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REVIEW

Experience with the long-term use of desmopressin for nocturnal enuresis in children and adolescents

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Introduction

The burden of nocturnal enuresis (NE) on children and their families is great, resulting in low self-esteem [1]. In adults, bedwetting is associated with several psychosocial problems and may affect both personal relationships and career development [2]. Hägglof *et al.* [3] showed that enuretic children had significantly impaired self-esteem, increasing to normal levels after 6 months of treatment. In addition, the total cost of managing an enuretic child has a considerable effect on the family economy [4]. Therefore, it has been suggested that active treatment should be instituted early (i.e. as soon as the child wants to sleep dry) to prevent psychosocial consequences and favour the normal development of the child [1,5].

Desmopressin

Desmopressin, an analogue of ADH (vasopressin), has gained increasing popularity as the treatment of choice for NE. Night-time administration of desmopressin increases water reabsorption in the collecting ducts of the kidneys, resulting in a low nocturnal urine volume [6]. The efficacy of desmopressin in NE is believed to be the result of this reduction in urine production.

Desmopressin, originally formulated as a nasal spray, is now available in tablet form for patients who prefer oral administration or who have trouble with intranasal administration (i.e. nasal irritation or colds). The ease of administration and relative convenience of desmopressin treatment has resulted in its wide acceptance. Although consistent use of the wetting alarm has the best evidence in support of its long-term efficacy, both physicians and patients often reject this treatment [7]. This reluctance to use a wetting alarm is attributed to the demanding preconditions for successful treatment, e.g. lengthy instructions, a high degree of compliance, close co-operation among family members, the motivation required to overcome the impatience associated with the slow onset of action of treatment, and the annoyance of waking other family members [8]. Furthermore, adolescent and adult enuretics usually prefer pharmacotherapy [9,10]. Therefore, alarm therapy has a poor chance of success in families that are not motivated to adhere to the demanding guidelines required, or where there is parental intolerance of the enuresis [1,11].

A comprehensive summary of many randomized, controlled trials has established the efficacy and safety of both desmopressin intranasal spray and tablets [12]. Desmopressin treatment usually gives a response rate of $\pm 70\%$, with a rapid onset of action, and is relatively free from side-effects [6,13]. However, the main disadvantage of desmopressin is that its efficacy may not be maintained on discontinuing treatment, with the recurrence of symptoms after ceasing treatment in 50–95% of patients [14].

Objectives of the present review

Because of the high rates of relapse on discontinuing desmopressin treatment, there are suggestions that desmopressin should be administered for longer or that treatment should be re-started on relapse. Until recently the main support for the efficacy and safety of desmopressin treatment in NE was based on short-term studies, i.e. 2–12 weeks. To induce long-term dryness with desmopressin, greater attention has been focused on the possibility of prolonged treatment. There are concerns about possible decreasing efficacy (tachyphylaxis) and increased occurrence of adverse events with the long-term use of desmopressin, and thus the maintenance of efficacy and safety during prolonged treatment should be established first. For this purpose, this review summarizes and discusses all eligible studies evaluating the efficacy and safety of desmopressin during prolonged use.

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Efficacy of long-term desmopressin treatment

Selection of long-term trials

To date, several studies have investigated the efficacy and safety of desmopressin during prolonged use; Table 1 [7,15–23] presents a survey of all qualifying long-term desmopressin studies. Studies were eligible for inclusion if patients prospectively entered the study, had monosymptomatic primary NE with no organic pathology and more than 2–3 wet nights a week, and if the (mean) duration of treatment was clearly indicated. The minimum duration of treatment for inclusion was 6 months, unless patients had achieved dryness during a previous treatment-free period. All reviewed studies were open and uncontrolled, except for one which had a double-blind placebo-controlled crossover design [15]. In that study a placebo period of 3 weeks was randomly placed throughout a 6-month treatment period with desmopressin. In most studies the (maximum) treatment period was determined in advance, whereas in two the treatment was given indefinitely and tapered (i.e. dose reductions of 10 μg increments) once total dryness had been achieved for a 2–4-week period [7,16]. Patients stopped treatment if they were poor responders or if they achieved 2–4 dry weeks with no treatment during the reduction phase [7,16] or during one of the treatment-free periods [17–19]. To compare the long-term studies more adequately, all response and cure rates noted in Table 1 were expressed as the percentage of the initial study population (including those not responding and who did not enter the long-term phase in most studies). Therefore, these percentages may differ from the percentages originally reported in the study.

Response rate

In all studies, desmopressin reduced the number of wet nights considerably over a period of ⩾6 months (Table 1). Usually, 50–85% of patients who entered the study showed at least a halving in the number of wet nights and 40–70% became almost completely dry during treatment. In five studies the patients were evaluated at regular intervals (0.5–6 months) [18–21,24]. In all studies it became evident that the efficacy of desmopressin continued or improved throughout the treatment period, indicating that the enuretics did not develop tolerance to desmopressin. In a recent Dutch long-term study, statistical time-trend analyses indicated that there was a statistically significant trend towards greater efficacy with treatment duration [18].

