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Low-dose desmopressin combined with serum sodium monitoring can prevent clinically significant hyponatraemia in patients treated for nocturia

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Objective

To explore risk factors for desmopressin-induced hyponatraemia and evaluate the impact of a serum sodium monitoring plan.

Subjects and Methods

This was a meta-analysis of data from three clinical trials of desmopressin in nocturia. Patients received placebo or desmopressin orally disintegrating tablet (ODT; 10–100 µg). The incidence of serum sodium <130 mmol/L was recorded by age, sex and dose. Potential predictors of clinically significant hyponatraemia were identified using multivariate analysis in a Cox proportional hazards model.

Results

Dose, age, baseline serum sodium level and kidney function, according to estimated GFR clearance, were significant risk factors for hyponatraemia in both sexes; similar to the known risk factors associated with hyponatraemia in the general population. In men, arthritis and use of drugs for bone disease were also predictive of hyponatraemia, while in women, raised monocytes and absence of lipid-modifying drugs increased the risk of hyponatraemia. Use of the proposed monitoring scheme and the minimum effective

dose would have omitted all patients with clinically significant hyponatraemia from further treatment.

Conclusions

The incidence of hyponatraemia can be reduced by using minimum effective gender-specific dosing with the ODT formulation of desmopressin (25 µg in women, 50 µg in men). A sodium monitoring plan is proposed whereby baseline sodium must be ≥ 135 mmol/L (especially important in the elderly), with additional monitoring at week 1 and month 1 for those at elevated risk because they are aged ≥ 65 years or receiving concomitant medication associated with hyponatraemia. This monitoring plan would help to prevent some at-risk patients developing hyponatraemia; retrospective application of the monitoring plan showed that, once at-risk patients were appropriately screened out, only mild, non-clinically significant hyponatraemia was observed, within ranges of other drugs associated with hyponatraemia and similar to the background prevalence in the treatment population.

Keywords

desmopressin, hyponatraemia, nocturia

Introduction

Hyponatraemia is a known risk associated with desmopressin therapy [1]. Desmopressin-induced hyponatraemia is usually mild and fully reversible, but has been identified as a limitation of nocturia treatment in the elderly [2–4].

It has been reported that there are significant gender differences in the incidence of drug-induced hyponatraemia and hyponatraemia-related complications

[5], with women at higher risk than men. Consistent with this, severe hyponatraemia occurs more frequently in women with nocturia receiving desmopressin compared with men [6]. Initial trials of desmopressin in patients with nocturia [7–10] used tablet doses (100–400 µg) that had been shown to be efficacious in the treatment of monosymptomatic nocturnal enuresis [11,12]. Bioequivalent doses of desmopressin orally disintegrating tablet (ODT) were therefore used when this formulation was introduced in 2005 (60–240 µg). Later trials

explored lower dose ranges to determine the minimum effective dose (MED), optimizing the balance between therapeutic effect and tolerability [13]. Using the MED ensures compensatory daytime diuresis between doses. Exploration of these lower doses showed that women have at least two times greater renal sensitivity to desmopressin than men [14], with the MED identified as 25 µg for women and 50 µg for men. Recent trials examining gender-specific doses have confirmed the efficacy and tolerability, including low incidence of hyponatraemia, of these low doses [15,16].

Hyponatraemia risk is known to be affected by various factors including certain other medications [17,18], water and serum sodium balance [3,19] and some illnesses [6,19]. In the present analysis, we explored the association of clinically significant hyponatraemia (defined as <130 mmol/L) with desmopressin dose, age and gender [6,14] in patients with nocturia. Other potential predictors of desmopressin-induced hyponatraemia, including baseline characteristics, concomitant medications and medical history were investigated. After a recent report [4] that a decreased level of haemoglobin was associated with an increased risk of desmopressin-induced hyponatraemia in patients with nocturia with Nocturnal Polyuria, baseline leukocyte levels were investigated in this study. The effects of a serum sodium monitoring plan were retrospectively evaluated to investigate the impact on incidence of clinically significant hyponatraemia in patients with nocturia when receiving gender-specific low-dose desmopressin.

