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Oral Desmopressin Lyophilisate Formulation (MELT): Efficacy and Safety in Children and Adults

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ABSTRACT

Nocturnal enuresis (NE) is a common disorder in childhood and desmopressin is one of the most widely and well-tolerated medications for NE. The recent oral lyophilisate formulation of desmopressin (MELT) is effective in the treatment of NE in children and nocturia in adults. A MEDLINE literature search MEDLINE (2000-July 2017) was performed using the search terms MELT enuresis, MELT desmopressin, sublingual desmopressin, lyophilisate desmopressin. Twenty articles were analyzed with a number of patients of 3448. In 12 articles were reported 1275 pediatric patients (<18 years old), and in 8 articles 2213 adult patients. In pediatric population the indication was enuresis in 1269 patients and central diabetes insipidus in 6 patients. In adult population the indication was nocturia in 1941 patients, renal colic in 259 patients, healthy volunteers 13 patients. In 17 studies desmopressin was administered alone while in 3 studies in association respectively with Tolterodina, Ketorolac and Tamsulosin. In 7 studies were reported side effects in only 81 patients, 60 in pediatric population and 21 in adult population. The reported side effects in pediatric population were nausea, lethargy, lower limb weakness, headache, diarrhea, viral gastroenteritis. The reported side effects in adult population were asymptomatic hyponatriemia, nausea, diarrhea, dizziness, symptomatic hyponatriemia. 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 the first line and safety treatment for nocturnal enuresis and nocturia.

Key words: Enuresis, Desmopressin, Efficacy.

INTRODUCTION

Nocturnal enuresis (NE) is a pediatric disorder and many scientific studies have established decreased secretion of ADH and a reduced response to antidiuretic hormone in children affected[1,2]. 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,

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well-tolerated, rapid acting prescribed medications for MNE (level 1, grade A, according to ICCS).

Pharmacokinetics and pharmacodynamics

dDAVP is produced replacing a residue of L-arginine with D-arginine in position 8 and removing an amino group in position 1 in the cysteine molecule. It was launched for the first time in 1966. It led to a considerable increase in the anti-diuretic action and a longer plasmatic half-life[6,7]. dDAVP has a vasopressor effect because is a selective V2 receptors-agonist with no effect on V1-receptors. The activation of these receptors on the cells of the distal renal tubules and collecting ducts, causes the opening of acquaporin-2 type water channels (water channels), responsible for increased reabsorption of free water. In enuretics, there is altered expression of aquaporins.

dDAVP was first marked in 1974 as an intranasal solution, then it was released in 1981 as an injectable solution for intravenous, subcutaneous or intramuscular usage and finally as an oral solid tablet formulation in 1987. Recently, has been developed an oral lyophilisate formulation (MELT)[8]. Moreover, data suggest that there is no significant difference between the clinical effects of MELT compared to the tablet, due to its higher bioavailability [8,9].

The limit of using the nasal spray formulation is the great variations in absorption due to any modification of upper respiratory tract (infections, allergy, nasal congestion etc)[10].

In Japan, nasal spray had been the formulation for the treatment of central diabetes insipidus until Kataoka *et al*. demostrated 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 an effective therapy for NE and water intoxication is an infrequent adverse event associated[8, 12, 13]. Although, we can prevent this dangerous reaction managing risk factors associated with hyponatremia[12]. However, the risk for this deadly adverse event could be reduced by following guidance. The most important indication is to adhere to the dose recommendations when prescribing dDAVP. Literature suggests not exceeding the recommended dose and to restrict fluid intake, especially during the evening[8, 9, 12-15]. Many studies demonstrate that the onset of hyponatraemia is more common in younger patients and during the first administration of therapy.

