**Desmopressin treatment in nocturia; an analysis of risk factors for hyponatremia.**

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**ABSTRACT**

**Aims:** To explore the incidence, severity, time course and risk factors of clinically significant hyponatremia in desmopressin treatment for nocturia.

**Methods:** Data from three multi-centre phase III trials were pooled. Hyponatremia was categorised as borderline (134-130 mmol/L) or significant (<130 mmol/L). Risk factors were explored with logistic regression and subgroup analysis performed to explore threshold values for contraindication.

**Results:** In total 632 patients (344 men, 288 women) were analysed. During dose-titration, serum sodium concentration below normal range was recorded in 95 patients (15%) and 31 patients (4.9%) experienced significant hyponatremia. The risk increased with age, lower serum sodium concentration at baseline, higher basal 24-h urine volume per bodyweight and weight gain at time of minimum serum sodium concentration. Age was the best single predictor. Elderly patients (≥65 years of age) with a baseline serum sodium concentration below normal range were at high risk (75%). Limiting treatment in elderly with normal basal serum sodium concentration to those below 79 years and with a 24-hour urine output below 28 mL/kg would reduce the risk from 8.1 to 3.0% at the cost of 34% fulfilling the contra-indication.

**Conclusions:** The majority of nocturia patients tolerate desmopressin treatment without clinically significant hyponatremia. However, the risk increases with increasing age and decreasing baseline serum sodium concentration. Treatment of nocturia in elderly

patients with desmopressin should only be undertaken together with careful monitoring of the serum sodium concentration. Patients with a baseline serum sodium concentration below normal range should not be treated.

**Key words:** Elderly, serum sodium, safety.

## INTRODUCTION

Oral desmopressin, a vasopressin analogue, has shown efficacy in treatment of nocturia (the complaint that the individual has to wake at night one or more times to void (van Kerrebrock et al., 2002)) due to nocturnal polyuria (Lose et al., 2003; Mattiasson et al., 2002). The safety profile of desmopressin treatment in diabetes insipidus and nocturnal enuresis is well established (Drincic and Robertson, 1999; Glazener and Evans) and the only potentially serious adverse effect, hyponatremia, is a rare occurrence (<1/10 000). The incidence of hyponatremia reported in nocturia has been significantly higher, with 12-22% of patients experiencing one or more episodes of serum sodium concentration below normal range (Lose et al., 2003; Lose et al., 2004; Mattiasson et al., 2002; Rembratt et al., 2003). Serum sodium concentration has been assessed in many clinical trials involving desmopressin, but rarely as frequently as in the large nocturia trials published by Mattiasson et al and Lose et al. Consequently, it is expected that these trials unearth a higher frequency of non-symptomatic low serum sodium concentration. The aim of this database analysis was to explore the incidence, severity, time course and risk factors of significant hyponatremia in nocturia patients.

## MATERIALS AND METHODS

Data from three multicentre phase III trials (one in men (Mattiasson et al., 2002), one in women (Lose et al., 2003) and one recruiting both men and women (van Kerrebroeck et al., 2002)) were pooled. The studies were performed by urologic and gynaecologic clinics in Sweden, Denmark, France, Germany, the Netherlands, UK and USA. All studies consisted of a three-week open-label dose-titration, one week each on 0.1, 0.2 and 0.4 mg

of oral desmopressin, followed by a one week wash-out and a three-week, randomised, double-blind, parallel group comparison with placebo. Patients were required to have ≥ 2 voids per night during a one-week screening. Nocturnal urine volume exceeding largest voided volume was an inclusion criterion in two out of the three studies. However, 97% of patients in the third trial also fulfilled this criterion. Patients with urinary tract infection, congestive heart failure, glucosuria, obstruction, diuretic medication or a 24-h urine output exceeding 40 mL/kg bodyweight were excluded. If a patient obtained zero nocturnal voids during a dose-titration week, this dose was chosen as the optimal dose for the double-blind treatment period, and the patient would not proceed to the next dose level. In patients not achieving zero nocturnal voids to any of the doses, the tolerated dose giving the lowest nocturnal diuresis was selected. Serum sodium concentration was measured before screening, after each period in dose titration, after washout (except in the mixed gender study) and after the double-blind period. Patients who experienced a serum sodium concentration below 125 mmol/L were to be withdrawn from the study (Lose et al., 2003; Mattiasson et al., 2002; van Kerrebroeck et al., 2002).