Subjects/Patients and Methods

Patients

Patients were involved in three published placebo-controlled trials of desmopressin ODT for nocturia (NCT00477490, NCT01223937 and NCT01262456) [13,15,16]. Included patients were aged ≥ 18 years, with serum sodium >135 mmol/L and ≥ 2 voids/night at baseline. All studies were approved by the institutional review board or ethics committee for each site, the Declaration of Helsinki was followed, and informed consent obtained from all patients.

Study Design and Procedures

Data were collated from three randomized, double-blind trials: (1) a 4-week trial in men and women with nocturia (10, 25, 50, 100 µg; ClinicalTrials.gov Identifier: NCT00477490) [13] with an open-label extension for up to 2 years [20][data on file]; (2) a 12-week trial in women (25 µg; ClinicalTrials.gov Identifier: NCT01223937) [15]; and (3) a 12-week trial in men (50 and 75 µg; ClinicalTrials.gov Identifier: NCT01262456), with a 4 week open-label extension (100 µg) [16]. Overall, 1443 patients were treated with desmopressin ODT or placebo in these trials.

Endpoints

Serum Sodium Concentration and Clinically Significant Hyponatraemia

Serum sodium was measured at baseline, day 4, day 8 and week 4, and then monthly [15,16] or at those time points and also weeks 2 and 3 [13]. The threshold for clinically significant hyponatraemia events was defined as serum sodium <130 mmol/L. Serum sodium ≤ 125 mmol/L (severe hyponatraemia) was also assessed.

Predictors Evaluated

The effect of treatment/dose on hyponatraemia risk was evaluated by gender. Associations between the development of hyponatraemia and patient demographics and baseline characteristics including age, body mass index, body weight, serum sodium, creatinine clearance, leucocytes, concomitant medication and medical history were explored. Concomitant medications during the trial were coded using the WHO drug anatomical therapeutic chemical classification.

Statistical Analysis

The incidence of clinically significant hyponatraemia was calculated by dosing occasion and by highest dose level received by each patient because some patients received higher doses during trial extensions. The probability of experiencing a clinically significant hyponatraemia event was analysed using the Cox proportional hazard model using data from the initially assigned dose groups. A stepwise model was built for each gender on all available demographic variables and baseline characteristics. These variables were entered into the model as either factors (e.g. treatment/dose) or covariates (e.g. age, weight, renal creatinine clearance), under the assumption that the probability of developing clinically significant hyponatraemia at any given time (hazard rate) for the first time is proportional in their risk factors. Results were reported as hazard ratios with associated 95% CIs based on the Wald test. Time to clinically significant hyponatraemia was plotted using Kaplan–Meier methodology, and differences between dose groups and placebo were tested using the log rank test.

SAS version 9.2 service pack 3 was used.

Results

Patient Demographics

A total of 1443 patients from the three trials were included in the analysis set, of whom 820 (57%) were men. Their mean (SD; range) age was 61.1 (13.4; 19–89) years, with men being slightly older (mean 62.9 years) than women (mean

58.8 years). Overall, 49% of patients were aged ≥ 65 years. The mean serum sodium level at baseline was 140 mmol/L for men and women. Three patients with serum sodium levels < 135 mmol/L were included, despite this being an exclusion criterion. The mean creatinine clearance rate at baseline was 101 mL/min, with 117 patients (8%) having baseline creatinine clearance (estimated GFR) < 60 mL/min. The median (SD) creatinine clearance rate for women was slightly lower (91.4 [39.4] mL/min) compared with men (96 [32.7] mL/min).

Post-baseline sodium data during exposure to first dose were collected in 1431/1443 patients.

Incidence of Clinically Significant Hyponatraemia

A total of 68 patients experienced clinically significant hyponatraemia (< 130 mmol/L). Table 1 shows the number of patients affected according to sex, age group (< 65 or ≥ 65 years) and highest desmopressin dose received (or placebo). Overall, the total number of patients with serum sodium levels < 130 mmol/L was 68/1431 (4.8%); amongst those on active treatment (10–100 μg desmopressin), 67/1005 (6.7%) had serum sodium levels < 130 mmol/L. Data were identical for number experiencing clinically significant hyponatraemia according to dosing occasion. Clinically significant hyponatraemia was more frequent in patients aged ≥ 65 years than in those aged < 65 years in all dose groups, including those receiving the MED for desmopressin (11% of men aged ≥ 65 years vs 0% of men aged < 65 years receiving 50 μg ; 4% of women ≥ 65 aged years vs 2% of women aged < 65 years receiving 25 μg). Severe hyponatraemia, defined as ≤ 125 mmol/L serum sodium, was rare, affecting 22/1431 (2%) patients overall.

