









# The adverse effects of oral desmopressin lyophilisate (MELT): personal experience on enuretic children

## Oral desmopressin liyofilizatın (MELT) advers etkileri: enüretik çocuklarda kişisel deneyim

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**Cite this article as:** Ferrara P, Franceschini G, Mercurio S, Del Vescovo E, Ianniello F, Petitti T. The adverse effects of oral desmopressin lyophilisate (MELT): personal experience on enuretic children. Turk J Urol 2018; 44(1): 51-5.

### ABSTRACT

**Objective:** The aim of this study was to evaluate adverse effects of oral desmopressin lyophilisate (MELT) in enuretic children.

**Material and methods:** We enrolled 260 children with nocturnal enuresis (NE) referred to the Pediatric Service, 'Campus Bio-Medico' University of Rome, from April 2014 to April 2017 in the study, of these 23 were excluded. The study was characterized by 2 phases. During Phase 1 a careful patient's medical history was obtained and physical examination was performed. After 3 months of treatment with MELT (Minirin/DDAVP®) at the dose of 120 mcg a day, a micturition diary was kept, adherence to therapy and any possible adverse effects were checked during the Phase 2. The study was carried out in compliance with the Helsinki Declaration.

**Results:** Among 237 patients included in the study 11 male and 6 female (n=17; 7.2%) patients with a mean age 10.06±2.49 years, reported 22 adverse effects, with an absolute risk of 7.17%. In particular, 5 neurological symptoms, 3 gastrointestinal effects, 4 sleep disturbances, 8 psycho-behavioral disorders, 2 symptoms of fatigue were reported.

**Conclusion:** In our study MELT with its higher bioavailability guaranteed lower frequency of adverse effects which resolved spontaneously and rapidly. The MELT formulation actually represents the first line and safe treatment for the NE.

**Keywords:** Adverse effects; desmopressin; enuresis.

### ÖZ

**Amaç:** Bu çalışmanın amacı enüretik çocuklarda MELT'in advers etkilerini değerlendirmektir.

**Gereç ve yöntemler:** Nisan 2014 ile Nisan 2017 arasında Roma Üniversitesi Çocuk Sağlığı ve Hastalıkları Servisi Biyomedikal Bölümüne sevk edilen 260 noktürnal enürezli çocuğu çalışmaya aldık, bu hastalardan 23'ü çalışma dışı bırakılmıştır. Çalışma iki evreden ibaretti. Birinci evre dikkatli bir hasta öyküsü ve fizik muayeneden ve ikinci evrede 3 ay günde 120 mcg MELT (Minirin/DDAVP®) tedavisi sonrası işeme günlüğü, tedaviye uyum ve herhangi olası olumsuz etkiler kontrol edilmiştir. Çalışma Helsinki Bildirgesine uyum içinde yürütülmüştür.

**Bulgular:** Toplam 237 hasta çalışmaya dahil edilmiş, 11 erkek ve 6 kız, yaş ortalaması 10,06±2,49 yıl olan toplam 17 (%7,2) hasta, %7,17'lik mutlak risk ile 22 advers olay bildirmiştir. Özellikle 5 nörolojik semptom, 3 gastrointestinal etki, 4 uyku bozukluğu, 8 psikososyal bozukluk ve 2 yorgunluk yakınması bildirilmiştir.

**Sonuç:** Çalışmamızda daha yüksek biyoyararlanımla MELT kendiliğinden ve hızla geçen daha düşük advers etki bildirimini garanti etmektedir. MELT formülasyonu gerçekte NE'nin ilk basamak ve güvenli tedavisini temsil etmektedir.

