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DESMOPRESSIN HAS AN INFLUENCE ON THE AROUSABILITY OF CHILDREN WITH PRIMARY NOCTURNAL ENURESIS

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ABSTRACT

Purpose: Several studies provide evidence regarding the effect of desmopressin (DDAVP) on the sleep of adults. Therefore, we investigate whether this effect has a role in children with primary nocturnal enuresis treated intranasally with DDAVP.

Materials and Methods: A prospective, randomized, placebo controlled, double-blind, crossover study was performed. Patients were assigned to 2 groups by lottery. Arousability was determined by a special bell apparatus with an adjustable sound pressure level. The wet nights per week and the results of the arousal tests were compared using the signed rank test.

Results: A total of 20 children with primary nocturnal enuresis 6 to 15 years old were enrolled in the study, 2 of whom had to be excluded. There were no marked differences in age or weight between the groups. The number of wet nights per week decreased significantly with DDAVP treatment. Moreover 14 patients slept more soundly with DDAVP and only 4 were more difficult to awake after the medication. This difference was significant.

Conclusions: This study revealed an effect of DDAVP on arousability of enuretic children as well as its previously known action for the treatment of primary nocturnal enuresis. This result is consistent with the known action of DDAVP on sleep of elderly adults. It suggests that the cause of primary nocturnal enuresis lies in the structure of sleep of the affected patients.

KEY WORDS: desmopressin, enuresis

An accepted therapy of primary nocturnal enuresis (PNE) is treatment with desmopressin (DDAVP).[1] This treatment is based on the hypothesis that affected children have insufficient secretion of antidiuretic hormone at night[2] and, in combination with a relatively low bladder capacity, nocturnal enuresis occurs.[3] However, this concept has been contradicted.[4–6] An emerging hypothesis supported by increasing data indicates that not only renal, but also a central effect of DDAVP may be, at least partially, responsible for the therapeutic effectiveness of DDAVP on children with PNE.[7] In the current literature studies provide evidence regarding the effect of DDAVP on sleep of adults.[8,9] Therefore it seems possible that DDAVP also affects the sleep of children treated for PNE. We determined if DDAVP has an influence on the arousability of children with primary nocturnal enuresis.

METHODS

A prospective, randomized, placebo controlled, double-blind, crossover trial was conducted to determine whether DDAVP has an influence on the arousability of children with PNE. The children were tested under DDAVP and placebo conditions. Children were recruited through the enuresis clinics and those with a documented history of PNE were enrolled in the study. Physical examination, urinalysis, blood test and renal ultrasound were performed at the first visit. Eligible children were older than 6 years with monosymptomatic PNE, normal bladder capacity and a minimum of 2 wet nights a week for 2 consecutive weeks. Children with frequent urinary tract infections and urological or neurological abnormalities were excluded from study. No patient was allowed to take medication such as DDAVP or use conditioning therapy to treat PNE during the 3 months before study entry.

Design. The study consisted of a 1-week placebo (medication 1) period (placebo controlled) and a 1-week drug (medication 2) period. Subjects were randomly assigned to either group 1 or 2 (randomized). Group 1 started with medication 1 and switched to medication 2 after 1 week, while group 2 was treated in analogous fashion (crossover). During all periods identically appearing nasal sprays containing 30 μg DDAVP or placebo were taken shortly before bedtime. Neither the study personnel, children nor parents knew the assignment of drug or placebo to medication 1 or 2 (double-blind). After the first 1-week period (group 1 received medication 1, group 2 received medication 2) the first arousal trial was conducted. After the first arousal trial the groups switched medications (group 1 received medication 2, group 2 medication 1) and after a second 1-week period a second arousal trial was performed.

Arousability. Arousability was measured at home by a special bell apparatus that produced a tone of 1,000 Hz for 3 seconds and adjustable sound pressure level (SPL). To ensure that sleep was not disturbed before the actual arousal trial the apparatus was operated by study personnel from a separate room. The arousal test began near midnight with repetitions of tones of 3-second durations each at a SPL of 50 dB. If the child awoke, the number of repetitions at this lowest sound pressure level was taken as a measure of arousability. If the child did not awake after 10 repetitions, the loudness was increased to 60 dB. Again 10 repetitions 3 seconds each were used to try to awake the child. The loudness of the tone was increased in 5 steps (50, 60, 70, 80, 85 dB). To confirm that the child was fully awake he/she had to repeat a code word that was given before going to sleep. If the patient did not awake after 20 repetitions at a SPL of 85 dB the trial was stopped.

