

Desmopressin melt improves response and compliance compared with tablet in treatment of primary monosymptomatic nocturnal enuresis

Kristian Vinter Juul · Charlotte Van Herzele ·
Pauline De Bruyne · Sandra Goble ·
Johan Vande Walle · Jens Peter Nørgaard

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Abstract Primary nocturnal enuresis is a prevalent childhood condition that can persist into adulthood. Desmopressin is an antidiuretic available as orally disintegrating lyophilisate (melt) or solid tablet. Recent findings suggesting different food interactions and clinical characteristics, including compliance, between desmopressin melt and tablet motivated a post hoc analysis of a previously reported randomised, crossover study. The efficacy of desmopressin melt compared with tablet was evaluated using the International Children's Continence Society (ICCS) responder definitions. Compliance was further analysed using detailed criteria, and the association between efficacy and compliance was examined. In total, 221 patients aged 5–15 years, already receiving desmopressin tablets were randomised to the treatment sequence melt (120/240 µg)/tablet (0.2/0.4 mg) or tablet/melt in two consecutive 3-week periods. The probability of being a responder (partial or full) during either period was significantly more likely with desmopressin melt compared with tablet (odds ratio, 2.0; confidence intervals, 1.07–3.73; $p=0.03$). There was no period effect on compliance in the tablet/melt sequence and no difference in the number of completely compliant patients in each formulation group; however, more patients were >75 % compliant in period 1 compared with period 2 in the melt/tablet sequence.

Increased compliance was associated with greater reductions in the number of wet nights for both formulations. Conclusions: Desmopressin melt, compared with tablet, improves the probability of being a responder. Switching from tablet to melt formulation increased patient compliance. Increased compliance was associated with increased efficacy. Switching to desmopressin melt may benefit patients with suboptimal responses to desmopressin tablet.

Keywords Enuresis · Desmopressin · Compliance · Formulation

Introduction

Monosymptomatic nocturnal enuresis (MNE), bedwetting without any other lower urinary tract symptoms (LUTS) [10], is a distressing problem that affects 6–10 % of 7-year-old children [5]. It has an annual spontaneous resolution rate of approximately 10–15 % [5], but not all cases resolve spontaneously. Nocturnal enuresis persists in up to 3 % of adolescents [21] and 1 % of untreated adults [5]. Given the huge impact of enuresis on self-esteem, quality of sleep, performance at school and social and familial life [4, 15], timely and adequate treatment is mandatory. Enuresis is essentially caused by a mismatch between nocturnal bladder capacity and the amount of urine produced during the night in children or adults who do not awake from sleep in response to a full bladder [5]. Nocturnal polyuria (NP), due to insufficient arginine vasopressin hormone release at night, is a major cause of MNE [12].

There are only two first-line treatments of MNE available, the enuresis alarm and desmopressin, both of which have level 1 grade A recommendations from the International Consultation

K. V. Juul (✉) · S. Goble · J. P. Nørgaard
Ferring International PharmaScience Center, Kay Fiskers Plads 11,
2300 Copenhagen, Denmark
e-mail: KristianVinter.Juul@ferring.com

C. Van Herzele · J. V. Walle
Pediatric Nephrology Unit, Ghent University Hospital, Ghent,
Belgium

P. De Bruyne
Department of Pediatrics and Medical Genetics, Ghent University,
Ghent, Belgium

on Incontinence [14]. Desmopressin is a selective vasopressin receptor type 2 agonist that retains the antidiuretic properties of vasopressin without inducing pressor activity. Recent guidelines recommend an individualised treatment based on parameters obtained using a voiding diary to assess important factors, such as whether nocturnal enuresis is monosymptomatic or present with additional LUTS symptoms, and whether patients have NP [17]. Amongst those with MNE with underlying NP, desmopressin is the recommended therapy due to its antidiuretic action [17]. However, despite a significant percentage of full responders in trials, there exist subpopulations of patients that are only partial responders or appear desmopressin resistant [16]. Up to 60 % of patients demonstrate less than a 50 % decrease in wet nights in trials [8].

