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Original Article

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What Affects Relapse After Desmopressin Treatment in Monosymptomatic Nocturnal Enuresis?

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ABSTRACT

Background: Desmopressin is an important treatment option for monosymptomatic nocturnal enuresis (MEN), yet relapse after discontinuation remains a major problem. This study aimed to compare the outcomes of different desmopressin formulations (orally fast-dissolving lyophilized vs. sublingual tablet) used in MEN treatment and to examine the recurrence rates of gradual versus sudden discontinuation.

Methods: Patients who received desmopressin treatment with a diagnosis of MEN from a single center (Dec 2022–Aug 2023) were retrospectively analyzed. Desmopressin treatment (136 in fast-dissolving lyophilized form, 98 in sublingual tablet) was started in 234 patients (75 girls, 159 boys) (mean age 9.26 years) (preschooler 72, preadolescent 135, adolescence 27), was given for an average of 3.1 months, and was terminated (suddenly 204, gradually 30 patients). Afterwards, the patients were evaluated with follow-up visits in the first and third months, and statistical analyses were performed.

Results: There were no significant differences in relapse rates among patients with different drug formulations or discontinuation methods. However, preschool children (5-7 years of age) had significantly lower relapse rates than older age groups ($P = .004$ and $P = .018$). No dose-related differences in relapse were found.

Conclusion: Age was the main determinant of relapse, with preschool children exhibiting better sustained responses. Drug formulation and discontinuation method did not significantly affect relapse. The fast-dissolving form may improve treatment adherence due to ease of administration.

Keywords: Age, child, desmopressin forms, enuresis, recurrence

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INTRODUCTION

Enuresis is defined as involuntary urinary incontinence during sleep for at least 3 consecutive months in children older than 5 years of age. The terminology used in this study follows the updated recommendations of the International Children's Continence Society (ICCS).[1] Monosymptomatic enuresis nocturna (MEN) is defined as nighttime bedwetting without daytime urinary incontinence in children without any pathology in the urinary system[1] and has a prevalence of 3.8% (10% in young children and around 1% in adolescents), and is not only common but also highly likely to recur after treatment. Desmopressin is the main first-line treatment for MEN patients with nocturnal polyuria and normal bladder function. Since 1972, it is preferred because it is easy to administer and does not cause any long-term harm. Since 2005, an orally fast-dissolving lyophilized form is also available. The most prominent problem of desmopressin treatment is the high recurrence rate of MEN, which is 83% after drug discontinuation.[2] Although the treatment of MEN patients is specified in guidelines, there is no consensus on how it should be terminated. Termination of treatment may be immediate or with a gradual reduction. In this study, the aim was to

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evaluate the results of the drug forms of desmopressin (orally fast-dissolving lyophilized form and sublingual tablet) used in the treatment of MEN and to compare the MEN recurrence rates after gradual/sudden discontinuation of treatment.

MATERIALS AND METHODS

This retrospective study analyzed patients diagnosed with MEN and treated with desmopressin at Gaziantep Cengiz Gökçek Maternity and Child Diseases Hospital Pediatric Urology Clinic between December 2022 and August 2023. Patients with Dysfunctional Voiding Scoring System scores above 15 were excluded to ensure inclusion of pure MEN cases.

All patients with MEN with nocturnal polyuria, defined according to ICCS guidelines as nocturnal urine output > 130% of expected bladder capacity for age based on a 2-3-day frequency–volume chart, were given desmopressin.

Two hundred thirty-four patients (75 girls, 159 boys) (mean age: 9.26 years) (72 patients in preschool age [5-8 years old]; preadolescent [8-12 years old] 135 patients; adolescent [12-17 years old] 27 patients) were started on oral desmopressin treatment (136 of them received fast-dissolving forms and 98 of them received tablets) (Table 1). Treatment response was assessed monthly. Those who missed the follow-up examination were called and received information by phone. The mean duration of oral desmopressin treatment was 3.1 months. A 50% reduction in enuresis was considered as non-response to treatment, and no enuresis for at least 3 weeks was considered as complete response. Dose escalation to 240 µg/day was implemented in 6 patients with persistent nocturnal polyuria who did not respond to treatment in the first month (Table 2).

The choice of desmopressin formulation was determined by the availability of the drug in the pharmacy at the time of prescription, along with physician preference and family convenience. No randomization was performed. In 204 patients who achieved complete response to MEN treatment, the medication was discontinued abruptly.

