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THE EFFECT OF DESMOPRESSIN ON SHORT-TERM MEMORY IN CHILDREN WITH PRIMARY NOCTURNAL ENURESIS

DOMINIK MÜLLER, HELKE FLORKOWSKI, KERSTIN CHAVEZ-KATTAU, GÖRAN CARLSSON AND PAUL EGGERT

From the Children's Hospital, University of Kiel, Kiel, Germany

ABSTRACT

Purpose: The use of desmopressin in patients with primary nocturnal enuresis is based on the hypothesis of a nocturnal lack of endogenous arginine vasopressin. However, in addition to the kidney, other targets of desmopressin are known. Therefore, we examined whether the administration of desmopressin influences central nervous function in children with primary nocturnal enuresis.

Materials and Methods: Our prospective, randomized, double-blind, placebo controlled cross-over study was performed on 40 children with nocturnal enuresis. Patients were randomly assigned to receive either 20 µg. desmopressin intranasally or 0.9% saline solution. Each group comprised 19 and 21 to children, respectively. After 2 weeks the groups were switched. The children were tested for short-term memory and reaction time to both treatments. Statistical analysis was done using the Wilcoxon matched pairs test.

Results: Median patient age was 8.0 years (range 6 to 13). During desmopressin treatment children in both groups had a significant decrease of wet nights (5.3 to 3.2 per week). In contrast to reaction time, short-term memory was significantly different between both groups ($p < 0.05$).

Conclusions: Our results demonstrate an increase in short-term memory after desmopressin treatment in children with nocturnal enuresis. This finding indicates the central nervous system as a target involved in the pathogenesis of nocturnal enuresis as well as the therapeutic benefit of desmopressin treatment.

KEY WORDS: enuresis; desmopressin; memory, short-term; arousal

Primary nocturnal enuresis or nightly bed-wetting affects about 5% of all children at the beginning of school age.¹ Desmopressin, a synthetic analogue of arginine vasopressin (AVP), has been established as efficient treatment for this condition based on the hypothesis of a nocturnal lack of endogenous AVP.² However, other studies failed to confirm this pathophysiological background,³ and we also had additional concerns about the hypothesis of nocturnal AVP deficiency. First, other therapeutic regimens, such as the bell pad or tricyclic antidepressants (imipramine), are known to be as effective as desmopressin although their mechanisms of action are thought to be different.⁴ Second, affected children exhibit other striking symptoms that can hardly be explained by a nocturnal renal concentration defect. They often experience a markedly deep sleep, and enuresis occurs in the afternoon sleep as well.⁵ These latter points implicate involvement of the central nervous system in the pathophysiology of the disorder as well as the therapeutic success of desmopressin. Since it has been demonstrated that desmopressin exhibits stimulating effects on the central nervous system, we evaluated the influence of desmopressin on central nervous functions represented by reaction time and short-term memory in children with primary nocturnal enuresis.⁶ For this purpose we designed a prospective, randomized, double-blind, placebo controlled cross-over study design.

PATIENTS AND METHODS

Enuresis was defined by 3 or more wet nights a week. The study included 11 girls and 29 boys with nocturnal enuresis who had never been dry for longer than 2 months. The patients had never received therapy for enuresis before entering the study. Diagnosis was confirmed by exclusion of

anatomical abnormalities on ultrasound, and unremarkable urinalysis and serum analysis. At study entry the children were randomly assigned to group 1 (20 µg. desmopressin) or group 2 (0.9% saline solution placebo). Desmopressin and placebo were given as intranasal spray. The patients received either desmopressin or placebo in double-blind fashion. After 2 weeks the groups were switched.

All children were tested before, and during placebo and desmopressin. To assess short-term memory patients were asked to listen to 10 words given by a blinded examiner. The child had the chance to learn these words in a course of up to 10 repetitions. After 30 minutes the children were asked to recall as many words as possible. The number of words the child was able to recall was used as a measure of short-term memory. During each test period the words given were the same for every child.

A standardized computer program was used to determine reaction time. Managed by this program, targets (monsters) appeared randomly on the screen. The children were asked to hit as many targets as possible in a limited time span by pressing on a button on a joystick. To hit the targets they had to press the button within a limited (0.5 second) time span. The younger children (6 to 8 years old) "played" for 5 minutes during which 60 targets appeared, and the older children had a test period of 10 minutes with 160 targets. The ratio of the sum of all single reaction times (time of target appearance until pressing the button) and total number of the targets was used to measure reaction time. Desmopressin and placebo were given 30 minutes to 1 hour before the tests, and before going to bed on all other days.

The results are presented as median values, 95% confidence intervals (CI) of the median and ranges. Differences were tested using the nonparametric Wilcoxon signed rank test, with $p = 0.05$ considered significant. After receiving

detailed information, all parents provided written consent, and the ethical committee of the Christian Albrechts University of Kiel approved the study.

RESULTS

A total of 14 boys and 5 girls were assigned to group 1 and 15 boys, 6 girls were assigned to group 2. Mean patient age was 8.7 years (median 8.9, range 6 to 13) in group 1 and 8.6 years (median 8.0 and range 6.3 to 11.9) in group 2. Neither group differed significantly in regard to gender, weight and height.

