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Abbreviations and Acronyms

ICCS = International Children's Continence Society

MNE = monosymptomatic nocturnal enuresis

PD = pharmacodynamic

U = urine collected after desmopressin administration

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Study received local ethics committee approval (CE2009/653).

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Purpose: Desmopressin is a standard treatment for monosymptomatic nocturnal enuresis. Different formulations are promoted as bioequivalent, although these claims are not supported by comparative pharmacodynamic data in children. Food interaction is known to influence the bioavailability of desmopressin. We compared the pharmacodynamics of the 2 most frequently used desmopressin formulations, tablet and lyophilizate, with a standardized meal, allowing extrapolation to clinical reality, where the interval between evening meal and medication intake is limited for school-age children. We hypothesized there would be a faster pharmacodynamic response, and greater concentrating and antidiuretic activity for the fast dissolving (melt) formulation compared to the tablet with simultaneous food intake.

Materials and Methods: Two tests were performed on separate days in identical standardized conditions, starting with a 15 ml/kg water load. After achieving maximal diluting capacity a standardized meal was administered, followed by desmopressin tablet (t test) or melt (M-test). Diuresis rate and urinary osmolality were measured hourly. Paired data from 4 girls and 15 boys with a mean age of 12.1 years were obtained.

Results: In the early response phase more than 25% of patients had a higher diuresis rate with tablet vs melt formulation, reaching statistical significance in the plateau phase (urine collected at hours 3 to 5, $p < 0.02$) and in duration of action (urine collected at hours 5 to 8, $p < 0.005$). For desmopressin melt smaller standard deviations in diuresis rate were remarkable. Concentrating capacity demonstrated no significant differences between formulations in the early response phase, in contrast to the plateau phase ($p < 0.036$) and duration of action ($p < 0.001$).

Conclusions: With meal combination desmopressin melt formulation has a superior pharmacodynamic profile to tablet, making it more suitable for the younger age group with a limited interval between meal and drug administration.

Key Words: administration, sublingual; biological availability; deamino arginine vasopressin; food-drug interactions; freeze drying

DESMOPRESSIN is the only drug therapy with evidence level 1, grade A recommendation for the indication of monosymptomatic nocturnal enuresis.[1,2] Of children treated with desmopressin only 24.5% achieve complete dryness,[3–5] leaving up to 75% as incomplete responders or nonresponders. Several pathogenic mechanisms have been proposed to have a role in desmopressin

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resistance, including hypercalciuria, high osmotic load, increased prostaglandin synthesis, sleep disturbance and impaired sensitivity to desmopressin.[6–11] However, these pathophysiological differences alone cannot explain the high variability in desmopressin response. Therapy compliance, and pharmacodynamic and pharmacokinetic properties of the different desmopressin formulations deserve further exploration.[12,13]

Three different formulations of desmopressin are promoted as being bioequivalent for the indication of MNE—nasal spray (20 μg), oral tablet (400 μg) and recently the oral lyophilizate formulation (melt, 240 μg).[14] Due to safety issues, desmopressin nasal spray no longer has Food and Drug Administration approval, leading to its worldwide withdrawal for this indication and necessitating a switch to the tablet or melt in the majority of countries.

Direct comparative data on melt and tablet bioequivalence are lacking. Moreover, comparative research in this field is complicated primarily due to the subdivision of PD effects into 3 levels, ie the effect on renal concentrating capacity, measured as urinary osmolality (often referred to as intrinsic effect),[15] the antidiuretic effect, measured as urinary volume per time unit, and the antienuretic effect, measured as wet nights per time unit. Also, most available pharmacodynamic data are drawn from adult study populations, including healthy men and patients with diabetes insipidus and nocturia.[16,17] To our knowledge only 2 comparative studies have been performed in a pediatric population with primary enuresis. Lottmann et al focused on safety, compliance and preference,[14] while Fjellestad-Paulsen et al reported differences in antienuretic effect.[17]

Differences in relation to food intake have not been considered in previous studies. While a fasting patient absorbs desmopressin quickly, concomitant meal intake delays absorption.[18] Additionally if intestinal motility is delayed, the absorption of desmopressin increases.[19] Since most pharmacodynamic studies are performed in a fasting state,[17,20,21] they are not representative of young children. In these patients, who have a short delay between meal and bedtime, tablet administration often coincides with the evening meal. Consequently less interference with nutrition can be expected if the desmopressin melt, in contrast to the tablet, is reabsorbed by oral and/or esophageal mucosa, as claimed.