Currently, two different formulations of desmopressin are approved in the USA and most of Europe for the MNE indication: oral tablet and orally disintegrating lyophilisate tablet (melt). These two formulations have been shown to be clinically bioequivalent at doses of 200/400 µg for the tablet and 120/240 µg for the melt in comparative studies in healthy young volunteers [data from unpublished clinical trial]. Primary analysis of the clinical anti-enuretic effect of the tablet and melt in the PALAT study (NCT00209261) supported this bioequivalence [9].

Stimulated by clinical observations that some patients with partial desmopressin response on the tablet benefitted from a switch to the melt, De Guchtenaere et al. published data from a pharmacodynamic study in children with enuresis, demonstrating superior antidiuretic effect and concentrating capacity with the melt 120 µg compared with the bioequivalent 0.2 mg tablet [2]. The design of the study involved a single-dose administration and a standardised meal aimed to reflect more closely the clinical reality for young children with enuresis who are likely not to take the drug on an empty stomach. The study demonstrated that more than 25 % of patients had a higher diuresis rate and lower concentrating capacity with the tablet vs melt formulation in the early response phase, and a statistically significant difference in diuresis was observed in the plateau phase and in duration of action [2]. This suggests that decreased food interaction might increase the bioavailability of desmopressin administered as the melt formulation compared with tablet due to mucosal absorption of the melt in the oral cavity and oesophagus [11, 20].

These recent findings on the potential interference of food administration and the indices of superior clinical characteristics of the melt (in an artificial setting of a single-dose pharmacodynamic study), as well as the importance of compliance, stimulated us to perform a post hoc analysis of existing data from the only multiple dose comparative clinical study of desmopressin melt vs tablet in children with nocturnal enuresis [9]. A comparative pharmacodynamic assessment in terms of anti-enuretic effect

was undertaken, using clinical response rates as currently recommended by the ICCS [10]. However, these data are from patients already receiving desmopressin tablet at baseline; thus, the responder analysis in this study examines response rates to desmopressin in addition to responses following 2 weeks of desmopressin therapy. We also reanalysed compliance data using the more detailed compliance criteria used by Van Herzeele et al. [16], and investigated the relationship between efficacy and compliance. While post hoc analyses are not as powerful as primary analyses, ethical considerations led us to pursue this course instead of setting up a new interventional study in children, since relevant data had already been collected. The current analyses also support power calculations for any prospective study protocols in MNE.

Methods

Clinical data were derived from an open-label randomised crossover study with daily doses of desmopressin melt and desmopressin tablet in children and adolescents with primary MNE (ClinicalTrials.gov Identifier: NCT00209261 [9]). The study was approved by the institutional review board or ethics committee for each site, the Declaration of Helsinki was followed, and informed consent was obtained from all patients.

Patients

The study was conducted in children and adolescents aged 5–15 years, with monosymptomatic primary nocturnal enuresis (PNE) who had been on a stable dose of 0.2 or 2×0.2 mg desmopressin tablet for at least 2 weeks. The use of non-pharmacological therapy (e.g. bed alarms) for nocturnal enuresis during the 60 days before the screening visit was not permitted for study participants. Inclusion and exclusion criteria are listed in full in Table 1.