Time to Clinically Significant Hyponatraemia

Time to clinically significant hyponatraemia was found to have a dose–response relationship, with the probability of clinically significant hyponatraemia occurring earlier increasing with desmopressin dose (Fig. 1). There was no difference in time to clinically significant hyponatraemia in women receiving desmopressin 10/25 μg and men receiving 10/25/50 μg compared with placebo (Fig. 1A and B). No dose–response relationship was seen in time to clinically significant hyponatraemia in patients aged < 65 years; however, in elderly women all doses > 25 μg increased time to hyponatraemia compared with placebo, while the same is true for elderly men at 50 μg and higher (data not shown).

Most clinically significant hyponatraemia events occurred within 2–3 weeks of treatment initiation. The time to return to serum sodium level ≥ 135 mmol/L after clinically significant hyponatraemia was short for most patients (median 17 days [95% CI 8–28]).

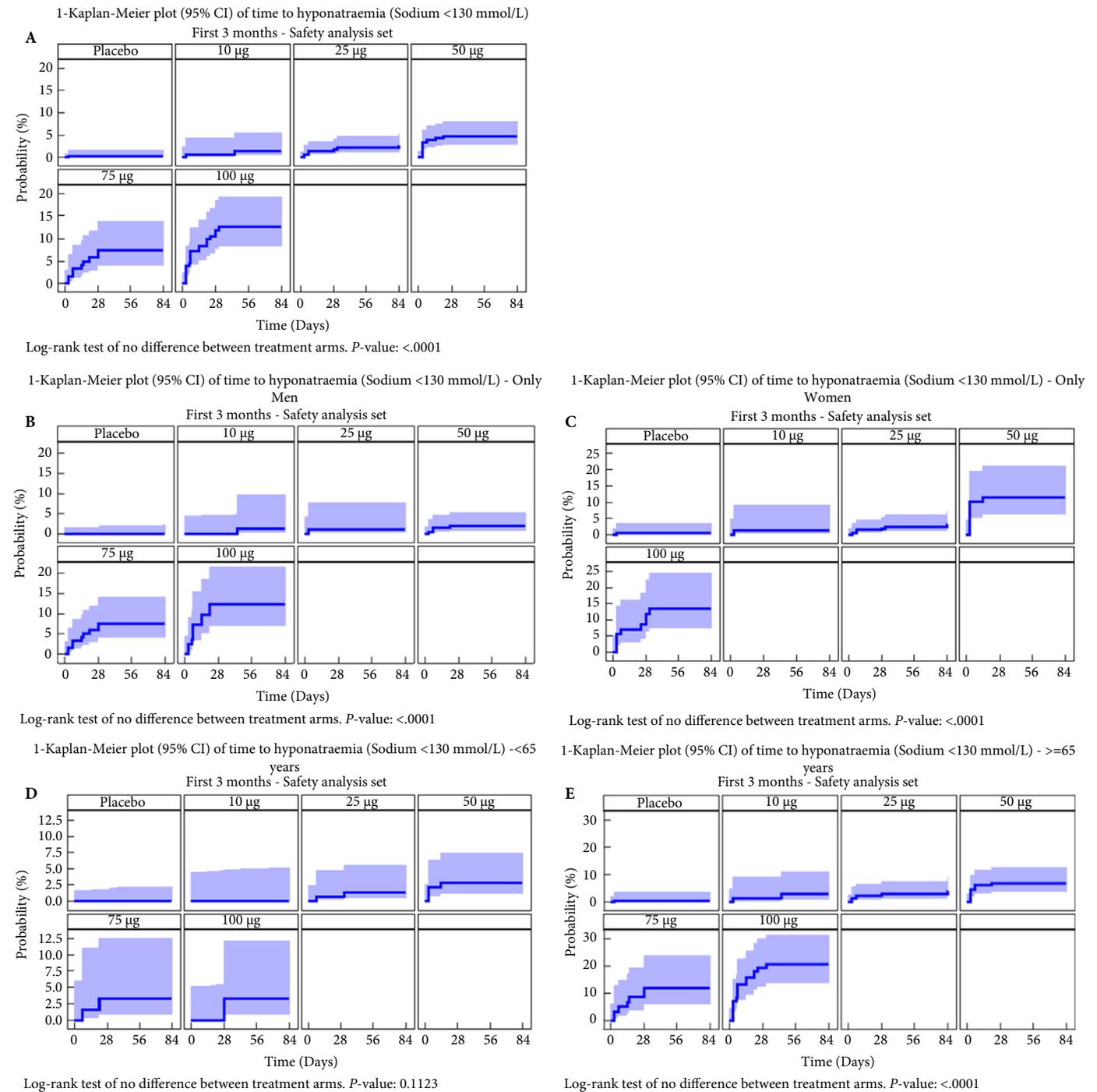
Predictors of Hyponatraemia

A stepwise Cox proportional hazard model was used to identify risk factors independently associated with clinically significant hyponatraemia (Table 2). Significant predictors of clinically significant hyponatraemia in both sexes were exposure to desmopressin doses above the sex-specific MED, baseline serum sodium < 135 mmol/L, age ≥ 65 years and impaired renal clearance (< 60 mL/min). In men, the use of drugs for bone disease and a history of arthritis were also significant predictors, and in women elevated monocytes and absence of lipid-modifying drugs at baseline significantly

Table 1 Number of patients experiencing clinically significant hyponatraemia (< 130 mmol/L) and severe hyponatraemia (≤ 125 mmol/L) by dose, sex and age group.

	Men				Women			
