SHORT REPORT

Desmopressin in the treatment of daytime urinary frequency in patients with multiple sclerosis

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Abstract

Twenty two patients with multiple sclerosis, complaining of frequency of day time micturition, completed a double blind crossover trial of desmopressin (DDAVP nasal spray) versus placebo. There was a significant decrease in micturition frequency in the 6 hour post-treatment period from 3.1 voids after placebo to 2.4 voids and a significant reduction in urinary volume after desmopressin. Eighty per cent of patients preferred the active treatment phase. Mean 24 hour urinary volume did not differ between active and placebo treatments and patients did not complain of increased night time frequency. Transient symptoms of hyponatraemia occurred in one patient but these resolved within 48 hours of stopping desmopressin. There were otherwise no side effects and mean serum sodium concentrations of the group remained unchanged throughout the study. The clinical indications for prescribing daytime desmopressin are discussed and the importance of patient compliance stressed.

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Desmopressin is a synthetic vasopressin analogue with a duration of action of 9.5-13 hours. First introduced for the treatment of neurogenic diabetes insipidus it was then shown to be effective in the management of primary nocturnal enuresis. Several studies then showed it to be effective in managing nocturia in patients with multiple sclerosis.¹⁻³ However, daytime urgency and frequency is also often highly distressing for patients with multiple sclerosis, seriously disrupting work and social activities. We found that many of the patients with multiple sclerosis given desmopressin to lessen night frequency with benefit, admitted on direct questioning that they had occasionally taken it during the day instead.

This study was to examine the effect on voiding frequency of desmopressin compared with placebo, the effect of desmopressin on 24 hour urine production, and the safety and

tolerance of desmopressin in patients with multiple sclerosis.

Patients and methods

Twenty eight patients with multiple sclerosis and neurogenic bladder dysfunction were screened, and 26 (10 men, 16 women) recruited into the study. Their ages ranged from 18-65 years with a mean age of 43. For patients to be able to collect their urine and measure the volume it was necessary that they should have sufficient lower limb power to stand and also that they should be cognitively unimpaired. The inclusion criterion was that a patient had eight or more episodes of voiding a day. Seventeen of the patients were already on treatment for neurogenic incontinence including full dosages of anticholinergic therapy and intermittent catheterisation if they had been shown to have incomplete emptying. Patients with diabetes, heart disease, hypertension, or renal disease or those taking diuretic therapy were excluded.

Four patients were withdrawn from the study, three for various reasons before starting the treatment phases. One patient developed headache and other symptoms of fluid retention and was found to be hyponatraemic after active treatment and was withdrawn. None of these four patients were subsequently considered in the analysis.

Desmopressin was given from a nasal spray providing metered doses of 10 µg per spray and the patients were instructed to use one spray in each nostril at the same time each day between 8 00 am and 2 00 pm.

The study took place over 6 weeks. Patients were assigned to placebo or desmopressin treatment in random order. The first 2 weeks were a "run in" phase during which they practised handling the spray bottle and filling in diary cards recording frequency of micturition as well as amounts voided. Baseline blood pressure was recorded together with weight and blood sodium concentrations. At the beginning of the 3rd week observations were repeated and bottle A was given. Patients continued to record voiding frequency and had to use the spray at the same time each day. Two weeks later, at the beginning of the 5th week, bottle A was replaced by bottle B. On the final day of the study blood pressure, weight, and blood sodium were measured again and

Urinary variables during placebo and desmopressin treatment

	Run in	Placebo	Desmopressin	p Value (placebo/ desmopressin)
Number of voids in 6 hours (after treatment where applicable):				
Mean	3.2	3.1	2.4	0.008*
SD	1.3	1.4	0.9	
Mean urine volume in 6 hours (after treatment where applicable):				
Mean	384	342	246	0.006*
SD	166	166	99	
Mean 24 hours urine volume (ml):				
Mean	1290	1272	1218	0.052
SD	436	482	455	
Number of night time voids:				
Mean	1.2	1.4	1.5	0.263
SD	1.2	1.1	1.2	
Serum sodium (mmol/l):				
Mean	139.9	139.7	139.2	
SD	3.0	3.0	3.3	

*Significant difference ($p < 0.05$).

patients were asked which study period treatment they had preferred.

