Desmopressin in the treatment of nocturia: clinical evidence and experience

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Abstract: Nocturia is a common and bothersome condition experienced by both men and women. Studies have suggested that nocturia contributes a level of morbidity to those who suffer from the condition, both young and old. Desmopressin has historically been utilized to treat conditions such as central diabetes insipidus, certain bleeding disorders and primary nocturnal enuresis. Recently, interest has increased as to the use of desmopressin (a vasopressin analog) in the treatment of adult nocturia, for whom nocturnal polyuria is prevalent. While desmopressin has been traditionally administered in tablet and bioequivalent high dose melt formulations, newer low-dose orally disintegrating sublingual desmopressin has been recently studied to determine safe and efficacious dosing strategies. In this review, nocturia and its associated morbidities are discussed, followed by a contemporary literature review regarding the safety and efficacy of desmopressin for its treatment.

Keywords: DDAVP, desmopressin, LUTS, nocturia, nocturnal polyuria

The International Continence Society has defined nocturia as waking at night to void, with each void preceded and followed by sleep [van Kerrebroeck *et al.* 2002]. Up to 61% of elderly women and up to 59% of elderly men report two or more voids per night; prevalence increases with age [Bosch and Weiss, 2010].

Nocturia is one of the most bothersome of the lower urinary tract symptoms (LUTS). It affects quality of both life and sleep, and is responsible for a significant amount of morbidity secondary to falls in the elderly [Asplund, 2005]. Nocturia has also been associated with increased risk of bone fractures in the elderly [Nakagawa *et al.* 2010]. Multiple studies have demonstrated an association of increased mortality risk with increasing nocturia severity episodes in the elderly [Asplund, 1999], despite controlling for comorbidities [Kupelian *et al.* 2005]. Other studies contradict such an association [van Doorn *et al.* 2012].

Vasopressin, also known as antidiuretic hormone (ADH), is produced by the posterior pituitary gland. Its role is to maintain serum osmolality and volume *via* free water excretion. Vasopressin, acts at the level of the collecting duct *via* interaction

with the V2 receptor. This relationship results in translocation of aquaporin channels associated with cytosolic vesicles to the apical/luminal membrane of collecting duct cells. Free water then passively reabsorbs from the nephron back into systemic circulation *via* basolateral membrane channels.

ADH is released from the posterior pituitary in states of hyperosmolality and hypovolemia. Detection of the aforementioned states is facilitated by chemoreceptors and baroreceptors located in the hypothalamus and carotid sinus, respectively. ADH also plays a small role in increasing systemic vascular resistance and increasing urea reabsorption in the medullary collecting tubule; the latter further enhances renal concentrating capacity [Shoskes and McMahon, 2011].

ADH analogs (in the form of DDAVP) have traditionally been used to treat central diabetes insipidus, bleeding disorders such as von Willebrand disease, and primary nocturnal enuresis. However, recent interest in its role for treating nocturia has spawned a growing body of literature examining the role and effect of desmopressin in its treatment.

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The utility of desmopressin depends on the pathophysiologic cause of nocturia, which in itself can be deduced by analysis of a 24-hour frequency volume chart. Five major categories exist: global polyuria; nocturnal polyuria; decreased functional bladder capacity; primary sleep disorders; and combinations, often known as 'mixed' nocturia etiology [Cornu *et al.* 2012].

Global polyuria is defined as greater than 40 ml/kg of urine produced over 24 hours [van Kerrebroeck *et al.* 2002]. Disease states such as diabetes mellitus, diabetes insipidus, hypercalcemia and primary polydipsia can be associated with global polyuria [Gulur *et al.* 2011]. Diabetes insipidus has many potential causes and is broadly divided between central (neurogenic) due to insufficient ADH synthesis by neurosecretory cells, and nephrogenic, in turn due to renal insensitivity to ADH.

Nocturnal polyuria is defined as excessive volume of urine produced during sleeping hours while 24-hour output remains <40 ml/kg. Nocturnal polyuria is generally defined in accordance with the Standardization Committee of the International Continence Society (ICS) as nocturnal urine volume (NUV) >20–33% (normal NUV increases with age) of total 24-hour urine production [van Kerrebroeck *et al.* 2002]. Excessive urine production remains a commonly reported cause of nocturia; up to 93% of elderly patients demonstrate nocturnal polyuria [Weiss *et al.* 2011].

