpoint, the clinical response was significantly greater in the desmopressin group with a success rate of 46% compared with 7% for placebo. This margin of success between desmopressin and placebo is influenced by the percentage cutoff point for episodes of nocturia. The choice of a 50% or greater reduction in episodes of nocturia as the primary endpoint was considered to be more clinically relevant rather than using a general measure of diuresis. The cutoff point of 50% was chosen arbitrarily. The results for the secondary end points support the observations from the primary analysis. The differences between desmopressin and placebo groups were found to be statistically significant in favor of desmopressin with respect to diuresis and the ratio of nocturnal urine volume relative to 24 hours and daytime urine volumes, which suggest a normalization of urinary values to within their physiologic range.[22,23]

It is important to note the correlation between the decrease in diuresis and the number of nocturnal voids after desmopressin therapy because this emphasizes the significant contribution from nocturnal polyuria to the problem of nocturia. It is unlikely that the decrease in diuresis could be improved any further because 0.9 mL/min is the normal rate in adults.[22]

One of the underrecognized aspects of nocturia relates to its impact on quality of life. The significant improvements in quality of life that were demonstrated put the issue of improvement versus cure into clinical perspective. The limitation of the BFLUTS questionnaire in relation to nocturia is recognized because it is designed only to record a symptom/quality-of-life score that is based on a summation of LUTS. It is recommended that, in the future, a more specific questionnaire is developed that is able to directly assess the impact of nocturia on quality of life. Nocturia is not only detrimental to the quality of sleep[24] and well-being but is also related to increased mortality[8] and risks of falling at night,[7] particularly in the elderly. Desmopressin significantly prolonged the duration of sleep until the first nocturnal void, which is an important indicator of quality of life.[25] Women with nocturia have been shown to take more sick leave compared with nonsufferers[26] and physicians need to be made more aware of the direct and indirect consequences associated with LUTS, such as nocturia.

Desmopressin appears to be a suitable candidate for the treatment of the nocturnal polyuria component of nocturia. It works by increasing the concentration capacity of the distal tubules decreasing urine output and improving the reabsorption of water in the kidney. The success of desmopressin can be explained by the fact that the kidney contains at least seven aquaporins (AQP), which are expressed at distinct sites. AQP2 is exclusively expressed in the principal cells of the connective tubule and collecting duct and is the predominant vasopressin-regulated water channel. Long-term efficacy has also been demonstrated for other indications where polyuria is a factor, such as nocturnal enuresis.[27]

With respect to safety, the randomized part of the study revealed that adverse events associated with desmopressin treatment were usually mild and comparable with placebo in terms of incidence. Bearing in mind that the randomized population represents a selected group in whom efficacy and safety was established during the uncontrolled dose titration in which approximately 50% (39 of 80) of the patients were excluded because of adverse events.

All cases of hyponatremia occurred during dose titration, and there were no serum sodium values below the normal range found during the double-blind period. Serum sodium levels were measured at each weekly visit during the dose-titration period; therefore, the presence of hyponatremia was established after 1, 2, or 3 weeks of treatment (or a week after treatment initiation or dose increase). The patients at higher risk of having hyponatremia develop were those aged 65 years or older. Therefore, special precautions are required when elderly patients begin desmopressin therapy, for instance, clinicians should perform regular assessments of serum sodium, most notably 3 days after commencing desmopressin treatment and after increasing the dose.

Regarding repeat assessments of serum sodium, providing sodium values are normal after the first few days of treatment, it is unlikely that these values will change significantly after longer-term treatment provided pa-

tients refrain from excessive drinking. Nevertheless, it is important to consider fluid retention and warn patients against such symptoms. Another useful precaution should be to ensure that patients do not exceed a daily fluid intake of 2.5 L. Although the frequency and severity of hyponatremia were low throughout the study, it is worth emphasizing that hyponatremia is associated with severe health risks, which, if untreated, can be fatal. It is therefore recommended that regular serum sodium measurements are performed in the elderly and the appearance of any symptoms characteristic of hyponatremia are fully investigated.

Although it may be important to provide advice on the management of nocturia, such as reducing liquids with a diuretic effect or limiting fluid intake before bedtime, these strategies are often insufficient to address the nocturnal polyuria component of nocturia. Recently, there has been considerable progress in the understanding and perception of nocturia as an independent condition. Both patient and physician need to become aware that it is not necessary to tolerate nocturia, particularly when there is an effective pharmacologic solution available.

Desmopressin treatment of male patients with nocturia has demonstrated similar results,[28] and a recent study shows that desmopressin is well tolerated during long-term treatment of nocturia.[29]

In summary, this study provides evidence for the efficacy and short-time safety of desmopressin in the treatment of nocturia in women.