Although hyponatraemia is not very common and it mostly depends on unappropriate somministration of the drug, there are some papers that describes this side effect. However, reported cases (14%) of this kind of side effect occurred in patients treated with dDAVP without an adequate indication for therapy or were definite contraindications to desmopressin use (polydipsia, dipsogenic diabetes insipidus)[16]. Moreover, none of the reported cases occurred in patients using an oral formulation of dDAVP.

dDAVP can be also administrated in adult with nocturia, but hyponatriemia is extremely correlated with age. Many studies underline that geriatric patients (> 65 years-old) with serum sodium under the lower limit are at high risk (>75%) of this adverse effect.

Only one report highlights the potentially life-threatening side effects associated with the co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) and dDAVP replacement therapy for CDI[19].

Van Herzeele *et al*. evaluate the safety of the oral dDAVP tablet in children with NE and report that dDAVP resulted to be well tolerated, independently of patient gender or age[20].

MELT formulation does not necessitate intake of water compared with the tablet, furthermore, at lower dosing levels it maintains comparable levels of efficacy and safety[21, 22]. Moreover, taking tablets can be difficult and may be hard for children to swallow. Significantly, MELT was well accepted by all ages.

Tablets formulation have also difficulties in administration due to their food interactions. Lower interactions are demonstrated with the oral

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

Reference	Patientsmean age	Number of patients	Dose	Indication	Side effects
Van Herzeele (2016)	10.4	18 12	120 µg Minirin Melt 240 µg Minirin Melt	MNE	No
Sharifiaghdas F (2016)	7.9	84 92	120-240 ìg desmopressin Melt 120-240 ìg desmopressin Melt	PMNE	At dose of 240 µg10 patientsnausea, lethargy and lower limb weakness
Juul KV (2016)	60.1	841	10-100 µg desmopressin Melt + 1-2 g Tolterodina	Nocturia	No
Pricop C (2016)	41.8 43.1 42.7	57 62 59	60 ìg Minirin Melt 120 µg Minirin Melt60 ìg Minirin Melt +30 mg ketorolac	Lithiasic renal colic	No
Ohtomo Y (2015)	10.5	157	120 µg Minirin Melt	PMNE	No
Keshvari Shirvani M (2015)	30.1	81	60 µg desmopressin Melt	Acute renal colic	No
Ahmed AF (2015)	70.1	123	60 µg desmopressin Melt + tamsulosin 0.4 mg	Benign Prostatic Hyperplasia and nocturia	7 patients mild asymptomatic hyponatremia
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 Minirin Melt	Central Diabetes Insipidus	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	No
Ohtomo Y (2013)	11.5	32	120 µg desmopressin Melt	MNE	No
Juul KV (2013)	9.6	72 149	120 µg desmopressin Melt+ 0,2 µg desmopressin tablets	MNE	No

			240 µg desmopressin Melt + 0,4 µg desmopressin tablets		
Weiss JP (2013)	60.8 60.1	119 124	50 µg desmopressin ODT* 100 µg desmopressin ODT*	Nocturia	Severe 2 pts at the dose of 50µg 2 pts at the dose of 100µg Serious 4 pts at the dose of 50µg 5 pts at the dose of 100µg
Sand PK(2013)	59.5	133	25 µg desmopressin ODT*	Nocturia	Severe 1 patient
Montaldo P (2012)	10.6	101 105	120 µg desmopressin Melt 240 µg desmopressin Melt	MNE	No
Weiss JP (2012)	61.7 62.4 61.6 62.1	155 152 148 146	10 µg desmopressin ODT* 25 µg desmopressin ODT* 50 µg desmopressin ODT* 100 µg desmopressin ODT*	Nocturia	nausea 2-5% diarrhea 1-6% dizziness 2-4blood sodium decreased 1–5%hyponatremia 0–6%
Fransén (2009)	26.6	13	240 µg sublingual desmopressin	Healthy volunteers	No
Lottmann H (2007)	9.6	221	120 - 240 µg desmopressin Melt	PNE	35 patients (headache 6 pts 2,7% nasopharingitis 4 pts 1, 8% diarrohea 3 pts 1, 4%viral gastroenteritis 3 pts 1,4%)
Vande Walle JG (2006)	8.0 9.4 8.7 8.4 9.1 9.1	12 12 11 12 13 12	30 µg desmopressin Melt 60 µg desmopressin Melt 120 µg desmopressin Melt 240 µg desmopressin Melt 360 µg desmopressin Melt 480 µg desmopressin Melt	PNE	15 patients reported 24 treatment-emergent adverse events23 pts at the dose of 480µg 1 at the dose of 240µg

