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Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men

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Objective To investigate the efficacy and safety of oral desmopressin in the treatment of nocturia in men.

Patients and methods Men aged ≥18 years with verified nocturia (≥two voids/night) and nocturnal urine production greater than their maximum functional bladder capacity were recruited. A 3-week dose-titration phase established the optimum desmopressin dose (0.1, 0.2 or 0.4 mg). After a 1-week ‘washout’ period, patients who responded in the dose-titration period were randomized to receive the optimal dose of desmopressin or placebo in a double-blind design for 3 weeks.

Results In all, 151 patients entered the double-blind period (86 treated with desmopressin, 65 with placebo). In the desmopressin group 28 (34%) patients and in the placebo group two (3%) patients (P < 0.001) had fewer than half the number of nocturnal voids relative to baseline; the mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7, respectively, reflecting a mean decrease of 43% and 12% (P < 0.001). The mean duration of the first sleep period increased by 59% (from 2.7 to 4.5 h) in the desmopressin group, compared with an increase of 21% (from 2.5 to 2.9 h) in the placebo group (P < 0.001). The mean nocturnal diuresis decreased by 36% (from 1.5 to 0.9 mL/min) in the desmopressin group and by 6% (from 1.7 to 1.5 mL/min) in the placebo group (P < 0.001). The mean ratio of night/24-h urine volume decreased by 23% and 1% (P < 0.001), and the mean ratio of night/day urine volume decreased by 27% and increased by 3% (P < 0.001) for the desmopressin and placebo groups, respectively. In the double-blind treatment period, similar numbers of patients had adverse events: 15 (17%) patients in the desmopressin and 16 (25%) patients in the placebo group. Most adverse events were mild. Serum sodium levels were < 130 mmol/L in 10 (4%) patients and this occurred during dose-titration.

Conclusions Orally administered desmopressin is an effective and well-tolerated treatment for nocturia in men.

Keywords nocturia, desmopressin, arginine vasopressin, nocturnal polyuria

Introduction

Nocturia, defined as waking at night to pass urine [1], can occur at any age in any population, although the prevalence of the condition increases with advancing age [2]. Studies show that nocturia is the most common lower urinary tract symptom (LUTS), reported by 72% of elderly people, and is considered to be a very bothersome condition [3,4]. Rising at night to void increases the risk of personal injury, particularly in the elderly where the condition is associated with a greater risk of falls [5] and hip fractures [6]. Nocturia has profound implications for sufferers, with detrimental effects on quality-of-life and sleep patterns, and increased mortality [7].

Nocturnal polyuria, or the over-production of urine at night, is an important cause of nocturia [8] that may result from age-related fluctuations in serum levels of the antidiuretic hormone arginine vasopressin (AVP). Advancing age is also associated with increased nighttime excretion of water, solutes and electrolytes [9,10]. However, regardless of age, most people with nocturia secrete less AVP nocturnally than do healthy subjects [8,11]. Treatments currently licensed to improve bladder function do not control nocturnal polyuria, which remains one of the most difficult LUTS to treat [12,13].

Desmopressin acetate (Minirin®, Ferring Pharmaceuticals, Sweden), a synthetic analogue of AVP, is effective against nocturnal polyuria when administered at bed-time, by decreasing nighttime urine production [14]. More potent than AVP, desmopressin is used in the treatment of several conditions where polyuria is a key symptom, e.g. diabetes insipidus and nocturnal enuresis, for which it remains a principal pharmacological treatment. Similarities between nocturnal enuresis

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in childhood and nocturia in adulthood have been described [15] and the opportunity for treating nocturia with desmopressin has also been investigated by others; these studies have provided support for the use of desmopressin in nocturia [16–19].

In the present study we compared the efficacy and tolerability of desmopressin with placebo in the treatment of nocturia in men. The primary endpoint was the proportion of patients with a reduction by more than half in the mean number of nocturnal voids in a 3-week double-blind treatment period; other secondary endpoints were also assessed.