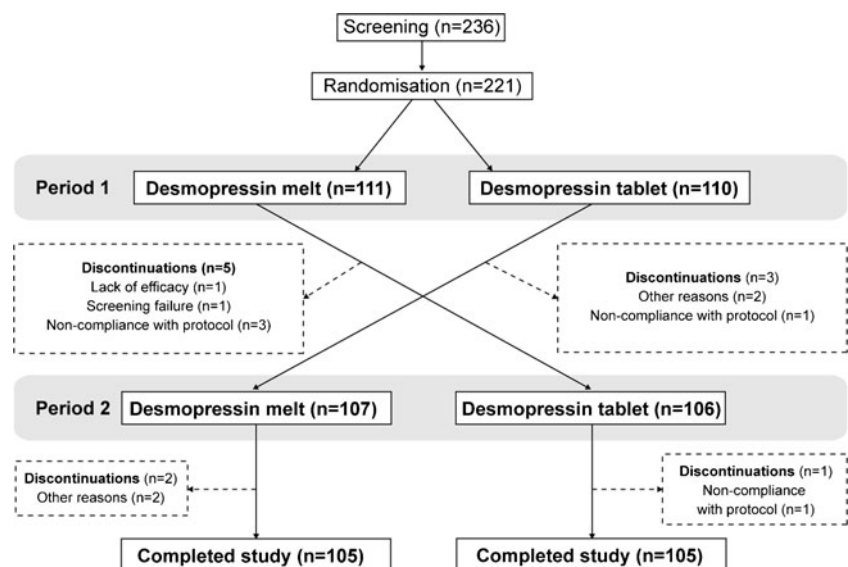
Study design

The study design has been described in detail elsewhere [7, 9]. Briefly, following a 2-week screening treatment period with 0.2 or 2×0.2 mg tablet, as defined by the clinician as the appropriate therapeutic dose for the patient, patients were randomised 1:1 to the sequence melt/tablet or tablet/melt (Fig. 1). Oral desmopressin tablets were administered at the same dose as during the screening period, and desmopressin melt was administered at claimed bioequivalent doses (0.2/0.4 mg tablet=120/240 µg melt). The intention to treat dataset, reported in the analysis, included all patients who had at least one post-randomisation assessment recorded.

Table 1 Inclusion and exclusion criteria

Number	Inclusion criteria	Exclusion criteria
1	Male or female, 5–15 years of age (inclusive; or according to the minimum age as specified in the marketing authorisation in each country)	Presence or history of organic urological disease, diurnal urinary incontinence, diabetes insipidus, ongoing urinary tract infection, clinically significant renal, hepatic, gastrointestinal, pulmonary, cardiovascular, endocrinological or neurological disease that would interfere with evaluation
2	Primary monosymptomatic nocturnal enuretic subjects	Ongoing systemic antibiotic use, use of diuretics or any drugs affecting urinary concentration, or medical treatment for hyperactivity
3	Stabilised (at least 2 weeks) on 0.2 or 2×0.2 mg desmopressin at the screening visit	Use of any experimental drug or device during 30 days before the screening visit
4	The subject was to have been free of diurnal symptoms such as urgency, frequency (more than seven micturitions during daytime), voiding postponement or infrequent voiding (less than three voidings during daytime), disordinated voiding (painful voiding or weak stream) and/or day wetting (more than once a week)	Use of non-pharmacological therapy (e.g. bed alarms) during 60 days before the screening visit
5	Female subjects must have been pre-menarchial or sexually inactive. Otherwise, contraception had to be used and a negative pregnancy test obtained	Abnormalities or disease in the oral cavity that might have affected the release and absorption of desmopressin from the oral lyophilisate formulation
6	Willing and able to comply with the protocol requirements for the duration of the study	The subject was a smoker
7	Parents of the child must have voluntarily signed a written informed consent agreement, after explanation of the nature and objectives of the study and prior to any study specific procedure and prior to treatment. It had to be thoroughly explained that the consent could be withdrawn at any time without prejudice. The institutional ethics committee (IEC) had to approve the informed consent agreement	Was hypersensitive towards any component of the investigational product
8	Where appropriate, participants were to assent to enrol in the study (age of assent to be determined by IECs or be consistent with local legal requirements)	The subject and/or the subject's parents had mental incapacity or language barriers precluding adequate understanding or cooperation
9		Had previously participated in this study
10		Was considered unsuitable by the investigator, for any other reason, to participate in the study

Fig. 1 Study design. Patients stabilised on 0.2 or 0.4 mg desmopressin tablets entered a 2-week screening period. Eligible patients were randomised 1:1 to receive melt or tablet for 3 weeks, then switched to the alternative formulation for 3 weeks



Responder analysis

The incidence of bedwetting episodes was recorded daily on diary cards. The mean incidence/week was calculated as the mean value of all data recorded between week -2 and 0 for period 0 (screening period), between week 0 and 3 (period 1), and between week 3 and 6 (period 2). The reduction in number of wet nights compared to baseline (week 0) in period 1 and 2 was categorised according to the ICCS response rates, modified to reflect the non-treatment naive baseline: non-response is defined as a 0–49 % decrease, partial response is defined as a 50–89 % decrease, response is defined as a ≥ 90 % decrease and full response is defined as a 100 % decrease or less than one symptom occurrence monthly [10]. These modified categories from a baseline of desmopressin treatment reflect additional responses with time to desmopressin, with the exception of full response that may reflect a stable response of < 1 symptom occurrence per month. The response rate for period 1 and 2 was summarised as a function of treatment and dose.