Table 1 Long-term efficacy (⩾6 months) of desmopressin in the management of NE

				Study duration, months		*Efficacy, %**	
Study	*Subjects,* N *APT/responders*	*Age at entry, years*	*Daily dose, μg*	*(mean)† treatment*	*follow-up*	*success >50%/ complete (>90%)*	*cure (after treatment period)*
[15]	34/28	8–45	10–40	6	3	82/70	18
[7]	55/36	6–17	40 T	3–42 (11–12)	6–84	65/51	27
[20]	65/54	7–17	20–40	6	0.5	77/58	38
[16]	155	5–19	20–50 T	3–>24 (6–7)	18 (median)	85/78	71
[17,22]	399/245	5–12	20–40	12‡	1	50/38	21¶
[23]	29	18–33	20–40	6	1	–/66	7
[19]	25/23	11–21	200–400	6‡	0.5	60/44	32§
[21]	232	6–17	200–600	6	–	47/33	–
[18]	89/71	11–39	200–600	21‡	0.5	73/44**	21

APT, all patients treated; in most studies only responders (⩾50% reduction of wet nights) from a previous dose-titration period entered the long-term phase. T, tapered dose.

* Responders (% partial and complete responders) and cure rate (% subjects who remained dry after ceasing medication), expressed in percentages of the initial study population (including nonresponders) were evaluated at the end of the treatment period.

† Subjects could stop earlier if dryness has been achieved during a 2-week treatment interruption.

‡ Interrupted for 1 or 2 weeks every 3–6 months to test for cure.

¶ 77 (19%) remained free during 1-week treatment interruption and 12 (3%) were free from relapse after tapering (nine) or abrupt cessation (three) of medication at end of the 1-year treatment period [22].

§ In the follow-up study [26] the total number of patients who achieved dryness without treatment were compared with the number of patients who were expected to be cured (assuming a 15% spontaneous cure rate per year in children; Table 2).

** According to last observation carried forward.

Cure rate

The cure rates (Table 1) represent the percentage of patients who achieved complete dryness after stopping treatment and who remained dry during the follow-up. Assuming an annual spontaneous cure rate of ≈ 15% in enuretic children [25], a considerable part of this recovery may be attributed to this spontaneous cure. However, in most studies the cure rate was higher than expected from spontaneous recovery [7,15,16,19,20, 22,23]. After 6 months of treatment the cure rates were 18–38% [15,19,20]. In the SWEET study [22] most of the recoveries (21%) occurred within 6 months from the start of treatment. At the end of the 1-year treatment period, the 73 complete responders were either randomized to gradual dose tapering or immediate cessation of treatment. Of these children, 23% in the tapered group and 9% in the group who stopped treatment immediately continued to be dry. This result is consistent with those of two other studies [7,16], indicating that gradual dose tapering decreases the frequency of relapse and thus improves outcome. Miller *et al.* [7] reported that the relapse rate was negligible and 27% of patients achieved persistent dryness with no treatment after a mean treatment period of 13.5 months. Riccabona *et al.* [16] reported that 71% of patients achieved dryness after stopping treatment, with no relapses. In a group of adult enuretics, 7% achieved complete cure after 6 months of desmopressin treatment; this is greater than would be expected, as spontaneous recovery is considered to be zero in adult enuretics [2].

The effect of 6 months of desmopressin treatment on the cure rate was assessed in a 7-year follow-up study [26]. The number of patients who achieved complete recovery (with or without desmopressin treatment in the follow-up period) was compared with the expected number of patients cured (assuming a 15% annual cure rate) at different times during the follow-up. The results (Table 2) suggested that long-term desmopressin treatment increased the cure rate and this was maintained after ceasing therapy. Similar results were reported in a 42-month study [27]. After 3 years (including a gradual dose-tapering period) 33 of 54 (61%) enuretic children became dry, while only 21 were expected to become completely dry over a 3-year period (assuming a 15% spontaneous annual cure rate).

Safety of long-term desmopressin treatment

Most studies have routinely investigated the safety profile of long-term desmopressin treatment (Table 1); laboratory data, vital signs and adverse events, evaluated at baseline and after various periods of treatment, are discussed.

Long-term treatment with desmopressin induced no clinically significant changes in mean values of blood chemistry (including serum sodium, potassium and osmolality) [7,15,18–22], nor significantly affected mean haematology [7,15,20,21] and urine analysis values [7,18,21,22]. Seven patients (1%) developed hyponatraemia with no clinical symptoms [21,22].

Mean BP values were not significantly changed during prolonged desmopressin treatment [7,15,18–22]. In two patients (0.3%) there was mild hypertension which may have been related to desmopressin treatment (Table 3).