**Anahtar Kelimeler:** Advers etkiler; desmopressin; enurezis.

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**Submitted:**  
29.08.2017

**Accepted:**  
16.11.2017

**Available Online Date:**  
08.01.2018

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Available online at  
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## Introduction

Nocturnal enuresis (NE) is a very common clinical disorder with a profound impact on affected children and their families. NE is defined as an intermittent (i.e., not continuous) bedwetting with any frequency during sleep in children more than or equal to five years old, according to the International Children's Continence Society (ICCS).<sup>[1]</sup> The DSM-5 has widened the scope of the criteria for enuresis. NE is the persistent inability to control urination that is not consistent with one's age of development.<sup>[2]</sup> The DSM-5 criteria for NE is as follows: repeated voiding of urine into bed or clothes whether involuntary or intentional. This bedwetting behaviour must be clinically significant as manifested by either a frequency of twice a week for at least 3 consecutive months or the presence of clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning. The patient's chronological age should be at least 5 years of age (or equivalent developmental level) and the behavior should not be attributable to the physiological effects of a substance (e.g., a diuretic, antipsychotic or selective serotonin reuptake inhibitor) or another medical condition (e.g., diabetes, spina bifida, a seizure disorder).<sup>[2,3]</sup>

The choice of treatment depends on the frequency and severity of symptoms, the child's age and motivation. Treatment options for NE are use of desmopressin, alarm devices, and imipramine. In particular, the main therapeutic effect of desmopressin is its antidiuretic activity. Since it rapidly reduces the number of wet nights per week compared with placebo and with homotoxicological remedies.<sup>[4]</sup>

The different formulations of desmopressin are an injectable solution, an oral tablet formulation and the recent oral sublingual lyophilisate (MELT) preparation. MELT with its higher bioavailability guarantees the same therapeutic response of other formulations with lower doses and represents the first-line and safe treatment for the NE.<sup>[5-7]</sup> The aim of this study was to evaluate adverse effects of MELT in enuretic children.

## Material and methods

According to the ICCS classification, we enrolled 260 children with NE referred to the Pediatric Service, 'Campus Bio-Medico' University of Rome, from April 2014 to April 2017 in the study, of these 23 were excluded. Patients aged >5 years with a diagnosis of primary NE without NE treatment within the last 3 months. The exclusion criteria included the presence of secondary NE, any known history of urinary infection, nephrogenic diabetes or congenital genitourinary anomalies. The children and their families were asked to participate in the study at the end of the clinical evaluation and, after a 3 months of observation period. The study was carried out in compliance with the Helsinki Declaration.

The study was characterized by 2 phases. Phase 1 consisted of taking a careful patient's medical history and performing physical examination (primarily urogenital examination) including monitoring blood pressure, cutaneous manifestation of occult spinal dysraphism (skin discoloration, dimples, hairy tufts, subcutaneous lipoma), lower extremity strength and sensation, deep tendon reflexes, state of bladder fullness and presence of fecal lumps. During the period of treatment, all patients and their parents were asked to keep a NE calendar depicting the wet and the dry nights. During the follow-up, families were called to verify their adherence and responses to the therapy.

Monosymptomatic patients were treated with MELT (Minirin/DDAVP<sup>®</sup>) at a dose of 120 mcg a day for 3 months combined with dietary recommendations.<sup>[8]</sup> If anamnestic history underlined non-monosymptomatic NE, oxybutynin (Ditropan<sup>®</sup>) was recommended in addition.

After 3 months, micturition diary, adherence to therapy and any possible adverse effects were checked. The association between the dependent (adverse effects) and independent variables (patient sex, combined desmopressin and oxybutynin) was determined using odds ratio. Data were expressed as mean±standard deviation and percentage. A paired-samples t-test and an independent-samples t-test were used for continuous variables; the chi-square test was used for categorical variables. The significance level was set at  $p < 0.05$ . Statistical analysis was carried out with the Stata Statistical Software program, Release 13 (StataCorp. 2013, College Station, TX, USA). The association between the side effects and the combined therapy of MELT + oxybutynin was determined by means of the odds ratio which was equal to 4.61 (IC 1.62-13) with a level of significance  $p < 0.05$ .

