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Oral desmopressin lyophilisate (MELT) for monosymptomatic enuresis: Structured versus abrupt withdrawal

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Abstract *Objective:* To investigate whether a structured withdrawal program from a sublingual formulation of fast-melting oral desmopressin lyophilisate (MELT) is superior to a sudden withdrawal from this formulation in the treatment of monosymptomatic nocturnal enuresis.
Materials and methods: One hundred and three children presented to our pediatric nephrology outpatient clinic for bedwetting. Eighty-one children, aged between 5½ and 14 years (mean age 8.64 years), were treated with MELT at a dosage of 120 mcg a day. Responders were randomized to been withdrawn from therapy, after 3 months, abruptly or in a structured withdrawal program (60 mcg/day for 15 days and then 60 mcg every second evening for another 15 days).

Main outcome parameter was relapse rate 1 month after the end of treatment. Relapse was defined as bedwetting occurring more than 2 nights per month after the 1-month treatment-free period.
Results: Relapse rate at 1 month after the end of treatment was 47.83% in the group on a structured program versus 45.83% in the abrupt termination group ($p = 0.89$).
Conclusion: Our study suggests that a structured withdrawal program from MELT therapy doesn't offer advantages compared to an abrupt termination in children with monosymptomatic nocturnal enuresis.

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Introduction

Nocturnal enuresis, in accordance with the International Children's Continence Society recommendations, is characterized by repeated involuntary voiding of urine into bed or clothes [1]. If bedwetting occurs without any other lower urinary tract symptom, enuresis is called monosymptomatic (MNE). Above 10% of 6-year-old children, around 5% of 10-year-old children, and 0.5–1% of teenagers and young adults suffer from MNE [2–7]. Overall MNE prevalence is 3.8%, and it decreases proportionately with age [8]. Even though spontaneous remission is frequent, MNE may have such deep psychological and social impact on the affected children and their families that proper management of this condition is mandatory [5,9]. Pharmacological, psychological/behavioral and alternative interventions are commonly used. The first-line therapy for a subgroup of patients with MNE associated with nocturnal polyuria and normal bladder function is desmopressin (dDAVP) [10,11].

dDAVP is an effective treatment for MNE in children, since it rapidly reduces the number of wet nights per week compared with placebo and with homotoxicological remedies [3,12]. It has been employed clinically for >30 years in a range of formulations: intranasal solution (since 1972), injectable solution (since 1981), tablets (since 1987), and most recently a fast-melting oral desmopressin lyophilisate (MELT) (since 2005) [13]. While there is consensus that therapy with dDAVP tablets should be discontinued in a structured withdrawal program [14], no data about withdrawal are yet available for MELT.

The aim of this study was to compare relapse rates after a 1-month treatment-free period between two different withdrawal programs for children given MELT for the treatment of MNE.

Materials and methods

Between January 2009 and December 2011 a total of 103 children presented with bedwetting to the pediatric nephrology outpatient clinic of "A. Gemelli" University Hospital in Rome.

The inclusion criterion was MNE defined as bedwetting at least twice a week in the last 3 months by children >5 years old. Exclusion criteria were the presence of daytime urgency, frequency (>7 micturitions during daytime), voiding postponement, infrequency (<3 voiding during daytime), painful voiding, weak stream, day wetting (more than once per week), therapy with dDAVP tablets in the last 6 months, secondary enuresis, and any form of bedwetting related to other diseases.

Children were treated for a period of 3 months with MELT at a dose of 120 mcg a day. After 3 months of therapy, patients who were partial or full responders to MELT were enrolled in the study. According to the ICCS classification for initial success, the children were classified as non-responders if there was no or less than 50% decrease in wet nights compared to baseline; partial responders if there was 50% or more, but less than 90% decrease in wet nights compared to baseline; responders if there was a 90% or more decrease in wet nights compared to baseline; full responders if there was a 100% decrease or less than 1 symptom occurrence monthly [1].

Patients were randomized to undergo either an abrupt withdrawal or a structured withdrawal program: 60 mcg/day for 15 days and then 60 mcg every second evening for another 15 days (Fig. 1). Relapse was defined as bedwetting occurring more than 2 nights per month after the 1-month treatment-free period.

Statistical analysis

Data are presented as frequency and percentage. Paired-samples t test and independent-samples t test were used for continuous variables; the χ^2 test was used for categorical variables. The significance level was set at $p < 0.05$.

Results

We enrolled 103 patients with bedwetting. Of these, 22 (21.36%) were excluded for the following reasons: 14 because of presence of daytime symptoms, 3 were lost to follow up, 3 had undergone therapy with dDAVP in the last 6 months, 1 patient was diagnosed with diabetes insipidus, 1 patient had secondary enuresis.

So we included in our study 81 children, aged between 5½ and 14 years (mean age 8.64 years). These patients were treated with MELT: 34/81 (41.98%) had no response in terms of a decreased number of wet nights, reflecting values in the literature, so only 47/81 (58.02%), who responded to therapy, were included in the paired statistical analysis and underwent random allocation. The demographic characteristics and outcome data of these patients are shown in Table 1.

Of the 47 patients, 24 (51.06%) were randomly assigned to withdraw suddenly and 23 (48.94%) to withdraw gradually. There were no differences in gender, age or number of wet nights/week between groups. The baseline severity of MNE was similar in the two groups.

One month after the end of treatment, relapse occurred in 11/23 (47.83%) of the structured withdrawal program group and in 11/24 (45.83%) of the abrupt termination group ($p = 0.89$).

