NOCTURNAL ENURESIS: RESULTS FROM A NON-INTERVENTIONAL STUDY COMPARING DESMOPRESSIN TABLET AND MELT

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PURPOSE

Treatment with desmopressin in nocturnal enuresis is regarded as first-line treatment (Grade A/Level 1) or alternatively an alarm treatment. Desmopressin is available in different formulations such as nasal, oral tablet and melt (oral lyophilisate), however nasal formulation is not indicated in a number of countries for the treatment of nocturnal enuresis, since it bears a risk for overdosing. Desmopressin tablets and melt formulation have been shown to be bioequivalent. Published studies indicate benefits with the melt formulation over conventional tablets (Lottmann et al. 2007). It was shown by van de Walle (2010) that melt formulation results in a more predictable pharmacodynamics when a standardized meal was taken at the same time of the drug treatment. Furthermore de Guchtenaere et al. (2011) showed a superior response rate and a lower rate of non-response for MINIRIN®-melt formulation in a comparative study versus tablet.

The objective of this study was to compare real-life data of patient satisfaction with the two formulations of desmopressin. Moreover the efficacy of melt formulation and tablet was compared.

MATERIAL AND METHODS

A multi-center 3-months non-interventional study, including 3 visits, was conducted between 30/05/2011 and 28/03/2013. Patients who had given their consent were included in this non-interventional study in a consecutive manner. Inclusion in the study was allowed when treatment of primary enuresis nocturna was indicated according to Summary of Product Characteristics (SMPC) of MINIRIN®.

Primary endpoint was patient/parent treatment satisfaction as descriptive comparison between the two treatment groups.

Secondary endpoints included compliance, number of wet nights and adverse drug reactions (ADR).

Patient/parent satisfaction was measured via *a visual analogue scale (VAS)* and difficulties while taking the medication were also assessed. Patients answered the question:

Did your child have difficulties taking the medication? Possible answers were: never, rarely, occasionally and frequently.

Data on maximal voided volume, nocturnal diuresis volume and number of wet nights were documented.

The study design included 3 visits:

At inclusion and first treatment, at week two and after 3 months all endpoints were evaluated and the closing documentation was done. The closing documentation was also filled in when the study participation was prematurely terminated by any patient.

Statistical analysis was done with descriptive statistics (minimum, maximum, median, mean, standard deviation and frequency distributions). Comparative methods of two or more subgroups of the ITT were done with t-test, U-test and variance analysis, fishers exact t-test and c 2-test.

Table 1 Demographics and patients' characteristics

	Tablet	Melt	Total
Patients included	49	84	134
Taking a study medication	49	84	134
Study therapy finished	43 (87.8 %)	67 (79.8 %)	111 (82.8 %)
Finished ahead of schedule	6 (12.2 %)	17 (20.2 %)	23 (17.2 %)
Medium period of observation [Weeks (SD)]	90.2 (27.3)	80.8 (26.9)	84.3 (27.3)
Medium period of observation [Weeks]	83.0	86.0	88.5
Male [%]	65.3	77.4	72.4
Female [%]	34.7	22.6	27.6
Age [Jahre]	8.5	8.7	8.7
Age-groups [%]			
0 – 5 years	12.2	14.3	13.4
5 – 10 years	69.4	57.1	61.2
>10 years	18.4	28.6	25.4
BMI, median	16.8	18.2	17.4
Weight, median [(kg]	30.0	29.0	30.0
Duration of PEN, median [years]	0.59	0.42	0.54
Average drinking quantity daytime, median [mL]	900	800	875
Maximal voided volume, median [ml]	180	200	200
Nocturnal diuresis volume, median [ml]	255	280	265
Daytime symptoms [%]	18.4	14.5	16.5
Urge [%]	20.4	21.7	21.8
No pre-treatment, first diagnosis [%]	30.6	33.3	32.1
Only watchful waiting so far [%]	32.8	32.1	35.1
Pre-treatment total [%]	30.6	34.5	32.8
Propiverin HCl [%]	12.2	11.9	11.9
Oxybutynin HCl [%]	0.0	1.2	0.7
Desmopressin [%]	16.3	11.9	13.4
Non-medical treatment [%]	2.0	7.1	5.2
Concomittant therapy			
Propiverin HCl [%]	4.1	2.4	3.0
Oxybutynin HCl [%]	0.0	1.2	0.7
Non-medical	6.1	7.1	6.7
- apparative VT	6.1	4.8	5.2
- psychotherapy	0.0	2.4	1.5
- bladder training	0.0	1.2	0.7

RESULTS

134 children were included **(tablet = 49; melt = 84).** One of those was treated with both treatment forms and therefore excluded from the analysis. 111 patients (82.8 %) completed the study, 43 (87.8 %) in the tablet group and 67 (79.8 %) in the melt group. There were no study terminations due to ADR. The majority of study participants (72.4 %) were male. At inclusion, approximately 1/3 already received enuresis therapy before inclusion; another third was being followed carefully without treatment/newly diagnosed, respectively.

