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Authors: P Abrams, J Weiss, A Mattiasson, P van Kerrebroeck, S Walter, G Robertson, J Blaivas and the Nocturia Study Group
Institution: Department of Urology, Southmead Hospital
Title: THE EFFICACY AND SAFETY OF ORAL DESMOPRESSIN IN THE TREATMENT OF NOCTURIA IN MEN.

Aims of Study:

Nocturia, defined as waking at night to void, is caused by a number of factors including nocturnal polyuria. The aims of this study were to investigate the efficacy and safety of oral desmopressin, an antidiuretic agent, in the treatment of nocturia in males.

Methods:

The study was a multi-centre, multi-country, phase III trial. Male patients aged ≥ 18 years were screened using frequency-volume charts. Patients were deemed eligible for the study if they had verified nocturia (defined as ≥ 2 voids/night) and a nocturnal urine production greater than maximum functional bladder capacity. Optimal dose was established through an open-label dose-titration using 0.1 mg, 0.2 mg and 0.4 mg of desmopressin (Minirin®, DDAVP®) for one week each. After a one-week wash-out period, patients were randomised to receive either their optimal dose or placebo for three weeks in a double-blind fashion. Optimal dose and placebo were compared for the primary endpoint; proportion of subjects with a 50% or greater reduction in the mean number of nightly voids. Secondary endpoints included reduction in the mean number of voids per night, increase in the number of hours from bedtime until the first nocturnal void and decrease in nocturnal diuresis. Safety parameters assessed included incidence of adverse events, vital signs and serum sodium levels. A follow-up protocol enabled patients to continue with optimal dose treatment for 10 or 12 months.

Results:

The number of patients entering the dose-titration period was 224. Seventy-three (33%) patients were withdrawn from the dose-titration period and the most frequent reasons for withdrawal were failure of nocturnal diuresis to return to pre-treatment levels during wash-out (16 patients), lack of efficacy (16 patients) and adverse events (14 patients). One hundred and fifty-one patients were randomised into the double-blind period (drug: n=86, placebo: n=65). The proportion of patients showing at least a 50% reduction in number of voids per night was 34% in the desmopressin group compared with 3% in the placebo group ($p<0.0001$). Secondary endpoints also showed significant differences between the two groups. The mean number of voids per night changed from 3.01±0.91 at baseline to 1.74±0.89 during treatment in the drug group and from 3.16±1.30 to 2.73±1.20 in the placebo group. The first sleep period (mean values) was prolonged by 108±88 minutes in the drug group, and by 25 ±61 minutes in the placebo group when compared to baseline values. The mean nocturnal diuresis decreased from 1.50±0.58 ml/min at baseline to 0.91±0.33 ml/min during treatment in the drug group and from 1.67±0.62 ml/min to 1.53±0.64 ml/min in the placebo group.

A total of 237 adverse events were reported by 107 (48%) patients during the trial. The most frequently reported treatment-related adverse events were headache, nausea, and dizziness. Forty-nine (22%) patients had serum sodium levels below normal range at some point during the study. Serum sodium levels below 130 mmol/L were seen in 10 patients (4%). In most patients, the low serum sodium values occurred during the dose-titration period. The majority of the patients with serum sodium levels below the normal range were above 65 years of age. Serious adverse events judged as treatment-related were reported in one patient (0.4%), who developed

thrombocytopenia during the wash-out period.

More than 75% of the patients chose to continue in the follow-up trial of open-label desmopressin treatment for 10 or 12 months.

Conclusions:

Orally administered desmopressin is an effective and well tolerated treatment for nocturia with a polyuric component. Desmopressin reduces the frequency of nocturnal voids, prolongs the time to first void after bedtime and reduces nocturnal diuresis. Adverse events were mainly mild and comparable with the established safety profile of desmopressin in other indications. Development of hyponatraemia mainly seems to affect the elderly (above 65 years of age).