	Age < 65 years		Age ≥ 65 years		Age < 65 years		Age ≥ 65 years	
	N	Affected, n (%)	N	Affected, n (%)	N	Affected, n (%)	N	Affected, n (%)
Clinically significant hyponatraemia								
Placebo	113	0 (0)	121	0 (0)	108	0 (0)	84	1 (1)
10 μg desmopressin	35	0 (0)	49	1 (2)	48	0 (0)	27	2 (7)
25 μg desmopressin	37	0 (0)	53	1 (2)	113	2 (2)	89	4 (4)
50 μg desmopressin	94	0 (0)	103	11 (11)	49	5 (10)	30	7 (23)
75 μg desmopressin	63	2 (3)	59	7 (12)	–	–	–	–
100 μg desmopressin	32	0 (0)	53	14 (26)	40	2 (5)	31	9 (29)
Total	374	2 (< 1)	438	34 (8)	358	9 (3)	261	23 (9)
Severe hyponatraemia								
Placebo	113	0 (0)	121	0 (0)	108	0 (0)	84	1 (1)
10 μg desmopressin	35	0 (0)	49	1 (2)	48	0 (0)	27	0 (0)
25 μg desmopressin	37	0 (0)	53	0 (0)	113	0 (0)	89	0 (0)
50 μg desmopressin	94	0 (0)	103	3 (3)	49	3 (6)	30	3 (10)
75 μg desmopressin	63	1 (2)	59	3 (5)	–	–	–	–
100 μg desmopressin	32	0 (0)	53	5 (9)	40	0 (0)	31	2 (6)
Total	374	1 (< 1)	438	12 (3)	358	3 (< 1)	261	6 (2)

Fig. 1 Kaplan–Meier curves of time to serum sodium concentration <130 mmol/L during first 3 months of treatment.



predicted clinically significant hyponatraemia. There was also a significantly lower risk with the lowest dose (10 µg) of desmopressin, which is consistent with its lack of efficacy.

Of the three patients who were included with baseline serum sodium levels <135 mmol/L, one woman discontinued as a result of somnolence, one woman was lost to follow-up and

had an adverse event of hyponatraemia, and one man discontinued because of hyponatraemia.

Effect of Sodium Monitoring

A monitoring plan is proposed in order to minimize the risk of hyponatraemia (Fig. 2). In its most conservative form, this plan requires baseline serum sodium to be checked in all

Table 2 Cox regression model through stepwise selection for predictors of clinically significant hyponatraemia.