## Results

Of the 260 initially enrolled patients, 23 (8.8%) were excluded for the following reasons because 15 patients had undergone therapy with desmopressin within the previous 3 months, 5 were lost to follow up, and 3 cases needed a further period of observation. Thus, 237 children were included in our study. Of these, 164 (69.2%) were male and 73 (30.8%) were female, aged between 5 and 18 years (mean age  $10.32 \pm 2.52$  years).

Among 237 patients included in the study, 11 male and 6 female cases ( $n=17$ ; 7.2%) with a mean age  $10.06 \pm 2.49$  years, reported 22 adverse effects, with an absolute risk of 7.17%. In particular:

- neurological symptoms (headache and migraine) ( $n=5$ ; 2.1%)
- gastrointestinal side effects (abdominal pain, nausea and vomiting) ( $n=3$ ; 1.3%)
- sleep disturbances (difficulty falling asleep, nocturnal awakening) ( $n=4$ ; 1.7%)
- psycho-behavioral disorders (irritability, aggression, poor attention) ( $n=8$ ; 3.4%)
- fatigue ( $n=2$ ; 0.8%) (Table 1).

**Table 1. Adverse effects in enuretic children treated with MELT**

	n
Gastrointestinal symptoms (abdominal pain, nausea, vomiting)	3
Neurological symptoms (headache, migraine)	5
Sleep disturbances (difficulty in falling asleep, nocturnal awakening)	4
Psycho-behavioral disorders (irritability, aggression, poor attention)	8
Fatigue	2
Total	22

**Table 2. Adverse effects and treatment**

Therapy	Males	Females
	n	n
Desmopressin	5	3
Desmopressin + Oxybutynin	3	2
Desmopressin + Melatonin	2	0
Desmopressin + Oxybutynin + Melatonin	1	1

Of the 17 children who reported side effects, 8 (47%, 5 males and 3 females) patients were treated with MELT monotherapy with absolute risk of 3.68%. Five (29.4%, 3 males and 2 females) cases were treated with MELT combined with oxybutynin, while 2 (11.8%, 2 males and 0 females) cases were treated with MELT combined with melatonin 1 mg/day, and 2 (11.8%, 1 male and 1 female) received treatment with MELT, oxybutynin and melatonin (Table 2). The association between the adverse effects and therapy with MELT combined with melatonin was determined by the Odds ratio which was 0.47 with a level of significance  $p=0.2$ . The evidenced association between the side effects and the treatment with MELT combined with oxybutynin was determined by the odds ratio which was 4.61 (IC 1.62-13) with a level of significance  $p<0.05$ . The association between side effects and sex was determined by the odds ratio which was 1.30 with a level of significance  $p>0.05$ . The underlined association between side effects and age was studied with Student t-test. Mean difference between mean age of the patients with and without side effects was calculated at a significance level  $p>0.05$ .

With the onset of adverse effects, the patients stopped the treatment with a complete disappearance of the symptoms within 48 hours.

## Discussion

Nocturnal enuresis is a multifactorial disorder with a genetic predisposition and there are some factors that worsen NE, including family history, sleep disorders, overactivity of the detrusor muscle, male gender, attention deficit/hyperactiv-

ity disorder (ADHD), low socio-economic status, poor school performance, and constipation.<sup>[9-11]</sup> Current therapies for NE include desamino-D-arginine vasopressin (DDAVP, desmopressin) treatment, use of an alarm device, oxybutynin, tricyclic antidepressants (imipramine) and behavioural techniques, or a combination of treatments. In this study we analyzed the adverse effects of MELT therapy in enuretic patients. Data have shown an absolute risk of 7.17% for the development of side effects with desmopressin treatment possibly associated with other therapies (oxybutynin/melatonin).

