Increased urinary calcium excretion in enuretic children treated with desmopressin

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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 Desmopressin was then withdrawn and reintroduced after 2 weeks.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 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
standard deviation, median, 95% confidence interval of the median and range. Differences were tested using the non-parametric 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 \( \mu \text{mol/mmol} \) and decreased without therapy to 262 \( \mu \text{mol/mmol} \), which was significant (\( p = 0.047 \)). At restart of therapy the Ca\(^{2+}\)-concentration increased significantly to 364 \( \mu \text{mol/mmol} \) (\( p = 0.003 \), 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 microharmuria 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 xulate 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 calcitomin.

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