Randomized comparison of long-term desmopressin and alarm treatment for bedwetting

Jonathan Evans a,*, Birgitta Malmsten b, Alison Maddocks c, Harbans Singh Popli d, Henri Lottmann e, on behalf of the UK study group

a Children’s Renal & Urology Unit, Nottingham Children’s Hospital, Nottingham University Hospitals NHS Trust, Queens Medical Centre Campus, Nottingham NG7 2UH, UK
b Ferring Pharmaceuticals A/S, Copenhagen, Denmark
c National Public Health Service for Wales, PO Box 108, St David’s Park, Carmarthen SA31 3WY, UK
d Swindon Primary Care Trust, Chatsworth House, Bath Road, Swindon SN1 4BP, UK
e Service de Chirurgie Viscerale Pédiatrique, Hôpital Necker-Enfants Malades, Paris 74015, France

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Abstract Objective: To compare the efficacy of long-term primary nocturnal enuresis (PNE) treatment using desmopressin versus enuresis alarm.

Materials and methods: A 6-month randomized trial was performed with patients from 29 enuresis clinics: 251 patients ≥5 years in age with severe PNE (mean 5.5–5.6 wet nights/week) were randomized to desmopressin (0.2–0.4 mg daily) or alarm. Efficacy was assessed by percentage reduction in mean number of wet nights/week; patients achieving dryness, mean initial duration of sleep and compliance were evaluated. Efficacy analyses were performed using the intent-to-treat population (all patients) and excluding patients who withdrew; 12-month follow-up data were collected.

Results: Data could not be evaluated for the 32% of alarm patients and 7% of desmopressin patients who withdrew early. In intent-to-treat analyses, a similar proportion of patients across groups showed a ≥50% reduction in wet nights/week (desmopressin: 37.5%, alarm: 32.2%) and achieved dryness (desmopressin: 32%, alarm: 37%). Compliance was higher with desmopressin: 95–98% of patients took >75% of tablets; 50–78% used alarm >75% of nights. Initial sleep duration was 1.02 h longer at the end of treatment with desmopressin (95% CI: 0.045, 1.99).

Conclusion: Desmopressin and alarm demonstrated comparable efficacy in the treatment of PNE. Withdrawal from the alarm group was high, indicating the importance of considering family motivation before selecting treatment, for optimal outcome.

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Introduction

Primary nocturnal enuresis (PNE) is the term used for bedwetting in children, who have never been consistently dry at night, for ≥6 months continuously [1,2]. It is a common condition, affecting around 7–22% of 7–8-year-old children [2–6]. Patients are at increased risk of socio-emotional problems, resulting from embarrassment and low self-esteem [2,7,8]. Parents also experience a multifaceted burden, including emotional stress, practical difficulties of overnight stays away from home, and cost/time implications of frequent laundering of bedclothes [9]. Annually, enuresis spontaneously resolves in ~15% of patients [10], but if left untreated can persist into adulthood for around 3% [11,12], with the overall prevalence in adults reported to be up to 2.3% [13].

Bedwetting is multifactorial, although there are believed to be three principal contributing factors. In approximately two-thirds of monosymptomatic PNE patients, the circadian rhythm of arginine vasopressin (AVP) is underdeveloped, causing excessive nighttime urine production [14,15]. In around one-third of patients, the bladder is unstable and contracts during sleep [16]. In addition, patients either cannot suppress bladder contractions whilst asleep, or awaken in response to bladder fullness [17].

The two main treatment types are pharmacological and conditioning. At their meeting held in 2008 (report published in 2009), the International Consultation on Incontinence (ICI) recognized the synthetic analog of AVP, desmopressin, as the only evidence-based pharmacological therapy for bedwetting of polyuric origin (Level 1, Grade A) [18]. It has a sufficient duration of antidiuretic action and is V2-receptor specific, avoiding pressor activity associated with stimulation of V1-receptors by AVP [3]. Overall, studies show that desmopressin reduces nocturnal urine output and is well tolerated [e.g., [19–21]]. A Cochrane review also concluded that desmopressin rapidly reduces the number of wet nights, but that limited evidence from short-term trials in small numbers of patients suggests this effect may not be sustained after treatment withdrawal [22]. Longer-term trials, though uncontrolled, indicate improved maintenance effects however [23], and evidence is mounting that structured withdrawal of medication may encourage the persistence of improvements [24]. In a recent randomized controlled study, abrupt withdrawal was compared with structured withdrawal. After one treatment-free month, significantly more patients undergoing gradual withdrawal experienced <2 wet nights/month than those undergoing abrupt withdrawal (80% vs 57%, P < 0.0001) [25].