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Authors: G Lose, P Van Kerrebroeck, T Bäckström, R Freeman, G Robertson, J Blaivas and the Nocturia Study Group
Institution: Department of Gynaecology, Glostrup Hospital
Title: THE EFFICACY AND SAFETY OF ORAL DESMOPRESSIN IN THE TREATMENT OF NOCTURIA IN WOMEN.

Aims of Study:

Nocturia, defined as waking at night to void, is caused by several factors including nocturnal polyuria. The aims of this study were to investigate the efficacy and safety or oral desmopressin, an antidiuretic agent, in the treatment of nocturia in females.

Methods:

The study was a multi-country, multi-centre, phase III trial. Women aged ≥ 18 years were screened using frequency-volume charts and were eligible to take part if they had verified nocturia (defined as ≥ 2 voids per night) and a nocturnal urine production greater than maximum functional bladder capacity. An open-label dose-titration period established the optimal dose for each patient using 0.1 mg, 0.2 mg and 0.4 mg of desmopressin (Minirin®, DDAVP®) for one week each. After a one-week wash-out period, patients were randomised to receive either placebo or drug at the optimal dose for a three-week double-blind period. Optimal dose and placebo were compared for the primary end-point; proportion of patients with a 50% or greater reduction in the mean number of nightly voids. Secondary endpoints included reduction in the mean number of voids per night, increase in the number of hours from bedtime until the first nocturnal void and decrease in nocturnal diuresis. Safety parameters evaluated included incidence of adverse events, vital signs and measurement of serum sodium levels. A follow-up protocol enabled patients to continue with optimal dose treatment for 10 or 12 months.

Results:

The number of patients entering the dose-titration period was 224. Eighty (36%) patients were withdrawn from the dose-titration period and the most frequent reasons for withdrawal were failure of nocturnal diuresis to return to pre-treatment levels during wash-out (33 patients), adverse events (22 patients) and lack of efficacy (8 patients). The population for the main analysis (i.e. the Intention To Treat population) consisted of 72 patients receiving

desmopressin and 70 patients on placebo. The proportion of patients who showed a reduction of 50% or more in the number of nightly voids was significantly greater ($p<0.0001$) in the drug group (n=33 or 46%) than in the placebo group (n=5 or 7%). Significant differences between the two patient groups were also observed for secondary endpoints. The mean number of nocturnal voids was reduced from 2.92±0.75 at baseline to 1.61±0.84 during treatment with desmopressin, compared with a decrease from 2.91±0.87 to 2.36±0.87 in the placebo group. The mean duration of the first period of sleep was prolonged in the treatment period compared to baseline, by 130±102 minutes in the drug group compared to 37±74 minutes in the placebo group. Mean nocturnal diuresis decreased from 1.51±053 ml/min at baseline to 0.82±0.36 ml/min during treatment in the drug group compared to 1.44±0.50 ml/min to 1.35±0.50 ml/min in the placebo group.

A total of 398 adverse events were reported by 158 (71%) patients during the trial. Headache, nausea, hyponatraemia, abdominal pain, and dry mouth were the most frequently reported treatment-related adverse events. Serum sodium levels below the normal range were recorded at least once for 27 (12%) patients, of which 13 (6%) patients had serum sodium levels below 130 mmol/L. All cases of hyponatraemia were reported within the dose-titration period and were mainly in patients above the age of 65 years. Serious adverse events judged as treatment-related were reported by 3 (1%) of the patients; all cases were seen during the dose-titration period. Two patients developed hyponatraemia requiring hospitalisation. One patient experienced respiratory insufficiency and pulmonary infection.

The follow-up trial of open-label desmopressin treatment for 10 or 12 months was accepted by more than 70% of the patients.

Conclusion:

Orally administered desmopressin is an effective treatment for nocturia with a polyuric factor. It not only reduces the number of nocturnal voids and nocturnal urine volume, but also prolongs sleep duration to the first void. Oral desmopressin compared to placebo was well tolerated. The type of reported adverse events were comparable with previous experience with desmopressin in other indications. The elderly (over 65 years), in particular, seem to be more susceptible to developing hyponatraemia.

Source of funding: Ferring Pharmaceuticals and Aventis.