However, this absolute risk is reduced to 3.38% if patients were treated with MELT monotherapy. According to a recent review, which collected data from various clinical trials, the overall average incidence of side effects among 1083 enuresis-treated children with desmopressin was 5%.<sup>[12]</sup> The difference between the incidence rates of our sample and the reference study in the literature can be explained by several factors. First of all, two studies differ according to the number and age of the study participants (1083 children and adults in the first case vs. 237 children in our study).

In addition, while the incidence data of our study refer to MELT monotherapy or in some cases to combination treatment with MELT, oxybutynin and/or melatonin. However, Van Kerrebroeck used desmopressin monotherapy in tablet or nasal spray formulation in patients with a diagnosis of monosymptomatic NE. Any statistically significant correlation between desmopressin treatment and variables such as sex ( $p=0.61$ ), age of patients ( $p=0.32$ ) and concomitant melatonin intake ( $p=0.2$ ) was not detected in our study, although melatonin treatment may appear to be a possible protective factor from the development of side effects (OR=0.47).

Desmopressin is a synthetic analogue of vasopressin or ADH that reacts on kidney V2 receptors on the renal collecting tubuli, supporting water reabsorption and reducing the volume of urine produced. The most commonly encountered adverse reactions in our study were psycho-behavioral disorders, gastrointestinal disorders, headache, sleep disturbances and less commonly fatigue. These effects are outnumbered and more debilitating than those mild adverse effects commonly reported in the literature.<sup>[13]</sup> They are probably associated with excessive fluid intake or an inappropriately high dose of medication even though any experimental evidence does not exist on this issue. Currently, desmopressin is available in several formulations. Data gathered in the literature and post-marketing studies which evaluated the safety profile of the oral and sublingual lyophilisate formulations by emphasizing a lower incidence of side effects (primarily hyponatremia) of these two formulations compared to nasal spray. This is probably explained by the longer duration of the treatment (up to 24 hours) and/or by interindividual pharmacokinetic differences between different formulations. Considering

the administration of MELT in our study, the incidence of adverse events was reduced to about 3%, which is even less than 5% incidence rate reported in the major studies concerning the safety profile of different formulations of the drug.

Finally, a useful statistical issue to be determined is the association between adverse effects and combined treatment of desmopressin and oxybutynin ( $p<0.001$ ) the latter being a possible causal factor ( $OR=4.61$ ). Oxybutynin, an anticholinergic drug, which acts on M1, M2 and M3 receptors at smooth muscle of bladder may be responsible for numerous side effects including nausea, vomiting, xerostomia, constipation, headache and insomnia. In addition oxybutynin, probably causing xerostomia, promotes increased absorption of fluids, which, is one of the main underlying mechanisms responsible for the appearance of desmopressin side effects.

The incidence rate of side effects of each formulation of desmopressin is not easy to estimate, and it is often complicated by the concomitant administration of other treatments. Our data hypothesize a low incidence of side effects related to MELT compared to an oral administration. In addition, the incidence of these effects increases if oxybutynin is combined to the MELT treatment.

However, it is not possible to attribute for certain the occurrence of adverse effects, directly to the desmopressin treatment, or to the combined treatment of desmopressin and oxybutynin. The literature studies have demonstrated that DDAVP is a safe and effective medication for NE. In our study MELT with its higher bioavailability guaranteed a lower rates of adverse effects which resolved spontaneously and rapidly. The MELT formulation actually represents the first- line and safe treatment for the NE. Larger scale studies are needed to confirm the authors' observation.

**Ethics Committee Approval:** The study was carried out in compliance with the Helsinki Declaration and was approved by the Service of Pediatrics of Campus Bio-Medico University, Rome.

**Informed Consent:** Informed consent was obtained from parents of the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - P.F.; Design - P.F.; Supervision - P.F., F.I.; Resources - S.M., G.F., E.D.V.; Materials - F.I., S.M.; Data Collection and/or Processing - S.M., G.F.; Analysis and/or Interpretation - T.P.; Literature Search - E.D.V.; Writing Manuscript - P.F., G.F., S.M.; Critical Review - P.F., F.I., T.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Etik Komite Onayı:** Çalışma Helsinki Bildirgesine uyum içinde yürütülmüş ve Roma Üniversitesi Çocuk Sağlığı ve Hastalıkları Servisi Biyokimya Bölümü tarafından onaylanmıştır.