We sought to investigate the bioequivalence of desmopressin administered as tablet and oral lyophilizate for the 2 major PD properties, antidiuresis and concentrating capacity, with a concomitant standardized meal in children with MNE. We hypothesized there would be 1) a faster PD response, 2) greater concentrating activity and 3) greater antidiuretic activity for desmopressin melt formulation compared to tablet with simultaneous food intake. This design allowed us to extrapolate the data to clinical reality, where the majority of young patients take the drug less than 1 hour after the evening meal on a stomach that is not yet empty.

PATIENTS AND METHODS

Subjects

A total of 19 patients were selected at a tertiary enuresis center, all of whom fulfilled ICCS criteria for monosymptomatic nocturnal enuresis partly responding to desmopressin tablet. Partial response was defined according to ICCS definition as a 50% to 89% decrease in number of wet nights weekly. Exclusion criteria consisted of history of urological disease, daytime incontinence, diabetes insipidus, ongoing urinary tract infection, desmopressin hypersensitivity and any clinically significant disease likely to interfere with evaluation; use of antibiotics, diuretics or any drug affecting urine concentration; and abnormalities of the oral cavity.

Children of appropriate intellectual maturity signed a specially designed form, and written informed consent was obtained from all parents and legal guardians. The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice, and approval was obtained from our local ethics committee (CE2009/653).

Protocol

Blood was sampled on arrival and 6 hours after desmopressin administration, and serum sodium was evaluated for safety reasons. Urine samples were collected by voiding hourly from arrival, with exclusion of post-void residual by bladder ultrasound. Osmolality, volume and creatinine concentration were assessed for each urine collection.

Oral hydration was started immediately after admission to the hospital. Children were asked to drink 15 ml/kg water in 15 minutes.[22] If complete dilution was reached (defined as urinary osmolality less than 200 mosm/l), a standardized 510 Kcal meal was administered, containing 12 gm protein, 23 gm fat and 63 gm carbohydrate (McDonald's® Happy Meal™ containing 4 Chicken McNuggets™ and french fries). The meal was immediately followed by desmopressin administration. Subsequently all urinary voids were compensated with an identical amount of water, to maintain fluid homeostasis. To maintain hydration, 8 hours of insensible loss (estimated as 500 ml/m^2 per body surface area per 24 hours) was compensated at 5 hours after medication by oral water administration (166 ml/m^2 per body surface area).

Identical tests were performed with desmopressin tablet and melt with a 14-day interval between tests (fig. 1). All spontaneously reported adverse events were recorded, as were those routinely surveyed at the end of each study day.

Laboratory Assessments

Hourly diuresis volume, urinary osmolality and urinary creatinine were measured. Diuresis volume per weight and time unit was calculated as a parameter for antidiuretic effect. Concentrating capacity was evaluated by urinary osmolality. Osmotic excretion was calculated by

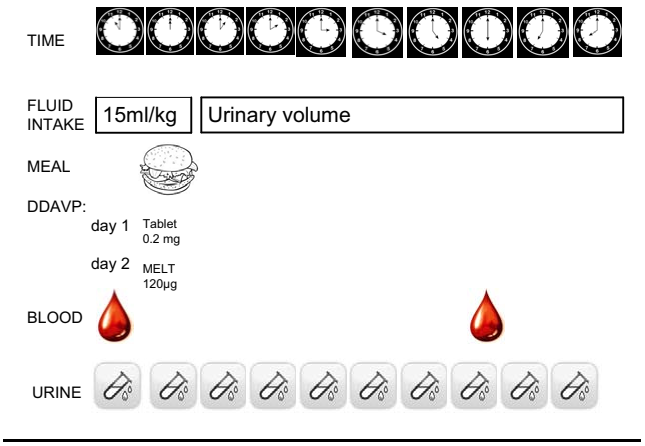

Figure 1. Study design. *DDAVP,* desmopressin.

osmolality × volume per time unit. Serum sodium was determined twice.

Study Drugs

The first formulation, 200 µg desmopressin tablet (Desmotab®, Ferring N. V., Aalst, Belgium), was administered orally immediately after the meal. The second formulation, 120 µg desmopressin melt (Minirin® Melt, Ferring), was given under identical circumstances.

Statistics

SPSS®, version 17 statistical software was used to perform analysis. Since osmolality and diuresis are not identically distributed, nonparametric testing (paired Wilcoxon signed rank test) was used. All tests were performed using a 5% level of significance.

RESULTS

Four patients were excluded from paired statistical analysis for the following reasons. One patient had mental retardation and did not succeed in taking the melt or the tablet properly, 1 did not reach maximal diluting capacity before desmopressin administration, 1 took desmopressin the evening before test 2 and 1 had collection errors.

