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Long-term treatment of nocturnal enuresis with desmopressin

A follow-up study

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Summary. Eight patients with monosymptomatic nocturnal enuresis (age 11–24 years) were investigated prior to and after 24 weeks of desmopressin treatment in order to evaluate the impact on the endogenous vasopressin secretion and urinary output. No effect on plasma vasopressin, diurnal urinary volume, and urinary osmolality were found after this long-term treatment. Overall no changes in either body weight, blood pressure, or hematological variables were demonstrated. This supports previous findings that the treatment appears to be well tolerated and free of side effects in longer term.

Key words: Nocturnal enuresis – Plasma vasopressin – Urinary excretion

Individuals suffering from monosymptomatic enuresis have been shown to lack a diurnal rhythm in vasopressin (AVP) secretion and urinary output with a large and poorly concentrated nocturnal urine production [1, 4].

The synthetic antidiuretic drug desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP) has long been the drug of choice in central diabetes insipidus but optimistic results with desmopressin also have been reported both in children and adult patients with enuresis [5, 8]. However, before desmopressin can be considered the drug of choice among the enuretics, safety and possible side effects have to be determined too.

Concern has been expressed that endogenous AVP secretion is affected during desmopressin treatment, although desmopressin does not cross the blood-brain barrier [7], and acute intravenous injection of desmopressin does not influence endogenous AVP secretion [9]. Indirectly, using the water-deprivation test Rew and Rundle [3] found that desmopressin did not influence endogenous AVP secretion after 4–13 months of treatment. However, no studies have measured the direct influence of long-term treatment on plasma AVP or on the diurnal variation of urinary output.

No major acute side effects of signs of fluid retention have been found in clinical trials with desmopressin treatment for periods as long as 6 months [5].

The aim of this study was to establish the effects and to evaluate the safety of 6 months treatment with desmopressin on endogenous AVP production, diurnal urinary output as well as body weight, blood pressure, and other hematological variables.

Materials and methods

Eight patients with monosymptomatic nocturnal enuresis (3 girls, 5 boys) aged 11–24 (mean 15.8 years) entered the study (Table 1). They were randomly chosen from 28 patients who entered a 24-week treatment period as described by Rittig et al. [5]. The selected patients did not differ significantly in the sex ratio, age, weight, weekly enuretic episodes, or dose of desmopressin from the others. Prior to treatment all had at least three wet nights per week both according to history and a 2-week observation period. The patients had normal urinary flow, bladder capacities, and no diurnal urological problems. No evidence of bacteriuria, proteinuria, or glucosuria was found either before or after treatment. No medication besides desmopressin was administered during the investigation, and neither desmopressin nor any other treatment for enuresis had been used 3 months prior to the study.

The treatment period consisted of a dose titration period of 2–4 weeks on 20–40 μg desmopressin intranasal spray at bedtime, followed by 24 weeks of continous treatment at the effective dose of desmopressin, apart from a 3-week randomly placed placebo period [5]. Three patients received 20 μg, two 30 μg, and three 40 μg desmopressin during the treatment period (Table 1).

The diurnal studies were performed before and 12 weeks after the treatment period. To ensure a fluid steady state during each diurnal study all subjects received a total fluid intake of 25 ml/kg per 24 hours 3 days before and on the actual investigation day. Plasma AVP was measured at 8 a.m. and 12 noon on both investigation days and determined by radioimmunoassay after extraction of plasma [2]. Separate assays were used before and after treatment. The coefficient of variations of the assays were 12% interassay and 9% intraassay, respectively. Urinary output was measured every fourth hour during the day and compared to the total night output. Blood pressure, body weight, and hematological parameters were measured before and after the treatment period.

Table 1. Demographic data of eight patients with nocturnal enuresis investigated before and after 24 weeks of treatment with desmopressin.

Patient	Sex	Age (years)	Body weight (kg)	Dose (μg DDAVP)	Weekly enuretic episodes	
					Before treatment	After treatment
1	M	11	62	20	5.5	6.0
2	F	16	69	40	3.0	6.0
3	M	15	70	20	4.0	5.0
4	F	12	30	30	4.5	3.5
5	M	13	65	40	5.5	6.5
6	M	18	93	40	6.5	–
7	M	17	55	30	5.0	0.5
8	F	24	62	20	4.0	1.5

The weekly enuretic episodes are the mean of the 2 weeks prior to each investigation, both before and after treatment
DDAVP, 1-desamino-8-D-arginine vasopressin

All eight patients were dry under desmopressin treatment apart from the placebo period. The efficacy data of desmopressin during the treatment period and dose titration period have been described in detail elsewhere [5].

