TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1328-1332
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doi:10.3906/sag-1610-72

The effect of antidiuretic hormone on urine and serum electrolyte levels in children with primary monosymptomatic nocturnal enuresis

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Received: 13.10.2016 • **Accepted/Published Online:** 27.03.2017 • **Final Version:** 13.11.2017

Background/aim: The data concerning the effects of desmopressin on water/electrolyte disturbances of children with primary monosymptomatic nocturnal enuresis (PMNE) are limited. In the present study we aimed to evaluate the effect and tolerability of desmopressin on blood and urine electrolytes and osmolality in PMNE.

Materials and methods: Thirty-five children with PMNE between the ages of 5 and 15 participated in the study. Patients collected urine during the daytime and acknowledged the night time fluid restriction before starting to use the desmopressin tablets. The medication was taken orally at least 1 h before bedtime. Blood and urine samples were collected before the introduction of the treatment (day 0) and on the third and seventh days of the administration of desmopressin to determine osmolality and electrolyte levels.

Results: Thirty-five patients participated in the study. Twenty-one patients (60%) were male and 14 (40%) were female. The mean age was 9.6 ± 2.7 years. There were no significant changes in serum osmolality, urine osmolality, and serum sodium concentration. Mean urine calcium/creatinine ratio was 0.03 ± 0.01 mg/mg at the beginning, 0.06 ± 0.02 mg/mg on the third day, and 0.04 ± 0.01 mg/mg on the seventh day of the study. No significant changes were seen in urine calcium/creatinine ratio before and after treatment.

Conclusion: Desmopressin appeared to be a well-tolerated drug and provided a safe and effective treatment for children who were following fluid intake restriction for PMNE.

Key words: Nocturnal enuresis, antidiuretic hormone, electrolyte, osmolality

1. Introduction

Nocturnal enuresis (NE) is defined as involuntary leakage of urine during sleep (1). Intermittent incontinence of urine in a sleeping child who has previously been dry for less than 6 months without any other lower urinary tract symptoms is considered to be primary monosymptomatic nocturnal enuresis (PMNE) (2). The prevalence of enuresis varies according to age groups. In general, the rate of NE is 15%–20% around the age of 5, 7% at the age of 10, and 3% at the age of 12; it is reduced to 1% in subjects aged 15 and older (3). The etiology of NE is not yet fully elucidated. Multiple factors may play a role in its etiology. Factors leading to the pathophysiology of NE are genetic factors, wake up disorders, night-time low bladder capacity, detrusor overactivity, and nocturnal polyuria (4). According to the 2002 International Continence Society definition, nocturia is defined as waking at night to void and production of an abnormally large volume of urine during sleep (5). Electrolyte disturbances also may cause NE. Pace et al. (6) showed that hypercalciuria, especially the absorptive type, may lead to NE. Disturbances of secretion of antidiuretic hormone (ADH) is another factor causing NE (7,8). The majority of the children with monosymptomatic nocturnal enuresis do not show a normal circadian rhythm of the ADH arginine vasopressin (AVP). i.e. the expected increase of vasopressin is not observed in them (8). Rittig et al. (9) showed that vasopressin has a diurnal rhythm of constant levels during the day (0800–2200 hours) and a highly significant increase during the night (2200–0800 hours) in normal subjects. In contrast, enuretics showed a significantly less pronounced nocturnal increase in vasopressin with significantly lower nocturnal levels than normal subjects. Normal subjects showed a diurnal rhythm in urinary excretion rate reciprocal to urinary osmolality with a low and highly concentrated nocturnal urinary output. In enuretics, however, this normal diurnal rhythm was absent.

Different treatment methods such as medical treatments (imipramine, desmopressin, anticholinergics), behavioral interventions, and enuresis alarm therapy are

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used in cases of NE (10). Desmopressin is a synthetic analog of arginine vasopressin that has an antidiuretic effect and reduces the production of urine and increases the urine concentration. The half-life of desmopressin is 1.5–3 h. An increasing number of reports show that administration of desmopressin seems to improve nocturia (11). Desmopressin is involved in management of primary nocturnal enuresis according to guidelines that have been developed by the International Children's Continence Society, the National Institute for Health and Care Excellence, and the Paediatric Society of New Zealand (12). Desmopressin is produced in tablet, melt, and nasal spray forms. Since the sublingual melt form of desmopressin melts readily, it is efficient and easy to use. The recommended melt dose is 120–240 μg (maximum: 360 μg). The risk of side effects is very low in patients with night time fluid restriction. The risk of water intoxication and hyponatremia can be prevented by limiting fluid intake. Due to its prolonged duration of action, occasionally desmopressin may lead to hyponatremia by blocking the mechanism of compensatory diuresis (13). The most serious side effects associated with hyponatremia are cerebral edema and convulsion. Headache and nausea in nasal applications and epistaxis, nasal congestion, and rhinitis can also be added to its side effects (14). However, data on the effects of desmopressin on water/electrolyte disturbances in children with PMNE are limited. There are few studies about its unfavorable side effects and safety of application. Although its effects are well recognized, the possible side effects still constitute an important source of risk.