In four studies there was an increase in mean body weight [15,18–20] or body mass index (BMI) [18] during desmopressin treatment. In two other studies the mean body weight did not change throughout treatment [7,21]. The increases in mean body weight range from 3–5% over a 6-month period [15,19,20] to 7% over a 2-year period [18]. However, only in the last study did both the increase in mean body weight and BMI reach statistical significance [18]. As reference standards [28–31] indicate that a mean BMI increase of 0.6–1.3 kg/m^2 per year is normal in adolescents, these reported body weight increases during desmopressin treatment could (at least partly) be attributed to the natural gain in these adolescents.

Table 3 shows all adverse events (reported in all studies in Table 1) which were considered to be related to

Table 2 The comparison of cure rates with the expected rate of spontaneous resolution reported in [26]

	Treatment during follow-up (no. of patients cured)			*Total cured*	
Follow-up	*none (%)*	*short-term*	*long-term*	*observed*	*expected*
2 weeks	8 (32)	–	–	8	2
1–12 months	11 (44)	1	1	11	4
1–3 years	11	2	2	15	8
3–5 years	12	3	2	17	13
5–6 years	12	4	3	19	16

Table 3 Adverse events, considered to be related to desmopressin

Adverse event	N	*References*
General		
Headache	20	[15,16,18,19,21]
Mild hypertension	2	[18,19]
Aggressive reactions	4	[22]
Nightmares	2	[22]
Fatigue	1	[18]
Body odour	1	[21]
Vertigo	1	[19]
Oral haemorrhage	1	[22]
Gastrointestinal system		
Abdominal pain	10	[19,22]
Nausea	2	[19,21]
Dyspepsia	1	[21]
Increased appetite	1	[22]
Gastric complaints	1	[18]
Diarrhoea	1	[18]
Urinary system		
Urinary frequency	1	[21]
Respiratory system		
Rhinitis	2	[16,22]
Skin		
Eczema	1	[22]
Electrolyte balance		
Fluid retention	1	[18]
Total number of adverse events	53	
All patients treated	1083	

desmopressin treatment. Of the 1083 patients treated with desmopressin spray or tablets, 53 (5%) patients experienced an adverse event that could be treatment-related. For most of these patients this did not justify discontinuing treatment. The most frequent adverse event was headache, affecting 2% of patients. Only one of the adverse events (i.e. fluid retention) was considered to be a serious adverse event, and this subject had a history of hypertension and used atenolol treatment before and during the study [18]. After discontinuing desmopressin treatment there was a rapid recovery. Two review studies, investigating the risk of desmopressin-associated hyponatraemia, showed that the occurrence of water intoxication during desmopressin treatment is rare and that most of these cases were ascribable to excessive fluid intake (against the instructions of the marketing authorization holder) or other conditions (e.g. cystic fibrosis) contributing to this complication [32,33].

In one study the incidence of adverse events was assessed at regular intervals (3–6 months) throughout treatment [18]. The incidence of all adverse events was 16–17% during the first two periods and decreased to 14 and 10% during periods 3 and 4, respectively. Statistical trend tests showed borderline statistical evidence ($P = 0.05$) for the decreased incidence of adverse events and no significant difference for the doses. Further analyses suggested that the observed decrease in the incidence of adverse events was partly a result of those subjects who did not have any adverse events generally remaining longer in the study.

Endogenous ADH secretion

Although desmopressin does not cross the blood–brain barrier [34], concern has been expressed that long-term desmopressin treatment may affect endogenous ADH secretion. Indirectly, using the water-deprivation test, desmopressin intranasal spray did not influence endogenous ADH secretion in a group of seven patients with NE after a mean treatment period of 13 months [35]. In addition, Knudsen *et al.* [36] showed that long-term desmopressin treatment (20–40 μg intranasal spray during 24 weeks) did not directly affect endogenous ADH secretion in eight enuretic patients. These studies also showed that there were no abnormal variations in body weight, BP, routine haematological and biochemical values [35,36] or in urinary excretion rate or urinary osmolality [36].

Conclusions

Various studies, mainly conducted over the last 10 years, have provided more information about the long-term efficacy and safety of desmopressin treatment (both intranasal spray and tablets) in NE. The main conclusions are:

- The efficacy of desmopressin treatment is sustained throughout long-term use ($\geqslant 6$ months);
- Long-term desmopressin treatment does not affect mean values of haematology, biochemistry and BP;
- Adverse events are usually minor and the incidence does not increase throughout prolonged desmopressin use;
- Regular treatment interruptions are recommended (e.g. for 1–2 weeks every 3–6 months) to test if further treatment is necessary;
- A stepwise reduction of the dose may decrease the risk of relapse;
- Several studies indicate that long-term desmopressin treatment may accelerate the cure rate;
- Long-term desmopressin treatment does not affect the endogenous ADH secretion.

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Abbreviations: **NE**, nocturnal enuresis; **BMI**, body mass index.