Conditioning treatment predominately uses an alarm which sounds when the patient’s clothes or sheets become wet. This is thought to improve arousal to a full bladder and increase bladder capacity [26]. Enuresis alarms also have an ICI Level 1, Grade A recommendation for bedwetting. Usage involves substantial disruption to patients’ and parents’ sleep patterns and results are not immediate — treatment is usually required for at least 6–8 weeks before efficacy can be determined; these factors can lead to poor compliance [27] and high discontinuation rates. However, alarms represent a non-pharmacological treatment and studies suggest improvements may be sustained after treatment withdrawal, at least in the short-term [28].

In studies of response rates for each treatment, drop-outs and patients who do not respond during dose titration have sometimes been excluded from analyses [23,28], inflating estimates of treatment success. Furthermore, direct comparisons between desmopressin and alarm are few [27,29,30]. In the current study, these treatments are compared and analyses of response include all patients randomized to a treatment group, thus comparing treatments in a clinically meaningful way and gaining efficacy estimates reflecting results in everyday practice. Since treatment using either desmopressin or enuresis alarm is recognized to be superior to no treatment or ‘watchful waiting’ [22,27], no placebo arm was included.

Methods

This was an open-label, multicenter, randomized, phase IV study, performed in the UK with patients from 29 enuresis clinics. The study was in accordance with the Declaration of Helsinki [31], Good Clinical Practice, applicable regulatory requirements and the approved protocol. Freely written consent was obtained from the patient, or parent/guardian where appropriate. Recruitment occurred between 15/04/2002 and 27/07/2004. The last patient completed 12-month follow up in July 2006.

Patients

Patients with previously untreated PNE, or who had been treated >1 year ago and/or for <4 weeks, were enrolled. Inclusion criteria included ≥6 wet nights over 2 weeks during screening and age 5–16 years. To select for children with monosymptomatic PNE, patients were excluded if they had diurnal symptoms (e.g., urgency, frequency and/or day wetting), encopresis, renal or central diabetes insipidus, or a urinary tract infection within the past month. Also excluded were patients with the syndrome of inappropriate antidiuretic hormone secretion and/or cardiac failure, clinically significant diseases or medication that could interfere with evaluation of the study or with treatment.

Study design

Fig. 1 summarizes the study design. Baseline characteristics were recorded during screening (2 weeks, 2 days). A randomization code was generated in SAS®, by center, using a block size of four. Patients were randomized 3:1 by phone to desmopressin or alarm, based on an estimated response rate of 60%, and 98% power to detect a significant difference (P < 0.05). Planned sample sizes were 110 in the alarm and 330 in the desmopressin group. Patients could withdraw from the study at any point. Due to the nature of the interventions, there was no blinding to group assignment.

Desmopressin treatment

During the 2-week run-in period, patients received 0.2 mg desmopressin daily, and then entered the first 3-month
treatment period. Those with \( \leq 1 \) wet night during run-in received 0.2 mg daily desmopressin and those experiencing >1 received 0.4 mg daily desmopressin in both treatment periods.

Treatment period 1 was followed by a 2-week treatment-free washout. Patients dry at washout (14 consecutive dry nights) entered a 12-month follow-up period. Patients wet at washout entered a second 3-month treatment period before follow up.

Tablets were taken 1 h before bedtime. Patients were advised to drink only to satisfy thirst from 1 h before to 8 h after taking medication. Medication was not permitted if excessive fluid had been ingested, or was needed due to illness.

Diaries were completed by patients/parents from screening to end of treatment (EOT; final 2 weeks of treatment). Patients/parents recorded whether the preceding night was wet/dry and how many times the patient voided at the toilet. The investigator transferred diary data to the case report form.

**Alarm treatment**

Alarm patients were treated for \( \leq 6 \) months after screening until 14 consecutive dry nights were achieved or until the investigator believed treatment was of no further benefit. Patients then transferred to follow up. Patients attended the clinic for screening and treatment initiation; subsequent treatment assessment was performed according to the clinic’s normal practice. Patients receiving alarm treatment were required to keep a daily diary, as with the desmopressin group.

Compliance for both groups was measured by the investigator at each visit using the diary, and categorized: alarm used/tablets taken as instructed, used/taken >75% of nights, used/taken 50–75% of nights, used/taken <50% nights.
of nights. During follow up, patients in both groups were contacted by telephone after 1 month, 6 months and 12 months. Treatment during this phase was at the discretion of each patient’s own doctor.