Covariate/factor	HR estimate (95% CI)	P
Men (recommended dose 50 µg)		
Treatment (ref. 50 µg)		0.0013*
Placebo	0.00 (0.00; -) [†]	0.99
10 µg	0.117 (0.01; 0.96)	0.045
25 µg	0.162 (0.02; 1.29)	0.086
75 µg	3.996 (1.44; 11.10)	0.0078
100 µg	2.707 (1.08; 6.76)	0.0331
Baseline sodium <135 mmol/L	6.999 (1.28; 38.2)	0.025
Drugs for bone disease	6.097 (1.99; 18.70)	0.0016
Baseline creatinine clearance <60	4.967 (2.15; 11.48)	0.0002
History of arthritis	2.449 (1.15; 5.20)	0.020
Age ≥65 years	7.447 (1.71; 32.36)	0.0074
History of nasal preparations	1.633 (0.44; 6.03)	0.46
Women (recommended dose 25 µg)		
Treatment (ref. 25 µg)		<0.001*
Placebo	0.221 (0.03; 1.91)	0.17
10 µg	1.92 (0.36; 10.25)	0.45
50 µg	4.967 (1.79; 13.76)	0.002
100 µg	6.247 (2.07; 18.87)	0.001
Baseline sodium <135 mmol/L	16.457 (4.44; 60.98)	<0.001
Baseline creatinine clearance <60 (estimated GFR)	4.038 (1.69; 9.66)	0.002
Age ≥65 years	4.831 (2.07; 11.26)	<0.001
History of spinal column stenosis	2.659 (0.58; 12.12)	0.21
History of drug hypersensitivity	1.319 (0.56; 3.13)	0.53
Lipid-modifying drugs	0.241 (0.10; 0.59)	0.002
Elevated monocytes (vs 1%)	1.266 (1.14; 1.41)	<0.001

Bold values represent statistical significance below 0.05. *Overall factor effect. [†]No men receiving placebo s fell <130 mmol/L, thus the HR for placebo vs 50 µg is 0. CI based on Wald test.

patients before beginning treatment with the desmopressin MED, and desmopressin should not be initiated if serum sodium level is <135 mmol/L. Those with normal baseline serum sodium levels but aged ≥65 years or those using concomitant medications with risk of hyponatraemia (i.e. selective serotonin reuptake inhibitors, thiazides and anti-epileptic agents) should also be checked at week 1 and month 1 after treatment initiation. Any patients with serum sodium levels <135 mmol/L should have their treatment discontinued. To illustrate the effect of this monitoring plan, Fig. 3 shows the course of women (Fig. 3A) and men (Fig. 3B) treated with the MED with no sodium monitoring, and with the monitoring plan applied retrospectively. The grey lines show patients who did not develop hyponatraemia throughout the 3-month study. The coloured lines and blue dots indicate patients with at least one hyponatraemia event; the red dots show individual sodium levels <130 mmol/L.

During the trials, three women experienced a serum sodium level <130 mmol/L but >125 mmol/L. They were allowed to remain on treatment under continued sodium monitoring, so we could observe whether the serum sodium level would increase or decrease further.

Once we retrospectively apply the proposed monitoring plan, all women with clinically significant hyponatraemia (i.e. a laboratory value <130 mmol/L) during treatment would have

been discontinued. All except two with a value between 130 and 134 mmol/L (i.e. mildly hyponatraemic) would also have been discontinued. These two mildly hyponatraemic women (both aged <65 years) would have failed to be screened out by the monitoring plan (because normal baseline values and lack of risk factors would have excluded them from ongoing sodium monitoring) and would have continued on treatment, with occasional sodium levels in the mildly hyponatraemic range: one patient with mild chronic hyponatraemia (bottom green line) and one with type 2 diabetes and a single borderline low value of 134 mmol/L at the end of month 3 (top green line).

Similarly, all men with clinically significant hyponatraemia (consisting of two men with serum sodium 125–129 mmol/L) would have been omitted from further treatment if the monitoring plan was applied. All except four with mild hyponatraemia (130 and 134 mmol/L) would also have been discontinued from treatment. Of these four patients who would not have had treatment stopped by the monitoring plan, two had more than a single isolated low serum sodium level, and, of these two, one (green line) had two consecutive low sodium levels 30 days apart, and thus may have developed chronic mild hyponatraemia.