Mean drinking volume 928 (± 440) mL.

Mean (± SD) maximum voided volume 285 (± 259) mL.

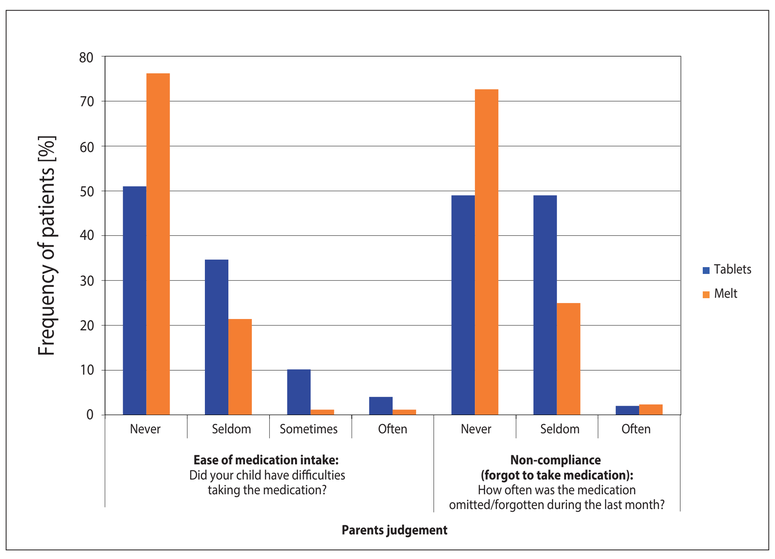
Mean (±S D) nocturnal volume 275 (± 131) mL.

16.5 % of the patients also suffered from daytime symptoms.

21.8 % had urgency.

Most patients received the by SMPC recommended dosage of 0.2 mg or 120 µg respectively at start of therapy. However one third of the patients received a lower starting dose of 0.1 mg in the tablet group and 9.5 % in the melt group.

Fig. 1 Parents judgement: Ease of medication intake



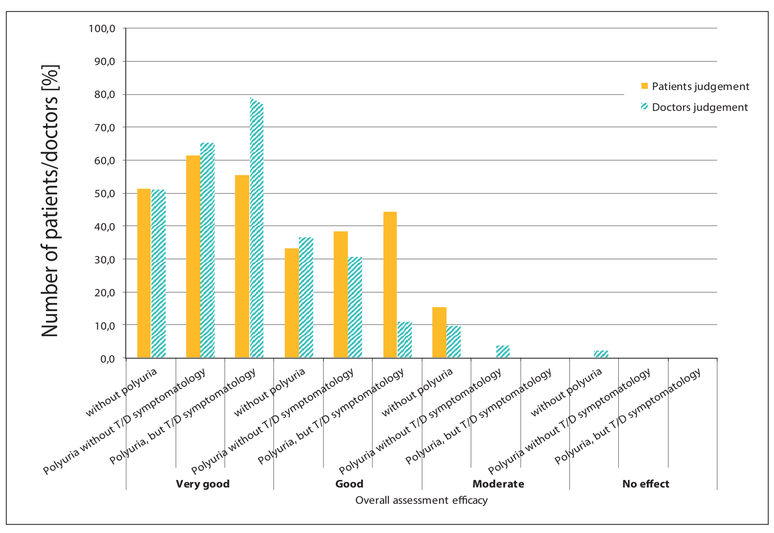
Primary endpoints favored the melt formulation:

Patient satisfaction, *VAS* evaluating difficulties with taking melt vs. tablet; mean (± SD): 85,0 ± 18,9 vs. 93,8 ± 12,1; **p < 0.001**

Parents satisfaction, *"Did your child have difficulties taking the medication":* (melt vs. tablet): **p = 0.005** (proportion stating "never problems" was 76 % vs. 51 %, Fig. 1)

Parents judgement compliance, *"How often was the medication omitted/forgotten during the last month"* and **p = 0.012** (proportion stating "never forgetting" was 73 % vs. 49 %, Fig. 1).