Patients and also their parents if the patients were under the age of 18, gave their consent to participate in the investigation after being informed of the nature and the purpose of the study according to the regulations of the local medical ethics committee.

Statistical analysis

Unless otherwise stated results are described as mean ± SD. For statistical analysis of the diurnal variation a nonparametric analysis of variance (Friedman's test) was used. Comparisons of pre- and posttreatment levels were made by Wilcoxon's signed rank test. Correlations were sought by Spearmans rank correlation test.

Results

After the 12-week follow-up period two patients (no. 7, male, 17 years, and no. 8, female, 24 years) had markedly reduced their nightly enuretic episodes, whereas the rest relapsed to their usual pattern of bed wetting (Table 1). Patient 6 had lost his posttreatment bed wetting records, but according to his information the frequency was unchanged.

The total diurnal urinary volume (Uvol), the ratio of diurnal fluid intake to urinary output, and the total diurnal urinary osmolality (Uosm) showed equal levels before and after treatment, indicating a stable fluid steady state (Table 2).

Plasma AVP

The AVP level shown as the median with an interquartile range after averaging the 8-a.m. and 12-noon samples are shown in Fig. 1. The levels were not significantly different before treatment (1.43 ± 0.82 pg/ml) and after treatment (1.34 ± 0.83 pg/ml). No correlation between the administered dose and the plasma level of AVP was found.

Table 2. Diurnal fluid steady state in eight enuretic patients investigated before and after 24 weeks of treatment with desmopressin

	Before treatment	After treatment
Total diurnal urinary excretion (ml)	1,512 ± 750	1,455 ± 608
Fluid intake per urinary output	1.20 ± 0.41	1.27 ± 0.72
Total diurnal Uosm (mosmol/kg)	649 ± 179	674 ± 200

All values are given as mean ± SD

Urinary excretion rate

The urinary excretion rate is shown in Table 3, and diurnal rhythm before and after treatment are illustrated in Fig. 2. No significant diurnal variation was found in Uvol at either diurnal studies. Also the day to night ratio of the urinary excretion rate was unchanged. Patients 7 and 8 had a nightly decrease in the urinary excretion rate of 51% and 67%, respectively, compared to a 7% decrease for the rest.

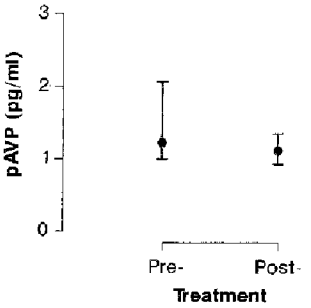

Fig. 1. Plasma vasopressin (AVP) values pre- and posttreatment. The values are the mean of the 8 a.m. and 12 noon levels, shown as median values with interquartile ranges

Table 3. Day and night urinary excretion rate and urinary osmolality in eight enuretic patients investigated before and after 24 weeks of treatment with desmopressin

	Day		Night		Day to night ratio	
	Before	After	Before	After	Before	After
Urinary excretion rate (ml/h)	64 ± 43	67 ± 35	54 ± 23	45 ± 20	1.24 ± 0.6	1.74 ± 1.2
Urinary osmolality (mosmol/kg)	622 ± 216	574 ± 246	646 ± 237	698 ± 217	1.19 ± 0.7	0.98 ± 0.3

All values are given as mean ± SD. Night values are from 10 p.m. to 8 a.m.

Urinary osmolality

Urinary osmolality is shown in Table 3, and diurnal variation before and after treatment is illustrated in Fig. 2. As for Uvol no significant treatment effect was found on the diurnal variation of Uosm in this group of eight patients as a whole. Neither did the day to night ratio of urinary osmolality change during treatment.

Hematological variables

Serum hemoglobin, white blood cell count and serum carbamide, creatinine, potassium, sodium, protein and osmolality were within normal range both before and after treatment and did not change after treatment. Specifically, no patients showed any signs of sodium imbalance or osmolality changes after the treatment period. Also, blood pressure and body weight were unchanged.

