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REVIEW

Desmopressin for the treatment of female storage lower urinary tract symptoms

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Abstract

Female storage lower urinary tract symptoms are prevalent and bothersome. They are usually attributed to an overactive bladder and treated with antimuscarinics. Nevertheless, failure of conventional treatment to alleviate nocturia in particular and epidemiological data suggesting that nocturnal polyuria is the only or a contributing factor to nocturia, has attracted interest in decreasing nighttime urine production as a method of managing nocturia. A reduction in urine production could also, at least temporarily, delay daytime storage symptoms by delaying bladder filling. Therefore, desmopressin, the synthetic analogue or naturally occurring antidiuretic hormone, could have a role in the management of female frequency, urgency and urgency incontinence. This work aims to review data on the use of desmopressin in females with storage symptoms. Available evidence indicates that desmopressin is efficacious in reducing nighttime urine production and episodes of nocturia, resulting in fewer sleep interruptions. This translates into improved quality of life. Desmopressin is also effective in postponing micturition, urgency and incontinence for several hours after being taken on demand. The tolerability profile of desmopressin is good and significantly improved compared to historical figures due to the introduction of new oral formulations, tailoring the dose according to gender and age and adhering to instructions for fluid restriction before administration. The incidence of hyponatremia, desmopressin's most important side-effect, is less than 3% in recent trials. The efficacy of desmopressin, combined with its improved safety profile, makes it an interesting method for treating female storage lower urinary tract symptoms.

Key words: Lower urinary tract symptoms; Storage; Nocturia; Overactive bladder; Desmopressin; Female; Nocturnal polyuria

Core tip: Recent data suggest that desmopressin in its oral formulations offers significant improvements in nocturia as well as daytime storage symptoms in female patients. The treatment rationale for nocturia is that nocturnal polyuria due to inadequate antidiuresis is a major contributing factor to nocturia. In the case of daytime storage symptoms, desmopressin taken on demand can postpone their manifestation by delaying bladder filling. Desmopressin is well tolerated and the risk of hyponatremia is low with appropriate dosing, based on a lower minimum effective dose in females compared to males.

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INTRODUCTION

Arginine vasopressin (AVP), a hormone produced by the neurohypophysis, is an integral part of the complex

mechanism regulating water homeostasis. AVP decreases urine production and increases its concentration by promoting osmotic reabsorption of solute-free water in the collecting tubules of the kidney[1] through activation of V2 receptors. AVP secretion is principally determined under physiological conditions by the osmotic pressure of plasma and mediated by specialized osmoreceptor cells in the hypothalamus.

Inadequate antidiuresis caused by a deficiency in AVP secretion or resistance to its action at the kidney level may lead to the development of clinical syndromes such as diabetes insipidus, primary nocturnal enuresis or nocturnal polyuria. Deficiencies or defects in vasopressin secretion can often be corrected by using desmopressin, a synthetic analogue of the naturally occurring hormone.

Desmopressin has increased potency and prolonged duration of action compared to AVP. Unlike AVP, desmopressin is V2-receptor specific so it reduces urine production without inducing pressor activity. It is the only available antidiuretic drug and has been used for over 30 years. Three different formulations of desmopressin have been available: nasal spray, hard oral tablet (0.1 and 0.2 mg) and since 2005 the desmopressin melt oral lyophylizate (administered sublingually without water) formulation (60 and 120 μg).

According to the International Urogynecological Association (IUGA) and the International Continence Society (ICS), female lower urinary tract symptoms (LUTS) include increased daytime urinary frequency, nocturia, urgency and urinary incontinence[2]. The symptom complex of urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology is defined as the overactive bladder (OAB) syndrome. The prevalence of female storage lower urinary tract symptoms is 59.2%, as shown in the EPIC study[3]. Nocturia in particular is a very common complaint in women. 54.5% of the female survey population had to wake up to void once or more per night and 24.0% at least twice.

