

Safety of the Recent Oral Lyophilisate Formulation (MELT) in Pediatric Patients- A Review

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ABSTRACT

To review the safety of the recent oral lyophilisate formulation of desmopressin (MELT) in the pharmacological therapy for nocturnal enuresis (NE) and diabetes insipidus in pediatric patients. We searched for published reviews and references from PubMed-MEDLINE, Embase, and CENTRAL and did also a new search spanning the period Jan 1, 2000, until July 31, 2017 by using the terms MELT enuresis, MELT desmopressin, sublingual desmopressin, lyophilisate desmopressin. We evaluated all studies about side effects and effectiveness of MELT in pediatric patients. Twelve articles were analyzed with 1275 pediatric patients (<18 years old). The indication was enuresis in 1269 patients and central diabetes insipidus in 6 patients. In 11 studies desmopressin was administered alone while in 1 study in association with Tolterodina. In 3 studies were reported side effects in only 60 patients. The reported side effects in pediatric population were nausea, lethargy, lower limb weakness, headache, diarrhea, viral gastroenteritis, hyponatremia. Our review confirm that the MELT formulation of desmopressin guarantee the same response of other formulations with a lower doses and a lowest number of side effects. We believe according with the literature that this formulation is actually an effective and safe treatment for NE.

Keywords: MELT, enuresis, safety.

INTRODUCTION


Nocturnal enuresis (NE) is defined as a repeated and uncontrollable leakage of urine into the bed or clothes without other symptoms of low urinary tract.¹

Decreased nocturnal antidiuretic hormone (ADH) excretion has been suggested to be a causative factor for NE in children affected.² Moreover, NE may be present with several comorbidities such as sleep

disorders, psychological problems, parasomnias, left-handedness, polythelia, language disorders and testicular pathology.³⁻⁵

The persistence of NE in teenagers causes feelings like anger, shame and low level of self-esteem. These considerations underline the need of an appropriate treatment during childhood. Desmopressin (dDAVP) is one of the most widely, well-tolerated, rapid acting prescribed medications for MNE (level 1, grade A, according to ICCS).



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Pharmacokinetics and pharmacodynamics

dDAVP is a well-known synthetic analogue of the antidiuretic hormone vasopressin.⁶ It was produced in 1966 by removing an amino group from the cysteine molecule in position 1 and replacing a residue of L-arginine with D-arginine in position 8. It led to a considerable increase in the anti-diuretic action and a longer plasmatic half-life.⁷

dDAVP has selectively effect on V2 receptors-agonist (vasopressor effect). These receptors are located on the cells of the distal renal tubules and collecting ducts: their activation determines the opening of water channels, aquaporin-2 type water channels, responsible for increased reabsorption of free water. Altered expression of aquaporins is detected in enuretic children.^{7,8}

Vande Walle *et al.* suggested that the new oral lyophilisate formulation (MELT) is responsible for the decrease of urine output and an increase in mean urinary osmolality.⁸ Moreover, the clinical effects between MELT at lower doses and tablets are similar because the MELT formulation has a better bioavailability.^{8,9}

dDAVP intranasal solution is also available in children but has many unknowns regarding its bioavailability, especially when children are affected by upper respiratory infections, allergies and rhinitis.¹⁰

In Japan, intranasal desmopressin had been the only formulation for the treatment of central diabetes insipidus (CDI) until 2012 until Kataoka *et al.* demonstrated that orally disintegrating tablet (ODT) is superior to intranasal desmopressin in controlling water balance. Nowadays the efficiency and safety of desmopressin ODT have been clear, and oral formulations are preferred for administration.¹¹

Safety of dDAVP

dDAVP is a well established and effective therapy for NE. Hyponatremia is a possible adverse event associated with dDAVP. It is the most severe complication due to water intoxication, though it is infrequent.^{8,12,13} Risk factors for hyponatremia are identifiable and preventable: high fluid intake,

increment of the recommended dose, young age (less than 6 years) and concomitant administration of another medication.¹²

In many clinical trials of PNE, changes in blood chemistry values (serum sodium, calcium and potassium, alanine aminotransferase and aspartate aminotransferase and osmolality), were not clinically significant.⁸ Moreover, there were no difference between the reported incidences of adverse events in treatment and control groups.