Nocturnal polyuria may be secondary to changes in circadian release of ADH, mobilization of peripheral fluid during sleep hours, or increased nocturnal atrial natriuretic peptide release [Gulur *et al.* 2011]. Thus, fluid overload states such as congestive heart failure, liver disease with hypoalbuminemia, nephrotic syndrome or lower extremity venous stasis are associated with nocturnal polyuria [Cornu *et al.* 2012]. Central nervous system lesions contributing to a change in circadian release or action of ADH have also been implicated in causing nocturnal polyuria [Gulur *et al.* 2011]. Obstructive sleep apnea and excessive evening fluid intake also contribute to nocturnal polyuria.

The frequency volume chart (see Figure 1) is useful in evaluating nocturnal bladder capacity so as to determine whether the bladder can accommodate NUV. Reduced nocturnal bladder capacity

can be due to structural or functional abnormalities of the lower urinary tract, namely obstruction, overactive bladder, neurogenic bladder, calculi or cancer [Cornu *et al.* 2012].

Patients with nighttime micturition unassociated with awakening because of the desire to pass urine are categorized as having a primary sleep disorder such as insomnia or arousal disorders, neurologic conditions such as Parkinson's disease or dementia, psychiatric conditions such as depression, or abuse of drugs or alcohol [Cornu *et al.* 2012].

A growing body of literature regarding nocturia as a bothersome and potentially morbid condition, often of polyuric origin, has led to consideration of antidiuretic therapy as a mechanistically desirable treatment option. Mattiasson and colleagues performed a short-term, multicenter, international double-blind placebo-controlled trial for adult men who suffered from nocturia, defined as at least two voids per night and a nocturia index (NUV/maximum voided volume) >1 based on voiding diary data [Mattiasson *et al.* 2002]. An initial dose titration period occurred over 3 weeks, with a 1-week washout period followed by a 3-week randomized, double-blind, placebo-controlled study. Patients who did not report >20% reduction in number of nightly voids despite maximal dosing at 0.4 mg *via* desmopressin tablet were classified as nonresponders and were not randomized. Those who failed to return to $\geq 78\%$ of baseline during the washout phase were also excluded. The primary endpoint included a reduction in the number of nightly voids by at least 50% as based on voiding diaries. Secondary endpoints included the number of nightly voids, effect on quality of life and safety (specifically adverse effects and incidence of hyponatremia). Ultimately, 143 patients completed the study after 151 patients were randomized. There was a statistically significant difference in clinical response in the intent-to-treat population between the treatment and placebo arms (34% *versus* 3%, respectively; $p < 0.001$), with an odds ratio (OR) of 20 for response (defined as $\geq 50\%$ reduction in the mean number of nocturnal voids) with desmopressin use [95% confidence interval (CI) 4.0–105.2]. This was confirmed in the population of subjects who were ultimately randomized after the washout period (33% *versus* 2%, respectively; $p < 0.001$; OR 22.4; 95% CI 2.5–203.5). Secondary endpoints favored desmopressin as well, with statistically significant differences in change in number of nocturnal voids (43% *versus* 12% decrease, respectively;

Figure 1. Diary-based differential diagnosis of etiology of nocturia.

$p < 0.001$) and duration of first sleep period (59% versus 21% increase, respectively; $p < 0.001$). Regarding safety, while 48% of patients described an adverse effect (15 in the desmopressin group and 16 in the placebo group; a similar number), 94% of adverse events were mild or moderate. The five patients who experienced serious adverse events were not deemed to have experienced those events secondary to the medication, and three were in the placebo arm. Ten (4%) patients experienced hyponatremia, four (40%) of whom were asymptomatic.