Four girls and 15 boys (mean ± SD age 12.1 ± 2.5 years) with normal body weight (48.7 ± 16 kg) were eligible for the study. All patients completed tablet and melt testing under identical circumstances. Patients were properly hydrated, with no significant difference in minimal osmolality at the start of the test (table 1).

Figures 2 and 3 show individual data regarding antidiuretic effect. Statistical significance was obtained for diuresis in urine collected at hour 6. Statistical difference not being reached at U 7 and U 8 may be related to ceasing the test once dilution capacity was regained. This observation is supported by statistical differences in U 6 and U 7 for urinary osmolality, revealing that the effect of desmopressin melt was superior to tablet during urine collected at hours 5 to 7.

Although not statistically significant for median diuresis rate, mean diuresis rate was 25% lower with desmopressin melt during the first hour after administration (2.8 vs 3.7 ml/kg per minute), with more than 25% of patients having a higher diuresis rate than the melt controls. For desmopressin melt smaller standard deviations in diuresis rate were remarkable in the early phase, as well as after 5 hours. In the plateau phase there was only a tendency toward superior effect of desmopressin melt.

Pharmacodynamic data, expressed as concentrating effect and antidiuretic effect, are outlined in tables 1 and 2. Values of diuresis are presented as absolute value, diuresis rate and diuresis-to-creatinine ratio. For clarity and clinical interpretation we arbitrarily subdivided the time course into 3 different phases—early response (urine collected at hours 1 and 2), plateau (3 to 5) and duration of action (5 to 8), with the latter demonstrating the most significant differences.

Figure 3 illustrates the overall better effect of desmopressin melt on concentrating capacity, which was most pronounced at U 5. No significant differences were found in the early response phase. In this phase the importance of the osmotic load was shown by the significant correlation between osmotic excretion and diuresis rate after the standardized meal (tablet $p = 0.007$, melt $p = 0.005$).

No significant differences were identified in mean serum sodium either before or 6 hours after desmopressin administration, or between different formulations (140 vs 138 mmol/l with tablet, 140 vs 139 mmol/l with melt). No serious adverse events were noted. One patient experienced minor headache and vomited once without hyponatremia in the safety laboratory.

DISCUSSION

This is the first study with paired data in children with MNE revealing that there is bioequivalence between the lower dose of desmopressin melt (120 µg) and tablet (200 µg), as well as superiority of the

Table 1. *Urinary concentration expressed by urinary osmolality*

	Tablet	Melt	p Value
Mean ± SD min urinary osmolality (mOsm/l)	78 ± 32	88 ± 31	0.87
Mean ± SD urinary osmolality (mOsm/l) by hour:*			
U 1–2	498 ± 238	525 ± 279	0.58
U 3–5	682 ± 250	763 ± 192	0.036
U 5–8	403 ± 315	513 ± 293	0.001

* U 1 to 2 was defined as early response phase, U 3 to 5 as plateau phase and U 5 to 8 as duration of action.