The reference ranges for serum sodium concentration varied between centres. For the analysis all values for sodium concentration were standardised by conversion to z-scores using the local centre normal range and subsequent conversion back to mmol/L using a common normal range of 135-145 mmol/L. Hyponatremia was categorised by severity as borderline (134-130 mmol/L) or significant (<130 mmol/L). Since no significant hyponatremia was recorded in the double-blind period, patients were classified as non-hyponatremic, borderline hyponatremic or significantly hyponatremic based on the lowest serum sodium concentration recorded in dose-titration. A specific search of the

adverse event database was performed to elicit the prevalence of clinically significant hyponatremia, defined as all cases with a serum sodium concentration below reference range with at least one of the symptoms headache, nausea, vomiting, fatigue, dizziness, ataxia or weight increase reported in the preceding week.

Logistic regression, using best subset selection, to find predictors for hyponatremia was performed for significant vs. non- and borderline hyponatremics. The models included baseline parameters and changes from baseline (Table I). Subgroups were identified based on the best predictive baseline characteristics. To determine the best classification of patients at high risk of significant hyponatremia a stepwise discriminant analysis with an F-test entry criterion of 0.2 followed by a full, cross-validated discriminant analysis was performed. To obtain easier-to-use cut-off points a heuristic splitting algorithm was also applied.

## RESULTS

A total of 632 patients (344 men, 288 women: 97% Caucasians) entered the dose titration phase of the three trials and were included in the analysis. The median age was 62 years (range 19-94 years) and 283 patients (45%) were elderly (≥65 years). Mean body mass index was 27.2 (SD 4.6).

The distribution of values for serum sodium concentration in the different phases of the studies are shown in Figure 1.

In total 95 patients (15%) experienced at least one episode of serum sodium concentration below normal range during dose-titration and for 29 of those, hyponatremia was reported as an adverse event (Table II). During dose-titration a total of 44 values of serum sodium concentration below 130 mmol/L were registered.

For all values of serum sodium concentration taken throughout the three studies, possible symptoms of hyponatremia were reported in conjunction with 40% of those below, and 10% of those above or equal to 130 mmol/L.

Two serious adverse event of hyponatremia were reported, one each on 0.1 and 0.2 mg. Both patients recovered without sequelae.

No significant hyponatremia occurred during the double-blind period.

The basal characteristics in patients experiencing significant hyponatremia differed in several ways from the borderline and non-hyponatremics (Table III). On average, they were older and smaller, had lower creatinine clearances, higher total and nocturnal urine volumes and had a tendency to lower basal serum sodium concentration.

In the best predictive model for significant hyponatremia the risk increased with age, increasing baseline 24-h urine volume per bodyweight, decreasing baseline serum sodium

concentration and weight gain at time of minimum serum sodium concentration (see table IV). Adding more than these four characteristics had less effect on the predictability of the model ($\chi^2 = 67$). All patients with significant hyponatremia were above 55 years of age and all but three were over 65 years ($\chi^2$ for model with age alone = 30; Figure 2). Creatinine clearance, which is strongly and inversely related to age, was almost as good a predictor of hyponatremia when investigated alone ($\chi^2 = 23$).

The population was split into four groups (see table V) based on age and baseline serum sodium concentration. Discriminant analysis in the subgroup of elderly patients with normal basal serum sodium concentration gave age and 24-h urine volume per bodyweight as the best predictors for risk. Using a neutral approach (i.e. a prior probability of significant hyponatremia of 0.5) the risk of significant hyponatremia was reduced from 8.1 to 3.4% in this group, at the cost of 80 patients (31%) being contraindicated - of which 65 patients (81%) did not develop significant hyponatremia in dose-titration. Using the cut-off points obtained with the heuristic splitting algorithm, age above 79 years and 24-h urine volume above 28 mL/kg bodyweight, reduced the risk of significant hyponatremia to 3.0% at the cost of 89 patients (34%) not receiving treatment due to the contra-indication, of which 73 patients (82%) did not develop significant hyponatremia in dose-titration.