Hyponatremia can be classified as 'asymptomatic borderline' (serum sodium of 130-134 mmol/l), 'symptomatic class I' (serum sodium 125-129 mmol/l), or 'symptomatic class II' (serum sodium <125 mmol/l). The onset of hyponatremia was found to be more frequent in younger patients and during the first administration of therapy and two trials of oral dDAVP in MNE, reported asymptomatic reductions in serum sodium levels.⁸

Many papers underline that the risk for this severe adverse reaction can be reduced by following some advertisements. The most important are: adhere to the indications and dosing recommendations when prescribing dDAVP and restrict inappropriately fluid intake, especially during the evening.^{8,9,12-15}

It is important to underline that 14% of reported cases of this type of side effect were arisen in patients treated with dDAVP without an adequate indication for therapy (e.g. secondary NE, global polyuria) or in patients with definite contradictions to desmopressin use (polydipsia, dipsogenic diabetes insipidus).¹⁶ Moreover, none of the reported cases occurred in patients using an oral formulation of dDAVP.

Many studies underline that dDAVP side effects are deeply correlated with age. dDAVP can be also administrated in adult with nocturia, but elderly patients (> 65 years-old) with low serum sodium, are at high risk (>75%) of hyponatremia.^{17,18}

There is only one report that highlights the potentially life-threatening side effects associated with the administration of non-steroidal anti-

Table 1: Summary Data From Published Reports on oral lyophilisate formulation of desmopressin (MELT) and side effects

Reference	Patients mean age	Number of patients	Dose	Indication	Side effects
Van Herzele -2016	10.4	18	120 µg Mimirin Melt	MNE	No
Sharifiaghdas F -2016	7.9	12 84	240 µg Mimirin Melt 120-240 µg desmopressin Melt	PMNE	At dose of 240 µg 10 patients nausea, lethargy and lower limb weakness
Ohtomo Y -2015	10.5	157	120-240 µg desmopressin Melt + 1-2 g Tolterodina 120 µg Mimirin Melt	PMNE	No
Onol FF -2015	8.7	73	120 - 240 µg desmopressin lyophilisate	PMNE	No
De Waele K -2014	12 days 62 days	1 1	60 µg Mimirin Melt	Central Diabetes Insipidus MNE	No
Ferrara P -2014	8.64	81	120 µg desmopressin Melt	MNE	No
Korkmaz HA -2014	Newborns	4	5 µg pro kg oral desmopressin lyophilisate	Central diabetes insipidus MNE	No
Ohtomo Y -2013	11.5	32	120 µg desmopressin Melt	MNE	No
Juul KV -2013	9.6	72	120 µg desmopressin Melt + 0,2 mg desmopressin tablets	MNE	No
		149	240 µg desmopressin Melt + 0,4 mg desmopressin tablets		

Author	Year	Age (years)	Patients	Dose	Formulation	MNE	No
Montaldo P	-2012	10.6	101	120 µg	desmopressin Melt	MNE	No
			105	240 µg	desmopressin Melt		
Lottmann H	-2007	9.6	221	120 - 240 µg	desmopressin Melt	PNE	35 patients (headache 6 pts 2,7% nasopharyngitis 4 pts 1,8% diarrhea 3 pts 1,4% viral gastroenteritis 3 pts 1,4%)
			12	30 µg	desmopressin Melt	PNE	15 patients
Vande Walle JG	-2006	8	12	60 µg	desmopressin Melt		23 pts at the dose of 480µg 1 at the dose of 240µg
			12	120 µg	desmopressin Melt		
			11	240 µg	desmopressin Melt		
			12	360 µg	desmopressin Melt		
		9.1	13	480 µg	desmopressin Melt		
		9.1	12				

inflammatory drugs (NSAIDs) during dDAVP replacement therapy for CDI.¹⁹

Van Herzeele *et al.* in the "DRIP" study (desmopressin response in PNE), evaluates the safety profile of the oral dDAVP tablet in children with MNE. dDAVP tablet treatment resulted well tolerated in children with MNE, regardless of patient gender or age.²⁰

Overall, 222 (30%) patients experienced 404 treatment-emergent adverse events. Although most of these treatment-emergent adverse events were considered unrelated to the study drug. They were experienced mostly as gastrointestinal disorders; infections and infestations; respiratory, thoracic and mediastinal disorders.