Lose and colleagues utilized an identical short-term, double-blind, placebo-controlled study design for women, and included dose titration, washout and a randomization period for responders only [Lose *et al.* 2003]. Inclusion criteria, dosing, and time frames were the same as that of Mattiasson and colleagues [Mattiasson *et al.* 2002]. Primary and secondary endpoints were also analogous to the aforementioned study. In total, 141 women completed the short-term study. In the intent-to-treat population, a clinical response ($\geq 50\%$ reduction in the mean number of nocturnal voids) was reached in 33 (46%) of

patients in the treatment arm versus 5 (7%) in the placebo arm ($p < 0.0001$; OR 13.4; 95% CI 4.6–39.2). This statistical significance was confirmed in the randomized population, which consisted only of subjects who clinically responded to desmopressin during the dose-titration period (44% versus 4%; $p < 0.0001$; OR 33.2; 95% CI 6.0–183.6). All secondary endpoints, specifically first sleep period and number of nightly voids, favored the treatment arm over the placebo arm (78% versus 20% increase, and 46% versus 17% decrease, respectively; $p < 0.0001$). Regarding safety, despite 71% of patients reporting an adverse event, 90% of the events were reported as mild or moderate. Similar rates were reported between the treatment and placebo arms (36% versus 35%; respectively). Five (2%) patients reported serious adverse events; two deaths were reported as well, one cardiac related and one of unknown cause, which were not thought to be medication-related. A total of 27 (12%) patients recorded serum sodium levels below normal range, half (13) of which were below 130 mmol/l. A total of 11 of these were over the age of 65. All cases of hyponatremia occurred during the dose-titration period.

Table 1. Summary of outcomes of clinical trials in nocturia patients treated with desmopressin.

Study	Target population	Mean age (range)	Effective doses	Route of delivery	Clinical responders in treatment arm (%)	Clinical responders in placebo arm (%)	p value	Incidence of hyponatremia (%)
Mattiasson <i>et al.</i> [2002]	Men	65.1 [24.2–87.6]	0.1, 0.2, 0.4 mg (dose titration)	Oral	34	3	<0.001	8
Lose <i>et al.</i> [2003]	Women	57.1 [20.6–88.7]	0.1, 0.2, 0.4 mg (dose titration)	Oral	44	4	<0.0001	12
Lose <i>et al.</i> [2004]	Men and women	60.5 [21–88]	0.1, 0.2, 0.4 mg (dose titration)	Oral	67	N/A	N/A	14
Van Kerrebroeck <i>et al.</i> [2007]	Men and women	63.4 [19.8–94.0]	0.1, 0.2, 0.4 ng (dose titration)	Oral	33	11	0.0014	3
Weiss <i>et al.</i> [2012]	Men and women	62.0 (N/A)	100 µg (25 µg in women)	Sublingual	71	47	<0.0001 ^a	3
Rembratt <i>et al.</i> [2003]	Men and women	75.5 ^b [66–90]	0.2 mg	Oral	82	N/A	N/A	5
Kuo [2002]	Men and women	75.4 [65–84]	0.1 mg	Oral	66.7	N/A	N/A	3
Wang <i>et al.</i> [2011]	Men	74.0 [65–88]	0.1 mg	Oral	61.4	13.8	<0.001	16
Weiss <i>et al.</i> [2013]	Men	60.4 (N/A)	50 or 75 µg	Sublingual	2.04 ^c	N/A	0.0004	3

^aFor 100 µg dose only.^bMedian age.^cOdds ratio for achieving >33% decrease in number of nocturnal voids at 75 µg.

Lose and colleagues extended the data sets from the aforementioned studies towards 12 months after randomization and examined long-term safety as the primary endpoint [Lose *et al.* 2004]. Inclusion criteria included at least two voids per night with a nocturia index >1. Dose titration using tablets at 0.1, 0.2 and 0.4 mg was performed, each patient ultimately taking their optimal dose. The authors took specific interest in serum sodium values, having performed periodic assessment of laboratory values, vital signs and weight at each follow-up visit. Secondary endpoints included response to desmopressin in number of nightly voids, time between nightly voids and quality of life. Overall, 95 men and 87 women completed the 11-month followup. Some 25% of men and 68% of women completed 13 months of desmopressin. During long-term treatment, 92 men and 90 women reported adverse effects (70% and 77%, respectively); however, nearly 90% of these were mild or moderate. Adverse effects led to withdrawal in 12% of patients. Four men experienced six serious adverse effects, namely, dizziness in one, cardiac failure, headache and vomiting in two, and chest pain and hypertension in one. One woman experienced four serious adverse effects, namely hyponatremia, headache, vertigo and nausea. Some 14% of patients experienced hyponatremia; however, of the 35 cases, 33 were asymptomatic and borderline (serum sodium not lower than 130 mmol/l but below normal range). The remaining two patients experienced symptomatic class I hyponatremia (serum sodium greater than 125 mmol/l but less than 130 mmol/l). Patients 65 years and older were found to be more susceptible to treatment related adverse events and hyponatremia.