Fig. 2 Parents and doctors judgement: Overall efficacy



In a post-hoc subgroup analysis it was shown, that

37 % (n=41) patients had no polyuria,

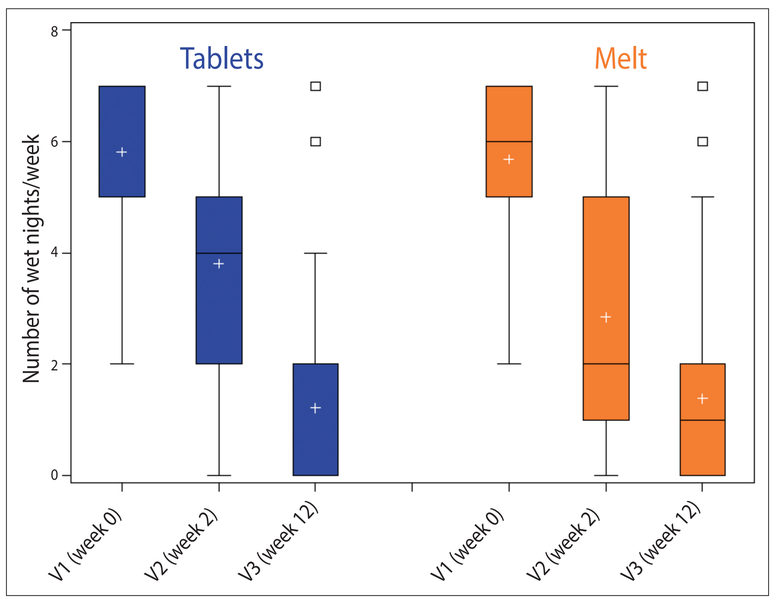
26 % (n=28) patients suffered from polyuria alone,

9 % (n=10) suffered both from polyuria and daytime or urgency symptoms,

28 % (n=31) were not evaluable from the documentations made.

The best overall assessment for efficacy was seen in the polyuria group (Fig. 2)

Fig. 3 Number of wet nights



Reduction of wet nights equal at the end of documentation period for both formulations (average of just below 6/week at inclusion to just above 1/week after 3 months, Fig. 3).

Children treated with melt benefitted from a faster reduction in the number of wet nights (at week 2 a significantly reduced number of wet nights for melt vs. tablet was shown, mean = 2.8 wet nights/week vs. mean = 3.8 wet nights/week).

During treatment dosage was increased in 40.8 % of tablet and 23.8 % of melt treated patients.

Some children had combination therapy:

4.1 % (tablet) and 3.6 % (melt) additionally received antimuscarinic.

6.1 % (tablet) and 4.8 % (melt) additionally received alarm.

24.3 % of the patients finished treatment after 12 weeks.

74.8 % continued therapy.

Most of the children continuing with treatment did so with normal (0.2 mg/120 mg) dosage. 12.5 % switched from tablet to melt, whereas none switched from melt to tablet.

Table 2 Overall assessment tolerability

	Study population			
Overall assessment tolerability	Tablet (N = 49) n %	Melt (N = 84) n %	Total (N = 133) n %	Test
Patients' judgement				
Very good	28 (58.3 %)	67 (80.7 %)	95 (72.5 %)	0.006
Good	19 (39.6 %)	15 (18.1 %)	34 (26.0 %)	
Moderate	1 (2.1 %)	1 (1.2 %)	2 (1.5 %)	
Bad	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Missing values	1	1	2	
Physicians judgement				
Very good	30 (62.5 %)	67 (82.7 %)	97 (75.2 %)	0.009
Good	17 (35.4 %)	14 (17.3 %)	31 (24.0 %)	
Moderate	1 (2.1 %)	0 (0.0 %)	1 (0.8 %)	
Bad	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Missing values	1	3	4	

No discontinuations were caused by adverse events (AEs); one ADR ("headache") was reported (tablet group), the patient recovered after 8 days without any changes in treatment. Patient evaluation of tolerability was better in the melt group as compared to tablet group (Tab. 2, p = 0.006).

DISCUSSION

A non-interventional study has its general limitation but pictures daily practice. In the data presented only 26 % (n = 28) of patients had nocturnal polyuria and should have been treated with desmopressin following the EAU/ICCS guidelines. All other patients did not have nocturnal polyuria or had daytime symptoms, so by definition were NMNE patients or were not well documented. This reflects the need for improvement in the quality of care through education of HCP.

Patient satisfaction as the primary endpoint showed a clear favor for the melt formulation. This finding is in line with earlier data showing a preference of melt in children younger than 12 years.

Compliance is a key aspect in treatment success of PNE and was found to be clearly superior in the melt group of this study. The switch of 12,5 % of patients from tablet to melt when continuing treatment also supports that the melt formulation is more favorable compared to tablets.

Despite the above discussed limitations the treatment outcome was surprisingly good. Efficacy data are comparable in both treatment groups but a faster reduction of wet nights was found in patients treated with melt. This is in accordance with de Guchtenaere et al. who showed better efficacy of melt vs. tablet treatment and in accordance with other published data. MNE patients with nocturnal polyuria showed the best treatment response. Furthermore again favorable safety data for the melt formulation was approved.

CONCLUSION

- **What can we learn from this study? In daily live practice still a substantial number of patients do not receive guideline conform PNE treatment assumable due to a lack of proper diagnosis.**
- **Patient satisfaction is significantly higher in the melt group vs. tablet desmopressin group.**
- **Children with PNE benefit from a treatment with melt by a faster reduction in wet nights.**
- **Compliance with melt treatment is better than in patients treated with tablets**
- **Tolerability was significantly better in the melt group.**

Overall efficacy was comparable between different forms of desmopressin treatment, several other aspects such as patient satisfaction, compliance and tolerability were superior in the melt group suggesting the preferential use of the melt formulation in patients with PNE. This is in line with the EMA recommendations for treatment in children below 12 years of age.

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