**Patients and methods**

This randomized, double-blind, placebo-controlled, parallel-group, multinational, phase III study evaluated the efficacy and safety of desmopressin in men with nocturia. The study comprised the following periods: screening (1 week), dose-titration (1–3 weeks, followed by a 1-week ‘washout’), and a 3-week double-blind treatment period. For the first week of dose-titration, all patients received desmopressin 0.1 mg orally at bedtime. For those who then had no nocturnal voids (a full treatment response), 0.1 mg was selected as the optimal dose for the double-blind treatment period. These patients received no higher doses of desmopressin. Patients who did not respond during the first dose-titration week received desmopressin 0.2 mg. Patients then having no nocturnal voids or ≥20% reduction in nocturnal diuresis were maintained on 0.2 mg. The dose was increased to 0.4 mg (2 × 0.2 mg tablets) in the third week in those who did not respond to 0.2 mg (i.e. had <20% decrease in nocturnal diuresis). Patients who experienced a <20% decrease in nocturnal diuresis at all doses during dose-titration were classified as not responding and did not continue in the study. If treatment-related adverse events were experienced during dose-titration, patients were allocated to the maximum tolerated dose that showed the best pharmacodynamic response (i.e. reduction in nocturnal diuresis).

Only patients who obtained a ≥20% reduction in nocturnal diuresis during the dose-titration period were randomized to either placebo or active treatment. The study design and schedule of evaluations are shown in Fig. 1. The study duration ranged from 6 weeks for those achieving optimal response during the first dose-titration week, to 8 weeks for those completing all three dose-titration weeks. Clinical and laboratory assessments were undertaken throughout the study (height, weight, physical examination, BP, blood and urine analysis, concomitant medication/diseases, serum sodium monitoring and adverse event reports).

Men aged ≥18 years with symptoms of nocturia were recruited and screened. Patient-maintained diaries were used to record the following throughout the study; bedtime, time of rising, 24-h fluid intake and urine recording, time and volume of nocturnal voids and time of tablet intake. During the study, from 1 h before bedtime until 8 h after taking of either desmopressin or placebo, patients drank only to satisfy thirst, avoiding liquids with a diuretic effect.

The following inclusion criteria were used: a mean of two or more voids per night, with Nocturia Index scores of >1 [6] (mean nocturnal volume/functional bladder capacity; the latter being the largest single volume of urine measured at any time). The main

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**Fig. 1.** The study design and treatment schedule. Green triangles show serum sodium measurements and red squares the recording of adverse events.
exclusion criteria were: nocturia arising from other well-defined causes of increased urinary frequency, e.g. diagnosed or suspected diabetes insipidus, primary polydipsia (40 mL/kg/24 h) or multiple sclerosis, urge incontinence or recently commenced medical or surgical treatment for BPO; conditions characterized by fluid and/or electrolyte imbalance where anti-diuresis was inappropriate (e.g. cardiac failure, use of diuretics); serum sodium levels below the normal range, and uncontrolled hypertension.

Patients who showed no response during dose-titration (i.e. <20% reduction in nocturnal diuresis) and patients who failed to return to ≥78% of baseline nocturnal diuresis values after the 1-week washout period did not enter the double-blind treatment period. 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; protocol deviation; failure to co-operate; a condition developed which jeopardised the welfare of the patient; at the discretion of the investigator; at the request of the patient.

The primary efficacy endpoint was the proportion of patients who had a reduction by more than half in the mean number of nocturnal voids after treatment compared with baseline. Several secondary endpoints were also assessed: the number of nightly voids; the duration of the sleep period until the first void; nocturnal diuresis; night-time/24 h and night-time/day urine volume; effect on quality of life and the safety of desmopressin treatment.

The efficacy assessments were based on data in the patients’ diaries and endpoints were derived for the 3-week double-blind period. Safety was evaluated from reported adverse events and laboratory data, with emphasis on serum sodium levels. The quality of life and the prevalence of LUTS were assessed using an abbreviated form of the ICSMale questionnaire [20], completed by patients during screening and after the double-blind treatment period.

The intent-to-treat (ITT) population comprised all randomized 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 period. The per-protocol (PP) population comprised the subset of the ITT patients who fulfilled all inclusion criteria, met none of the exclusion criteria, took ≥80% of the study medication for the double-blind period, and who were not categorized as protocol violators at any time. The safety population comprised all patients taking at least one dose of study medication. For the primary endpoint, the analysis was based on the ITT population (primary analysis) and the PP population (secondary analysis). The analyses of all the secondary endpoints were based on the ITT population. The evaluation of adverse events and laboratory variables was based on the safety population.

The primary objective was tested using a stratified Cochran-Mantel-Haenszel test controlling for country. If the country-specific odds ratio was homogeneous (based on Breslow-Day and Zelen’s tests) the common odds ratio was presented with an approximate 95% CI. Results were presented using P values based on the two-sample t-test. Analysis of the ICSMale questionnaire results 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 (≥50% reduction in mean nocturnal voids) while a placebo response would be observed in ≤7% of patients. A sample size of 55 patients per treatment group was needed to allow for the detection of a 23% (30% vs 7%) difference calculated with a power of 90% and α = 0.05 (two-sided).

