Neurourology and Urodynamics

Desmopressin Orally Disintegrating Tablet Effectively Reduces Nocturia: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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Aims: The primary objective was to investigate the efficacy of desmopressin orally disintegrating tablet versus placebo in patients with nocturia. Pharmacodynamics, safety and patient-reported quality of life (QoL) outcomes were also evaluated. One of several benefits of the new formulation is increased bioavailability. Exploring lower doses allows for a better evaluation of therapeutic effect versus tolerability. **Methods:** This was a 4-week, randomized, double-blind study comparing 10, 25, 50, or 100 μg desmopressin versus placebo in adults with defined nocturia. **Results:** The intent to treat population comprised 757 patients experiencing ~3 voids/night and a high prevalence of nocturnal polyuria (~90%). Increasing doses of desmopressin were associated with decreasing numbers of nocturnal voids and voided volume, greater proportions of subjects with >33% reduction in nocturnal voids, and increased duration of first sleep period. The lowest dose reaching statistical significance ($P < 0.05$ vs. placebo) varied by endpoint. Improvements were clinically meaningful, meaning that patients actually had fewer nightly voids. Post hoc analyses by gender suggested a lower minimum effective dose for women. Desmopressin was generally well tolerated. Reductions in serum sodium to <125 mmol/L in six women (taking >25 μg desmopressin) and two men (aged 67 and 82) taking 100 μg, support lower and gender-specific dosing to reduce the small but clinically significant risk of hyponatraemia. Each void reduced/hour of sleep gained was associated with significant improvements in QoL. **Conclusions:** Desmopressin orally disintegrating tablet is an effective and well-tolerated treatment for patients with nocturia. Further exploration of the lower dose range is warranted. *Neurourol. Urodynam.* © 2012 Wiley Periodicals, Inc.

Key words: desmopressin; nocturia; nocturnal polyuria; sleep; urinary bladder

INTRODUCTION

Nocturia is defined as the need to wake to void once or more per night.[1] It is a remarkably prevalent condition[2] that is considered to be clinically significant when ≥2 nightly episodes are experienced.[3,4] Associated chronic fragmentation of sleep and impaired sleep efficiency can have profound consequences for alertness, mood, functioning, cognitive performance and work productivity, and may also affect health and mortality.[5]

Treatment approaches include conservative management via fluid restriction, and pharmacological therapy using anticholinergics and/or drugs for benign prostatic hyperplasia (BPH). However, while these may be effective for daytime overactive bladder (OAB) or BPH symptoms, they are generally ineffective for nocturia.[6,7]

Around 80% of patients with nocturia have nocturnal polyuria (NP), which is reported to be associated with decreased nocturnal secretion of arginine vasopressin (AVP).[8–12] This may be a primary cause of NP or may occur secondary to other conditions (e.g., sleep apnea and third spacing). Desmopressin acetate, a synthetic analog of AVP, mimics the action of the natural hormone, and desmopressin tablets have been shown to be a well-tolerated and effective treatment for nocturia in adults with NP in clinical trials.[13–17]

Desmopressin has most recently been formulated as an orally disintegrating tablet (oral lyophilisate/melt/orodispersible formulation) (MINIRIN® Melt, Ferring Pharmaceuticals A/S, Copenhagen, Denmark), which is administered sublingually without water. This formulation is associated with increased bioavailability, allowing lower dosing than with the original solid tablets. The primary objectives of this study were to evaluate the efficacy and tolerability of desmopressin orally disintegrating tablet versus placebo. The minimum effective dose (MED) was investigated with a view to further optimizing the balance between therapeutic effect and tolerability in patients of all ages.

The study was monitored by an external, independent Data Safety Monitoring Board and was approved by the institutional review board or ethics committee for each site. The study was registered on www.clinicaltrials.gov (NCT00477490, NCT00615836) on 22 May 2007.

MATERIALS AND METHODS

Patients

Patients were ≥18 years of age, with an average of ≥2 voids per night determined via a 3-day frequency–volume chart

Christopher Chapple led the review process.
Conflict of interest: J.P. Weiss has been working with Ferring Pharmascience for more than 10 years acting in the capacity of paid consultant and scientific advisor. N.R. Zinner has been involved in clinical trials and has received speaker honoraria and consultancy fees from Ferring Pharmaceuticals and Astellas. B.M. Klein and J.P. Nørgaard are employees of Ferring Pharmaceuticals.
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and change from baseline in nocturnal voids and the baseline QoL score as covariates. This analysis was performed for the overall score and for each of the two domains. The impact of the change in initial period of undisturbed sleep on QoL was analyzed in a similar manner.

Two-sided tests using a step-down strategy from highest to lowest dose were used for all efficacy endpoints. Missing values for nocturnal voids at Days 8, 15, 22, and 28 were imputed using last observation carried forward.

SAS version 9.1.3 service pack 4 was used.