MAIN POINTS

- Preschool-aged children (5-7 years) have lower relapse rates after desmopressin treatment for monosymptomatic nocturnal enuresis.
- No significant difference exists between fast-dissolving lyophilized and sublingual tablet forms regarding relapse rates.
- Gradual versus sudden discontinuation of desmopressin does not significantly impact relapse risk.
- Treatment adherence may be improved with fast-dissolving formulations.
- Age-specific counseling is crucial to minimize relapse in older children.

Table 1. Patient Demographics

		n/Mean ± SD	%/Median (Min-Max)
Gender	Female	75	(32.1)
	Male	159	(67.9)
Age (years)		9.26 ± 2.62	9 (5-17)
Age group	Preschool	72	(30.7)
	Preadolescent	135	(57.6)
	Adolescent	27	(11.5)

Recurrence was defined as ≥ 2 wet nights per week after treatment cessation, and withdrawal from treatment referred to discontinuation of desmopressin either abruptly or gradually.

Ethics committee approval was obtained from Gaziantep University Clinical Research Ethics Committee (Decision no: 2023/407, Date: December 29, 2023). Informed consent was obtained from all participants' parents/guardians.

SPSS version 25.0 program (IBM SPSS Corp.; Armonk, NY, USA) was used for data analysis. The conformity of the variables to normal distribution was analyzed by histogram plots and the

Table 2. Treatment Responses of Patients

		n/Mean ± SD	%/Median (Min-Max)
Drug	Melt (sublingual lyophilized)	136	(58.1)
	Sublingual tablet	98	(41.8)
Time (months)		3.09 ± 0.59	3 (3-4)
1st month follow-up	No recurrence[a]	145	(61.9)
	Recurrence[b]	46	(19.6)
	Withdrawal from treatment[c]	43	(18.3)
3rd month follow-up	No recurrence[a]	117	(50)
	Recurrence[b]	38	(16.2)
	Withdrawal from treatment[c]	79	(33.7)
Drug discontinuation	Sudden discontinuation*	204	(87.1)
	Gradual discontinuation**	30	(12.8)
Doubling the dose	No	228	(97.4)
	Yes	6	(2.5)

[a]<2 wet nights/week for ≥3 consecutive weeks after treatment cessation.
[b]≥2 wet nights/week after treatment cessation.
[c]Discontinuation of desmopressin.
*Complete cessation of the dose without tapering.
**Tapering the dose to half before complete cessation.

Table 3. Statistical Analysis of Patients' Treatment Responses

		Drug							
		Melt (Sublingual Lyophilized)		Sublingual Tablet					
		n	%	n	%	$P^{a,b,c}$	$P^{a,b}$	$P^{a,c}$	$P^{b,c}$
1st month follow-up	No recurrence[a]	90	66.1	55	56.1	.008*	.700*	.004*	.008*
	Recurrence[b]	30	22	16	16.3				
	Withdrawal from treatment[c]	16	11.7	27	27.5				
3rd month follow-up	No recurrence[a]	77	56.6	40	40.8	.018*	.554*	.005*	.130*
	Recurrence[b]	23	16.9	15	15.3				
	Withdrawal from treatment[c]	36	26.4	43	43.8				

*Pearson chi-square test, adjusted with Bonferroni correction.
[a]<2 wet nights/week for ≥3 consecutive weeks after treatment cessation.
[b]≥2 wet nights/week after treatment cessation.
[c]Discontinuation of desmopressin.

Kolmogorov–Smirnov test. Mean, SD, median, and minimum-maximum values were used to present descriptive analyses. Statistical analyses included the Pearson chi-square test, post hoc Bonferroni correction, and calculation of odds ratios (OR) with 95% CIs for significant categorical variables. *P*-values below .05 were considered statistically significant.

RESULTS

The gender and age distribution of 234 patients with MEN receiving desmopressin drug treatment are shown in Table 1, and the first- and third-month responses after treatment are shown in Table 2.

There was no correlation between the use of different forms of desmopressin and the likelihood of subsequent recurrence of MEN. There was no significant difference in the likelihood of recurrence with the rapidly dissolving sublingual lyophilized form compared to the sublingual tablet form at first and third months follow-up ($P = .70$ and $P = .55$). However, the melt group has a lower proportion of withdrawal from treatment (Table 3).

After oral desmopressin treatment, the probability of recurrence at the first- and third-month follow-up visits was found to be lower in the preschool age group (P =004 and $P = .018$) (Table 4).