**Hasta Onamı:** Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Yazar Katkıları:** Fikir - P.F.; Tasarım - P.F.; Denetleme - P.F., F.I.; Kaynaklar - S.M., G.F., E.D.V.; Malzemeler - F.I., S.M.; Veri Toplanması ve/veya İşlenmesi - S.M., G.F.; Analiz ve/veya Yorum - T.P.; Literatür Taraması - E.D.V.; Yazıyı Yazan - P.F., G.F., S.M.; Eleştirel İnceleme - P.F., F.I., T.P.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Finansal Destek:** Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

## References

1. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. *Neurourol Urodyn* 2016;35:471-81. [CrossRef]
2. A.P.A. - American Psychiatric Association, "DSM-5 - Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition", American Psychiatric Publishing, Washington DC, 2013.
3. Nevés T. Pathogenesis of enuresis: Towards a new understanding. *Int J Urol* 2017;24:174-82. [CrossRef]
4. Ferrara P, Marrone G, Emmanuele V, Nicoletti A, Mastrangelo A, Tiberi E, et al. Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial. *Pediatr Nephrol* 2008;23:269-74. [CrossRef]
5. Ferrara P, Romano V, Cortina I, Ianniello F, Fabrizio GC, Chiaretti A. Oral desmopressin lyophilisate (MELT) for monosymptomatic enuresis: Structured versus abrupt withdrawal. *J Ped Urol* 2014;10:52-5. [CrossRef]
6. Gökçe MI, Hajjiyev P, Süer E, Kibar Y, Sılay MS, Gürocak S, et al. Does structured withdrawal of desmopressin improve relapse rates in monosymptomatic enuresis? A prospective randomized placebo controlled multicenter study. *J Urol* 2014;192:530-4. [CrossRef]
7. Juul KV, Van Herzele C, De Bruyne P, Goble S, Walle JV, Nørgaard JP. Desmopressin melt improves response and compliance compared with tablet in treatment of primary monosymptomatic nocturnal enuresis. *Eur J Pediatr* 2013;172:1235-42. [CrossRef]
8. Ferrara P, Del Volgo V, Romano V, Scarpelli V, De Gara L, Miggiano GA. Combined dietary recommendations, desmopressin, and behavioral interventions may be effective first-line treatment in resolution of enuresis. *Urol J* 2015;12:2228-32.
9. Oguz U, Aykac A, Demirelli E, Sancak EB, Resorlu B, Sarikaya S, et al. The time of spontaneous resolution of monosymptomatic nocturnal enuresis (mne) is familial. *Urol Int* 2015;94:459-63. [CrossRef]

10. Ferrara P, Ianniello F, Romani L, Fabrizio GC, Gatto A, Chiaretti A. Five years of experience in nocturnal enuresis and urinary incontinence in children: where we are and where we are going. *Urol Int* 2014;92:223-9. [\[CrossRef\]](#)
11. Ferrara P, De Angelis MC, Caporale O, Malamisura M, Del Volgo V, Vena F, et al. Possible impact of comorbid conditions on the persistence of nocturnal enuresis: results of a long-term follow-up study. *Urol J* 2014;11:1777-82.
12. van Kerrebroeck PEV. Experience with the long-term use of desmopressin for nocturnal enuresis in children and adolescents. *BJU Intern* 2002;89:420-5. [\[CrossRef\]](#)
13. Guzelsoy M, Demirci H, Coban S, Belkiz Gungör B, Ustunyurt E, Isildak S. Impact of urinary incontinence on quality of life among residents living in Turkey. *Urol J* 2014;11:1447-51.