RESULTS

Patient Disposition and Demographics

Only 799/1,412 subjects were randomized (Fig. 1). The most common reasons for screening failure were renal insufficiency (15%) and averaging <2 nocturnal voids during screening (10%). Other reasons included diabetes insipidus (5%), hyponatremia (4%), suspected urinary disorders (4%), and uncontrolled diabetes mellitus (4%) or hypertension (3%). Reasons for exclusion were not given in 35% of cases.

The ITT population included 757 subjects and 710 (89%) completed the study. Across treatment groups, 6–16% of subjects discontinued prematurely. The most common reasons for discontinuation were withdrawal of consent (4%), AEs (2%), and lost to follow-up (2%).

Overall, treatment groups were well balanced (Table I).

Change in Mean Number of Nocturnal Voids

A greater decrease in nocturnal voiding was observed with increasing dose of desmopressin (−0.83 to −1.43) (Table II). Reductions were significant versus placebo for 100 μg

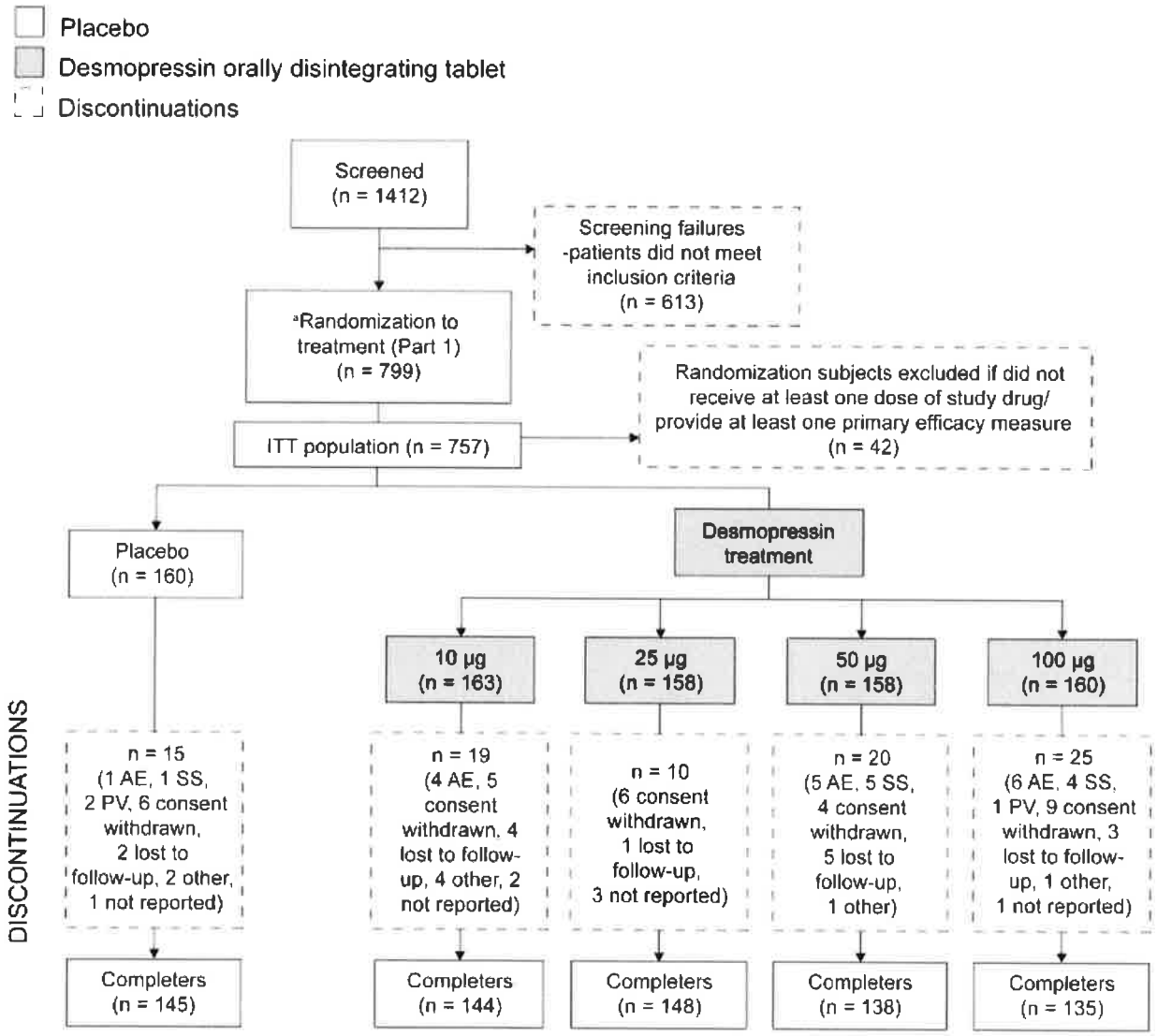

Fig. 1. Patient disposition. [a]Randomization stratified by age (<65, ≥65 years), presence/absence NP. ITT, intent to treat; AE, adverse event; SS, serum sodium; PV, post-void residual volume.