Multicenter study conducted in Sweden (Umea, Uppsala, Göteburg, Borås, Varberg), Denmark (Glostrup, Århus, Odense, Kolding, Ålborg), The Netherlands (Maastricht, Leiden, Winterswijk, Zwolle, Almelo, Tilburg, Heerlen, Amsterdam), the United Kingdom (Plymouth, Southampton, Blackburn, Kettering, Glasgow), and the United States (Las Vegas, Nev, Lawrenceville, NJ, Los Angeles, Calif, Laurel, Md). An identical study conducted in male patients is due to be published in the *British Journal of Urology*.

REFERENCES

1. Van Kerrebroeck P, Weiss J. Standardisation and terminology of nocturia. BJU Int 1999;84:14.
2. Miller M. Nocturnal polyuria in older people: pathophysiology and clinical implications. J Am Geriatr Soc 2000;48:1321-9.
3. Peters TJ, Donovan JL, Kay HE, Abrams P, de la Rosette JJ, Porru D, et al. The International Continence Society "Benign Prostatic Hyperplasia" Study: the bothersomeness of urinary symptoms. J Urol 1997;157:900-1.
4. Donahue JL, Lowenthal DT. Nocturnal polyuria in the elderly person. Am J Med Sci 1997;314:232-8.
5. Barker JC, Mitteness LS. Nocturia in the elderly. Gerontologist 1998;28:99-104.
6. Hale WE, Perkins LL, Marks RG, Stewart RB. Symptom prevalence in the elderly. J Am Geriatr Soc 1986;34:333-40.
7. Stewart RB, More M, May FE, Marks RG, Hale WE. Nocturia a risk factor for falls in the elderly. J Am Geriatr Soc 1992;40:1212-20.
8. Asplund R. Mortality in the elderly in relation to nocturnal micturition. BJU Int 1999;84:297-301.
9. Asplund R. The nocturnal polyuria syndrome. Gen Pharmacol 1995;26:1203-9.
10. Rembratt A, Norgaard JP, Andersson K-E. Nocturnal polyuria: an inescapable consequence of aging. Neurourol Urodyn 2001;20: 460-2.
11. Lose G, Alling-Moller L, Jennum P. Nocturia in women. Am J Obstet Gynecol 2001;185:514-21.
12. Matthiesen TB, Rittig S, Nørgaard JP, Pedersen EB, Djurhuus JC. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. J Urol 1996;156:1292-9.
13. Hjälmås K, Hanson E, Hellstrom A-L, Kruse S, Sillen U. Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multi-center study. BJU Int 1998;82:704-9.
14. Vilhardt H. Basic pharmacology of desmopressin: a review. Drug Invest 1990;2:28.
15. Asplund R, Åberg H. Desmopressin in elderly subjects with increased nocturnal diuresis: a two-month treatment study. Scand J Urol Nephrol 1993;27:77-82.
16. Asplund R, Sundberg B, Bengtsson P. Oral desmopressin for nocturnal polyuria in elderly subjects: a double blind, placebo-controlled randomised exploratory study. BJU Int 1999;83:591-5.
17. Eckford SD, Carter PG, Jackson SR, Penney MD, Abrams P. An open, inpatient, incremental safety and efficacy study of desmopressin in women with multiple sclerosis and nocturia. BJU Int 1995;76:459-63.
18. Seiler WO, Stahelin HB, Hefti U. Desmopressin reduces night time urine volume in geriatric patients: implication for treatment of the nocturnal incontinence. Clin Investig 1992;70:619.
19. Weiss JP, Blaivas JG. Nocturia. J Urol 2000;163:5-12.
20. Jackson S, Donovan J, Brookes S, Eckford S, Swithinbank L, Abrams P. The British Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. Br J Urol 1996;77:805-12.
21. Asplund R, Sundberg B, Bengtsson P. Desmopressin for the treatment of nocturnal polyuria in the elderly: a dose titration study. Br J Urol 1998;82:642-6.
22. Kirkland JL, Lye M, Levy DW, Banerjee AK. Patterns of urinary flow and electrolyte excretion in healthy elderly people. BMJ 1983; 287:1665-7.
23. Saito M, Kondo A, Kato T, Yamada Y. Frequency volume charts comparison of frequency between elderly and adult patients. Br J Urol 1993;72:38-41.
24. Asplund R. Daytime sleepiness and napping amongst the elderly in relation to somatic health and medical treatment. J Intern Med 1996;239:261-7.
25. Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D. Sleep deprivation: effect on sleep stages and EEG power density in man. Electroenceph Clin Neurophysiol 1981;51:483-93.
26. Asplund R, Aberg H. Nocturnal micturition, sleep and well-being in women of ages 40-64 years. Maturitas 1996;24:73-81.
27. Djurhuus JC, Mathiesen TB, Rittig S. Similarities and dissimilarities between nocturnal enuresis in childhood and nocturia in adults. BJU Int 1999;84(1 Suppl):9-12.
28. Mattiasson A, Abrams P, van Kerrebroeck P, Walter S, Weiss J. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind, placebo-controlled study in men. BJU Int 2002;89: 855-62.
29. Lose G, Matthiasson A. Long-term treatment of male and female nocturia patients with oral desmopressin. Int Urogynecol J 2002;13 (1 Suppl):5.