Efficacy assessments and statistical methods

The primary objective was to compare treatment efficacy evaluated by the percentage reduction in mean number of wet nights/week from baseline to EOT. Responses at EOT were subdivided into three categories of reduction in wet nights, according to International Children’s Continence Society (ICCS) recommendations: ≥90%, 50–89% and <50%. As defined by the ICCS, those with ≥50% reduction were considered ‘responders’. Reduction was calculated in two ways.

1) Excluding dropouts with no evaluable diary data (except those who withdrew due to lack of efficacy); patients were included if ≥7 evaluable nights over ≤2 weeks during screening and the treatment period were available. These analyses will hereafter be referred to as ‘excluding early dropouts’.
2) Using the intent-to-treat (ITT) population (all randomized patients); early dropouts with no evaluable data after screening were assumed not to have responded to treatment (<50% reduction).

For the difference in response between treatment groups (desmopressin minus alarm), 95% confidence intervals (CIs) were calculated according to the Altman et al. method [32], with a lower limit of ≥20% demonstrating non-inferiority. Mean number of wet nights/week was also investigated ([number of wet nights/number of evaluable nights] × 7 days, assuming availability of ≥4 evaluable nights for a 1-week, and 7 for a 2-week interval) in repeated measures analyses. Analysis of covariance (ANCOVA) was performed for the number of wet nights at EOT, including screening values as a covariate, and investigation center and treatment group as factors.

Patients achieving dryness and time to dryness (from visit 2 until the first day of the first 14-day period of dryness), were assessed using diary data, and analyzed using Kaplan–Meier curves and a log-rank test to compare groups. Mean initial duration of sleep (from bedtime until first trip to toilet/bedwetting) was assessed using diary data and analyzed as described for the mean number of wet nights/week.

Follow-up data were explored to determine: a) the proportion of patients who maintained response to treatment after treatment discontinuation, b) treatment choices and response during follow up, c) maintenance of dryness, and d) mean number of wet nights/week during follow up.

Safety assessments

Treatment-emergent adverse events (TEAEs) — defined as any unfavorable and unintended sign, symptom or disease temporally (not necessarily causally) associated with use of the product — were monitored throughout the study. TEAEs were rated as mild, moderate or severe; and as unrelated to treatment, or unlikely, possibly, or probably related to treatment.

Results

Baseline demographics and patient disposition

Table 1 shows patient demographics and baseline characteristics. Fig. 1 shows patient flow through the study; overall, 58% of alarm patients withdrew before study completion (2% due to TEAEs, 14% lack of efficacy, 22% patient preference, 20% other reasons), compared to 41% of desmopressin patients (5% due to TEAEs, 15% lack of efficacy, 10% patient preference, 11% other reasons). A further seven patients (4%) withdrew from the desmopressin group during follow up (1% due to lack of efficacy, 3% other reasons).

A large proportion of alarm patients (19/59 (32%) vs 13/192 (7%) with desmopressin) did not provide sufficient evaluable data to allow calculation of the reduction in wet nights. Most of these patients dropped out from the study very early, providing no diary data under treatment, mainly due to lack of efficacy (n = 0 and n = 3 for desmopressin and alarm), patient preference (n = 5 and n = 7), or being lost to follow up (n = 5 and n = 6).

Response to treatment

Excluding early dropouts, the proportion of patients responding (achieving ≥50% reduction in wet nights/week) was greater with alarm (47.5%; 95% CI: 32.9, 62.5) vs 39.1%; 95% CI: 32.3, 46.4 with desmopressin). However, the ITT analysis shows similar efficacy for desmopressin and alarm (Fig. 2): 17% and 21% of patients receiving desmopressin achieved ≥90% reduction and 50% to <90% reduction, respectively; 27% and 5% of patients receiving alarm treatment achieved ≥90% reduction and 50% to <90% reduction, respectively. The proportion of patients achieving ≥50% reduction in wet nights/week was therefore higher with desmopressin (37.5%; 95% CI: 31.0, 44.5) than alarm (32.2%; 95% CI: 21.7, 44.9), giving an estimated 5.3% (95% CI: −9.0%, 17.9%) difference in response rate between treatments, and demonstrating the statistical non-inferiority of desmopressin.

