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ORIGINAL PAPER

Desmopressin 120 mcg, 180 mcg, 240 mcg: The right treatment for the right patient

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Summary ***Background: The first-line drug therapy for patients with nocturnal enuresis (NE) associated with nocturnal polyuria and normal bladder function is desmopressin (dDAVP).***
Objective: To evaluate if increasing dose of oral desmopressin lyophilisate (MELT) can improve response rates to dDAVP and is useful in enuretic children.
Materials and methods: We enrolled a total of 260 children all diagnosed with NE. Enuretic children were treated with increasing MELT at a dose of 120, 180 and 240 mcg a day.
Results. We included in our study a total of 237 children, 164 males (69.2%) and 73 females (30.8%) aged between 5 and 18 years (mean age 10.32 ± 2.52 years). Of the 237 patients enrolled in the study and treated with MELT 120 mcg, a full response was achieved in 135 (56.9%). A partial response was achieved in 21 (8.9%) patients, therefore the dose was increased up to 180 mcg, with further improving symptoms (14.3%) or full response (9.5%), and up to 240 mcg, without usefulness.
Conclusions: MELT at the dose of 120 mcg resulted efficacy and safety; the increased dose up to 180 mcg resulted poorly efficacy; finally, the further increase up to 240 mcg did not improve the symptoms with the increased risk of side effects.

KEY WORDS: Desmopressin; Nocturnal enuresis.

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INTRODUCTION

Nocturnal enuresis (NE) is a very common pediatric disorder. According to recent *International Children's Continence Society* (ICCS), NE is defined as intermittent incontinence occurs exclusively during sleeping periods. NE should not be used to refer to daytime incontinence (1).
In children without any other lower urinary tract symptoms and without a history of bladder dysfunction is defined as *mono-symptomatic NE* (MNE).
NE is a multifactorial disorder. It has 3 main pathophysiological determinants that are nocturnal polyuria, detrusor overactivity and failure to awaken in response to bladder sensations. When organic disease is not suspected and children suffer from MNE that causes a significant problem, it should be treated (2).
The first-line drug therapy for patients with MNE associated with nocturnal polyuria and normal bladder function is desmopressin (dDAVP) for a period of 3 months following by withdrawal. dDAVP is associated with a response rate of about 40-60%, however its effect may not be maintained on discontinuing treatment, and symptoms have been found to recur in about 50-80% after stopping treatment (3).
The different formulations of dDAVP are an intranasal solution, an oral tablet formulation and the recent oral sublingual lyophilisate (*MELT*). The aim of this study is to evaluate if increasing dose of *MELT* (120, 180, 240 mcg/day) can improve response rates to dDAVP in enuretic children.

MATERIALS AND METHODS

We enrolled a total of 260 children all diagnosed with NE, between April 2014 and April 2017, at the *Paediatric Service of Campus Bio-Medico Hospital in Rome*.
Inclusion criteria were: age > 5 years and a diagnosis of *primary MNE* (PMNE) without NE treatment in the last 3 months. Exclusion criteria were the presence of secondary NE, any provided story of urinary infection, nephrogenic diabetes or congenital genitourinary anomalies. The children and their families were asked to participate in the study. This study was conducted in accordance with the regulatory standards of *Good Clinical Practice* and the *Declaration of Helsinki*.
We carefully evaluated each patients with medical history and physical examination, including monitoring blood pressure, possible sign of spinal dysraphism or polythelia, neurological reflexes and genital examination.
During the period of treatment, all patients and their parents were asked to keep a NE calendar depicting the wet and the dry nights and in addition, we educated both child and parents with dietary advices (4).
During the follow-up, families were called to verify their adherence and responses to the therapy and dietary recommendations.
Enuretic children were initially treated for a period of 3 weeks with *MELT* (*Minirin®*) at a dose of 120 mcg a day and after this observation period, the responders or full responders continued treatment up to three months, the

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partial responders increased *MELT* at a dose of 180 mcg and non responders were excluded. Patients who had increased the dose to 180 were observed for 3 weeks and even in this observation period, the responders or full responders continued treatment up to three months, the partial responders increased *MELT* at a dose of 240 mcg and non responders were excluded. Finally patients treated with *MELT* 240 mcg were observed for 3 weeks and even in this observation period, the responders or full responders continued treatment up to three months and non responders were excluded.
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.

Results

We enrolled 260 children with PNE. Of these, 23 were excluded for the following reasons: 15 had undergone therapy with *MELT*, 5 were lost to the follow up, 3 because of a further period of observation. We included in our study a total of 237 children, 164 males (69.2%) and 73 females (30.8%) aged between 5 and 18 years (mean age 10.32 ± 2.52 years).
Of the 237 patients enrolled in the study and treated with *MELT* 120 mcg, a full response was achieved in 135 (56.9%), a partial response was achieved in 21 (8.9%) and 81 (34.2%) had no response in terms of a decreased number of wet nights, reflecting values in the literature.
When the 21 partial responders increased *MELT* at a dose of 180 mcg, 16/21 (76.2%) had no further improvement and a mild improved response was achieved in 3/21 (14.3%); in these patients in which *MELT* dosage was increased to 240 mcg/day, a response or full response was achieved only in 2/21 (9.5%).
They were evaluated again after 3 weeks of pharmacological therapy combined with dietary advices. Of the 3 patients that increased the dosage to 240 mcg/day, no one had response in terms of a decreased number of wet nights.

Discussion

In our study we would like to highlight the importance of appropriate dDAVP administration and to clarify best practice in the use of this medication.
Reported response rates vary, only 41% of patients achieved ≥ 50% reduction in wet nights in the study by *Lottman et al.* (5), but 77% achieved > 90% reduction in the study by *Onol et al.* (6). It depends on the type of patients selected, suboptimal adherence rates, administration methods and doses and formulations used (7). Several studies have demonstrated decreased secretion of ADH and a reduced response to antidiuretic hormone in children affected. Moreover, NE may be present with several comorbidities such as sleep disorders, psychological problems, parasomnias, left-handedness, polythelia, language disorders and testicular pathology (8-10).
Various formulations of dDAVP are available (tablets, nasal spray) and many studies also showed that the dosage for *MELT* is more predictable due to the significantly smaller variance, however there is only limited information on the response to dDAVP in children relative to the dose required to produce an antidiuretic effect for the entire night. In a previous dose-ranging study, dDAVP tablets of up to 600 mcg at bedtime did not appear to reach a maximum effect (11, 12).
In our study only a small percentage of patients who had increased the dose of *MELT* to 180 mcg have further improved symptoms (14.3%) or was full responders (9.5%). No patient treated with 240 mcg had usefulness. It can suggests the importance of selecting the right treatment for the right patients.
Patients must be properly evaluated and diagnosed, and therapy must be used appropriately for the treatment to be successful. Data show that proper patient screening can predict treatment response, as well as failure rates.
A recent study, in fact, suggests that also the use of bladder diaries is highly recommended wherever possible (13).
Therefore, it is essential that the treating physician recognize that dDAVP will not work for all patients, and increasing dosage is not helpful if we do not use some tools to predict response. It is important that the most appropriate treatment strategy is selected as quickly as possible in order to minimize distress and difficulty for the patient and family.
MELT at the dose of 120 mcg resulted efficacy and safety; the increased dose up to 180 mcg resulted poorly efficacy; finally, the further increase up to 240 mcg did not improve the symptoms with the increased risk of side effects.

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