The pathophysiology of OAB is not completely elucidated but detrusor overactivity, the finding of involuntary detrusor contractions during the filling phase of the micturition cycle, is still considered to play an important role. The symptom of nocturia from a pathophysiological point of view is as complex as overactive bladder; even although it is traditionally attributed to a decreased bladder functional capacity in the context of OAB, the role of nocturnal polyuria is increasingly recognized[4]. Nocturnal polyuria is defined as a nocturnal urine output greater than 20% of the total daily in young people and 33% in the elderly, with the value for middle age falling between the two extremes[5]. Fifty-seven percent to sixty-four percent of patients with nocturia have confirmed nocturnal polyuria with the percentage increasing to as high as 89% in patients treated with a blockers or anticholinergics for benign prostatic hyperplasia (BPH) or OAB[4,6,7].

Based on the current knowledge of the physiology of lower urinary tract and the pathophysiology of lower urinary tract dysfunction, the amount of urine produced cannot be an etiological factor but may exacerbate underlying pathology. Therefore, the rationale for the use of desmopressin in the treatment of OAB patients is that through a decrease in urine production, it will increase the time taken to reach functional bladder capacity between micturitions, thereby reducing frequency and urgency and offering symptomatic improvement. This is very similar to the rationale for use of desmopressin in nocturia patients. An inadequate antidiuresis may have an etiological role in cases where nocturnal polyuria is present and then the rational of using desmopressin is most obvious.

This review aims to investigate the use of desmopressin for the treatment of female storage LUTS. Only papers in peer-reviewed journals that reported results on female populations were considered.

DESMOPRESSIN FOR NOCTURIA

Prospective studies investigating the efficacy and safety of desmopressin in women with storage LUTS are summarized in Table 1.

In a phase-Ⅲ, randomized, double blind study investigating the safety and efficacy of oral desmopressin in the treatment of nocturia[8], women with at least 2 episodes per night and a nocturia index score of more than 1 (defined as the mean nocturnal volume divided by largest voided volume) entered a dose-finding phase starting at 0.1 mg orally administered desmopressin, with weekly dose increments to 0.2 and 0.4 mg, if necessary. Patients who experienced a complete response to any of the doses or a greater than 80% response on the maximum tolerated dose followed a one week washout. Provided that their washout voiding diary values returned to at least 78% of their baseline ones, they were randomized to receive their optimal desmopressin dose or placebo in a double-blind fashion for another 3 wk. Eighty patients withdrew during the dose-finding and washout phases (adverse events 27.5%, failure of diuresis to return to baseline values 37.5%, lack of response 10%) and 144 were finally randomized.

After 3 wk of treatment, 46% of patients on desmopressin had a 50% or greater reduction in nocturnal voids compared with 7% on placebo ($P < 0.0001$). The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis and ratios of nocturnal to 24 h and nocturnal to daytime urine volumes changed significantly in favor of desmopressin *vs* placebo ($P < 0.0001$).

As far as safety is concerned, headache and nausea were reported by 22% and 8% of patients during the dose titration. Clinically relevant hyponatremia was reported in 6% of the population but serum sodium levels were below the normal range during the study in 12%. All cases of hyponatremia occurred during the dose titration period. Two deaths occurred during the same period but neither could be directly associated with the study

