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INCREASED URINARY CALCIUM EXCRETION IN ENURETIC CHILDREN TREATED WITH DESMOPRESSIN

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ABSTRACT

Purpose: The use of desmopressin in the treatment of primary nocturnal enuresis (PNE) is accepted and based on the fact that this drug leads to renal water reabsorption. However, recent findings have also implicated that desmopressin regulates other molecules, such as sodium and potassium. We investigate if desmopressin influences renal Ca^{2+} handling.

Materials and Methods: A total of 32 children with PNE were enrolled in a prospective study. Patients received a standard 30 μg desmopressin intranasally before going to bed. All patients were treated for at least 4 weeks. Desmopressin was then withdrawn and reintroduced after 2 weeks. Urine samples were collected during all 3 phases of the study. Ca^{2+} measurement was performed in single morning spot urines as well as in 24-hour collections. Additionally, blood was sampled for analysis of Ca^{2+}. The Wilcoxon signed rank test was used for statistical analysis.

Results: Wet nights decreased an average of 4.75 to 1.0 per week with desmopressin treatment. While blood concentrations did not change with or without medication, urinary Ca^{2+} excretion was significantly higher while patients were treated with desmopressin. This significant result was the same in single spot as well as in 24-hour samples.

Conclusions: This study demonstrated the increased excretion of Ca^{2+} by desmopressin treatment in children with PNE. Since Ca^{2+} is a crucial molecule in growth and development, this finding indicates the necessity of larger followup studies concerning Ca^{2+} handling and growth in children on long-term desmopressin treatment.

KEY WORDS: desmopressin, calcium, kidney, enuresis

Primary nocturnal enuresis (PNE) is one of the most frequent complaints in pediatric practice. Several different factors such as reduced functional bladder capacity, and endocrinological and neurological disorders are attributed to PNE.[1–3] The use of desmopressin (DDAVP), a synthetic analogue of the endogenous hormone arginine vasopressin, for the treatment of nocturnal enuresis is based on its antidiuretic action.[4] Desmopressin binds to the renal V_2-receptor located at the basolateral side of renal cortical collecting duct cells. This leads to a cyclic adenosine monophosphate mediated insertion of the waterchannel aquaporin-2 into the apical membrane and subsequent reabsorption of H_2O.[5] However, recent studies provided evidence that desmopressin influences other renal transport systems as well.

In vivo studies demonstrated that arginine vaspression regulates the abundance of the furosemide sensitive sodium-2 chloride-potassium channel.[6] Other sodium transporters, such as the amiloride sensitive epithelial sodium channel, have also been shown to be regulated by desmopressin.[7] Moreover, use of gene expression profiling has shown that molecules not directly involved in transport processes are influenced by desmopressin administration.[8] These data implicate that desmopressin has far more complex primary or secondary regulatory activity on several renal transport systems than anticipated.

Since desmopressin proved to be an effective agent for PNE, its use is widely accepted but studies concerning the influence of this drug on renal ion handling in children with PNE are lacking. Especially for the mid-term and long-term use of desmopressin, it is not known whether this drug has other than isolated antidiuretic effects. This question is of special importance in children since several molecules are essential to guarantee adequate growth and development. Valenti et al demonstrated close correlation between hypercalciuria and aquaporin-2 excretion in children with PNE.[9] Likewise, the same authors were able to demonstrate a reduction in nocturnal enuresis episodes in hypercalciuric children when treated with a low calcium diet and desmopressin.[10] Controversely, Nevéus et al were not able to find a significant difference between the Ca^{2+} excretion in children with PNE and controls.[11] Therefore, we evaluate whether desmopressin treatment influences urinary excretion of Ca^{2+} in children with PNE.

PATIENTS AND METHODS

Enuresis was defined by 3 or more wet nights a week. The study included 15 girls and 17 boys 6.2 to 16.5 years old (median age 9.8) with primary nocturnal enuresis who had never been dry for longer than 3 months and had no daytime symptoms. No patient had received drug therapy for enuresis before entering the study. Diagnosis was confirmed by exclusion of anatomical abnormalities on ultrasound, and unremarkable urinalysis and serum analysis.

Patients received the standard 30 μg desmopressin intranasally before going to bed for at least 4 weeks. Desmopressin was then withdrawn, reintroduced after 2 weeks and continued for at least another 3 weeks. Urine samples were collected at the end of all 3 phases of the study. Ca^{2+} measurement was performed in single morning spot urines of 2 consecutive days as well as in 24-hour collections. The parents were asked to ensure that the collections were performed on dry nights. Additionally, blood was sampled for analysis of Ca^{2+}. The data are given as arithmetic mean with

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TABLE 1. *Ca (24-hour urine) excretion*

	DDAVP		No Therapy		DDAVP	
	Ca (mmol)	Vol (ml)	Ca (mmol)	Vol (ml)	Ca (mmol)	Vol (ml)
Mean	**2.93**	678	**2.32***	718	**3.05**	735
SD	1.57	292	1.43	284	1.66	237
Median	**2.58**	600	**2.29***	700	**2.49**	710
Min	0.99	185	0.31	110	0.73	380
Max	7.61	1,300	5.50	1,420	6.83	1,170
95% CI	2.25–2.91		1.23–2.93		1.87–3.82	

* Significant.