Discussion

This study addresses the influence of long-term treatment with desmopressin on the endogenous AVP secretion and urinary output. The results showed that long-term desmopressin treatment had no effect on plasma AVP, diurnal urinary volume, and urinary osmolality. Overall no changes in either body weight, blood pressure, or hematological variables were found.

Although several studies have indicated that desmopressin does not acutely influence endogenous AVP production [3, 9], no studies have dealt with the long-term effects of plasma AVP directly. However, such a long-term study presents methodological problems as one either has to use different assays or measure on samples which have been stored for variable periods. In the present study the total observation period was 9 months and the pre- and posttreatment samples were analyzed by different assays. The AVP levels before and after treatment were similar, and this may suggest that long-term administration of desmopressin has no effect on endogenous AVP production. Furthermore, no correlation was found between the administered dose of desmopressin and the plasma level of AVP. Besides, both the pretreatment (1.43 ± 0.82 pg/ml) and posttreatment levels (1.34 ± 0.83 pg/ml) were not significantly different than previously described in enuretic juveniles (1.73 ± 1.09 pg/ml, $n = 15$) and normal juveniles (1.94 + 1.03 pg/ml, $n = 11$) [4]. The AVP levels in the present study were also within the same range as in enuretic adults (1.55 ± 1.36 pg/ml, $n = 8$) [6].

The lack of influence of desmopressin treatment on endogenous AVP was further supported by unchanged

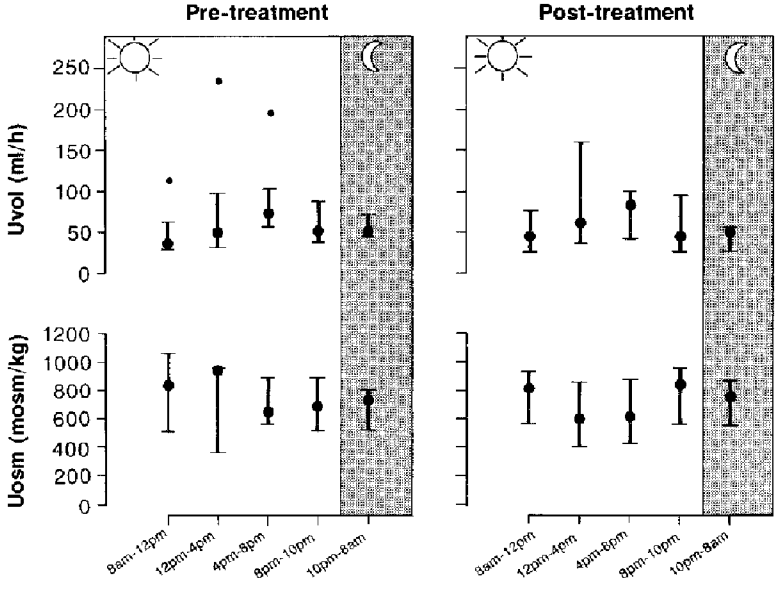

Fig. 2. Diurnal urine volume and osmolality pre- and post-treatment. Median values with interquartile ranges are shown

body weight, blood pressure, and hematological variables. In particular, no signs of diabetes insipidus or deficient ability to concentrate urine were found either clinically or in the hematological indices.

Long-term desmopressin treatment did not affect the diurnal urinary output. Overall the group lacked diurnal urinary rhythmicity as previous described [1, 4]. However, in the two patients whose nightly enuretic episodes were markedly reduced after treatment, the day-to-night variation of Uvol as well as Uosm changed from a lack of variation to a variation similar to what has been found in normal subjects [4]. This supports earlier findings that nocturnal urinary output is a major pathophysiological factor in nocturnal enuresis. Furthermore, a demonstration of a restitution of diurnal rhythm in plasma AVP in enuretic patients who have become dry further emphasizes the importance of this hormone in enuresis.

In conclusion, the study in this group of young patients indicates that regular use of desmopressin does not have a significant effect upon endogenous vasopressin production nor upon the other hematological parameters examined. This supports previous findings that the drug is safe in short-term use and also appears to be well tolerated and free of side effects in the longer term.

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