TABLE III. Change in N-QoL for Each Reduction of One in Number of Nocturnal Voids and for Each Increase of 1 hr in First Period of Undisturbed Sleep

	Change in N-QoL for each change of 1 in number of nocturnal voids estimate [95% CI]	Change in N-QoL for each change of 1 hr in first period of undisturbed sleep ESTIMATE [95% CI]
Sleep/energy domain	4.25 [3.11; 5.38]*	3.27 [2.52; 4.03]*
Bother/concern domain	5.03 [3.82; 6.24]*	4.05 [3.25; 4.85]*
Total score	4.68 [3.61; 5.75]*	3.68 [2.98; 4.38]*

*Statistically significant ($P \leq 0.05$, 95% CI does not contain 0).

Proportion With >33% Reduction in Mean Number of Nocturnal Voids

The proportion of subjects with >33% reduction in nocturnal voids increased with increasing dose (47–71%) (Table II). The effect was significantly greater versus placebo with 100 μg ($P < 0.0001$) and demonstrated a rapid onset. In females, the effect was significantly greater versus placebo for 100 μg ($P < 0.0001$), 50 μg ($P = 0.04$) and 25 μg ($P = 0.02$); in males, 100 μg was superior to placebo ($P < 0.05$). The results were consistent in both age groups.

The results of all analyses of voiding data are mutually supportive, indicating that the MED for desmopressin orally disintegrating tablets is 100 μg in men and 25 μg in women. Ten micrograms was sub-therapeutic for the co-primary endpoints (Table II).

Diuresis (Volumes)

At Day 28, nocturnal urine volume had decreased in all groups (Table II). Overall reductions were greater in the treatment groups than with placebo, being significant versus placebo ($P < 0.05$) at 25–100 μg. For females the difference was significant at 10–100 μg, and for males at 50–100 μg.

Sleep (Time From Falling Asleep to Waking for First Nocturnal Void)

The initial period of undisturbed sleep increased with desmopressin dose in all groups (Table II). Increases versus placebo were significant at 25, 50, and 100 μg (83, 85, and 107 min, respectively) (Table II). A significant increase was noted at 25–100 μg in females, and 100 μg in males.

QoL

One less nocturnal void was associated with an increase of 4.68 in total N-QoL score (5.03 for bother/concern, 4.25 for sleep/energy; $P < 0.05$) (Table III). Similarly, a 1-hr increase in first period of undisturbed sleep was associated with an increase of 3.68 in total N-QoL (4.05 for bother/concern score, 3.27 for sleep/energy; $P < 0.05$) (Table III). These changes support the notion that reducing nocturia increases QoL.

Safety and Tolerability

AE reporting. Table IV summarizes AE categories by treatment group. The four serious AEs reported were considered unrelated or unlikely to be related to the study drug and none were related to reductions in serum sodium. The incidence of AEs leading to discontinuation was highest in the 50 μg (8%) and 100 μg (9%) groups, primarily as a result of the protocol-defined withdrawal of patients with serum sodium <125 mmol/L. Individual AE terms did not reveal any unexpected findings, with respect to their prevalence. A relation to desmopressin dose was suggested for the following reported AEs: "nausea" (<1% in placebo group vs. 2–5% in desmopressin groups), "diarrhea" (1% vs. 1–6%), "dizziness" (0 vs. 2–4%), "blood sodium decreased" (<1% vs. 1–5%), and "hyponatremia" (<1% vs. 0–6%).

Laboratory serum sodium levels. Overall, 24 patients (3.0%) had serum sodium levels <130 mmol/L during the study. Of these, nine (1.1% of total), including six women and two men on active treatment, had reductions in serum sodium to <125 mmol/L. These drops all occurred within a week of treatment initiation. Patients ≥65 years were more frequently affected than those <65 years (Table V). No woman receiving 25 μg desmopressin had serum sodium <125 mmol/L. No man under the age of 65 years had serum sodium <130 mmol/L.

DISCUSSION

The objectives of this large randomized trial were to investigate whether a new formulation of desmopressin was superior

TABLE IV. Summary of Treatment-Emergent Adverse Events

		Active				
	Placebo	10 μg	25 μg	50 μg	100 μg	Total
n	160	163	158	158	160	799
All AEs, n (%)	76 (48%)	92 (56%)	78 (49%)	92 (59%)	99 (62%)	437 (55%)
Serious AEs, n (%)	1 (<1%)[a]	1 (<1%)[b]	1(<1%)[c]	1 (<1%)[d]	—	4 (<1%)
AEs leading to discontinuation, n (%)	7 (4%)	6 (4%)	2 (1%)	13 (8%)	14 (9%)	42 (5%)
Severe AEs, n (%)	2 (1%)	6 (4%)	3 (2%)	11 (7%)	7 (4%)	29 (4%)
ADRs, n (%)	47 (29%)	55 (34%)	57 (36%)	69 (44%)	73 (46%)	301 (38%)

[a]Prostate cancer.
[b]Diverticulitis.
[c]Myalgia.
[d]Metastasis.

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