The MELT formulation retains similar levels of efficacy and safety at lower dosing levels, and requires no intake of water compared to the tablets.^{21,22} Moreover, taking tablets can be inconvenient and may be difficult for children to swallow.²² Significantly, MELT was well accepted by all ages and facilitates the early initiation of treatment in children with MNE.²²

Another advantage of MELT compared to tablets can be observed in food interaction. The dDAVP tablet and oral lyophilisate should be administered 60 min before bedtime and at least 2 h after the evening meal, which may be impractical in school-aged children.²³ The oral lyophilisate reduce difficulties posed by this short interval. Furthermore, oral lyophilisate it is less affected by intestinal motility because it is believed to be absorbed by oral and/or oesophageal mucosa.²³

dDAVP is also used in severe and inherited bleeding disorders. Stooft *et al.* included 108 patients, median age 30 years, affected by Von Willebrand disease type 1 (76%).²⁴ No patients presented severe hyponatremia. Some adverse events emerged after dDAVP infusion (hypotension and tachycardia), but none of them sustained at 24h. In conclusion, this study supports dDAVP use as a safe treatment option in patients with various bleeding disorders.²⁴

Ferrara *et al.* reported that dDAVP was effective and safety in reducing bedwetting during treatment, compared with placebo and with homotoxicology.²⁵

Post marketing safety data analysis, revealed 151 cases of hyponatremia in children with NE: 145 with intranasal formulations and 6 with tablets.¹² The difficult administration of a spray formula, can be a possible cause of overdose in patients treated with intranasal dDAVP. In conclusion, there is a decreased risk of hyponatremia with oral compared with intranasal dDAVP.^{12,22,26}

We performed a MEDLINE literature search (January 2000-July 2017) using the search terms MELT enuresis, MELT desmopressin, sublingual desmopressin and lyophilisate desmopressin, to review the safety of MELT and its effectiveness in the treatment of NE and CDI in pediatric patients. Additional references were identified from a review of literature citations. All english-language observational studies and case reports about side effects and effective of MELT in pediatric patients were evaluated.

Twelve articles were analyzed with 1275 pediatric patients (<18 years old). The indication was NE in 1269 patients and CDI in 6 patients. In 11 studies dDAVP was administered alone while in 1 study in association with Tolterodina.

In 3 studies were reported side effects in only 60 patients. The reported side effects in pediatric population were nausea, lethargy, lower limb weakness, headache, diarrhea, viral gastroenteritis, hyponatremia.

CONCLUSIONS

Our review confirms that the MELT formulation of dDAVP guarantee the same response of other formulations with a lower doses and a lowest number of side effects. We believe, according with the literature, that this formulation is actually the first line and safety treatment for NE in pediatric patients.^{27,28}

Finally we can resume that it is necessary to educate patients to avoid an inappropriately high fluid intake when dDAVP is prescribed, not ingest a higher than recommended dose and promptly discontinue the medication at the onset of signs like headache, nausea or vomiting, prodroms of hyponatremia, especially during the first 2 weeks following treatment initiation when hyponatremia is most likely.^{21,23} Fluid restriction is important both for the safety and efficacy of dDAVP therapy.²³ According to ICCS recommendations, an evening fluid intake of d"200 ml and then no drinking until morning is a safe guideline to minimize risk of hyponatremia; in general practice, it is commonly advised that patients should stop drinking 2 h before bedtime, with dDAVP administration up to 1 h before bedtime.²³

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