Both men and women experienced a decreased number of nightly voids (3.1–1.6 and 2.9–1.3, respectively), as well as at least a 50% decrease in number of nightly voids from baseline (37–67%, and 46–67%, respectively). In addition, time duration of first sleep period and quality of life improved for both men and women. There were no differences for either adverse effects or efficacy based on medication dose. Lose and colleagues concluded that desmopressin tablets are largely safe and effective for use in adults; however, caution must be used for those beyond the age of 65 [Lose *et al.* 2004].

Van Kerrebroeck and colleagues described an international, multicenter, double-blind,

placebo-controlled trial with 127 patients who reported at least two voids per night [Van Kerrebroeck *et al.* 2007]. Median age was 65.2 years and 35% of the patient population was female. Tablet doses began at 0.1 mg and were titrated up weekly to a maximum dose of 0.4 mg, with a washout period prior to randomization. The authors reported a statistically significant decrease in the number of nocturnal voids in the desmopressin arm *versus* placebo (33% *versus* 11%; $p < 0.0014$). All secondary endpoints, including time between voids, favored the desmopressin group. Patients in the desmopressin arm gained 108 minutes in the first sleep period compared with 41 minutes in the placebo arm, for a difference of 67 minutes ($p < 0.0001$). Self-reported quality of sleep in the form of one question, specifically, 'During the last week, did you often feel fresh in the mornings when you got up?' favored the desmopressin group as well (OR = 2.71; 95% CI 1.16–6.35; $p = 0.02$). Desmopressin was generally well tolerated: there was no statistically significant difference between the treatment and placebo arms (15 patients each) in adverse effects and 67% of adverse effects were classified as mild. Six cases of hyponatremia were recorded, five of which (83%) occurred in patients ≥ 2 years of age. Only one was symptomatic with headache. A total of 20 more patients experienced a postbaseline serum sodium level below normal, while an additional 17 patients experienced borderline hyponatremia (no serum sodium level < 130 mmol/l); 16 of these 17 were asymptomatic. The authors concluded that desmopressin tablets were largely effective and well tolerated.

Weiss and colleagues reported outcomes on a 4-week multicenter, randomized, double-blind placebo-controlled trial aiming to determine the efficacy of orally disintegrating sublingual desmopressin (i.e. 'melt' formulation) [Weiss *et al.* 2012]. The authors randomized patients to various doses, specifically 10, 25, 50 and 100 μg . Approximately 90% of the subject population reported production of at least 33% of their daily voided volume at night, which classified them as nocturnal polyurics. Patients were included if they reported two or more voids at night, and had normal baseline serum sodium and renal function [glomerular filtration rate (GFR) ≥ 60 ml/min]. Patients with urinary retention, elevated postvoid residual, or evidence of bladder outlet obstruction were excluded. Primary endpoints included change in

mean number of nocturnal voids from baseline and proportion of subjects with $>33\%$ decrease in mean number of nocturnal voids. Secondary endpoints included duration of first sleep period, nocturnal and total urine volume, and nocturnal quality of life. The ultimate intent to treat population consisted of 757 patients randomized to placebo *versus* desmopressin at various doses; 710 patients ultimately completed the study.