Table 1 Summary of studies investigating desmopressin in female storage

Study	Indication	Design	Desmopressin dose/formulation	Comparator	*n*	Primary end-point	Result
Lose *et al*[8], 2003	Nocturia	RCT	0.1, 0.2, 0.4 mg oral, hard tablet	Placebo	144	Percent of patients with > 50% reduction in nocturia	Significant *vs* placebo
Weiss *et al*[9], 2012	Nocturia	RCT	10, 25, 50, 100 μg oral lyophylizate	Placebo	341	Reduction in no of voids, patients with > 33% reduction in nocturia	Significant *vs* placebo for both co-primary end-points
Yamaguchi *et al*[11], 2013	Nocturia	RCT	10, 25, 50, 100 μg oral lyophylizate	Placebo	58	Reduction in nocturia episodes	Significant *vs* placebo for 25 and 50 mg
Sand *et al*[13], 2013	Nocturia	RCT	25 μg oral lyophylizate	Placebo	261	Reduction in nocturia episodes, percent of responders (> 33% reduction)	Significant *vs* placebo
Hilton *et al*[14], 1983	Nocturia (MS)	RCT, crossover design	20 μg nasal	Placebo	16	Reduction in nocturia episodes	Significant *vs* placebo
Eckford *et a*[15], 1994	Nocturia (MS)	RCT	20 μg nasal	Placebo	22	Reduction in nocturia episodes	Significant *vs* placebo
Eckford *et al*[16], 1995	Nocturia (MS)	Open label, non-randomized, placebo controlled, incremental dose	20, 40 , 60 μg nasal	-	8	Nocturnal urinary volume and osmolarities	Significant *vs* placebo No significant for 40 and 60 *vs* 20 μg
Robinson *et al*[18], 2004	Daytime incontinence (any type)	RCT, crossover design	40 μg nasal	Placebo	60	4-h post-dose periods with no urine leakage	Significant *vs* placebo
Hashim *et al*[19], 2009	OAB	RCT, crossover design	0.2 mg oral, hard tablet	Placebo	41	Time to various OAB symptoms in 8 h post dose	Significant *vs* placebo
Han *et al*[20], 2011	OAB	Open label, randomized	Desmopressin 0.2 mg plus solifenacin 5 mg	Desmopressin 0.2 mg	68	Time to first frequency or urgency episode	Significant for combination *vs* desmopressin monotherapy

RCT: Randomized controlled trial; OAB: Overactive bladder.

drug. As was expected, adverse events associated with desmopressin treatment were usually mild and comparable with placebo in the selected population of women entering randomization for whom efficacy and safety were established during the uncontrolled dose titration. It is worth mentioning that overall, 50% of the patients were excluded during the study because of adverse events.

The authors of the study concluded that oral desmopressin is an effective and well-tolerated treatment for nocturia in women. Nine years later, in a 4 wk, randomized, double-blind study comparing 10, 25, 50 or 100 μg desmopressin orally disintegrating tablet (melt) *vs* placebo in adults with at least two episodes of nocturia per night but no formal requirement for documented nocturnal polyuria[9], 341 women were recruited. The study had two co-primary endpoints: change in mean number of nocturnal voids and proportion of subjects with > 33% reduction in mean number of nocturnal voids from baseline. The study also investigated the minimum effective dose (MED) of desmopressin.

A greater decrease in number of nocturnal voids and a greater increase in the proportion of subjects with > 33% reduction in nocturnal micturitions were observed with increasing doses of desmopressin. The effect was significant *vs* placebo for all desmopressin doses except the 10 μg for both the co-primary endpoints. Significant effects were also noted for the reduction of nocturnal urine volume and the increase in initial period of undisturbed sleep *vs* placebo. The improvements in quality of life outcomes, including self-rated sleep quality and the Nocturia Quality of Life questionnaire, were also significant.

The incidence of adverse events increased for increasing doses of desmopressin and was within the expected range. As far as hyponatremia is concerned, six women on active treatment had reductions in serum sodium to < 125 mmol/L, none in the 25 μg group. These drops all occurred within a week of treatment initiation.

The results of all analyses of voiding data in this study indicated that the MED for desmopressin orally disintegrating tablets is 25 μg in women and the 10 mg dose was sub-therapeutic. The MED for the 416 men also included in the study was 100 μg.

The influence of concurrent voiding dysfunction on the efficacy of desmopressin in the treatment of female nocturia was examined in a retrospective analysis of 84 women with more than 2 episodes of nocturia at initial evaluation[10]. Women were treated with 100 μg desmopressin for 1 mo and were escalated to 200 μg for another month in case of lack of effect of the initial dose. Among the 84 patients, 51 (60.7%) complained of concomitant OAB symptoms and were treated with anticholinergics. As far as nocturia etiology is concerned, 59 patients (70.2%) had nocturnal polyuria, 6 (7.1%) had reduced nocturnal bladder capacity, and 19 (22.6%) had both. A dose escalation in 39.3% women was required.

Overall, 73 women (86.9%) showed improvement of nocturia and the mean number of nocturia episodes (1.4 ± 1.5) was significantly reduced compared to baseline (3.7 ± 1.3) ($P < 0.05$). A ≥ 50% reduction in the number of nocturnal voids compared with baseline was observed in 41 of 84 women (48.8%). The 41 women with a ≥ 50% reduction in the number of nocturnal voids had a lower baseline urgency grade (according to the urinary sensation scale) compared to the 32 women who showed smaller improvements.