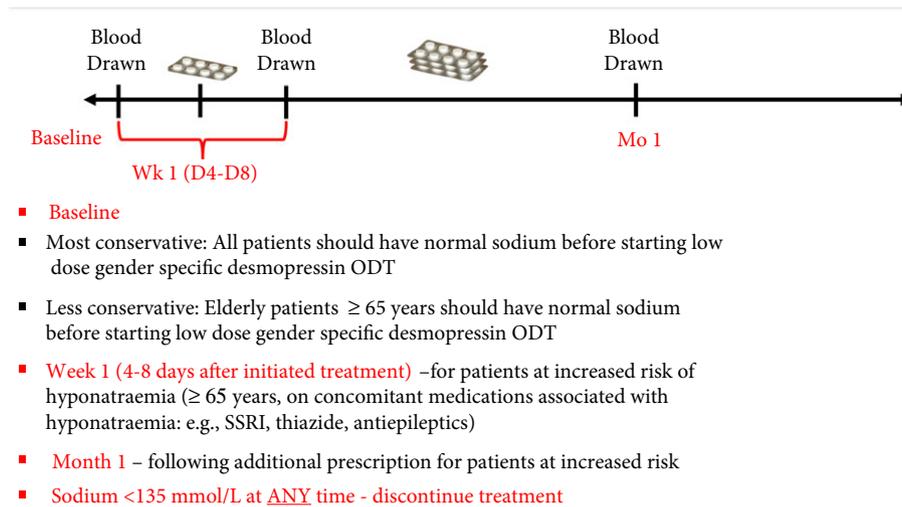
An alternative, less conservative monitoring plan could be considered, in which only those at risk because of their age (≥65 years) or other risk factors (e.g. concomitant medications known to induce syndrome of inappropriate antidiuretic hormone) are monitored for serum sodium levels at baseline, week 1 and month 1 (Fig. 2).

Discussion

Hyponatraemia is a potentially serious side effect of desmopressin therapy in adults with nocturia. It is therefore important to identify baseline predictors of hyponatraemia in patients with nocturia who are prescribed desmopressin in order to minimize its incidence. The present findings contribute to identifying patients at risk, which may help to guide treatment choices for patients with nocturia.

Analysis of the combined data from three trials of desmopressin ODT, comprising >1400 patients with nocturia, shows that desmopressin dose, patient age, baseline serum sodium levels, and kidney function according to estimated GFR clearance were significant risk factors for hyponatraemia in both sexes. Drugs for bone disease and arthritis were also predictive of hyponatraemia in men, while elevated monocytes and absence of lipid-modifying drugs were significant predictors in women.

The finding that women receiving desmopressin at higher doses have an elevated risk of clinically significant hyponatraemia concurs with our previous report [14], which showed that decreases in serum sodium level were

Fig. 2 Proposed monitoring plan to minimize risk of hyponatraemia.

approximately twofold greater in women aged >50 years receiving desmopressin ODT 25–100 μg than in men. This supports gender-specific dose recommendations. The optimum dose for women is 25 μg , whilst men require 50 μg to obtain clinically meaningful efficacy with minimal side effects [15,16]. Rembratt et al. [21] also found increasing age and low serum sodium concentration at baseline to be predictors of hyponatraemia with desmopressin oral tablets. Older people have a greater risk of hyponatraemia as a result of age-related alterations in fluid and electrolyte balance caused by increased sensitivity to arginine vasopressin and decreased renin-angiotensin pathway activity [22]. Increasing age and female gender are known risk factors for hyponatraemia induced by drugs other than desmopressin [23].

In addition to age-, sex- and dose-dependent risk, the present analysis suggests that certain factors, including low baseline serum sodium level and impaired renal clearance, increase the risk of clinically significant hyponatraemia.