Compliance rate

Treatment compliance was verified based on diary records and by review of empty blisters and unused study medication. Patients returned empty medication packages. Study drug compliance was calculated as a percentage of the number of doses taken as instructed in each study period. Compliance was categorised as 100, > 75 –99, 50–75 and < 50 %, in line with a recent study of desmopressin compliance [16], and compliance rate by treatment and dose was summarised.

Statistical analysis

Power calculations have been presented for this study previously [9]. In brief, allowing for a 10 % dropout rate, a sample size of 200 subjects would yield 80 % power to detect a true preference proportion as low as 61 %. Statistical evaluation was performed using Statistical Analysis Software (v9.2). The number and proportion of patients was summarised by responder status (non-responder, partial responder, responder and full responder) for the two different treatment sequences. The compliance rate was categorised according to the following: missing, < 50 , 50–75, > 75 –99 and 100 %, and summarised with number and proportion of patients for each treatment sequence. The distribution of proportions was compared using chi-square tests. The probability of having an amelioration (i.e. reduction in bedwetting; defined as partial responder, responder or full responder) during period 1 and 2 was analysed using a repeated logistic regression model with terms for sequence, age, treatment, dose group, period and a random factor for subject. Using error variance from the logistic model, the odds ratio (OR) and 95 % confidence intervals (CI) of the overall treatment effect (melt vs tablet) was estimated. The association between

compliance rate and response was explored using an analysis of covariance (ANCOVA) model with terms for sequence, age, treatment, dose group, treatment by dose group interaction, compliance group, treatment by compliance group interaction, period and a random factor for subject. Using error variance from the ANCOVA model, the compliance by treatment effect was estimated and reported with 95 % CI.

Results

Patient characteristics

A total of 236 patients fulfilled the inclusion criteria and following screening, 221 patients were randomised initially to receive melt ($n=111$) or tablet ($n=110$) formulation (Fig. 1). Of the 221 patients randomised, 72 patients were in the low-dose group (120 μg melt and 0.2 mg tablet) and 149 patients were in the high-dose group (240 μg melt and 2×0.2 mg tablet). The mean number of wet nights per week during screening was 1.54 ± 1.75 and 2.39 ± 2.02 in the low- and high-dose groups, respectively. For both groups, the minimum incidence of wet nights per week was zero and the maximum incidence was seven. The majority of enrolled patients were male (71.6 %) and the mean age was 9.6 ± 2.4 years.

Responder analysis

The probability of having an amelioration was significantly greater for desmopressin melt compared with desmopressin tablet as assessed by the repeated logistic regression model (OR=2; 95 % CI, 1.07–3.73; Table 2). The dose of desmopressin also significantly increased the probability of amelioration, with an OR of 3.05 favouring the lower dose melt 120 μg /tablet (0.2 mg) compared with the higher dose melt 240 μg /tablet (0.4 mg; Table 2).

Approximately 80 % of the patients were non-responders, with < 49 % further decrease in symptoms with continuing desmopressin treatment, after completing period 1 in both

Table 2 Responder analysis: repeated logistic regression model with terms for sequence, age, treatment, dose groups, period and a random factor for subject

Parameter	Odds ratio	95 % confidence interval of odds ratio	<i>p</i> value
Sequence	0.75	0.37–1.53	0.4334
Age (1 year increase)	1.17	0.95–1.30	0.1795
Formulation (melt vs tablet)	2.00	1.07–3.73	0.0288*
Dose group (low vs high)	3.05	1.63–5.70	0.0005*
Period	3.04	1.61–5.72	0.0006*

* $p \leq 0.05$, statistically significant difference between groups

sequences (Table 3). There were slightly more responders during the first period in the melt (6.5 %) compared with tablet (1.9 %) group. In addition, there was a significant period effect for both formulations ($p=0.0006$) with more full responders and fewer non-responders in period 2 compared with period 1 (Tables 2 and 3). Increased time on desmopressin therapy increased responders, irrespective of formulation.