## DISCUSSION

A minor, asymptomatic decrease in serum sodium concentration, resulting in a value below normal range, does not represent a health hazard unless it progresses. The same is true for a larger fall in serum sodium concentration that does not result in an absolute value below normal range. However, in 4-6% of patients in the published trials the serum sodium concentration decreased below 130 mmol/L (Lose et al., 2003; Mattiasson et al., 2002). Hyponatremia of this magnitude can have a variety of adverse effects ranging from mild headache, anorexia, nausea and vomiting to loss of consciousness and seizures. Unless properly diagnosed and treated hyponatremia can even be fatal. Because of this, and the relatively benign nature of the clinical indication, the problem of hyponatremia during desmopressin therapy for nocturia cannot be ignored. In the present studies desmopressin was well tolerated by the majority of patients both based on adverse events in general and electrolyte balance in specific. In 83% of the patients the serum sodium concentration remained within normal range throughout the study. Among the patients with serum sodium levels below normal range 2/3 never dropped below 130 mmol/L. The prevalence of hyponatremia found is similar to that described in a recent meta-analysis (Weatherall, 2004), which among other trials included the all male study in the present analysis. A previous trial in elderly indicated that the risk of desmopressin-induced hyponatremia increased with age, cardiac disease and increasing 24-hour urine volume (Rembratt et al., 2003). Patients with cardiac disease were excluded from the present trials, however, the findings on age and 24-hour urine volume were confirmed. Age is a risk factor for hyponatremia in the use of several drugs (Chan, 1997) as well as in general (Ledingham et al., 1987; Miller, 1997). However, most elderly patients did not develop

any hyponatremia, indicating that the predisposing factor is not age per se but one or more dysfunctions that occur more frequently in the elderly.

In the present analyses patients were classified based on their values of serum sodium concentration during dose-titration. Since all significant hyponatremia episodes occurred in that period no bias pertaining to this definition is expected.

Because of the design of the dose-titration, the relation of hyponatremia to dose cannot be reliably assessed.

The treatment of elderly patients presents a difficult dilemma. Although the elderly have a significantly higher risk of hyponatremia, the majority of patients over 65 still tolerate desmopressin without adverse effects. Also, the elderly have a greater need for therapy, at least in terms of the frequency and severity of nocturia (Jackson, 1999). Judging from the present results, patients with basal a serum sodium concentration below the normal range should not be treated. Applying restrictions on 24-hour urine volume (not > 28 mL/kg) and age (not > 79 years) would reduce, but not eliminate, the risk. It would also exclude a large number of patients who could benefit safely from desmopressin therapy. As of today, no sufficiently selective criteria enabling identification of risk patients prior to treatment have been identified. Further studies on the mechanisms on desmopressin-induced hyponatremia are therefore indicated.

## CONCLUSIONS

The majority of nocturia patients tolerate desmopressin treatment without clinically significant hyponatremia. However, the risk increases with increasing age and decreasing baseline serum sodium concentration. Should treatment of an elderly person be

undertaken, dose titration with monitoring of the serum sodium concentration 3 to 7 days after starting desmopressin or increasing the dose is strongly recommended. Symptoms of hyponatremia should not be relied upon in lieu of laboratory measurements because many hyponatremic patients are asymptomatic. Patients with a baseline serum sodium concentration below normal range should not be treated.

**ACKNOWLEDGEMENTS**

We thank Gary L Robertson for help with design and interpretation of results, Lene Holdrup for collating the data on symptomatic hyponatremia and Klaus Juel Olsen for performance of the statistical analyses.

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Table I: Parameters incorporated in the logistic regression and discriminant analysis of risk for significant hyponatremia.

| **Demographics** | **Baseline values** |
|---|---|
| • gender | • weight (kg) |
| • age (years) | • body mass index (kg/m$^2$) |
| • diabetes mellitus [1] | • 24h urine volume/bodyweight (mL/kg) |
| | • largest voided volume (mL) |
| **Dose-titration data**[1] | • nocturnal urine volume (mL) |
| • hypernatremia (>145 mmol/L) on treatment | • nocturnal urine vol. / largest voided vol. |
| • max reduction of nocturnal diuresis (mL/min) | • nocturnal diuresis (mL/min) |
| • reduction in nocturnal diuresis on 0.1mg (mL/min) | • serum sodium (mmol/L) |
| • weight gain at time of minimum s-sodium (%) | • serum potassium (mmol/L) |
| | • serum creatinine (µmol/l) |
| | • creatinine clearance (mL/min) |

[1] Only used in logistic regression.

