

Desmopressin in nocturnal enuresis

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SUMMARY The response of desamino-D-arginine vasopressin (DDAVP) was investigated in 32 enuretic children in a double-blind clinical study. The 15 children treated with DDAVP showed a significant reduction in the incidence of bed wetting—from 18.7 ± 6.5 to 6.5 ± 9.2 wet nights per 30 days. In 6 children bed wetting stopped entirely, in 6 there was a satisfactory response, and in 3 the response was marginal or there was none. When DDAVP was stopped most children reverted to their earlier bedwetting habits (15.7 ± 8.9 nights a month). Response to DDAVP was significantly better in children aged more than 10 years (mean age for the entire group). The administration of DDAVP was not associated with any appreciable change in morning urine osmolalities. No adverse effects were noted. It is concluded that DDAVP is effective in nocturnal enuresis, particularly in older children. It is suggested that the cessation of bed wetting may, in part, reflect functional properties of DDAVP rather than antidiuresis.

Enuresis nocturna (EN) is a common, age-related complaint in childhood.^{1,2} for which there is as yet no clear treatment. Antidepressant drugs³ and electrical conditioning devices⁴ have been used with a modicum of success, despite side effects.

Recently DDAVP was administered with considerable success to children with EN,^{5–7} and its beneficial effects were attributed to antidiuretic properties.^{6,7} The aim of this study was to evaluate the response of children with EN during and after the administration of DDAVP, and to assess the effect of this drug on morning urine concentration.

Material and methods

Thirty-two (15 boys and 17 girls) children with EN, whose ages ranged from 7 to 15 years, took part in a double-blind study. Any child known to have an organic disease of the urinary tract was excluded; however, 3 patients had a history of urinary tract infections and of healed vesicoureteric reflux.

A complete case history was taken and physical examination, urine analysis, and urine culture were performed at the start of the study, and repeated thereafter.

The children were studied during three 30-day periods, before, during, and after the treatment. The treatment consisted of DDAVP (desamino-D-arginine vasopressin, Ferring AB, Sweden), 10 µg, or placebo, administered intranasally, before bedtime, every day, for 30 days. The study was randomised

and the code was known to neither participants nor investigators. Bed-wetting episodes were recorded every morning for 90 days. A night in which bedwetting had occurred at least once was called a 'wet' night.

Since the first morning urine in children with persistent EN is probably the product of the last hours of the night, its osmolality may be higher than the first morning urine produced throughout the entire night by the children who do not wet their beds. For the purpose of assessing concentration capacity we therefore measured the osmolality of the second morning urine sample before any fluid intake.

Informed consent was obtained in each case from one of the parents.

Data were analysed by the Student's *t* test and are presented as mean \pm SD.

Results

Fifteen (7 boys and 8 girls) children received DDAVP, and 17 (8 boys and 9 girls) children received placebo (Table 1). In the DDAVP group 12 children had been treated previously with chlorimipramine hydrochloride, 2 of whom had responded; in the placebo group 3 of the 11 patients who had been treated in the past with chlorimipramine hydrochloride had responded well to the drug.

A familial history of EN was elicited in 4 children

Table 1 Clinical data and second morning urine osmolalities in the DDAVP and placebo-treated children

	DDAVP (n=15)	Placebo (n=17)
Boys	7	8
Girls	8	9
Age (years)	10.5 ± 2.2	10.0 ± 2.5
Patients with a family history of enuresis	4	6
Urine osmolality		
Before treatment	1032 ± 147	920 ± 135
During treatment	1006 ± 210	918 ± 164
After treatment	919 ± 181	911 ± 165

of the DDAVP group, and in 6 of the control group. Mean age was 10.5 ± 2.2 (median 10.0) and 10.0 ± 2.5 (median 9.5) years in the DDAVP and control groups respectively.

Second morning urine osmolalities before, during, and after treatment were 1032 ± 147, 1006 ± 210, and 919 ± 181 mmol/l in the DDAVP group and 920 ± 135, 918 ± 164, and 911 ± 165 mmol/l in the placebo group. There were no significant differences in urine osmolality between the two groups in any of the study periods. Morning urine osmolality did not change after administration of DDAVP.

Placebo administration was not associated with any significant change in the number of wet nights: 21.3 ± 8.5, 18.8 ± 8.3, and 16.9 ± 9.4 during the three periods—before, during, and after the administration of the placebo.

In the group of children on DDAVP the number of wet nights decreased significantly from 18.7 ± 6.5 to 6.5 ± 9.2 (P < 0.01). Response was prompt and could be seen as early as 1–3 days after drug administration. When the treatment was stopped the number of wet nights rose to 15.7 ± 8.9, a value not significantly different from that observed before DDAVP (Figure).

Results were assessed as excellent (no wetting), satisfactory (fewer than 7 wet nights per 30-day period), or as unsatisfactory. The administration of DDAVP resulted in excellent results in 6 children, and in satisfactory results in 6 others. In 3 patients the results were unsatisfactory: the number of wet nights was changed from 27 to 12 in one child, from 28 to 25 in another, and from 24 to 30 in the third. In the children of the placebo group only one child had an excellent response and one had a satisfactory response (Table 2).

