

A randomised study comparing a new, convenient and more readily absorbed desmopressin formulation (Minirin® MELT) with the tablet formulation in primary nocturnal enuresis

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Introduction

- Primary nocturnal enuresis (PNE) or bedwetting is a common condition, affecting approximately 6–10% of children aged 7 years.^{1,2} PNE can have an adverse effect on the sufferer's life; socially, emotionally and behaviourally⁴
- Nocturnal polyuria due to insufficient nighttime release of antidiuretic hormone (vasopressin) is one of the principal causes of PNE²
- Desmopressin acetate (Minirin®) is a selective vasopressin receptor type 2 (V₂) agonist, retaining the antidiuretic properties of vasopressin without inducing pressor activity⁵
- In children who respond to desmopressin, once-daily administration at bedtime reduces the number of wet nights per week by more than 80% during long-term treatment⁷
- The International Consultation on Incontinence endorse the use of desmopressin as a first-line treatment for PNE⁸
- A new oral fast-melting (lyophilisate) formulation of desmopressin (Minirin® MELT) has been developed. This convenient formulation dissolves almost instantly in the mouth and allows lower dosing than the conventional tablet due to higher bioavailability⁹
- Development of lyophilisate formulations is recommended by regulatory bodies such as the European Medicines Agency (EMA) as an approach to improve the acceptability of medicines by children¹⁰

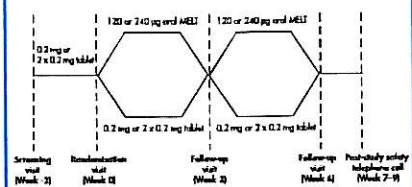
Objectives

- To compare the oral MELT and conventional tablet formulations of desmopressin in children and adolescents in terms of:
 - Efficacy
 - Tolerability
 - Compliance with medication
 - Preference

Methods

- This was an open-label, randomised, cross over study involving children and adolescents (aged 5–15 years) with PNE
- Subjects who had been taking desmopressin tablets for a minimum of 2 weeks and who were stabilised on a dose of either 0.2 mg or 0.4 mg (2 x 0.2 mg) entered a 2-week screening period during which baseline enuretic characteristics were determined (Figure 1)

Figure 1. Study design



- Eligible subjects were then randomised 1:1 to receive MELT or tablet for 3 weeks at bedtime, after which they crossed over to receive the alternate formulation for another 3 weeks (Figure 1)
- Daily diary cards recording medication use and whether the subject had experienced a dry or wet night the preceding night were completed

- Information on adverse events was obtained by the investigator using non-leading questions at each visit
- Subjects were asked which treatment they preferred at the end of 6 weeks' treatment
- Statistical analyses were performed using the intention-to-treat (ITT) dataset. All statistical tests were 2-sided with a significance level of 5%. Allowing for a 10% dropout rate, it was estimated that 200 subjects would yield 80% power to detect a true preference proportion as low as 61%

Results

- 221 subjects from 26 European centres in 5 countries were randomised to receive the MELT (n=111) or tablet (n=110) formulation for 3 weeks before switching to the alternate formulation

Table 1. Baseline demographics (ITT population, n=218)

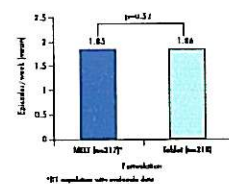
Variable	Mean (SD)
Age [years]	9.6 (2.4)
Height (cm)	143 (16)
Weight (kg)	39.0 (14.4)
BMI (kg/m ²)	18.4 (3.7)
Variable	%
Sex	
Male	71.6
Female	28.4
Age group	
5–8 yrs	34.4
9–11 yrs	40.8
>12 yrs	24.8

- 6 subjects (5.4%) initially receiving the MELT and 5 subjects (4.5%) initially receiving the tablet discontinued treatment before the end of the 6-week treatment period. No discontinuations were due to adverse events

Efficacy

- For the ITT population, efficacy was similar between the two formulations, as illustrated in Figure 2. The number of bedwetting episodes/week (mean [SD]) was: MELT 1.85 (1.89) and tablet: 1.86 (1.83). The estimated difference was -0.05 episodes/week (95% confidence interval [CI]: -0.21–0.10)

Figure 2. Mean number of bedwetting episodes/week (ITT population)



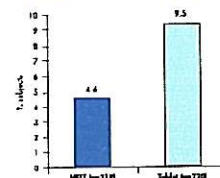
Tolerability

- No serious or severe adverse events were reported. Nasopharyngitis was the most frequently reported adverse event, reported by 4 subjects (1.8%) receiving the MELT and 2 subjects (0.9%) receiving the tablet

Compliance with medication

- Compliance was numerically greater in those receiving the MELT than in those receiving the tablet (Figure 3)

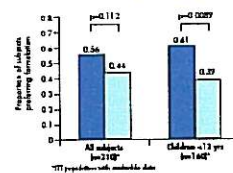
Figure 3. Non-compliance with therapy (<80%, safety population)



Preference

- Preference for the MELT was strongly age-dependent (p=0.006), with children <12 years showing a statistically significant preference for the lyophilisate (60.6%; 95% CI: 52.6–68.2%, p=0.0089) (Figure 4)

Figure 4. Subjects' preferred formulation (ITT population)



Conclusions

- The new lower-dose desmopressin MELT formulation retains similar levels of efficacy and tolerability as bioequivalent doses of the original tablet formulation
- The MELT formulation is associated with greater compliance than the tablet formulation
- Preference for the MELT is strongly age-dependent (p=0.006)
- In children (<12 years of age) there is a statistically significant preference for the MELT formulation compared with the tablet formulation (p=0.0089)
- The new convenient MELT formulation facilitates the early treatment of PNE

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