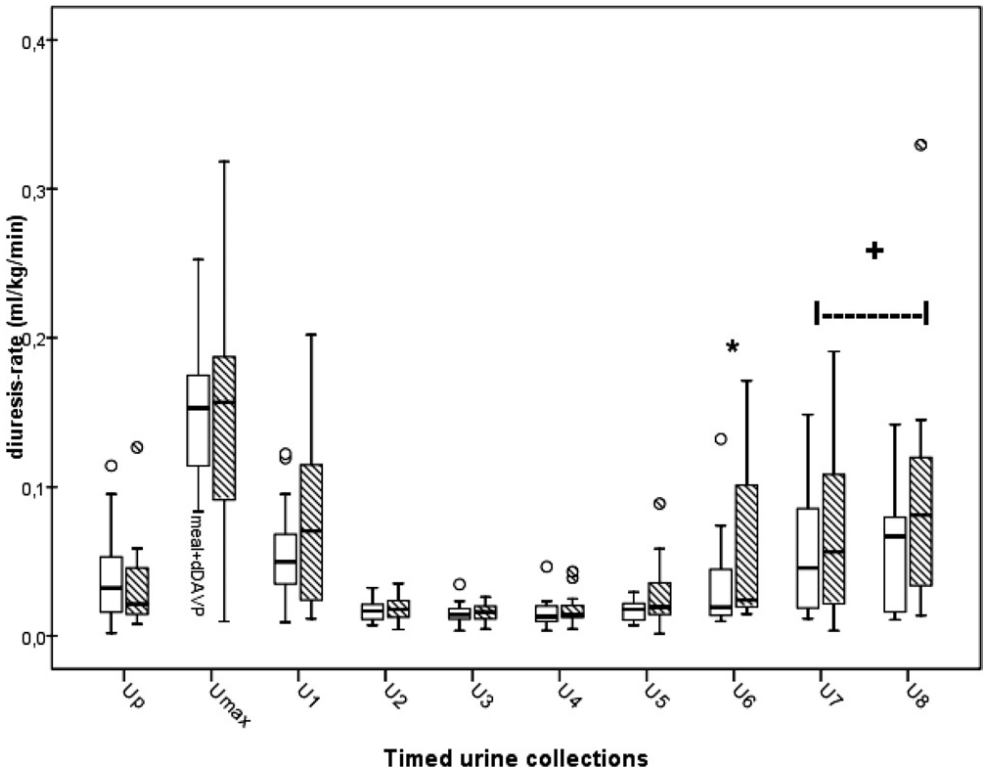

Figure 2. Antidiuretic effect in terms of diuresis rate (ml/kg per minute). White bars represent desmopressin melt. Striped bars represent desmopressin tablet. Asterisk indicates p <0.05. Plus sign indicates paired analysis of 17 patients at U 7 and 9 patients at U 8. *dDAVP*, desmopressin. *Umax*, urine collected with maximal dilution. *Up*, urine collected before dilution.

melt regarding prolonged duration of action (U 5 to U 7) for diuresis rate and/or concentrating capacity. This phenomenon cannot be explained by the difference in gastrointestinal reabsorption for these 2 oral formulations, but rather favors the theory of mucosal absorption of the melt in the oral cavity and esophagus.[22,23] To facilitate further analysis, it is necessary to divide the discussion according to the 3 major phases of activity—early response, plateau and duration of action (regaining diluting capacity). A superior pharmacodynamic effect results in 1) a shorter time to reach maximal effect, reducing total nocturnal diuresis volume and filling rate, both of which have a role in the pathogenesis of enuresis, and 2) a more predictable duration of action, including longer duration of action compared to tablet in cases where it is too short, without losing the ability to regain diluting capacity in the early morning (6 to 12 hours after administration), since this is a major consideration for the safety profile of the drug.

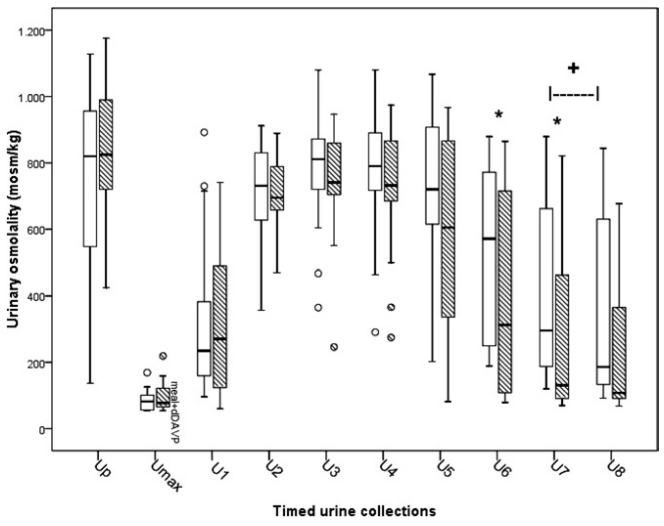

Figure 3. Urinary concentration expressed by urinary osmolality (mosm/kg). White bars represent desmopressin melt. Striped bars represent desmopressin tablet. Asterisk indicates p <0.05. Plus sign indicates paired analysis of 17 patients at U 7 and 9 patients at U 8. *dDAVP*, desmopressin. *Umax*, urine collected with maximal dilution. *Up*, urine collected before dilution.

Table 2. *Antidiuretic effect expressed by diuresis rate*

	Tablet	Melt	p Value
Mean ± SD max diuresis rate (ml/kg/min)	7.6 ± 3.7	7.2 ± 2.7	0.77
Mean ± SD diuresis rate (ml/kg/min) by hour:*			
U 1–2	2.4 ± 2.5	1.8 ± 1.8	0.13
U 3–5	1.3 ± 1.65	0.89 ± 0.88	0.02
U 5–8	3.2 ± 4	2.1 ± 2.1	0.005

* U 1 to 2 was defined as early response phase, U 3 to 5 as plateau phase and U 5 to 8 as duration of action.