A statistically significant difference in number of nocturnal voids was seen for all patients with 100 μg ($p < 0.0001$) and 50 μg ($p < 0.02$). Women responded to 25 μg as well ($p < 0.02$); however, for men, there was only a statistically significant difference with 100 μg ($p < 0.005$). The proportion of patients with at least a 33% reduction in the number of nocturnal voids increased with dosage; however, there was only a significant effect at 100 μg ($p < 0.0001$) for all patients (i.e. both sexes). A stronger response was seen in women at 25 μg ($p = 0.02$), 50 μg ($p = 0.04$) and 100 μg ($p < 0.0001$). At the conclusion of 4 weeks, NUV had significantly decreased in a dose-dependent manner in all groups for all doses ≥ 25 μg ($p < 0.05$). All patients also reported an increase in the time period of initial sleep from 25 μg ($p < 0.001$) as well as improved quality of life ($p < 0.05$). Four serious adverse effects were noted amongst the study population; none were thought to be related to the study. A total of 24 patients (3.0%) experienced hyponatremia, nine of whom measured at <125 mmol/l. Patients ≥ 65 years of age were more likely to develop hyponatremia. The authors concluded that orally disintegrating desmopressin melt is both well tolerated and effective, especially for those under the age of 65.

A significant amount of literature examining the safety and efficacy of oral desmopressin has focused on the elderly, given this group's predilection towards hyponatremia. Rembratt and colleagues recruited 72 patients with a median age of 75.5 (range 66–90), all of whom experienced two or more voids per night and completed frequency–volume charts for 72 hours while taking 0.2 mg of desmopressin tablets [Rembratt *et al.* 2003]. Primary endpoint was safety in regard to serum sodium. Despite the fact that 34 patients (47%) reported a total of 49 adverse events, headache being most frequent (16%), only four patients experienced serum sodium <134 mmol/l, and all were at least 79 years of age. There were no serious adverse effects. The authors concluded that desmopressin tablets were well tolerated in the short term;

however, clinicians must be prudent in trending serum sodium during the early phase of treatment.

Kuo aimed to examine the efficacy of desmopressin tablets in patients >65 years old, safety and adverse effects being reserved as secondary endpoints [Kuo, 2012]. He recruited patients with more than three episodes of nocturia as well as nocturnal polyuria (>35% of total voided volume at night) according to frequency–volume charts. Those with normal serum electrolytes and complete frequency–volume charts (72 hours of data) were eligible. Desmopressin tablets at a dose of 0.1 mg were administered for 4 weeks; a visit at the 2-week mark was carried out in order to collect another 3-day frequency–volume chart, as well as urine for specific gravity and serum electrolytes. The patients were followed for 4 weeks after stopping desmopressin. Quality of life was also examined. A total of 30 patients ultimately underwent medication administration; 25 men and five women, mean age 75.4 ± 6.6 years, range 65–84. Five patients (16.7%) reported side effects, namely dizziness and headache, generalized erythema, general weakness and increased urinary frequency. Two patients discontinued themselves from the study secondary to side effects. All 28 patients who completed the study reported improved NUV, nocturia frequency and quality of life index ($p < 0.0001$), with no significant change in serum sodium (139.7 ± 4.06 mEq/l *versus* 138.9 ± 4.73 mEq/l; $p = 0.364$). Kuo concluded that desmopressin tablets were safe and effective for administration in the elderly in the short term.

Wang and colleagues expanded the use of desmopressin to elderly men with a clinical diagnosis of BPH, as well as two or more voids per night as well as nocturnal urine production $\geq 30\%$ of 24-hour urine volume [Wang *et al.* 2011]. In a randomized, double-blind, placebo-controlled trial using 0.1 mg of desmopressin tablets, 115 men over the age of 65 received placebo or desmopressin daily at bedtime for 12 months. Follow-up visits at 1, 3, 6 and 12 months were performed, at which time the authors collected frequency–volume charts, urine sodium, urine osmolality, serum electrolytes and quality of life questionnaire responses. The primary endpoint was the proportion of patients who had a reduction by two in the mean number of nocturnal voids after long-term treatment as opposed to baseline. Many secondary endpoints were also examined, namely the number of nightly voids, initial sleep duration, nocturnal volume and nocturnal