Preschool-aged children had significantly lower odds of recurrence than adolescents at both the first-month (OR = 5.89, 95% CI: 1.97-17.59, $P = .002$) and third-month follow-ups (OR = 4.80, 95% CI: 1.68-13.71, $P = .003$). Differences between preschool and preadolescent groups were not statistically significant at either time point. Sudden discontinuation of desmopressin was associated with lower recurrence rates than gradual tapering, although these differences did not reach statistical significance at the first (OR = 0.44, $P = .166$) or third month (OR = 0.59, $P = .339$) (Table 4).

Table 4. Treatment Responses According to the Age Distribution of Patients

		Age Group (years)							
		Preschool 5-7 y		Preadolescent 8-12 y		Adolescent 13-17 y			
		n	%	n	%	n	%	P*	OR/CI notes**
1st month follow-up	No recurrence	53	73.6	83	61.4	9	33.3	.004*	Preschool vs Adolescent: OR = 5.89, $P = .002$); Preschool vs Preadolescent: OR = 1.39, $P = .441$
	Recurrence	11	15.8	24	17.7	11	40.7		
	Withdrawal from treatment	8	11.1	28	20.7	7	25.9		
3rd month follow-up	No recurrence	40	55.5	69	51.1	8	29.6	.018*	Preschool vs Adolescent: OR = 4.80, $P = .003$; Preschool vs Preadolescent: OR = 1.19, $P = .669$
	Recurrence	7	9.7	21	15.5	10	37		
	Withdrawal from treatment	25	34.7	45	33.3	9	33.3		

Values >1 indicate higher odds of recurrence compared to reference group.
**P*, Pearson chi-square test, adjusted with Bonferroni correction.
***OR, odds ratio.

Table 5. The Effect of the Type of Discontinuation of Treatment on Recurrence

		Drug Discontinuation							
		Sudden Discontinuation		Gradual Discontinuation					
		n	%	n	%	$P^{a,b,c}$	$P^{a,b}$	$P^{a,c}$	$P^{b,c}$
1st month follow-up	No recurrence[a]	119	58.3	26	86.6	.005*	.134*	.003*	.048*
	Recurrence[b]	42	20.5	4	13.3				
	Withdrawal from treatment[c]	43	21	0	0				
3rd month follow-up	No recurrence[a]	92	45.1	25	83.33	<.001*	.266*	<.001*	.001*
	Recurrence[b]	33	16.1	5	16.6				
	Withdrawal from treatment[c]	79	38.7	0	0				

*Pearson chi-square test, adjusted with Bonferroni correction.
[a]<2 wet nights/week for ≥3 consecutive weeks after treatment cessation.
[b]≥2 wet nights/week after treatment cessation.
[c]Discontinuation of desmopressin.

There was no statistically significant difference in the likelihood of subsequent recurrence of MEN with gradual or sudden discontinuation of oral desmopressin therapy (P = .134 and P = .266) (Table 5).

No statistically significant result was found between oral desmopressin use and dose-related recurrence (Table 6).

DISCUSSION

Monosymptomatic nocturnal enuresis (MNE) is a common and heterogeneous pediatric condition with a multifactorial background, including a genetic predisposition. The prevalence of enuresis in Türkiye is reported to be around 25.9%. Given its high frequency and negative impact on social and psychosocial functioning, timely and effective treatment is important.[3,4] According to Yeung et al., approximately one third of children with nocturnal enuresis at the age of 5 years may not achieve continence before adulthood.[5] Adherence to desmopressin therapy can be enhanced by structured monitoring (e.g., a written checklist), which may improve treatment success.[6] In our study, the easy-to-use, fast-dissolving formulation was associated with higher treatment success, particularly in preschool-aged children.

Desmopressin and alarm therapy are used in the first-line treatment of MEN. Alarm treatment administered to selected families with high sociocultural level and strong compliance yields good results with low relapse rates. Desmopressin, on the other hand, reduces nocturnal polyuria by decreasing nighttime urine production and has been widely used for many years. However, the probability of recurrence in a short time after discontinuation of treatment remains high.[7] In this study, desmopressin treatment was preferred over alarm therapy due to families' low socioeconomic status and the presence of multiple children per household.

Table 6. The Relationship Between Desmopressin Dose and Recurrence

		Doubling the Dose							
		No		Yes					
		n	%	n	%	$P^{a,b,c}$	$P^{a,b}$	$P^{a,c}$	$P^{b,c}$
1st month follow-up	No recurrence[a]	140	61.4	5	83.3	.446*	.666*	.217*	.331*
	Recurrence[b]	45	19.7	1	16.6				
	Withdrawal from treatment[c]	43	18.8	0	0				
3rd month follow-up	No recurrence[a]	112	49.1	5	83.3	.178*	.648*	.063*	.148*
	Recurrence[b]	37	16.2	1	16.6				
	Withdrawal from treatment[c]	79	34.6	0	0				

*Pearson chi-square test, adjusted with Bonferroni correction.
[a]<2 wet nights/week for ≥3 consecutive weeks after treatment cessation.
[b]≥2 wet nights/week after treatment cessation.
[c]Discontinuation of desmopressin.