In the present prospective study we aimed to evaluate the effect and tolerability of desmopressin on blood and urine electrolytes and osmolality in PMNE.

2. Materials and methods

Patients attending the pediatric nephrology unit with the complaint of enuresis were the participants of this prospective study. The study protocol was approved by the local ethics committee and informed consent was obtained from the parents of all patients prior to the beginning of the study. At the first visit, information on the patient's medical history and voiding diaries were collected, and physical examinations concerning liver and renal function tests were performed. Based on clinical indications, laboratory and imaging studies were completed.

Children with PMNE between the ages of 5 and 15 years were included in the prospective study. The physical examinations of these patients were normal. None of these patients had hypertension or renal dysfunction. They did not have any symptoms of neurological or urological diseases. They also did not have any diurnal symptoms. Desmopressin melt antidiuretic hormone at 120 μg was prescribed. To obtain optimum antidiuresis during sleep the medication was applied by mouth to the subjects at least 1 h before bedtime. We gave directions to the subjects about limiting excessive water consumption after dinner and they were limited to fluid intake of 200–300 mL according to their weight after 2100 hours until morning. We also informed the patients about the side effects including headache, vomiting, dizziness, edema, hyponatremia, and seizures that might occur during the study. These patients were diagnosed with primary nocturnal enuresis for the first time and they had not received any drug treatment before. The exclusion criteria were patients with daytime enuresis, age of less than 5 and greater than 18, and having symptoms of secondary enuresis (urination dysfunction, urinary tract infection, urethral obstruction, ectopic ureter, obstructive sleep apnea, diabetes mellitus or insipidus, hyperthyroidism). The patients were asked to collect daytime urine and were informed about the night time fluid restriction before starting to take the desmopressin melt tablets. Between 0800 and 0900 hours, blood and urine samples were collected before the introduction of the treatment (day 0) and on the third and seventh days of the administration of desmopressin to determine osmolality and electrolyte levels. The study subjects were not allowed to eat or drink prior to the blood and urine sample collections on days 3 and 7.

We used SPSS 11.5 for Windows for the statistical analysis. The Shapiro–Wilk test was used to investigate whether the distribution of the continuous variables was close to normal distribution. Differences between the means of continuous variables in two and three groups were evaluated by using Student's t-test or the Mann–Whitney U test and the Kruskal–Wallis test or ANOVA test, respectively, where applicable. Descriptive statistics for continuous variables are shown as mean ± standard deviation, and for nominal variables they are shown as the number of cases and as (%). Repeating measures were investigated with variance analysis. $P < 0.05$ was considered to indicate statistical significance. Serum sodium levels between 135 and 145 mmol/L were considered normal, and levels under 135 mmol/L were defined as hyponatremia.

3. Results

In total 35 patients (21 males, 14 females) participated in this study. The mean age was 9.6 ± 2.7 years. Sixteen patients were prepubertal and 19 were postpubertal. Daily liquid intake and urine volume were 1635 ± 734 mL/m^2 and 1270 ± 607 mL/m^2, respectively (Table 1). There was no significant difference in blood sodium, potassium, and osmolality between prepubertal and postpubertal children ($P = 0.552$). Blood sodium values were 137.0 ± 1.85 mEq/L before the treatment and 138.0 ± 2.07 mEq/L and 137.0 ±

Table 1. Demographic characteristics of the patients.

Variables	Total n = 35	Prepubertal n = 16	Postpubertal n = 19
Age, years	9.6 ± 2.7	7.5 ± 1.4	11.3 ± 1.5
Range of age, years	5.5–16	5.5–9.5	10–16
Males, n (%)	21 (60%)	13 (81.25%)	8 (42%)
Females, n (%)	14 (40.0%)	3 (18.75%)	11 (58%)
Daily liquid intake, mL/m^2*	1635 ± 734	1480 ± 694	1740 ± 730
Daily urination, mL/m^2*	1270 ± 607	1125 ± 551	1383 ± 589

*Mean ± SD.

1.95 mEq/L on the third and seventh days of treatment, respectively. Blood osmolality values were 254.9 ± 20.15 mOsm/kg H_2O at the beginning and 260.5 ± 23.9 mOsm/kg H_2O and 260.4 ± 24.47 mOsm/kg H_2O on the third and seventh days of the study, respectively (Table 2). Urine calcium/creatinine values were 0.03 ± 0.01 mg/mg at the beginning, 0.06 ± 0.02 mg/mg on the third day, and 0.04 ± 0.01 mg/mg on the seventh day of the study. There were no significant changes of serum sodium level, serum osmolality, urine osmolality, or urine calcium/creatinine ratio (P = 0.618, P = 0.135, P = 0.088, and P = 0.423 respectively). No significant changes were seen in urine potassium level between the beginning and the seventh day of the study (P = 0.448) (Table 2). Two weeks after the initiation of treatment, effects of the medication were observed. In the follow-up period, the NE complaints of 80% (n = 28) of the patients had been successfully treated with desmopressin melt tablets. None of the patients had symptomatic side effects of headache, vomiting, dizziness, edema, or fatigue.