Table II: Classification of patients based on severity of hyponatremia in dose-titration and frequency of symptomatic and reported hyponatremia.

| | **All** | | **Male study** | | **Female study** | | **Mixed study** | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Exposed patients | 632 | 100 | 224 | 100 | 224 | 100 | 184 | 100 |
| Non-hyponatremic | 537 | 85 | 181 | 81 | 198 | 88 | 158 | 86 |
| Hyponatremic | 95 | 15 | 43 | 19 | 26 | 12 | 26 | 14 |
| Borderline (134-130 mmol/L) | 64 | 10 | 34 | 15 | 13 | 6 | 17 | 9 |
| Significant (<130 mmol/L) | 31 | 3 | 8 | 4 | 5 | 2 | 5 | 3 |
| *(<125 mmol/L)* | *13* | *2* | *1* | *<1* | *8* | *4* | *4* | *2* |
| Symptomatic hyponatremia | 27 | 4 | 11 | 5 | 13 | 6 | 3 | 2 |
| Adverse event | 29 | 5 | 9 | 4 | 14 | 6 | 6 | 3 |
| *Serious adverse event* | *2* | *<1* | *0* | *0* | *2* | *<1* | *0* | *0* |

Table III: Characteristics of patients with and without significant hyponatremia.

| | Non-hyponatremic [1] | | Significantly hyponatremic | |
|---|---|---|---|---|
| | **n** | **mean (SD)** | **n** | **mean (SD)** |
| **Demographics** | | | | |
| Age (years) | 601 | 61 (12) | 31 | 75 (8) |
| Weight (kg) | 601 | 80 (15) | 31 | 71 (13) |
| BMI (kg/m$^2$) | 601 | 27 (5) | 30 | 25 (5) |
| **Baseline values** | | | | |
| Nocturnal voids | 601 | 3.0 (1.0) | 31 | 3.2 (1.1) |
| 24-h urine vol./B.W. (mL/kg) | 599 | 24 (8) | 30 | 29 (7) |
| Nocturnal urine volume (mL) | 601 | 790 (311) | 31 | 940 (302) |
| Largest voided volume (mL) | 601 | 406 (144) | 31 | 465 (196) |
| Serum sodium (mmol/L) | 598 | 140 (2.2) | 31 | 138 (3.3) |
| Creatinine clearance (mL/min) | 597 | 86 (26) | 31 | 60 (15) |
| **On-treatment changes** | | | | |
| Weight gain at minimum s-sodium (kg) | 567 | 0.5 (1.9) | 30 | 1.9 (2.1) |

[1] Including patients with borderline hyponatremia.

Table IV: Results of logistic regression of risk of significant hyponatremia.

| | Odds Ratio | 95% Wald confidence limits | | P-value |
|---|---|---|---|---|
| Age (years) | 1.16 | 1.09 | 1.25 | <0.0001 |
| Baseline 24-h urine volume/bodyweight (mL/kg) | 1.09 | 1.04 | 1.16 | 0.0016 |
| Baseline serum sodium (mmol/L) | 0.76 | 0.64 | 0.91 | 0.0025 |
| Weight gain at time of minimum s-sodium (%) | 1.31 | 1.07 | 1.61 | 0.0106 |

N=594 as two patients with significant hyponatremia and 36 patients without were excluded due to missing values of one or more of the characteristics.

Table V: Subgroups based on age and basal serum sodium.

| Age | Basal s-sodium | n | No. of pts with significant hyponatremia | Risk |
|---|---|---|---|---|
| < 65 | Normal | 336 | 3 | <1% |
| | Low | 5 | 0 | - [1] |
| ≥ 65 | Normal | 260 | 22 | 8% |
| | Low | 8 | 6 | 75% |

[1] Risk not assessed due to insufficient data.