Mean number of wet nights/week

The mean number of wet nights/week decreased during treatment for both groups (median reduction from screening to EOT: 1.5 for desmopressin, 2.9 for alarm, excluding early dropouts; 1.32 and 0.5, respectively, for ITT population). The ANCOVA of mean number of wet nights/week at EOT (ITT population), showed that only the baseline number of wet nights had a significant effect (P < 0.001); the difference between treatment groups (desmopressin minus alarm: 0.0022; 95% CI: −0.6837, 0.6881) was not significant, indicating that the mean number of wet nights for the desmopressin group was not statistically significantly different from that of the enuresis alarm group at the end of treatment.
Patients achieving dryness

Excluding early dropouts, 34% treated with desmopressin (61/180) achieved 14 consecutive dry nights during the study (‘dryness’), compared with 56% (22/39) using alarm, a significant group difference (log-rank test: unstratified $P = 0.0004$, stratified by pool center $P = 0.00029$). However, in the ITT population, 32% of patients (61/192) treated with desmopressin achieved dryness, compared with 37% (22/59) in the alarm group. The difference between treatment groups was not significant in the ITT analysis (log-rank test: unstratified $P = 0.4485$, stratified by pool center $P = 0.3244$). Kaplan–Meier curves for time to dryness for the ITT population and excluding early dropouts are shown in Fig. 3.

Compliance

At all time points, 80–91% of desmopressin patients took medication as instructed, and 95–98% took >75%. With alarm, reported compliance was lower: 50–75% of patients used their alarms as instructed during visits 3–7 (only one patient attended at visits 8 and 9) and 50–78% used their alarms >75% of nights.

Mean initial duration of sleep

For patients who provided diary data whilst using the allocated treatment, mean initial duration of sleep averaged per week increased with desmopressin (0.43 h), but decreased with alarm (−0.38 h). The difference between treatment groups in initial sleep period was greater in the earlier weeks of treatment; for example, in the repeated measures ANCOVA, the estimated difference between desmopressin and alarm in week 2 was 2.85 h (95% CI: 2.080, 3.628). Baseline duration of sleep and treatment group were significant factors, and EOT initial sleep duration was 1.02 h longer.
with desmopressin (95% CI: 0.045, 1.988). If early dropouts without post-screening data were included in the analysis (screening values carried forward), only baseline initial duration of sleep/week was significantly associated with EOT initial sleep duration \((P < 0.0001)\); however, this analysis includes patients who were not using their treatment.

Safety evaluation

Overall, 30% of desmopressin patients and 14% of alarm patients reported TEAEs during the treatment period, the majority of which were mild. There were four TEAEs classed as severe in the desmopressin group: dysuria, micturition urgency (both in one patient, and possibly related to medication), appendicitis (unlikely) and rash (unrelated), and one in the alarm group: anxiety (probably). The only event considered drug related and occurring in more than one patient was headache (3/192) in the desmopressin group.

Follow-up period

There were difficulties in collecting follow-up data, particularly in the alarm group. This reduced sample sizes and made interpretation of the results difficult. No statistically significant differences were found between the desmopressin and alarm groups. Overall, between 56% and 64% of patients providing follow-up data at 1, 6 and 12 months were receiving no treatment for bedwetting.

Response during follow up

Of patients who responded to desmopressin during the treatment period \((n = 72, \text{ITT population})\), at least 50% had discontinued all treatment at 12 months and were considered responders (ITT, last observation carried forward (LOCF); treatment data missing for 13% of responders at 12 months). Of those who responded to alarm during the study period \((n = 19)\), at least 58% had discontinued all treatment and were considered responders at 12 months (ITT, LOCF; treatment data missing for 21% of responders at 12 months).

Using data from observed cases only, 39/62 patients who had responded to desmopressin during the treatment period were receiving no treatment at the end of follow up; 35 (90%) of these were considered responders and four (10%) were considered non-responders (had relapsed) at 12 months. For alarm, 13/17 patients who responded during the study were receiving no treatment at 12 months and all were considered responders at this time.

Treatment choice following non-response

Amongst patients who failed to respond to desmopressin during the treatment period and provided full follow-up data, 31/58 (53%) used alarm during follow up. Amongst patients who failed to respond to alarm during the treatment period and provided full data, 10/14 (71%) used desmopressin during follow up.

Response and treatment during follow up

Fig. 4 shows the distribution of response and non-response at each follow-up call, according to treatment received during follow up and response status at the end of the treatment period.

Dryness and maintained response

Of patients achieving dryness (14 consecutive dry nights) during the treatment period (observed cases), 89% in both groups were responders at the 12-month follow up. Of patients not achieving dryness during the treatment period with desmopressin, 54% (48/89) were responders at 12 months; of those not achieving dryness with alarm, 38% (6/16) were responders at 12 months. These differences were not statistically significant.