TABLE 2. *Ca (spot urine) excretion*

	Ca Creatinine (μmol/mmol)		
	DDAVP	No Therapy	DDAVP
Mean	**303**	**262***	**364**
SD	208	187	205
Median	**251**	**196***	**312**
Min	68	55	131
Max	1,105	902	1,091
95% CI	180–320	158–287	255–397

* Significant.

standard deviation, median, 95% confidence interval of the median and range. Differences were tested using the nonparametric Wilcoxon signed rank test, with $p = 0.05$ considered significant.

RESULTS

Without therapy the children had 4.75 wet nights per week versus 1 per week with desmopressin ($p < 0.001$). During the first 4 weeks of desmopressin therapy, withdrawal and second therapy course serum Ca^{2+} did not change significantly and remained in the range of normal, healthy children.

Urinary Ca^{2+} excretion per 24 hours decreased significantly during the first desmopressin (DDAVP) therapy ($p = 0.048$) and withdrawal, and increased with reintroduction of desmopressin ($p = 0.044$, table 1). The differences in Ca^{2+}-concentrations in the morning spot urines between therapy and withdrawal conditions were even more distinct. The creatinine related concentration measured in the first 4 weeks of therapy was 303 μmol/mmol and decreased without therapy to 262 μmol/mmol, which was significant ($p = 0.047$). At restart of therapy the Ca^{2+}-concentration increased significantly to 364 μmol/mmol ($p = 0.003$, table 2).

DISCUSSION

In this prospective study we confirmed that desmopressin in children with PNE influences urinary Ca^{2+} excretion. We reproduced the beneficial effect of desmopressin on nocturnal enuresis as wet nights decreased from 4.75 to 1.0 per week. According to our experiences and those published in the literature, the overall success rate of desmopressin treatment ranges from 35% to 65%.[12] This success is comparable to other treatments used for PNE, such as the bell pad and tricyclic antidepressants (eg imipramine).[13,14] From this point of view, our patients did not differ from others with PNE and, therefore, were considered as a standard patient group for this study.

From our prospective study we learned that desmopressin increases urinary Ca^{2+} excretion in children with PNE. This finding was unexpected, since studies of primary cultures of rabbit distal nephron cells showed increased transcellular Ca^{2+} transport.[15] In addition to these renal effects, there is evidence of nonrenal effects in the treatment of PNE.[16,17] From the clinical point of view it has been known for a long time that hypercalciuria is an important cause of frequent voiding and dysuria in children.[18] It is also established that hypercalciuria is one of the most frequent causes of microhematuria in childhood.[19] The influence of hypercalciuria on PNE itself has been demonstrated.[20] The hypothesis for this symptom is that microcrystallization of Ca^{2+}, PO_4^{3-} and oxalate occurs and causes microtrauma and irritation to the urethral and bladder mucosa, which is followed by spontaneous contractions and bladder emptying.

Our prospective study, which was controlled by withdrawal and reintroduction of desmopressin, is to our knowledge the first to describe renal Ca^{2+} handling during desmopressin treatment in children with PNE. While in vitro and animal studies suggest a positive effect of desmopressin on renal tubular Ca^{2+} reabsorption, our findings demonstrate the opposite effect in humans. To rule out the possibility that increased urinary Ca^{2+} values were just a result of a more concentrated urine, we measured Ca^{2+} excretion as the ratio of urinary Ca^{2+} and urinary creatinine (spot urines), and we obtained complete 24-hour urine samples and calculated absolute Ca^{2+} excretion daily. For both methods we obtained a slight but significant increase in urinary Ca^{2+} excretion while children were treated with desmopressin. In 30 of the 32 cases urinary Ca^{2+} excretion stayed within the normal range with and without desmopressin treatment. The remaining 2 patients already had hypercalciuria which was aggravated by desmopressin.

These data support the finding that desmopressin causes more than a simple antidiuretic effect by renal water reabsorption. Accordingly, Ca^{2+} must be added to the list of molecules that are influenced by desmopressin. This finding requires further investigation since Ca^{2+} is a crucial molecule in growth and development. Although desmopressin treatment did not increase Ca^{2+} excretion dramatically, the difference is significant if a long-term treatment is considered. Compensation mechanisms for renal Ca^{2+} loss include increased intestinal reabsorption but also Ca^{2+} resorption from bone.

CONCLUSIONS

Based on these findings, we include urinary Ca^{2+} excretion before and during treatment of PNE into the routine diagnostic followup. Long-term followup studies are needed to clarify the impact of desmopressin on Ca^{2+} excretion in children with PNE concerning different parameters such as bone densitometry, parathyroid hormone, osteocalcin or calcitonin.

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