The authors concluded that lower urinary tract symptoms (other than nocturia) and urgency in particular may reduce the effect of desmopressin in the treatment of nocturia and should be adequately addressed in order to maximize the efficacy of antidiuresis.

In another randomized, double-blind study comparing 10, 25, 50 or 100 μg desmopressin orally disintegrating tablet (melt) *vs* placebo in Japanese patients[11], the dose-response relationship of pharmacodynamic variables measured after a single dose of desmopressin was investigated along with the mean reduction of nocturia episodes after 28 d of treatment. Among the 111 patients completing the protocol, 58 were female. More than 50% but not all patients had nocturnal polyuria.

In the female population of the trial, there was an increase in the duration of antidiuretic action (DOA) of desmopressin, defined as the time with urine osmolality > 200 MOsm/kg after dosing. The DOA for the 25, 50 and 100 mg doses was 3, 4.41 and 5.59 h respectively; all significant compared with placebo. As far as a reduction of nocturia episodes is concerned, a significant reduction was seen in the 25 and 50 μg groups (mean reduction 1.81 and 1.70 respectively) but not the 10 or 100 μg compared with placebo. Significant changes were also observed for desmopressin over placebo in the secondary study outcomes: prolongation of initial undisturbed sleep, reduction in nocturnal diuresis and the ratio of nocturnal to 24 h urine volume.

The incidence of adverse events was within the expected range. No patients on active treatment had serum sodium < 130 mEq/L during any treatment period. Only two patients had serum sodium levels below 135 mEq/L, both of whom were male and > 65 years of age.

After analyzing both the female and male subpopulations of the study, the authors concluded that male patients require approximately 58 mg of desmopressin to achieve the duration of antidiuretic action that females achieve with 25 mg.

Taking into consideration evidence from previous trials[9,11,12] indicating that the effective dose of desmopressin may be lower in females than in males, a 3 mo, randomized, double-blind, placebo controlled study was designed to assess the efficacy and safety of a 25 mg orally disintegrating tablet of desmopressin in the treatment of women with at least 2 episodes of nocturia per night without significant daytime symptoms[13]. In all, 261 women were randomized. Desmopressin achieved a statistically significant reduction from baseline in mean number of nocturnal voids compared to placebo (treatment effect -0.22 voids, $P = 0.028$). The other co-primary endpoint, the percentage of responders, defined as the patients with a decrease of at least 33% in the mean number of nocturnal voids at each study visit compared to baseline using a longitudinal analysis, was also met: the odds ratio of responding to desmopressin compared to placebo was 1.85 ($P = 0.006$). The treatment difference was similar for patients younger than 65 and 65 years old or older, was evident from 1 wk into the study and maintained throughout the 3 mo treatment period.

Desmopressin was also shown to significantly increase the mean time to first nocturnal void by 49 min compared to placebo and decrease nocturnal urine volume at 3 mo. Significant increases in health related quality of life and sleep quality were also observed. Nevertheless, the percentage of patients with a decrease of at least 33% in the mean number of nocturnal voids at the 3 mo visit compared to baseline was not significantly different between treatment arms.

Desmopressin was well tolerated overall. Adverse events with an incidence of 2% or more in either treatment group included dry mouth, headache, medication error, somnolence and rash, leading to a 3% discontinuation rate in the desmopressin arm compared to less than 1% for placebo. As far as hyponatremia is concerned, sodium levels remained greater than 125 mmol/L throughout the trial and 3 transient decreases to less than 130 mmol/L were recorded which recovered in 2-4 d without requiring discontinuation of treatment.

The authors concluded that at a dose of 25 μg, desmopressin orally disintegrating tablet is an effective and well tolerated treatment for women with nocturia and supported recommendations for gender specific desmopressin doses.

The efficacy of desmopressin in the treatment of nocturia in female patients with neurogenic bladder dysfunction due to multiple sclerosis has been assessed in a randomized, double-blind, placebo controlled, cross-over study of 16 women, published 30 years ago[14]. Twenty microgrammes of desmopressin were administered intranasally at bedtime. Desmopressin achieved significant changes in early morning urine osmolality and nocturia episodes.