Compliance rate

At least 60 % of the patients in treatment sequence tablet/melt were 100 % compliant in both period 1 and 2 (Table 3). There was no difference in the distribution of compliance rate between the two different periods among the patients in this sequence ($p=0.2734$). A similar percentage of patients in the other treatment sequence, melt/tablet, were 100 % compliant in both period 1 (57 %) and 2 (60 %). However, significantly more of these patients were >75–99 % compliant in period 1 (melt) than in period 2 (tablet; 40 vs 28 %, respectively; $p=0.0425$; Table 4).

Across formulations, the reduction in mean number of wet nights/week was significantly greater for higher compliance rate compared with lower compliance rate groups (Fig. 2). However, the lower compliance rate groups had very low patient numbers. Compliance of >75 % appeared to be a natural cut-off level, since the only non-significant comparison was between the two lower compliance groups (<50 and 50–75 %; $p=0.86$).

Discussion

Bioequivalence of desmopressin melt 120 µg and desmopressin tablet 0.2 mg is supported by studies in healthy volunteers [data from unpublished clinical trial]. Primary analyses of the current

dataset, reported by Lottmann et al., not only confirmed the bioequivalence of the formulations at these doses, but added important data on the comparable safety profiles of desmopressin melt and tablet [9]. The anti-enuretic effect is directly related to antidiuretic effect and concentrating activity, at least in patients with high nocturnal diuresis, so superior antidiuretic effect should lead to fewer wet nights. We are aware that a secondary analysis can never reach the statistical power of the primary analysis, but it is unethical to perform another study in children when existing data can be used to test for differential clinical effects of, and compliance with, claimed bioequivalent doses of the two formulations.

This analysis compared the clinical response achieved with both desmopressin formulations using response groups as advised by the ICCS [10]. However, it should be noted that, to be eligible for inclusion in this study, patients were required to have already been receiving desmopressin tablets (0.2 or 0.4 mg) for at least 2 weeks prior to screening. Response rates reported are therefore only indicative of additional improvement achieved during this study, not of overall reduction in wet nights with desmopressin compared with frequency of wet nights experienced pre-treatment. Overall, 18 % of patients at period 2 receiving desmopressin tablet or melt were full responders with no wet nights and 13 % achieved a partial response (additional 50–89 % reduction in wet nights). The incidence of non-responders was higher than that usually reported in trials of desmopressin in MNE because the study population was treated with desmopressin at baseline. Analysis using the repeated logistic regression model, controlling for sequence of treatments, age, treatments, dose group and period, found that the probability of an amelioration in bedwetting (partial responder, responder or full responder) was significantly greater for patients receiving desmopressin melt compared with desmopressin tablet, with an OR of 2. This observation supports the theory that desmopressin melt

Table 3 Distribution of responders by treatment sequence

	Period 1 <i>n</i> (%)	Period 2 <i>n</i> (%)	Change in responders from period 1 to 2 %
Sequence tablet/melt			
Full responder	3 (2.83)	23 (22.33)	19.5
Responder	2 (1.89)	0 (0)	−1.89
Partial responder	17 (16.04)	14 (13.59)	−2.45
Non-responder	84 (79.25)	66 (64.08)	−15.17
Missing data	1	4	
Sequence melt/tablet			
Full responder	4 (3.74)	16 (15.53)	11.79
Responder	8 (7.48)	1 (0.97)	−6.51
Partial responder	12 (11.21)	15 (14.56)	3.35
Non-responder	83 (77.57)	71 (68.93)	8.64
Missing data	1	5	