Discussion

In this study we analyzed, in two groups with the same demographic characteristics and response rate to therapy with MELT, whether a structured withdrawal program was effective in lowering relapse rate after 1 month compared to an abrupt discontinuation of therapy. We observed a higher relapse rate in the structured withdrawal group, but the difference was not significant.

In a national, multicenter, retrospective survey, Marshall et al. suggested using a structured withdrawal program from dDAVP in order to reduce the incidence of relapse [14]. Similarly, Alloussi et al. asserted that, when compared to sudden withdrawal, structured withdrawal programs show better long-term success and lower relapse rates, with no difference between time- and dose-dependent programs [15]. Both these studies compared children

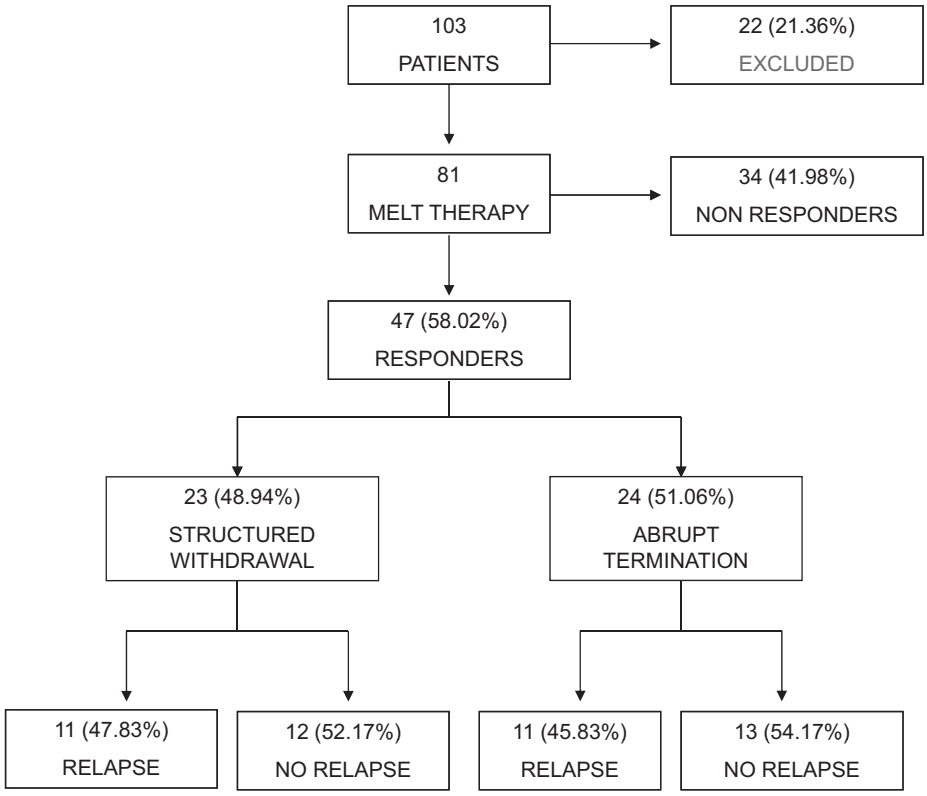

Figure 1 Patients enrolled and followed up.

treated with an oral dose of dDAVP in tablet form comprising between 0.2 and 0.4 mg/day. Recently, the new formulation (MELT) has been shown to have similar levels of efficacy and safety at lower dosing levels, since its bioavailability is approximately 60% greater than that observed for the tablet formulation [16]. De Guchtenaere et al. demonstrated that the increase in bioavailability is also related to a lower interaction with food, permitting children to take the drug nearer to the last meal and increasing compliance [17]. To date, no studies had been conducted to investigate whether a structured withdrawal program is superior to sudden withdrawal also with this formulation.

Table 1 Characteristics of the patients.

Variable	No withdrawal (%)	
	Structured	Abrupt
Overall	23	24
Male	15 (65.2)	17 (70.8)
Female	8 (34.8)	7 (29.2)
Age (yrs)		
5—7	8	9
8—10	9	10
11—14	6	5
No wet nights/wk		
7	14	16
3—6	7	7
2	2	1

A structured withdrawal program may impose a prolongation of therapy, usually for 1 month after the end of treatment, in children who already had a full response to dDAVP, and this may affect compliance to the treatment, which is a very important factor in the response to dDAVP [18]. The importance of compliance is fundamental, since adhering to behavioral guidelines may also further reduce side effects of dDAVP, in particular the occurrence of hyponatremia [18]. For this reason it is also important to promote health communication programs, such as for example toll-free numbers, to provide information and give advice on MNE and its related problems [19].

General advice we give to parents, according to the latest NICE guidelines [20], is to remember that bedwetting is not the child's fault, and to pay attention to fluid intake and restrict fluid for only a few hours before MELT treatment. We also encourage children to use the toilet regularly (4—7 times per day) and we use a rainy cloud/sun night diary as an incentive. We encourage parents to stop using nappies/pull-ups for a few nights if the child has been dry by day for some time.

Agreement to adhere to these simple guidelines for at least 1 month is a fundamental requisite for initiating pharmacological therapy for primary MNE, since lack of compliance can result in both a reduction in the success rate and a higher rate of side effects of dDAVP therapy [13,18].

Conclusions

Our study suggests that a structured withdrawal program from MELT therapy doesn't offer advantages compared to

an abrupt termination in children with MNE. This study, however, has a limitation due to the small sample size. Further studies are needed to determine whether the difference may become statistically significant with a larger sample size.

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This study was not funded.

Competing interests

None.

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