

## “DESMOPRESSIN RESPONSE IN THE TREATMENT OF PRIMARY NOCTURNAL ENURESIS IN THE UNITED KINGDOM” DRIP UK: AN OPEN-LABEL, RANDOMISED COMPARATIVE STUDY OF ORAL DESMOPRESSIN VERSUS ENURESIS ALARM

### Hypothesis / aims of study

Primary Nocturnal Enuresis (PNE) is a disease that affects around 10% of children between 5 and 10 years of age (1). Patients and their families experience substantial emotional distress as well as burden (2). The two main types of treatment for PNE are pharmacological or conditioning treatment. The International Consultation on Incontinence (2004) recognised desmopressin as the only evidence-based pharmacological therapy for nocturnal enuresis, and enuresis alarms as the most effective conditioning therapy (both level 1; grade A). However, alarm treatment involves a great deal of time, effort and inconvenience for both the child and his/her parents and therefore may not be suitable for many families. Furthermore, in PNE caused by nocturnal polyuria, trips to the toilet will still be required with alarm therapy. The current study compared the efficacy and safety of up to 6 months' treatment with either desmopressin or alarm therapy, in terms of reduction in the number of wet nights.

### Study design, materials and methods

This was an open-label, multicentre, comparative Phase IV study, performed in the UK with patients recruited from 29 sites. Patients included in the study suffered from PNE with no organic pathology, and experienced a minimum of six wet nights in 2 weeks. The main exclusion criteria for patients were: previous treatment with desmopressin, or with other medication for nocturnal enuresis within the past year, or use of enuresis alarms in the past year; where the treatment duration lasted for more than 4 weeks. Patients who had diurnal symptoms such as urgency, frequency and/or day-wetting were also excluded. After an initial 2-week screening period, patients who fulfilled inclusion criteria were randomised 3:1 to desmopressin or alarm treatment. Power calculations indicated that a total sample size of 440 was needed to give 98% power.

In the desmopressin arm, there was a 2-week run-in period during which all patients received 0.2 mg desmopressin. Patients then entered an initial 3-month treatment period, during which desmopressin was administered at a dosage of 0.2 or 0.4 mg dependent on the number of wet nights seen during the run-in period. Medication was taken once daily, orally at bedtime. The first treatment period was followed by a 2-week washout period with no study medication. Patients who were dry after the washout period entered a 12-month follow-up period, which consisted of telephone contact after 1, 6 and 12 months. Patients who were wet after the washout period continued to a second 3-month treatment period, after which they entered a 12-month follow-up period. If appropriate, treatment during the follow-up period was provided at the discretion of the investigator.

In the alarm group, patients were treated for a maximum of 6 months, until they experienced 14 consecutive dry nights, or until the investigator deemed the treatment of no benefit.

The primary objective was to compare the overall response to desmopressin versus enuresis alarm after 6 months of treatment. Daily diary cards were used to record night-time voiding. The efficacy analysis was based on the percentage reduction in the mean number of wet nights/week from the 2-week screening period to the final 2 weeks of treatment. Patients were categorised as having ≥90% reduction in mean number of wet nights per week (full responders), 50% to <90% reduction (partial responders), or <50% reduction or no reduction calculated (non-responders).

Secondary objectives of the study included an evaluation of time to dryness, patient well-being and number of trips to the toilet during the night.

### Results

251 patients were enrolled in the study, giving the study power of approximately 88%. A total of 192/251 patients were randomised to the desmopressin group, and 59/251 patients were randomised into the alarm treatment group. Table 1 shows the response rate when dropouts were regarded as non-responders (intention-to-treat population, ITT). Table 2 shows the response rate (partial or full) when dropouts were excluded.

Table 1: Response in ITT population (using diary data, and investigator's diary review data if necessary)

<b>Response status</b>	<b>Desmopressin N=192</b>	<b>Alarm N=59</b>
≥90% reduction (full responder)	32 (17%)	16 (27%)
50% to <90% (partial responder)	40 (21%)	3 (5%)
<50% or missing (non-responder)	120 (63%)	40 (68%)
<b>Total ≥50% reduction</b>	<b>72/192 (37.5%)</b>	<b>19/59 (32.2%)</b>

Table 2: Response in patient population, excluding dropouts (using diary data)

<b>Response status</b>	<b>Desmopressin N=192</b>	<b>Alarm N=59</b>
≥90% reduction (full responder)	32 (17%)	16 (27%)
50% to <90% (partial responder)	38 (20%)	3 (5%)

<50% (non-responder)	109 (57%)	21 (36%)
Missing	13 (7%)	19 (32%)
<b>Total ≥50% reduction</b>	<b>70/179 (39.1%)</b>	<b>19/40 (47.5%)</b>

No variables were significant in predicting treatment response. A total of 11 (6%) desmopressin patients and 3 (5%) alarm patients experienced drug-related treatment-emergent adverse events, although none of these were classed as serious.

'Time to dryness' profiles for those who completed the study period were similar between treatment groups. The mean initial period of sleep per week was significantly longer with desmopressin. The mean number of trips to the toilet per night during the treatment period was significantly higher in the alarm group.

#### Interpretation of results

Both desmopressin and enuresis alarms effectively reduced the number of wet nights experienced by children with PNE. A large proportion of patients in the alarm group dropped out of the study early but in the subgroup who did not drop out the response rate was higher in the alarm group. Overall, in the ITT population (with dropouts regarded as non-responders), the proportion of treatment responders was higher in the desmopressin group. Selecting treatment by "patient preference" and using pre-treatment predictive factors may result in better results than in this randomised clinical trial through fewer dropouts and greater compliance.

#### Concluding message

Treatment of PNE with desmopressin and with enuresis alarms effectively reduced the frequency of wet nights for those who completed the study. Both therapies have a good safety profile, but the success of alarm conditioning is hampered by the high number of patients who withdraw quickly from treatment. Successful training with alarms requires a high level of motivation, involvement from parents and children, and substantial disturbance to sleep patterns. It may therefore not be suitable for some families. Desmopressin, on the other hand, reduces the number of voids needed, has a fast onset of action and, as such, may be preferred by many patients and families.

#### References

1. Scand J Urol Nephrol, 1999;Suppl 202:66–69
2. J Child Psychol Psychiatry, 1990;31:447–454

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**HUMAN SUBJECTS:** This study was approved by the Local independent ethics committee and followed the Declaration of Helsinki Informed consent was obtained from the patients.