Results

There were no significant differences in demographic and baseline characteristics among study centres, or between the desmopressin and placebo groups, in the ITT population (Table 1). Baseline analysis of the ICSMale questionnaire showed a similar prevalence of LUTS

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**Table 1** Patient characteristics (intent-to-treat population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Desmopressin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>83</td>
<td>63</td>
</tr>
<tr>
<td>Mean (SD) [range]:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>64.5 (10.7) [37.4–87.6]</td>
<td>65.6 (10.2) [24.2–83.8]</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0 (3.7) [18.8–39.5]</td>
<td>27.3 (3.8) [22.0–37.3]</td>
</tr>
<tr>
<td>Nocturnal urine volume, mL</td>
<td>750 (273) [307–1479]</td>
<td>831 (300) [367–1650]</td>
</tr>
<tr>
<td>24-h urine volume per body weight, mL/kg</td>
<td>22.6 (7.3) [11.4–44.2]</td>
<td>21.8 (6.7) [10.8–48.2]</td>
</tr>
<tr>
<td>Functional bladder capacity, mL</td>
<td>376 (114) [100–650]</td>
<td>408 (133) [180–900]</td>
</tr>
<tr>
<td>Nocturnal voids, n</td>
<td>3.0 (0.91) [1.7–5.6]</td>
<td>3.2 (1.30) [1.6–9.6]</td>
</tr>
</tbody>
</table>
in both study groups, where nocturia, urgency, frequency, terminal dribbling and incomplete emptying were the most common and bothersome LUTS reported. Co-existing conditions reported were essential hypertension (61.27%); cardiac conditions (48.21%); lipid disorders (20.9%); diabetes mellitus (14.6%); symptomatic BPH (34.15%); and other prostate disorders (18.8%). Five patients (2%) had a history of malignant neoplastic disease and five (2%) reported inflammatory diseases of the prostate.

Withdrawals and exclusions

During the dose-titration and washout periods, 73 patients withdrew: 16 because there was no response during dose-titration; 14 because of adverse events; 16 because nocturnal diuresis failed to return to ≥78% of the baseline value at the end of the washout period; seven withdrew consent, four did not comply with the protocol and 16 for other reasons. During the double-blind period, five patients on desmopressin and three on placebo withdrew; one withdrawal in each group was for adverse events.

Five randomized patients were excluded from the ITT population as no efficacy data were available (three from the desmopressin and two from the placebo group). In addition, 49 patients were excluded from the PP population because of major protocol deviations (desmopressin group 34%, placebo group 33%). Most of these were patients who met a withdrawal criterion but were not withdrawn.

In all, 341 men (aged ≥18 years) were screened for entry into the study at 28 centres, i.e. Denmark (five), Sweden (five), The Netherlands (eight), UK (five) and USA (five). Of the patients screened, 117 were not enrolled into the study. Most of those failing the screening did not meet the inclusion criteria of ≥two voids per night, although most of those screened had urine production that exceeded their bladder capacity. Of the 151 randomized patients, 81 (94%) on desmopressin and 62 (95%) on placebo completed the study; the patient disposition is shown in Fig. 2.

Patient compliance was high, with 82 (95%) patients receiving desmopressin and 61 (94%) patients on placebo taking ≥80% of prescribed medication in the double-blind period.

A clinical response (fewer than half the mean number of voids per night during the double-blind period than in the screening period) was achieved by 28 (34%) patients receiving desmopressin and by two (3%) patients on placebo in the ITT population (P < 0.001). Compared with placebo, the odds of achieving a clinical response were 20 times greater for patients receiving desmopressin (95% CI 4.0–105.2). These findings were confirmed in the PP population, where 18 of 55 (33%) patients on desmopressin and one of 42 (2%) patients on placebo obtained a clinical response during the double-blind period (P < 0.001) with a common odds ratio of 22.4 (95% CI 2.5–203.5).

The reduction in the number of nightly voids in the ITT population is shown in Fig. 3. Using a threshold of a ≥40% reduction in nocturnal voids as a response (instead of ≥50%) 54% of the patients in the desmopressin and 16% in the placebo group obtained a response (Fig. 3). Two (2%) patients on desmopressin had no change or an increase in nocturnal voids, compared with 18 (29%) on placebo.