* ODT: orally disintegrating tablet

lyophilisate formulation, resolving the issue for young children to take the drug in a short interval between the evening meal and bedtime[23]. The dDAVP tablet and MELT should be administered 1 hour before bedtime.

dDAVP is also used in severe and inherited bleeding disorders. Stoof *et al*. included 108 patients (median age 30 yrs), most of them (76%) affected by von Willebrand disease type 1[24]. The Authors observed that adverse events coincided with the antidiuretic and vasomotor effects of dDAVP studied previously. Changes in parameters were transitory and not clinically relevant. In conclusion, this study confirms that dDAVP is a safe treatment in these patients too.

Ferrara *et al*. in another study reported that dDAVP was effective and safety patients with NE, compared with placebo and with homotoxicological remedies[25].

Analysis of post marketing safety data revealed 151 cases of hyponatremia in children with NE: 145 with intranasal formulations and 6 with tablets [12]. Other authors suggest that there is a decreased risk of hyponatremia with oral compared with intranasal dDAVP and one possible contributing cause is overdose in patients treated with intranasal dDAVP, because of the imprecise nature of administering a spray[12, 22].

To review the safety of desmopressin (MELT) and it is effective in the treatment of nocturnal enuresis and nocturia we performed a MEDLINE literature search MEDLINE (January 2000-July 2017) using the search terms MELT enuresis, MELT desmopressin, sublingual desmopressin, lyophilisate desmopressin. All English-language observational studies and case reports about side effects and effective of MELT in patients were evaluated.

Twenty articles were analyzed with a number of patients of 3448. In 12 articles were reported 1275 pediatric patients (<18 years old), and in 8 articles 2213 adult patients. In pediatric population the indication was enuresis in 1269 patients and central diabetes insipidus in 6 patients. In adult population the indication was nocturia in 1941 patients, renal colic in 259 patients, healthy volunteers 13 patients. In 17 studies desmopressin was administered alone while in 3 studies in association respectively with Tolterodina, Ketorolac and Tamsulosin.

In 7 studies were reported side effects in only 81 patients, 60 in pediatric population and 21 in adult population (Tab. 1). The reported side effects in pediatric population were nausea, lethargy, lower limb weakness, headache, diarrhea, viral gastroenteritis. The reported side effects in adult population were asymptomatic hyponatriemia, nausea, diarrhea, dizziness, symptomatic hyponatriemia. It is important to not underestimate other symptoms because particularly, for voiding disorders and abdominal pain is significant to rule out organic causes[26].

CONCLUSIONS

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 the first line and safety treatment for nocturnal enuresis and nocturia.

Finally we can resume that it is necessary to educate patients to avoid an inappropriately high fluid intake when dDAVP is prescribed, to adhere properly to the recommended dose and immediately suspend the medication at the onset of signs like headache, nausea or vomiting, prodroms of hyponatremia, especially if the symptoms develop during the first 2 weeks following treatment beginning when hyponatremia is more frequent. Fluid restriction is important both for the safety and efficacy of dDAVP therapy. ICCS recommendations underline to reduce fluid intake (d”200 ml) during evening, and then to avoid drinking until morning to reduce risk of hyponatremia; in general practice, it is generally advised that patients should avoid drinking 2 h before bedtime, with desmopressin administration up to 1 h before bedtime.

The future perspectives are to optimize MELT treatment associated with behavioral therapies to improve efficacy and further reduce side effects.

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