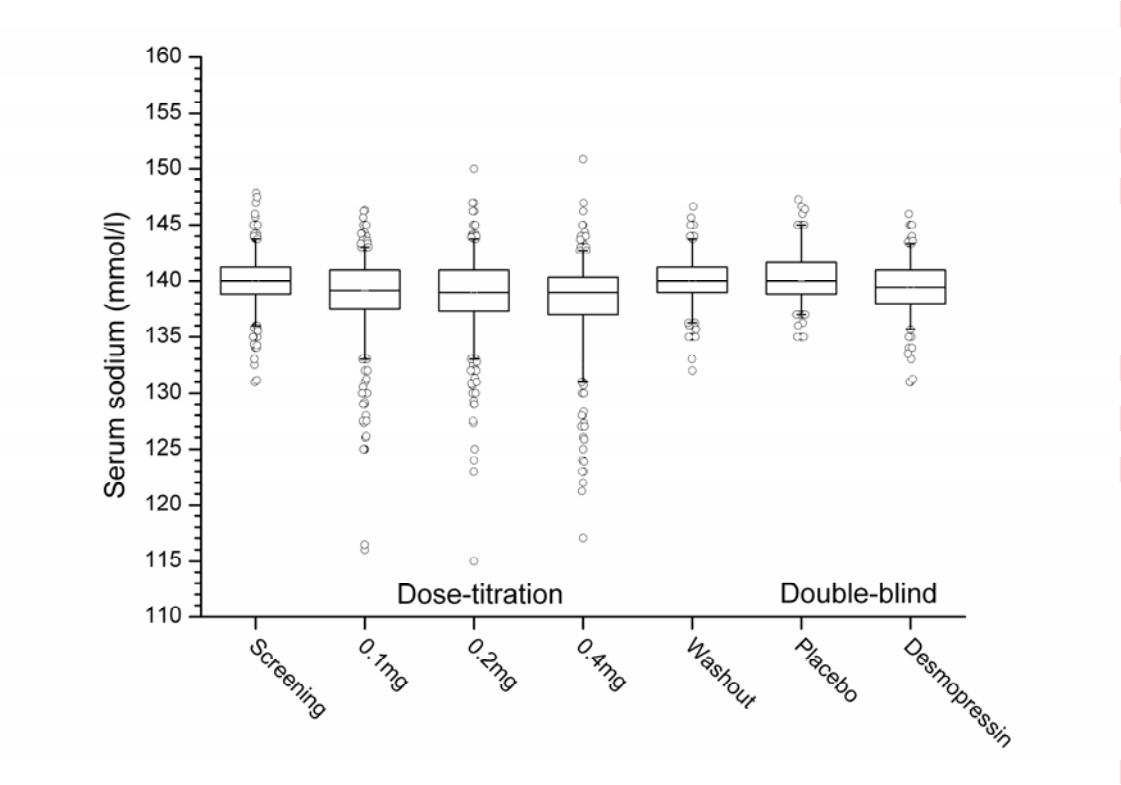


**Figure 1.** Serum sodium during the different phases of the studies. The central line is the median, the box the interquartile range, the bars the 5$^{th}$ and 95$^{th}$ centile and the points the observations outside these centiles.

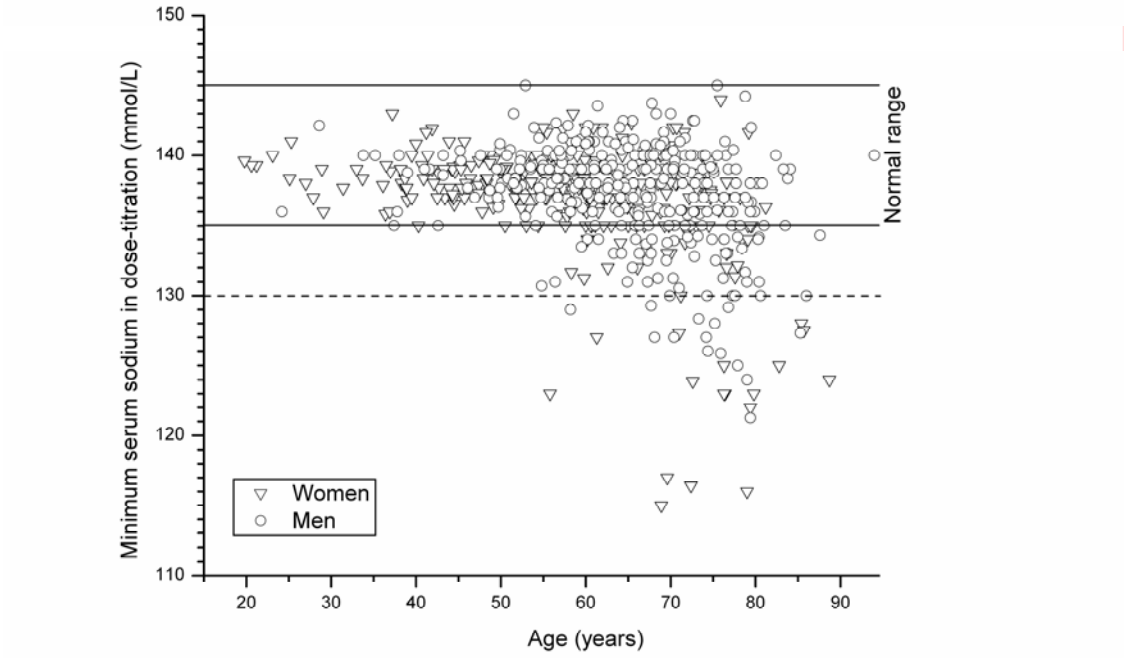


**Figure 2.** Minimum value on serum sodium in dose titration versus age.