ITT analysis of complete dryness during follow up revealed no statistically significant differences between the desmopressin and alarm groups. By month 12, 36/192 (18.8%) of patients in the desmopressin group and 13/59 (22%) of patients in the alarm group had achieved dryness.

Mean number of wet nights/week during follow up

The mean number of wet nights/week decreased during follow up for both groups. The median change from screening to 12-month follow up was \(-3.5\) (range \(-7.0\) to \(3.0\), \(n = 144\)) for the desmopressin treatment group, and \(-4.0\) (range \(-7.0\) to \(3.0\), \(n = 35\)) for the alarm group. This difference was non-significant.

Safety data during follow up

During follow up, four patients reported adverse events whilst using desmopressin (three unrelated to medication,
one possibly related and mild), and one patient reported an adverse event whilst using alarm (unrelated).

Discussion

This study of long-term PNE treatment showed comparable efficacy between desmopressin and alarm in ITT analyses of the 6-month treatment period. These analyses, including patients who withdrew early, represent outcomes that could be expected in the clinical setting, since patients in clinical practice are likely to discontinue treatment at least as frequently as those recruited to formal clinical trials. Our findings therefore indicate that, amongst unselected patients with severe PNE (mean: 5.5–5.6 wet nights/week in this study), the number of wet nights will be at least halved for around 30–40% if prescribed desmopressin or alarm. The proportion of patients achieving 14 consecutive dry nights during the study was also similar between treatment groups. Complete dryness may be an ambitious goal for some patients, and those with an appreciable reduction in wet nights are likely to consider treatment rewarding, be motivated to continue therapy and possibly achieve further improvements [23]. Clearly, the degree of...
success of each treatment will depend to some extent on the etiology of enuresis in the individual patient; for those who do not achieve resolution of their bedwetting using a single treatment, there may be value in considering combination therapy [18].

A striking observation in this study was that over half the alarm patients withdrew before completion, many doing so very early and providing no evaluable post-screening data. Partial compliance with alarm was also common. This study therefore underscores a major challenge to successful alarm treatment, that of poor adherence. The most common reason for withdrawal from alarm treatment was patient preference. Since alarms require the use of pads and wires, repeated sleep disruption, and strong parental involvement [33], a high level of commitment is essential if families are to continue treatment for a sufficient period. The mean duration of the first period of sleep was nearly 3 h longer using desmopressin than alarm at early stages of treatment, which is indicative of the considerable sleep disturbance during alarm treatment, especially during the early weeks.

Results from the 12-month follow-up period should be interpreted with some caution given the small numbers supplying data at some time periods, particularly for the alarm group. However, available data indicate that relapse rates were low in both treatment groups for patients who responded (≥50% reduction in wet nights) during the treatment period and took no further therapy during follow up. These low rates of relapse suggest that response to medication can be successfully maintained in patients and that response following withdrawal of treatment is similar for patients treated with either desmopressin or alarm. Patients who achieved dryness during the treatment period were less likely to maintain this more stringent level of response during follow up. A greater proportion of patients used desmopressin during follow up after failing to respond to alarm than used alarm after failing to respond to desmopressin, possibly indicating patients’ and families’ greater willingness to try pharmacological treatment than alarm therapy when bedwetting persists.

The initial selection of treatment for PNE patients may therefore have important implications for the child and family life. Because desmopressin treatment is relatively simple to take and can achieve results quickly, it may be a good first-line intervention for enuresis for some patients; note that the need for continued treatment should be reassessed at 3-monthly intervals. Although structured withdrawal of desmopressin may be valuable in increasing the likelihood of maintenance of improvements with desmopressin, the apparently lower risk of relapse with alarms seen in other studies [27,34] was not confirmed in this study. Given the persistence required and inconvenience associated with alarms, however, clinicians should heed families’ preferences and motivation when selecting treatment, to maximize compliance and achieve the optimum outcome for each patient.

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Conflicts of interest

In the past 5 years, Jonathan Evans and Henri Lottmann have received payment from Ferring Pharmaceuticals for advisory work and lecturing, and have received sponsorship to present research at educational meetings. Birgitta Malmsten is an employee of Ferring Pharmaceuticals. Alison Maddocks has received reimbursement of expenses for speaking at an educational meeting sponsored by Ferring. Harbans Singh Popli has received sponsorship from Ferring to present research at an educational meeting.

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Ethical approval

The study was in accordance with the Declaration of Helsinki. Good Clinical Practice, applicable regulatory requirements and the approved protocol.
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