Seventy-six (58%) patients included in the double-blind treatment period clinically responded during dose-titration; of these, 45 (59%) were randomized to desmopressin and 31 (41%) to placebo. The proportion of patients who had a clinical response during the double-blind period was significantly higher (P < 0.001) in the desmopressin (58%) than in the placebo group (6%), indicating a true treatment effect.

All secondary efficacy endpoints showed a highly significant difference in favour of desmopressin (Table 2). Analysis of the ICSMale questionnaire showed that
the prevalence of nocturia decreased from 99% to 63% in the desmopressin group, and from 100% to 93% in the placebo group. The degree of bother caused by nocturia and the proportion of patients considering nocturia to be ‘quite a problem’ or a ‘serious problem’ decreased in the desmopressin group but remained almost unchanged in the placebo group.

**Safety**

Of the 224 patients who entered the dose-titration period, 107 (48%) reported adverse events (Table 3). In the double-blind period, similar numbers of patients reported adverse events, i.e. 15 (17%) in the desmopressin group and 16 (25%) in the placebo group. Five patients had serious adverse events during the study; one had an exacerbation of a chronic lung infection during dose-titration and died 4 months after drug withdrawal, but this serious adverse event was considered unrelated to treatment. Another patient had thrombocytopenia, judged as treatment-related, during the washout period. After recovering the patient was randomized to placebo and completed the study. Afterwards the patient was re-challenged with desmopressin and the event did not recur. The remaining serious adverse events (two on placebo and one on desmopressin) occurred during the double-blind period and all were judged to be unrelated to the study medication.

Most of the adverse events reported were mild (67%); moderate and severe events constituted 27% and 6%, respectively. The most frequently reported and possibly treatment-related adverse events are listed in Table 3. No single treatment-related adverse event was reported in > 3% of the patients in the double-blind period.

Serum sodium levels were monitored closely during the study (Fig. 1). In all, 49 (22%) patients had one or more episodes of a serum sodium level below the normal range and in all 10 (4%) patients had sodium levels of <130 mmol/L. Four patients were asymptomatic and six were reported as hyponatraemic, which in three led to withdrawal. All cases of hyponatraemia occurred during dose-titration. Patients at the highest risk of developing hyponatraemia were those aged ≥65 years.

**Discussion**

Patients with nocturia who had a pharmacological response to desmopressin (defined as a reduction in nocturnal diuresis of >20%) were treated effectively with desmopressin. Desmopressin given orally at bedtime at doses of 0.1, 0.2 or 0.4 mg led to a ≥50% reduction in night-time voids in 34% of patients with nocturia, whereas only 3% receiving placebo had a

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Table 2: Secondary endpoint values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Desmopressin, mean (sd)</th>
<th>Placebo, mean (sd)</th>
<th>% change</th>
<th>Mean† (95% CI) change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Nocturnal voids, n</td>
<td>3.0 (0.9)</td>
<td>1.7 (0.9)</td>
<td>-43</td>
<td>3.2 (1.3)</td>
</tr>
<tr>
<td>Duration, first sleep period, h</td>
<td>2.66 (0.85)</td>
<td>4.5 (1.5)</td>
<td>+59</td>
<td>2.5 (0.9)</td>
</tr>
<tr>
<td>Nocturnal diuresis, mL/min</td>
<td>1.5 (0.6)</td>
<td>0.9 (0.3)</td>
<td>-36</td>
<td>1.7 (0.6)</td>
</tr>
<tr>
<td>Night/24-h urine volume, %</td>
<td>41.6 (10.2)</td>
<td>30.7 (11)</td>
<td>-23</td>
<td>44.5 (10.9)</td>
</tr>
<tr>
<td>Night/day urine volume</td>
<td>0.84 (0.5)</td>
<td>0.52 (0.3)</td>
<td>-27</td>
<td>0.95 (0.5)</td>
</tr>
</tbody>
</table>

*Percentage difference between end of treatment values vs baseline; †Difference between desmopressin and placebo as the absolute change in mean values; ‡P<0.001.

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clinical response. Desmopressin has been shown to decrease diuresis [14], but as a reduction in episodes of nocturia was the focus of the present study, the specific reduction in nocturnal voids was considered to be a more clinically relevant primary endpoint than measuring diuresis in general. The relevance and importance of a given endpoint is difficult to define; a threshold response of \( \geq 50\% \) reduction in night-time voids was chosen arbitrarily, but if a \( \geq 40\% \) reduction had been used the success rates would be 54\% in the desmopressin and 16\% in the placebo group. Nevertheless, the chosen primary endpoint provided a clinically valid and useful measure.