In the early response phase no significant difference in osmolality or diuresis rate could be identified. This finding is consistent with previous short-term studies (3 hours) in adults, which also failed to demonstrate differences in intrinsic pharmacodynamic effect when desmopressin tablet was administered with concomitant meal, despite significant differences in pharmacokinetics.[18] This result can partly be explained by the fact that urinary osmolality and diuresis are correlated not only with the concentrating activity of desmopressin, but also with the renal osmotic load by the meal. Furthermore, up to 25% of patients were observed to have a diuresis rate of more than 0.1 ml/kg per minute with the tablet (box plot, fig. 2) but not with the melt. Although no statistical difference was reached, the potential clinical importance cannot be denied. Extrapolating, for example, diuresis rates of 0.12 ml/kg per minute (tablet) and 0.08 ml/kg per minute (melt) in a child of 30 kg means a difference of $0.04 \times 30 \times 60 = 72$ ml, in other words, respective nocturnal urine productions of 260 ml and 330 ml, which might mean the difference between dry and wet.

It is not surprising that significant differences were not seen for antidiuretic effect or urinary osmolality for individual collections in the plateau phase, since 120 μg melt and 200 μg tablet are considered bioequivalent based on water loading tests (without meal).[22] Conversely when all values of collections U 3 to U 5 are taken together, a significant difference is reached in favor of the melt, with probably little clinical antienuretic benefit, since differences in absolute values are small.

The major point of interest is predictable duration of action. Our data clearly show that the pharmacodynamic effects are significantly more sustained with the melt in the region of interest, 4 to 8 hours. The lower diuresis rate is not only significantly different, but also probably clinically important, since the up to 50% increased diuresis rate with the tablet is likely to result in a diuresis volume greater than maximal functional bladder volume.

This superior duration of action, together with indices of a faster response in some patients and a higher maximal concentrating capacity/diuresis rate in the plateau phase, suggests that the bioavailability of the desmopressin melt is higher than that of the tablet. Nevertheless, it remains indirect evidence in the absence of pharmacokinetic data. Several studies support that this longer duration of action can only be explained by a superior pharmacokinetic profile. A higher desmopressin bioavailability does not change pharmacodynamic effects for the first 6 hours after dosing, but results in a longer duration of antidiuretic action.[18,24] This finding is congruent with a study revealing that increasing the oral dose from 200 to 400 μg in patients with diabetes insipidus did not increase the antidiuretic effect, but prolonged the duration of action.[21] Conversely prolonged duration of action should not result in an increased risk of water intoxication, as has been the case with desmopressin spray. Therefore, a pharmacodynamic test should demonstrate a regain of diluting capacity. It is reassuring that almost all patients started diluting after 6 hours.

The strength of the study design is that this is the first paired observation of pharmacodynamic effects of tablet vs melt in children with MNE and that the design with nutritional intake reflects more clinical reality in young children. Still, some issues require discussion. This is not a double-blind study, although the data and conclusions cannot be denied. No overall statistical difference was reached when comparing individual sample data, but only by combining them into plateau phase and duration of action. The low dosing allowed us to perform the study in an ambulatory state, since all children were expected to dilute within 12 hours, but decreased sensitivity to study differences in early and maximal response. Hence, it is not surprising that major differences were found in the duration of action.[22] Furthermore, the standardized meal was not standardized to body size parameters, nor was the nutritional or fluid intake before the test, which is reflected by the wide range in individual values at the start. The observation that a comparable minimal osmolality, reflecting diluting capacity, and maximal diuresis rate were obtained without statistical difference in osmotic excretion or diuresis volume shows the validity of the study design. All other criticisms may be valid but are largely addressed by the paired study design.

CONCLUSIONS

This study proves the superior pharmacodynamic characteristics of 120 μg desmopressin lyophilizate compared to 200 μg tablet, reaching significance for duration of action but also with indices of a shorter time to reach maximal antidiuresis and a higher concentrating capacity. These results can only be explained by superior pharmacokinetic characteristics.

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EDITORIAL COMMENT

The ICCS recommends alarm therapy (behavioral health therapy) and desmopressin as valid first-line treatments for enuresis (reference 3 in article).[1] A Cochrane review of the spray and tablet formulations concluded that children treated with desmopressin had an average of 1.3 fewer wet nights per week.[2]

Food interaction influences the bioavailability of desmopressin. For early elementary school-age children in North America the evening meal is often only 2 or 3 hours before bedtime, and many of these children also enjoy a bedtime snack. The pharmacodynamic data presented by the authors suggest that the melt formulation of desmopressin might result in 72 ml less urine produced during the interval studied. If a child experienced a comparable overnight reduction, 2.5 ounces might mean the difference between waking up wet and dry. Water is not necessary to swallow the melt, and in a child who aspires to dryness every ounce counts. When desmopressin does not work, a common reason is a low nocturnal functional bladder capacity, and behavioral health strategies to improve bladder and bowel health should be considered to achieve dryness (reference 3 in article).[1]

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