Enuresis. Before entering the study patients had a mean of 5.35 wet nights a week (median 5.5, 95% CI 4.5 to 6.0). Under study conditions there was a slight decrease of wet nights in group 2 to 4.9 wet a week (median 5.25, 95% CI 4.5 to 6.0) but the difference was not significant. Treatment with desmopressin led to a decrease of wet nights to 3.27 (median 3.0, 95% CI 2.0 to 4.0), and the difference between both groups was highly significant ($p < 0.001$).

Reaction time and short-term memory. Mean reaction times were 455 milliseconds (median 441, 95% CI 425 to 456) without any medication, 417 (median 403, 95% CI 381 to 415) with placebo and 418 (median 404, 95% CI 381 to 415) with desmopressin, which was not statistically significant.

Although in both groups the number of repetitions to learn the 10 items were nearly identical (mean 6.33 versus 6.17, median 6.0 versus 6.0, 95% CI 5 to 8 versus 4 to 8), the number of words the children were able to recall was significantly different. Of the 40 children 9 were able to recall more words under medication than placebo, and 1 child recorded less items. This difference in short-term memory was significant ($p = 0.012$).

DISCUSSION

Our study confirmed the known efficacy of desmopressin for nocturnal enuresis, as 27 patients (67.5%) were responders. We also learned from our study that children with primary nocturnal enuresis treated with desmopressin had significant improvement of short-term memory. Before discussing the latter regarding enuresis, it is necessary to determine whether systematic errors could have led to this finding.

Our 2 groups were created at random and were similar in regard to age, gender, weight and height. Although the study was performed in a cross-over manner, it seemed important to exclude unsymmetrical effects, and so the study had a double-blind design. To exclude the possibility of lifting the blinding, the examiner had no information about the order of the enuresis protocols which, as with all other data, was evaluated at the end of the study. To keep the patients blind the desmopressin dose was rather low compared to the recommended therapeutic dose.¹ Therefore, the effect was often not impressive but the children and their patients were unable to identify the medication.

It is important to determine whether our test actually measured short-term memory. Memory process can be divided into acquisition and retention. Retention (long-term memory) is usually studied as delayed recall score and acquisition (short-term memory) can be assessed as memory span or learning curve.⁷ Recalling verbal material, consisting of common and unrelated words, immediately after hearing has proved to be appropriate for this case.⁸ The choice of only 10 words for this test did not discriminate well because many children easily recalled all 10 items immediately. Therefore, optimal improvement between placebo and desmopressin was difficult to demonstrate. Possibly 15 or 20 words would have been more effective to differentiate between the groups. However, for statistical reasons it was impossible to increase the number of words during the study. Overall, after thorough consideration the influence of desmopressin on short-

term memory in children with nocturnal enuresis appears to have been proved.

In many studies AVP and its analogue, desmopressin, as well as their metabolites have been found to act as potent neurotransmitters in the central nervous system.⁹⁻¹¹ Their effects on behavioral consequences and on memory have been investigated extensively.^{12,13} Weingartner et al demonstrated in a cohort of patients with Korsakoff's syndrome that desmopressin increased short-term memory.⁶ Additionally, other investigators found that even while short-term memory was significantly improved, middle and long-term memory remained unaffected.

Short-term memory or working memory is dependent on attention functions, and associated with frontal lobe functions and the arousal system. Therefore, short-term memory may constitute an indirect measurement of "alertness" of an individual. This arousal system, or ascending reticular activating system,¹⁴ has originally been located in the brain stem but recent studies have focused on 4 major systems for the arousal effect, which can be characterized by their different neurotransmitters. Noradrenaline, serotonin, acetylcholine and histamine currently are known, with the noradrenaline dependent system involving the locus coeruleus being the most important.¹⁵⁻¹⁷ Furthermore, in the last few years feedback loops from the bladder to the central nervous system ending in these cerebral regions have been identified, establishing a functional link between arousal and bladder control.¹⁸

This mechanism exhibits important implications for nocturnal enuresis, since a delay of maturation of this system could explain the deep sleep, uncontrolled bed-wetting and self-limitation of the disorder. Furthermore, the known stimulatory effect of desmopressin on this system may explain its therapeutic benefit: This effect on the arousal system leads to a higher sensitivity for the signals emerging from the bladder. These signals are usually suppressed unless the bladder is filled completely, and when they are not suppressed, involuntary contractions and enuresis occur.¹⁹ This process has been defined as an instable bladder and often has been confused with small bladder volume. The fact that it has never been shown convincingly that children with nocturnal enuresis have higher urinary volumes than normal children supports this thesis well. This finding is in line with the results of the studies of Watanabe et al who reported²⁰ that sleep pattern of children with nocturnal enuresis did not differ from that of a control population as far as the classic sleep stages were concerned.²⁰ However, there was a difference in a waking, that is the arousability was reduced compared to a control population.²¹

The results of our investigation fully support the aforementioned hypothesis. We demonstrated that desmopressin influences the central nervous system in children with nocturnal enuresis. Our results suggest that the pathophysiology of nocturnal enuresis as well as the success of desmopressin treatment is not located primarily in the kidney and that its central action needs further investigation. Efforts are needed to clarify the exact basis of the disorder as well as the molecular action of desmopressin on the central nervous system.

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