Data management. Data (age, wet nights) are given as median and 95% confidence interval. Differences were tested

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Arousal test results

Arousal Test	Arousal Level*	Medication No.
Pt 1:		
1	1.1	1
2	3.1	2
Pt 2:		
1	1.1	1
2	1.4	2
Pt 3:		
1	3.3	2
2	1.9	1
Pt 4:		
1	5.20	2
2	4.1	1
Pt 5:		
1	5.13	1
2	5.20	2
Pt 6:		
1	5.20	2
2	5.10	1
Pt 7:†		
1	2.7	2
2	5.20	1
Pt 8:†		
1	4.7	1
2	3.1	2
Pt 9:†		
1	5.20	1
2	3.5	2
Pt 10:		
1	4.5	2
2	1.5	1
Pt 11:		
1	5.20	2
2	3.5	1
Pt 12:†		
1	5.20	1
2	5.1	2
Pt 13:		
1	3.5	1
2	5.20	2
Pt 14:		
1	2.1	1
2	2.2	2
Pt 15:		
1	4.4	1
2	5.20	2
Pt 16:		
1	4.4	1
2	5.20	2
Pt 17:		
1	1.4	2
2	0	1
Pt 18:		
1	2.1	1
2	2.8	2

* First number represents sound pressure level (eg 1 is 50 dB, 2 is 60 etc) and the second number represents the number of repetitions at this level (eg 4.10 corresponds to 10 signals of 3 seconds each at 80 dB).

† More difficult to awake under placebo conditions.

using the nonparametric Wilcoxon signed rank test. The results of the arousability tests were compared by the paired sign test, thus every patient was his/her own control. The level of significance was $p = 0.05$.

RESULTS

A total of 15 boys and 5 girls with PNE 6.2 to 14 years old (median age 8.3 years, 95% CI 7.3–9.5) fulfilled the study entry criteria. Patients were assigned to group 1 or 2, and both groups were comparable in regard to baseline characteristics (age, weight, sex). Medication 1 consisted of DDAVP and medication 2 was placebo. The average number of wet nights per week decreased significantly from 5.2 to 3.8 with DDAVP treatment ($p = 0.02$). Two subjects had to be excluded from study because they tried to cheat during the tests. Of the 18 remaining patients 14 were more difficult to awake with DDAVP treatment while only 4 slept more soundly under placebo conditions, which was significant ($p = 0.03$) (see table).

DISCUSSION

Since Trousseau's first description in 1868,[10] patients with PNE were characterized by a sound sleep. It is surprising that research has not confirmed that children with PNE are difficult to awake.[11–13] In 1997 Wolfish et al showed that enuretic boys were more difficult to arouse than age matched controls.[14] They assumed that the increased arousal thresholds may be due to delayed maturation and that treatment programs "that rely on awakening should be aware of these features."

Our data seem to be incompatible with the aforementioned results. Why should a child with PNE treated successfully with DDAVP sleep even more soundly than without therapy? This is not the important question, because 70% of enuretic children treated successfully with either drugs or alarm therapy will not awake to go to the bathroom but will remain asleep and stay dry the entire night. Therefore, it seems more likely that the therapy does not alter the ability to awake, but has an influence on the structure of sleep. Using this hypothesis as a basis, there is a broad correlation with findings that demonstrate an influence of vasopressin on adult sleep.[8,9,15] These findings show that elderly people have more sound sleep and the structure of sleep changes with a substantial reduction in rapid eye movement sleep. Although until now not consistent, there is growing evidence that not the depth, but the structure of sleep may be crucial in the pathogenesis of PNE.[16–18] However, until further studies based on these results are performed to confirm this hypothesis, the data suggest that the central effect of DDAVP is crucial to the treatment of PNE.

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EDITORIAL COMMENT

Arginine desmopressin was first used to treat primary nocturnal enuresis in 1977. Since that time, it has been a mainstay of medical therapy for bedwetting with a high efficacy but equally high relapse rate. The rationale in using DDAVP has been to decrease nocturnal urine output, which presumably should reduce wetting episodes whether the cause of the enuresis is relative nocturnal polyuria or decreased functional bladder capacity. However, there has been a paucity of evidence supporting decreased urine output or increased osmolality as correlating with efficacy of DDAVP in treating bedwetting.

Parents of children with enuresis also frequently report that the children are "heavy sleepers" and difficult to arouse. If this is the case (although there is little supporting evidence beyond the anecdotal), we would expect that a medication with a proven track record in treating nocturnal enuresis should increase arousability, making the children more likely to awaken to the stimulus of a full bladder. Eggert et al deliver just the opposite answer. In fact, in this excellent double-blind, placebo controlled study enuretic children were more difficult to awake after administration of DDAVP, despite a significant reduction in wet nights. A well-done prospective, randomized, controlled study such as this elevates the level of clinical science in pediatric urology and is ultimately the best way to answer the questions we all encounter in our daily practice.

To what then are we to attribute the effect of DDAVP on bedwetting? Enuretics have been shown to have a normal structure to sleep and wetting has been shown to occur in all stages of sleep. However, the authors correctly note that DDAVP has been shown to affect the sleep cycle. Specifically, it reduces the amount of rapid eye movement sleep, while not altering overall duration of sleep. DDAVP has also been shown to have other central nervous system effects, such as improvement in memory in humans and animals. This study lends further credence to the idea that nocturnal enuresis is a central nervous system disorder rather than simply a bladder disorder. Future investigations in the field of nocturnal and diurnal incontinence in children should center on the interaction of the central nervous system and bladder, rather than looking at the bladder in isolation.

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