If the children taking DDAVP are placed in two groups according to their ages, the older children (mean age > 10 years) had better results (6 children with excellent results and one in whom the response was satisfactory); in the younger group (mean age < 10 years) results were less satisfactory (5 had satisfactory responses and 3 failed to respond to

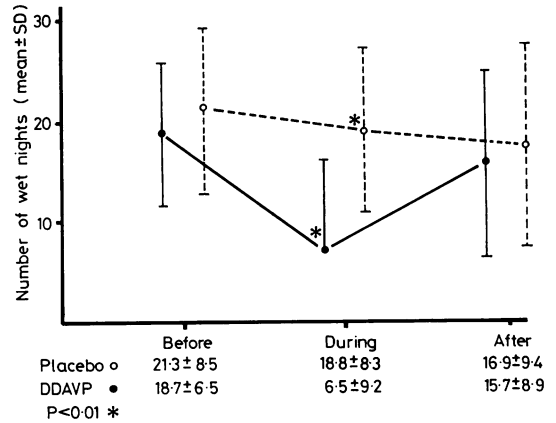


Figure Number of wet nights (per 30 days) before, during, and after administration of DDAVP or placebo.

Table 2 Response to DDAVP or placebo administration in 32 children with nocturnal enuresis

	Excellent	Satisfactory	Unsatisfactory
DDAVP	6	6	3
Placebo	1	1	15

Excellent = no bed-wetting, satisfactory = fewer than 7 wet nights a month, unsatisfactory = more than 7 wet nights a month.

Table 3 Age-related response to DDAVP administration in children with nocturnal enuresis

Age (years)	Excellent	Satisfactory	Unsatisfactory
< 10	—	5	3
> 10	6	1	—

P < 0.01 for the two age groups.

DDAVP) (Table 3). The difference between the responses in the two age groups was significant (P < 0.01).

None of the children treated with DDAVP had any side effects.

Discussion

This double-blind study, similar to several others^{5–7} shows again that DDAVP is a potent drug in the prevention of EN. There were minimal side effects or none at all after the administration of DDAVP in this series, as in others.^{5–7}

The response to DDAVP was particularly gratifying in children older than age 10 years. The results do not seem to favour the hypothesis of dose-related response curve. Response to treatment

was similar when 20 µg of DDAVP, double the dose we used, was administered by others.⁶ The significantly higher response rate among older children, despite a fairly low dose of DDAVP per kg, also argues against a dose-related response.

As in previous reports,^{5,6} most of our patients reverted to bed wetting once DDAVP was stopped.

It has recently been suggested that EN is associated with reduction in the nocturnal urinary concentrating ability of the subject; and that the effect of DDAVP on EN is due to its antidiuretic properties. However, none of the data presented so far showed an improvement in this respect after the administration of DDAVP⁷ and no evidence of a reduced urine concentration ability was shown in the children we studied.

If the good effect of DDAVP were entirely due to its antidiuretic properties, and since the degree of antidiuresis due to vasopressin is dose-dependent, better results should have been obtained in our lower age group rather than worse ones. However, since no overnight urine collections were taken it may be argued that DDAVP induces a state of antidiuresis in the first hours of the night which contributes to the cessation of bedwetting.

Our data show that DDAVP when administered daily for one month was effective in controlling EN during that period. Additional studies during longer periods of treatment need to be done in order to assess any permanent effects that DDAVP may have in controlling EN. Bed-wetting generally occurs during non-rapid eye movement sleep, a state associated with mental confusion, lack of response to a wide range of stimuli, retrograde amnesia, automatic behaviour, and poor response to efforts to provide behaviour wakefulness.⁸ It has been suggested that DDAVP effects the process of memory consolidation,⁹ improves attention, concentration, recognition, and recall¹⁰ and that it reverses amnesia.¹¹ It is tempting to relate, at least in part, the cessation of bedwetting to DDAVP induced improvement in these processes.

We conclude that DDAVP is a safe and useful tool in the treatment of EN, particularly in older children. We suggest that the effect of DDAVP on EN may not be solely due to its antidiuretic activity.

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Commentary

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The medical literature is littered with papers reporting the use of different drugs in the treatment of enuresis. There are few drugs that have not been tried! Unfortunately most of the drug trials have been conducted poorly. The authors of this paper have completed a carefully controlled trial. They found that DDAVP enabled a proportion of children to become dry while they were taking the drug. Previously the only clear evidence of successful drug therapy had come from the tricyclic antidepressant drugs—such as imipramine and amitriptyline. DDAVP can now be added to that list. However, as with the tricyclic drugs so with DDAVP, the beneficial effect appears to be temporary and once the drug is stopped the children start wetting again. No drug has yet been found to be effective in producing long-term cure for nocturnal enuresis. This limits the use of such drugs and many will feel that the drug should be used only for short periods—such as during an important visit or holiday.

It is interesting that the authors are unsure how the DDAVP is acting and in particular do not think it is related to its antidiuretic effect. Similarly with the tricyclic drugs it is not known why such drugs should be effective. It does not seem specifically to be related to any of their known properties—that is, why antidepressants don't work, other anticholinergics