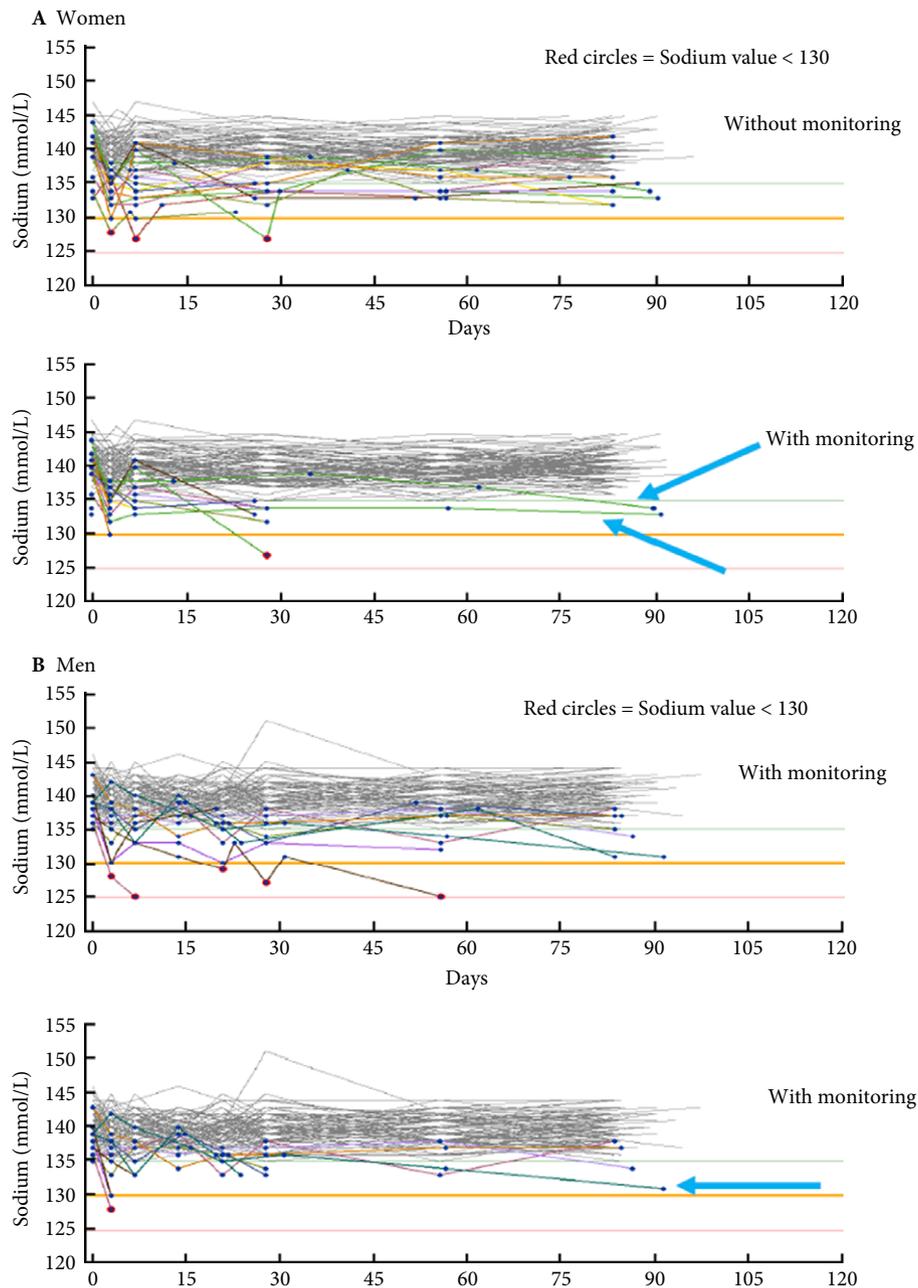
A serum sodium monitoring plan is therefore proposed, involving a serum sodium check at treatment initiation in all patients to exclude those with a low baseline value from treatment. Although not identified as risk factors in the present study, caution is advised when combining desmopressin with other drugs known to cause hyponatraemia, in particular selective serotonin reuptake inhibitors, thiazide diuretics and certain anti-epileptic drugs, such as carbamazepine. Further serum sodium monitoring at week 1 and month 1 is therefore recommended in elderly patients and those using other medications associated with hyponatraemia. If serum sodium level drops below 135 mmol/L, treatment should be discontinued.

When this plan was retrospectively applied to the trial data, all patients with clinically significant hyponatraemia were identified and would have been excluded from further

treatment. Care should be exercised in treating patients with other risk factors, including impaired renal clearance. Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance <50 mL/min), and poor renal function is therefore not included in the proposed monitoring plan; however, it may be appropriate to check renal clearance in individual patients before initiating desmopressin treatment if poor renal function is suspected but not yet diagnosed.