Results were analysed using ANOVA for crossover designs.

Results

Micturition frequency measured during the 6 hours after the use of the spray decreased significantly ($p < 0.05$) during the period of treatment with desmopressin to a mean of 2.4 voids, compared with both the run in period of 3.2 voids and placebo treatment 3.1 voids (table). There was a significant reduction ($p < 0.05$) in mean urine volume produced during the active treatment period to 246 ml from 384 ml and 342 ml during the run in and placebo periods respectively. The mean 24 hour urine volume did not differ significantly between the different periods, nor was there an increase in night time voiding frequency. Analysis of the preference data showed that 80% preferred the active to the placebo period of treatment, presumably because of the lessening of frequency of micturition.

The patient who was withdrawn on becoming hyponatraemic complained of general malaise, headache, and nausea and was found to have a serum sodium of 134 mmol/l. The symptoms resolved within 48 hours of discontinuing treatment and the blood sodium concentration returned to 141 mmol/l when checked a week later. There was no significant change in blood pressure during this period.

Discussion

In this study the effect of desmopressin has been shown to be only on the voiding frequency and urine volume in the 6 hour period after use of the medication. No other measurements differed between the run in period, placebo treatment, and active treatment. In particular there was no compensatory night time frequency nor evidence of water retention as the 24 hour urine volumes were the same in all three periods. The design and results of this study are almost identical to those reported by Fredrikson⁴ who also found the only significant change to be a reduction in number of voids in the 6 hours after the active treatment phase (from 3.1 to 2.6). Our study

found a somewhat higher patient preference for the active treatment phase—80% compared with Fredrikson's⁴ 68%. A placebo controlled trial study using oral desmopressin in 13 patients with multiple sclerosis and daytime urinary symptoms also showed a reduction in micturition frequency in the 6 hour period after active treatment.⁵

From these three studies there is conclusive evidence that patients with multiple sclerosis and urinary frequency and urgency can be safely provided with a period of some hours when urine production is reduced and voiding is lessened after the administration of desmopressin. This can be of considerable advantage when undertaking a long journey or attending a meeting or social occasion when access to a suitable toilet may be difficult.

The concern is the development of hyponatraemia. In our study one patient developed this problem but in a study of desmopressin in the management of night time frequency in patients with multiple sclerosis, four out of 17 patients developed symptomatic and biochemical hyponatraemia.³ The authors speculated that some patients with multiple sclerosis might have subtle hypothalamic defects in antidiuretic hormone control making them particularly susceptible to hyponatraemia. However in that study, as in ours the mean serum sodium concentration of the group did not change after desmopressin, suggesting that the development of hyponatraemia is an idiosyncratic response. How can this finding best be used to guide clinical practice? It is often not convenient to get the patient back 1 week after starting treatments to measure the sodium and a reasonable effective alternative is to warn patients clearly what the possible symptoms of hyponatraemia might be—namely, malaise, headache, and nausea—and to discontinue using desmopressin and contact their doctor should they develop any such complaints. A measurement of serum sodium can then be made and the patient advised to avoid the use of desmopressin in future if hyponatraemia is demonstrated.

The other question that arises is, when should desmopressin be prescribed to patients with multiple sclerosis and troublesome urinary symptoms? A patient with such disabling symptoms might reasonably be expected to be given any effective treatment and be unimpressed by the argument that their urinary symptoms were due to incomplete bladder emptying and detrusor hyperreflexia and therefore better treated by regular intermittent catheterisation and anticholinergic medication.⁶ In the author's practice, use of desmopressin is reserved for those already using first line therapy but who are occasionally in need of additional measures. It is prescribed to them after a strict warning about the possible risk of hyponatraemia and its symptoms and instructions that it must not be used more than once in 24 hours. It therefore seems reasonable to avoid prescribing it for patients in whom there is doubt about their possible compliance such as those with cognitive impairment. It should

probably also be avoided in those with severe immobility and dependent oedema.

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