Eleven years later, 22 women and 11 men, younger than 65 years of age with multiple sclerosis and nocturnal frequency, with or without enuresis, were recruited into a study assessing the efficacy and safety of desmopressin[15]. Following a two week placebo run-in to establish baseline values, patients entered a double-blind, placebo-controlled, cross-over study of 20 μg intranasal desmopressin at bedtime. Desmopressin achieved significant improvements in nocturia, reduced nocturnal urinary volume and the ratio nocturnal to 24 h urine volume. There were no cases of clinically significant hyponatremia and only two cases of asymptomatic hyponatremia were reported.

The same study team conducted an open-label, incre-

mental-dose safety and efficacy study of desmopressin in women with multiple sclerosis and nocturia[16]. Neither a significant decrease in nocturnal urinary volumes nor an increase in urinary osmolality was achieved by doses of desmopressin larger than 20 mg. A dose of 60 μg was associated with a decreased serum sodium level at the end of the 24 h period post administration. The authors concluded that as there were no benefits and a possibility of clinical hyponatremia with doses higher than 20 μg, these doses cannot be recommended.

A pooled analysis of data from three short-term, randomized, controlled efficacy studies of desmopressin orally disintegrating tablet or solid tablet, with treatment extension periods of 40-56 wk in patients with nocturia[17], indicated that efficacy was maintained and in some cases increased after long-term treatment compared with short-term for females as well as in males. This analysis also showed that long-term efficacy is not a result of early discontinuation of dissatisfied patients.

DESMOPRESSIN FOR DAYTIME STORAGE SYMPTOMS

The efficacy and safety of 40 μg doses of desmopressin nasal spray in managing daytime female urinary incontinence was explored in a multicenter, randomized, double-blind, placebo-controlled study with a cross-over design published in 2004[18]. Sixty women with mixed (32), predominantly urge (13), or predominantly stress (15) incontinence received study medication. The primary efficacy endpoint was the number of periods with no leakage for 4 h after dosing.

There was a significantly higher incidence of periods with no leakage in the first 4 h after dosing with desmopressin compared to placebo (62% *vs* 48%). There were no differences in outcome when analyzed according to type of incontinence. There was also a higher frequency of dry days on desmopressin than on placebo; 36% of patients had no leakage on virtually all treatment days for 4 h after dosing. The time from dosing to first incontinence episode was longer on desmopressin (6.3 *vs* 5.2 h), whilst the volume leaked per incontinence episode was lower on desmopressin than placebo. The total volume voided over the 24 h period after administration was consistently lower on desmopressin (1180 *vs* 1375 mL).

There were no serious or severe adverse events reported despite the relatively high dose used in the study and those most commonly reported on desmopressin were headache (36%) and nausea (10%). Three percent of women withdrew from the study because of mild adverse events.

A phase Ⅱb, double-blind, randomized, placebo-controlled study with cross-over design investigated the efficacy of 0.2 mg of oral desmopressin in patients with idiopathic OAB[19]. The rationale behind this "proof of concept" study was that desmopressin would postpone OAB symptoms by reducing the speed at which the bladder fills. Female and male patients were given 3 doses of 0.2 mg desmopressin on alternate days and 11 doses of placebo on all other days during the 2 wk double-blind phase. The primary endpoint was the time to the first OAB symptom episode (micturition, urgency, urge incontinence) during the first 8 h following treatment.

Forty-seven male and 41 female patients were randomized and results were not presented separately for each gender. There was an 8 min delay in the first post-dose micturition for desmopressin compared to placebo (92 min *vs* 84 min) which was not statistically significant. The delay in the second and third micturitions was statistically significant, resulting in one less micturition in the first 8 h post dosing for desmopressin compared to placebo. The time to the first and second urgency episodes was statistically significant on the drug compared to placebo. As far as urge incontinence was concerned, the majority of patients (78%) did not experience any leakage in the first 8 h following treatment, but no significant difference was found between drug and placebo days with regards to the number of UUI episodes in the first 8 h following dosing. However, if incontinence frequency was classified as severe (≥ 2 episodes/3 d) or mild (≤ 1 episodes/3 d), there was significantly less incontinence episodes with desmopressin in severe cases compared to placebo.