Preschool-aged children (5-7 years) in the cohort exhibited a markedly lower risk of relapse following desmopressin discontinuation, likely attributable to greater neurohormonal plasticity, earlier maturation of bladder control, and more intensive parental supervision. In clinical practice, older children often represent refractory cases with a history of suboptimal response to prior therapies, which may partly explain their higher relapse rates. Interestingly, relapse rates in the preschool subgroup were even lower than those reported in the DRYCHILD (DRYCHILD: multicenter prospective study of treatment response and relapse in monosymptomatic nocturnal enuresis) study, possibly due to earlier treatment initiation, sociocultural differences in family routines, and better adherence. While the DRYCHILD study[8] suggested that older children respond more favorably to first-line therapies such as desmopressin or alarm treatment for MNE, these results diverge from this pattern. This divergence may reflect differences in study populations and endpoints—DRYCHILD evaluated predictors of initial treatment success, whereas the study focused on relapse rates after achieving complete dryness. The sustained therapeutic benefit observed in younger children in this cohort may be reinforced by developmental and behavioral factors, including enhanced neurohormonal adaptability and consistent caregiver involvement, which support long-term maintenance of dryness. Given that 15%-20% of cases resolve spontaneously each year with age, the persistence of more treatment-resistant cases in older age groups is expected, making the higher responsiveness of younger children both clinically valuable and biologically plausible.

Since sublingual lyophilized (melt) form might be easier to take than the sublingual tablet form, the rate of discontinuation of the drug will be lower. Therefore, melt form is seen in this study that the possibility of discontinuing treatment is less. Although the difference in drug forms was expected to affect the recurrence of enuresis after treatment (first and third months), no significant difference was found between the 2 groups in this study. Although the *P*-value was statistically significant when evaluated collectively with those who dropped out of treatment ($P = .008$ and $P = .018$), the post hoc analysis value was insignificant when only the 2 drug forms were compared with each other ($P = .70$ and $P = .55$).

While sudden discontinuation of oral desmopressin was supported according to a study conducted in Germany in 2009, Gökçe et al[13] suggested that gradual discontinuation would result in a lower recurrence rate.[9] Some studies have even reported that there is no difference between these 2 forms of treatment termination.[10,11,12] Although the pathophysiology of the mode of treatment discontinuation has not yet been elucidated, the gradual reduction of oral desmopressin therapy may stimulate maturation of antidiuretic hormone production, as previously suggested by Marschall-Kehrel and Harms,[7,11,13,14] but it has not been proven. In patients treated with desmopressin, the pituitary gland may not need to produce antidiuretic hormone (ADH) for a long time because the water reabsorption is provided by exogenous desmopressin. If desmopressin is suddenly discontinued, it may take time for the pituitary gland to produce sufficient ADH. This can lead to issues such as polydipsia and polyuria. When discontinuation is gradual, it facilitates the pituitary's adaptation to producing natural ADH again. Gradual reduction of desmopressin is important to allow the pituitary gland to adapt to producing natural ADH. Increased diuresis could be expected for a short period. The fact that no relationship was found between the type of treatment discontinuation and recurrence of enuresis in this study supports this theory.

In this study, it was observed that children who responded to desmopressin were more effective in preschool age. It was hypothesized that regular desmopressin treatment was successful in treating MEN and that this was not dependent on drug forms and dose. No significant difference was found between the method of discontinuation of desmopressin and the possibility of MEN recurrence. However, the limitations of this study include the relatively short follow-up period and the high rate of voluntary treatment termination among children.

In conclusion, age was the main determinant of relapse after desmopressin treatment in MEN, with preschool children showing better sustained responses. Drug form or discontinuation method had no significant effect. However, the fast-dissolving form contributes to treatment continuity due to ease of administration.

Clinicians should consider age-specific counseling and close follow-up in older children to minimize relapse risk.

Limitations

This retrospective, single-center study was limited by its relatively short observation period, comprising approximately 3 months of treatment and 3 months of follow-up. In addition, the unequal distribution of patients between certain subgroups (e.g., only 30 children underwent gradual discontinuation) may have affected the robustness of some subgroup analyses. These factors should be considered when interpreting the findings, and future multicenter studies with longer follow-up are warranted to validate these results.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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