Arthritis and drugs for bone disease, for example, bisphosphonates, were found to be additional significant predictors of hyponatraemia in men, while elevated monocytes and absence of lipid-modifying drugs increased the risk in women. Bones are a reservoir for sodium, and chronic mild hyponatraemia is known to be associated with complications such as osteoporosis and fractures [24]; it is therefore possible that men in this study being treated for bone disease had chronic asymptomatic low serum sodium levels which increased their vulnerability to hyponatraemia with desmopressin therapy. The association of arthritis drugs with hyponatraemia in this study and the observation that use of lipid-modifying drugs may be in some way protective against hyponatraemia in women are, to our knowledge, novel findings and require further investigation and replication. It should be noted that investigation of associations between concomitant medications and hyponatraemia risk in patients taking desmopressin were inevitably limited to those drugs being taken by the study population, and there may therefore be other medications of relevance which have not been identified.

Our finding that increased levels of monocytes were highly significant predictors of increased hyponatraemia risk in women is concordant with a recent study in 172 patients prescribed desmopressin for nocturia and nocturnal polyuria

Fig. 3 Reduction in risk of hyponatraemia with proposed monitoring plan in (A) women and (B) men.

at a urology clinic [4], which found increased risk with lower haemoglobin levels. Raised white blood cell levels are probably indicative of recent infection, which may disturb salt and water balance, making patients more vulnerable to hyponatraemia associated with desmopressin use. Anaemia (low haemoglobin levels) can be associated with chronic inflammation, and the secretion of arginine vasopressin can be stimulated by inflammatory processes through the activation of interleukin-6, representing a possible mechanism by which risk of hyponatraemia with antidiuretic treatment may be increased if baseline levels of leukocytes are raised.

The desmopressin label states that treatment must be interrupted during intercurrent illnesses that predispose to fluid or electrolyte imbalance such as infection, fever or gastroenteritis, and as such it is important that these recommendations are adhered to in light of the current finding of increased risk with raised monocytes in women.

The present analysis also confirms a report based on 15 case histories [3] that desmopressin-induced hyponatraemia and decreases in serum sodium level generally occur within the first month of treatment initiation; therefore, particular

attention should be paid to hyponatraemia during this time, as detailed in our proposed monitoring scheme which includes serum sodium checks at baseline for all patients, as well as at week 1 and month 1 for those at increased risk because of advanced age or relevant concomitant medication.

The main limitation of the present study was that patients who had serum sodium levels ≤ 125 mmol/L were discontinued from the study according to the protocol [7–10], so follow-up data were not available. Only 22 patients (2%) had a serum sodium concentration ≤ 125 mmol/L, however, and this is therefore unlikely to have influenced our conclusions. The data included in the analyses were all taken from trials using the desmopressin ODT formulation and, as such, it is not known whether the findings can be extrapolated to other formulations of desmopressin.

In summary, in patients with nocturia treated with low-dose desmopressin combined with a sodium monitoring plan during the first month of treatment, mainly mild, non-clinically significant hyponatraemia was observed, within ranges of other drugs associated with hyponatraemia and similar to the background prevalence in the treatment population. In addition to higher desmopressin doses, predictors of clinically significant hyponatraemia include increasing age, low baseline sodium levels, impaired renal clearance (< 60 mL/min), as well as arthritis and drugs for bone disease in men, and raised monocytes and absence of lipid-modifying drugs in women. Use of gender-specific dosing (25 μ g in women and 50 μ g in men) and a serum sodium monitoring plan (baseline sodium check ≥ 135 mmol/L, especially in the elderly, with additional monitoring at week 1 and month 1 for those at increased risk because they are aged ≥ 65 years or on medication associated with hyponatraemia) will help to minimize the risk of desmopressin-induced hyponatraemia in patients with nocturia.

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Conflicts of interest

Kristian Vinter Juil, Jens Peter Nørgaard, Egbert van der Meulen, Anders Malmberg are employees of Ferring Pharmaceuticals. Johan van de Walle is a consultant to Ferring. The three published placebo-controlled trials of desmopressin ODT for nocturia [13 (NCT00477490), 15 (NCT01223937), 16 (NCT01262456)] included in this analysis were sponsored by Ferring.

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Abbreviations: ODT, orally disintegrating tablet; MED, minimum effective dose.