As found previously [16–19], the decrease in nocturnal diuresis with desmopressin treatment was associated with fewer nightly voids. In addition, the reductions in the ratios of night/24-h and night/day urine volumes after desmopressin treatment appeared to constitute a normalization to values within the physiological range [9]. The mean number of nocturnal voids reduced by 43\% in patients on desmopressin, compared with 12\% in those on placebo. There were reductions in nocturnal and 24-h urine volume in patients receiving desmopressin, possibly because of slight changes in drinking habits. Treatment with an antidiuretic agent such as desmopressin decreases urine production and increases the recycling of renal fluid. People with low nocturnal AVP levels often feel thirstier at night, but when they receive desmopressin they do not feel as thirsty and consequently night-time fluid intake is reduced. This observation is particularly relevant when the night/24-h urine volume ratio is interpreted; the decrease in mean ratio in patients on desmopressin would have been greater if they had maintained the same drinking patterns and therefore, the same 24-h urine volume.

Desmopressin prolonged the duration of the sleep period until the first void by 1.5 h; this initial period of sleep is important in determining the quality of sleep, and thereby has an effect on quality of life [21]. However, the quality-of-life results from the present study should be interpreted cautiously, as the ICSMale questionnaire is a general measure of LUTS and effect on quality of life, and was used here as there is no validated nocturia-specific questionnaire. Nevertheless, the present results indicate that patients’ perceptions were in line with the efficacy results, i.e. that desmopressin had a beneficial effect.

For safety, the study showed that adverse events associated with desmopressin treatment were usually mild and infrequent. These events were comparable with the established safety profile of desmopressin in the treatment of polyuria associated with other conditions. All episodes of hyponatraemia occurred during dose-titration. Patients at higher risk of developing hyponatraemia were those aged \( \geq 65 \) years. Therefore, special precautions are required when elderly patients begin desmopressin therapy, e.g. serum sodium should be measured 3 days after commencing desmopressin treatment and after any dose adjustment.

Although nocturia affects \( \geq 72\% \) of elderly people [4] the condition remains under-recognized by sufferers [22] and physicians [23]. Nocturia is the most difficult LUTS to alleviate or cure, persisting in 38\% of patients operated on for BPO [12,13]. The present findings indicate that nocturnal polyuria was the main cause of nocturia across the study population; most patients screened to enter the study had a nocturnal urine

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**Table 3** Summary of adverse events

<table>
<thead>
<tr>
<th>Events</th>
<th>Dose-titration</th>
<th>Double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>224</td>
<td>86</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>107 (48) [237]</td>
<td>15 (17) [28]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 (&lt;1) [1]</td>
<td>1 (1) [1]</td>
</tr>
<tr>
<td>Death*</td>
<td>1 (&lt;1) [1]</td>
<td>0</td>
</tr>
<tr>
<td>Adverse events related to study medication</td>
<td>60 (27) [139]</td>
<td>6 (7) [11]</td>
</tr>
</tbody>
</table>

Most frequently reported (>3\% patients) adverse events related to study medication:

- Nausea: 10 (4) [11]
- Diarrhoea: 9 (4) [10]
- Dizziness: 9 (4) [10]
- Hyponatraemia: 8 (4) [8]

N. number of patients with adverse events; *unlikely to be study-related (exacerbation of chronic lung infection).
production level that exceeded functional bladder capacity, even though not all of them had two or more episodes of nocturia each night. Nocturnal polyuria is clearly a major cause of nocturia, yet it can be diagnosed accurately using appropriate techniques [24].

Patients must be encouraged to seek further investigation when nocturia symptoms continue. While it is important for people with nocturia to receive general advice about the management of persistent nocturia, e.g. reducing alcohol and caffeine intake, and limiting fluid intake before bed-time, such strategies should not impose general fluid restrictions. Recently there has been a greater understanding of nocturia as an independent condition that is not always associated with other clinical conditions. Perceptions of this condition are also changing: it is unnecessary to tolerate nocturia when there is the potential to treat it effectively and safely. Desmopressin reduces nocturnal diuresis, thereby providing an effective means of therapy for nocturia. Further research into the pathophysiological mechanisms underlying nocturia and its effect on sufferers are required, and effective therapies including desmopressin need to become available. The present results from this pivotal study show that desmopressin is an effective and well-tolerated treatment for nocturia in men and highlight the need for a nocturia-specific, quality-of-life questionnaire.

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Abbreviations: AVP, arginine vasopressin; ITT, intention-to-treat; PP, per-protocol.