polyuria ratio, quality of life and safety. A total of 35 patients (61.4%) in the desmopressin arm achieved a clinical response (decrease of two or more voids per night) *versus* eight (13.80%) in the placebo arm ($p < 0.001$). The desmopressin-treated patients also demonstrated a decrease in total NUV and an increase in the initial sleep period *versus* placebo (392.1 ± 60.1 ml *versus* 533.1 ± 93.3 ml, and 120.0 ± 17.7 minutes *versus* 101.6 ± 19.5 minutes, respectively). Quality of life index increase was significantly greater in the desmopressin arm than in the placebo arm. There was no significant difference in the number of reported adverse effects or rate of asymptomatic hyponatremia between the desmopressin and placebo arms (17 *versus* 19 and 9 *versus* 10, respectively). These authors concluded that low-dose desmopressin is safe and well tolerated in the long term in patients with BPH and nocturia.

Weiss and colleagues recently examined the safety and efficacy of orally disintegrating desmopressin in men over the age of 18 in a randomized, double-blind, placebo-controlled, multicenter study [Weiss *et al.* 2013]. Nocturia included ≥ 2 voids per night per voiding diary analysis. Patients were randomized to desmopressin 50 μ g *versus* 75 μ g *versus* placebo if they did not meet exclusion criteria (most importantly, evidence of bladder outlet obstruction or incomplete emptying, renal dysfunction, or pre-existing hyponatremia). Randomization was stratified by age <65 *versus* age ≥ 65 , and subjects were instructed to take the study drug every night 1 hour before bed for the 3-month course of the study. Voiding diaries were collected monthly throughout the study period, as well as at randomization and at week 1. Primary endpoints included change from baseline in mean number of nocturnal voids and proportion of subjects who experienced at least a 33% decrease in the mean number of nocturnal voids at each visit. Secondary endpoints included mean initial sleep period time and mean NUV. Nocturnal quality of life and mean self-rated sleep quality were also assessed. A total of 395 patients were randomized, of whom 327 (83%) completed part I. Both desmopressin 50 and 75 μ g significantly decreased the mean number of nocturnal voids from baseline (-0.37 , $p < 0.0001$ and -0.41 , $p = 0.0003$, respectively) and increased the odds of obtaining >33% responder status (OR = 1.98, $p = 0.0009$ and OR 2.04, $p = 0.0004$, respectively). There was no significant difference between those younger than 65 years of age and those older than 65. Initial sleep period duration and NUV also improved with

both desmopressin 50 and 75 µg *versus* placebo at 3 months ($p \leq 0.009$). There was no difference in the number of patients who reported adverse effects amongst the three groups; however, the incidence of adverse drug reactions, as well as the incidence of patients with hyponatremia, was lower in the desmopressin 50 µg group compared with the 75 µg group. Eleven patients experienced serum sodium <130 mmol/l, of whom nine (82%) were >65 years; five of the six patients (83%) with serum sodium ≤ 125 mmol/l were >65 years. The authors concluded that desmopressin 'melt' 50 µg is the minimum effective and safe dose for use in men with nocturia.

Conclusion

Available data summarized in Table 1 support the use of desmopressin in both tablet and orally disintegrating formulations for patients with nocturia. Mechanistically, nocturnal polyuria as a major substrate of nocturia should respond to antidiuretic therapy using an ADH analog such as desmopressin in order to decrease the amount of urine production and thus alleviate nocturnal voiding. A number of studies have in fact demonstrated its efficacy in decreasing nocturia severity while improving quality of life as compared with placebo. The safety of desmopressin, however, is paramount to its clinical utility. Desmopressin is generally well tolerated, the newer 'melt' formulation at lower doses being nearly as effective and better tolerated than tablet ('high dose'). A minimum dosage of 25 µg orally disintegrating sublingual desmopressin appears to be ideal for women, whereas men may benefit from a minimum of 50 µg. Regardless of formulation or dosing, judicious care should be taken for elderly patients (≥ 65 years of age) due to the increased risk of hyponatremia in such vulnerable individuals.

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Conflict of interest statement

J.P.W. is a consultant for Ferring, Pfizer, Allergan, Astellas, Lilly and Drais.

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