According to the authors, this proof-of-concept study showed that desmopressin reduces OAB symptoms by increasing the time to the first OAB episode, with an overall improvement in QoL and minimal and tolerable side-effects, and therefore it represents a feasible method for symptomatic relief at least in the short-term. Its use as a per-needed tablet for management of OAB merits further assessment.

The use of a combination of anticholinergics and desmopressin in the treatment of overactive bladder was investigated in an open-label, randomized study[20]. Female patients with OAB and at least four voids in the first 8 h of the day after waking-up, excluding the first morning void, were recruited. Patients were randomly assigned to receive 5 mg of solifenacin (anticholinergic group) or 5 mg of solifenacin and 0.2 mg of desmopressin (combination group) for 2 wk. Patients were instructed to take the tablets after the first morning void. The primary efficacy endpoint was the increase in time to each of the first frequency or urgency episode. Thirty-one women in the anticholinergic group and 37 in the combination group completed the study.

Time to first micturition was 12 min later for the combination group compared to anticholinergic group (117 *vs* 105 min). This difference was not statistically significant in contrast to the difference in times to the second and third voids and time to the first urgency episode which were significant for the combination treatment compared to anticholinergic monotherapy. Combination treatment was also significantly better in reducing the total number of urinary frequency and urgency episodes during the first 8 h of the day as well as in improving quality of life scores. Age > 65 years and voided volume > 150 mL were predictors of improvement with combination treatment.

The authors concluded that the combination of desmopressin and an anticholinergic could be considered a feasible method for relief of symptoms in female patients with OAB.

CONCLUSION

Our review of the literature has revealed a renewed interest in the use of desmopressin for the treatment of female LUTS. Indeed, the majority of relevant trials have been published during the past 3-5 years.

Desmopressin has been available for over thirty years in the intranasal formulation for most of this period. Multiple reports of hyponatremia in elderly patients as well as in children have led to an increased awareness of this particular risk associated with desmopressin and have restricted its further clinical development. Due to this safety issue, desmopressin nasal spray lost Food and Drug Administration approval in 2007, leading to its worldwide withdrawal for the indication of nocturnal enuresis in children. Despite this, newer formulations of desmopressin are a well-established treatment in the management of childhood enuresis[21]. Drug dosing, variable absorption and misuse were major problems with the intranasal spray[22].

The switch to desmopressin tablet and more recently to the orally disintegrating formulation has been associated with a decrease in the incidence of hyponatremia[23,24]. Indeed, in all the recently reviewed trials for the role of desmopressin in the management of female storage LUTS, the incidence of hyponatremia and more specifically of clinically relevant hyponatremia was low. The superior pharmacokinetic and pharmacodynamic properties of the orally administered formulations are only one of the reasons for this observation[25-27]. Another reason is the identification of age and low baseline plasma sodium concentration as important risk factors for hyponatremia[23]. Finally, the awareness of a lower minimum effective dose in female patients compared to males[12] has led to more appropriate dosing.

The incidence of hyponatremia is currently less than 3%[23]. Evidence in this review suggests that desmopressin is currently a well-tolerated and safe treatment for females with LUTS.

Apart from the improved safety of oral formulations of desmopressin, another factor leading to a recent increase in the number or trials conducted in female populations is increased awareness of the prevalence and pathophysiology of nocturia. Nocturia in women was for many years attributed to OAB and was treated mainly with anticholinergics. The association of age with a reduction in the sensitivity of the osmoregulatory system resulting in inadequate production of AVP and a disturbance in the circadian rhythm of urine production has brought focus on nocturnal polyuria as an etiological factor of nocturia. Indeed epidemiological studies have found nocturnal polyuria in the vast majority of females with nocturia.

In our review, desmopressin administration achieved significant reduction in nocturia episodes and nocturnal urine production, which in most trials was translated to improvements in sleep and quality of life.

Trials conducted in females with daytime symptoms have confirmed that desmopressin is effective in at least postponing the development of storage symptoms and may be a useful on-demand medication for the management of OAB symptoms, particularly in combination with other treatments that address them around the clock.

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