Table 4 Compliance rates by treatment sequence

Compliance rate	<50 %		50–75 %		>75–99.9 %		100 %		Missing		Total	
	<i>n</i> (%)		<i>n</i> (%)		<i>n</i> (%)		<i>n</i> (%)		<i>n</i> (%)		<i>n</i> (%)	
Sequence tablet/melt ($p=2.743$) ^a												
Period 1 (tablet)	2	(1.83)	3	(2.75)	38	(34.86)	66	(60.55)	0	(0.0)	109	(100)
Period 2 (melt)	1	(0.92)	1	(0.92)	36	(33.03)	67	(61.47)	4	(3.67)	109	(100)
Sequence melt/tablet ($p=0.0425$) ^a												
Period 1 (melt)	1	(0.92)	2	(1.83)	44	(40.37)	62	(56.88)	0	(0.0)	109	(100)
Period 2 (tablet)	5	(4.59)	4	(3.67)	31	(28.44)	65	(59.63)	4	(3.67)	109	(100)

^a Chi-square test of difference in distributions of proportions

has an improved pharmacokinetic profile, due to reduced food interaction resulting in less variation of desmopressin plasma concentration, and an improved pharmacodynamic profile compared with desmopressin tablet as recently reported [1, 2].

Importantly, desmopressin melt offers a preferable administration method compared with desmopressin tablet [9]. The avoidance of fluid intake with drug administration helps to reduce the risk of water intoxication. This is important, especially in children with PNE, as swallowing 2 oz (60 mL) of fluid with a tablet is equivalent to about a quarter of the expected bladder capacity of a 7 year old [13]. This reduction in fluid intake was confirmed in the study of Lottman et al. where patients reported taking water (mean of 40 mL) with 13.1 % of desmopressin melt doses, compared with 76.9 % of tablet doses [9]. Avoiding the need for fluid intake with desmopressin administration is also likely to impact upon efficacy. A study of the pharmacodynamic effects of desmopressin nasal spray reported that urine concentration was reduced when fluid was not restricted before desmopressin administration [3].

In the treatment sequence tablet/melt, no difference in compliance rate between the two periods was observed ($p=0.2734$); while in treatment sequence melt/tablet, significantly more patients were >75 % compliant in period 1 (melt) than period 2 (tablet). In our opinion, although this finding is based on 16 patients reducing compliance by ≤ 75 % when switching

from desmopressin melt to tablet compared with three patients switching from tablet to melt, if similar compliance behaviour occurs in a real-life setting, it is of real clinical importance. The role of compliance is certainly underestimated in therapy resistance or partial response. In a substudy of the DRIP study [8], an international investigation of desmopressin tablet treatment for 6 months or less in children with PNE, compliance data were available on 723 patients [16]. During the initial run-in phases, 81–91 % of patients ingested all medication. However, this decreased to 77 and 71 % during the first and second 3-month treatment periods, respectively. High treatment compliance was associated with improved response and a narrower CI, indicating a greater response consistency achieved by more consistent medication [16]. Even with a study period of only 6 weeks in the present analysis, the same decreasing compliance over time was seen in patients receiving desmopressin tablet. It is notoriously difficult to measure patient compliance accurately, in almost all therapy areas. In this study, treatment compliance was verified based on diary records and by review of empty blisters and unused study medication. While this is an objective method of monitoring medication intake, it is possible that medication was lost or even thrown away, for example to attempt to demonstrate that investigators' instructions had been followed [16]. These factors may lead estimates of treatment compliance to be artificially inflated, and compliance rates in study populations, as well as clinical practice, are likely to be even lower than indicated.

Difficulties of compliance assessment aside, there are no studies with desmopressin tablet or melt available that have corrected their results for compliance in the individual patient. As the antidiuretic duration of action of desmopressin is limited to and only desirable during the night hours after drug administration, a high degree of compliance is essential to ensure consistent therapeutic effects [16]. However, the rapid pharmacodynamic effect of desmopressin supports conclusions on the efficacy of treatment in an individual compliant patient in 14 days [20]. Future research should include longer studies of desmopressin melt in patients with MNE and diagnosed NP to provide evidence of the long-term clinical benefit of desmopressin therapy in MNE. The additional responders seen