4. Discussion

The objectives of this study were to investigate the effect and tolerability of desmopressin on blood and urine electrolytes and osmolality in PMNE. In this sense, NE is an important public health problem for children and parents that affects the quality of life (15). Nocturnal polyuria (NP) and increased amount of urine during night time play a role in the pathophysiology of NE (4). NP may be caused by the disorder of the diurnal rhythm of secretion of ADH. NP is linked to decreased secretion of AVP (16–20). This is the basis of desmopressin response to treatment (7,8). AVP becomes effective on serum osmolality via V2 receptors. Aquaporin water channels of

Table 2. Serum and urine biochemical values at the beginning and after treatment on the 3rd and 7th days.

Variables*	Day 0	Day 3	Day 7	P-value
Serum calcium (mg/dL)	9.8 ± 0.34	9.8 ± 0.28	9.8 ± 0.33	0.941
Serum sodium (mEq/L)	137.0 ± 1.85	138.0 ± 2.07	137.0 ± 1.95	0.618
Serum potassium (mEq/L)	4.4 ± 0.43	4.3 ± 0.39	4.3 ± 0.46	0.631
Serum osmolarity (mOsm/kg H_2O)	254.9 ± 20.15	260.5 ± 23.9	260.4 ± 24.47	0.135
Urine sodium (mEq/L)	143.0 ± 51.95	154.5 ± 55.85	154.7 ± 79.93	0.714
Urine potassium (mEq/L)	67.2 ± 40.65	67.9 ± 39.38	79.1 ± 30.25	0.448
Urine osmolarity (mOsm/kg H_2O)	673.6 ± 244.4	798.3 ± 198.3	807.7 ± 198.1	0.088
Urine calcium (mg/dL)	4.5 ± 2.5	7.1 ± 3.1	6.1 ± 2.7	0.135
Urine creatinine (mg/dL)	121.6 ± 20.2	102.9 ± 16.4	122.2 ± 22.4	0.939
Urine calcium (mg)/creatinine (mg)	0.03 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.423

Mean ± SD.

the kidney present in epithelial cells of collecting ducts of type 2 are stimulated with the desmopressin V2 receptor and eventually provide water retention (21).

Desmopressin, a synthetic analog of AVP, treats enuresis by leveling the renal ion and water transport (7). Orally disintegrating tablets containing desmopressin (MINIRIN ® Melt, Ferring Pharmaceuticals, Saint-Prex, Switzerland), which are applied sublingually without water, have been available since 2005 and were recently approved for the treatment of nocturia in 57 countries (22). MINIRIN Melt is available in formulations of 60 µg, 120 µg, and 240 µg in Turkey. Vande Walle (23) et al. showed that to control diuresis for 7–11 h, which is a period similar to the sleeping time for children, 120 µg is better than the 60 µg form. Therefore, we prescribe the 120 µg oral form.

One of the most important side effects that may occur after desmopressin treatment is the antidiuretic effect caused by water retention and hyponatremia. Rembratt et al. carried out a metaanalysis study on 632 adult patients and among them 31 patients showed symptoms of hyponatremia, headache, nausea, vomiting, fatigue, dizziness, ataxia, and weight loss (24) due to urine osmolality increase after the administration of an antidiuretic hormone analog. Moreover, in other adult studies, there was also a significant change in the sodium levels (25,26). In our study, no significant hyponatremia developed in patients that received desmopressin treatment.

A placebo-controlled study by Rushton et al. (27) showed that there was an increase in urine osmolality in the desmopressin responsive group while there was no difference in the daily urinary osmolality. However, in our study, urinary osmolality did not change significantly after the desmopressin treatment. This could be related to the low number of patients.

Desmopressin treatment provides the regulation of ion and water transport (28). Chang et al. (25) and Kang et al. (26) showed that calcium excretion was increased in adult patients who used desmopressin. In our study, slightly increased urinary calcium excretion was determined, but it was not significant. Desmopressin may reduce the excretion of potassium by affecting the potassium Kir 1.1 channels located in the descending limb of Henle (29). However, in our study, there was no effect of desmopressin on potassium.

For ethical reasons, examining the effects of this agent in healthy children is not possible, so there was no control group in this study.

In our study, we found that urinary osmolality did not change significantly during the first days (days 3 and 7) of the treatment. In this short-term study of treatment of nocturia with antidiuretic hormone analogs, we observed no clinically significant adverse events caused by hyponatremia. It appears that this therapy can be safely used to treat nocturia patients. Unfortunately the number of patients (n = 35) and the follow-up period for blood and urine analysis (7 days) was limited. Therefore, to reach more reliable conclusions, there is a need for new studies including more patients and follow-up for longer periods. In this respect, for the long-term effect of desmopressin in these patients, prospective extension studies are needed.

Desmopressin appeared to be a well-tolerated drug and provided safe and effective treatment for children who were following fluid intake restriction proposals for PMNE.

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