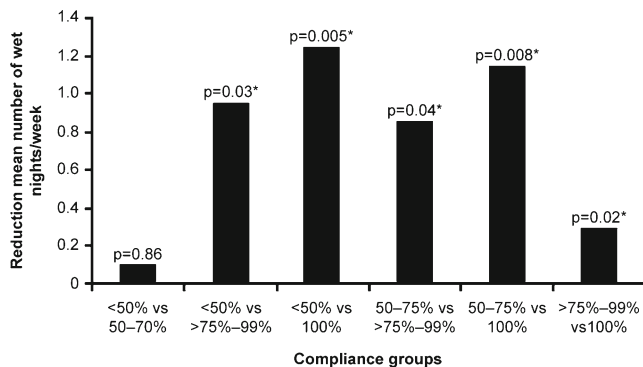


Fig. 2 Comparison between compliance groups on the reduction in mean number of wet nights, overall across formulations. * $p \leq 0.05$, statistically significant difference between compliance groups

in this study suggest that improved responses to desmopressin therapy are observed with increasing time on treatment.

Another reason for partial or no response to desmopressin treatment is that many studies enrol patients with only minimal screening, often in primary care settings, or do not use the new ICCS definitions [10] and fail to exclude patients with LUTS symptoms [18] suggestive of non-monosymptomatic nocturnal enuresis. The pharmacokinetics of desmopressin may also contribute to the findings of refractory enuresis in some patients since it is an oligopeptide with low bioavailability that may vary dependent on the administered formulation. Initial studies with desmopressin in enuresis were performed with the nasal spray, which had to be withdrawn from the market due to side effects, likely related to unpredictable bioavailability following absorption by the nasal mucosa [19].

The significant period effect in favour of greater efficacy in period 2 (i.e. the last 3 weeks of the six treatment weeks), might be a ‘learning’ effect. Whilst this is a clinical benefit, it is also a recognised methodological disadvantage of the crossover design, in which behaviour in the first period cannot be nullified for period 2. In this case, there was possibly a behavioural component, either by influences of the investigator, the patients themselves, their parents or a combination of these, reducing the number of wet nights over time. A learning effect in the treatment of PNE with desmopressin is sparsely described in the literature; however, Läckgren et al. showed that prolonged treatment with desmopressin has a pronounced effect on enuresis, especially during the period immediately after treatment cessation [6]. This finding deserves further exploration.

The significantly better response in patients receiving the lower desmopressin doses compared with the higher doses seems contrary to the intuitive expectation that a higher dose would be more effective. However, the study population comprised patients who had been on a stable dose level of 0.2 or 2×0.2 mg desmopressin tablet based on their clinician’s prescription prior to inclusion rather than a randomised assignment to dose. Thus, patients in the low-dose group (0.2 mg desmopressin tablet) at screening were probably highly polyuric patients with normal bladder capacity. In contrast, the patients prescribed the higher dose likely contained a larger proportion of desmopressin non- or partial responders. A potential weakness of our analysis is that other covariates such as age, weight and gender could correlate to final dose although former pharmacokinetic modelling showed that no such tested covariates provided a statistically significant model improvement [11].

Clinical implications

This study shows that the probability of having a reduction in bedwetting episodes is increased by a factor of two for patients

receiving desmopressin melt compared with desmopressin tablet. Thus, for patients with a suboptimal response to desmopressin tablets, there may be a clinical benefit to switching to desmopressin melt. As the antidiuretic effects of desmopressin tablet and melt are maintained for 6–11 h [5, 20] a high degree of compliance is essential to ensure consistent therapeutic effects. This study demonstrates that significantly better compliance is obtained with desmopressin melt, when switching from the tablet to melt formulation, which may partially explain the increased probability of having a reduction in bedwetting episodes for patients receiving desmopressin melt compared with tablet. Although the melt formulation is more expensive than the tablet in most countries, the reduction in bedwetting episodes results in savings in terms of laundry or diaper costs. Our findings are supportive of recent findings of better pharmacokinetic and pharmacodynamic characteristics for desmopressin melt compared with tablet [1, 2]. Additional exploration of predictors of clinical response may further optimise the dosage regimen of desmopressin in an individual PNE patient.

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