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Solute and Water Excretion Patterns in Patients with Nocturnal Polyuria

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Abstract

Background and Aims: Nocturia is a highly prevalent and troublesome lower urinary tract symptom, with 28-36% of adults usually voiding at least twice nightly. For many patients, nocturia arises from the presence of nocturnal polyuria (NP), usually defined as being present when more than 33% of the total 24-hour urine output occurs at night while the total 24-hour urine output remains normal. We report results of an innovative evaluation in a clinical sample of 29 nocturia patients found to have NP during evaluation of their nocturia symptoms.

Methods: Patients with nocturia collected 24-hour urine specimens split into two containers, one of which was collected during the daytime, the second collected during the nighttime. We analyzed patterns of solute and water excretion, comparing daytime to nighttime collections.

Results: Overall the group demonstrated remarkably abnormal patterns of solute and water excretion, with the rate of urine production dramatically greater at night (mean 118 mL/hr) than during the day (mean 56 mL/hr; $p<0.001$); solute excretion markedly increased at night (mean 41 mmol/hr) compared to during the day (mean 27 mmol/hr; $p=0.001$), and free water absorption marginally decreased at night (mean 18 mL/hr) compared to during the day (mean 33mL/hr; $p=0.053$). Within this broad pattern of abnormality, we found that patients fell into one of three categories: those with (1) Increased nocturnal solute diuresis, (2) Decreased nocturnal free water reabsorption, and (3) Nocturnal mixed diuresis.

Nocturnal water diuresis and solute diuresis have both been noted in other studies of nocturics. Our study enhances evidence that nocturic patients may benefit from a more sophisticated evaluation than is afforded by analysis of a simple frequency-volume chart.

Conclusions: A clinical categorization scheme based on these excretion patterns may help direct the clinician in choosing an appropriate therapy.

Keywords: Nocturia, Polyuria, Diuresis

Introduction

Nocturia, defined as "the complaint that the individual has to wake at night one or more times to void," (1) is a highly prevalent and troublesome lower urinary tract symptom. Epidemiologic data

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from several countries suggests that about 28-36% of adults usually void at least twice nightly with the odds of nocturia increasing with age, minority ethnicity, and female gender (2-5). Nocturia is associated with a decreased general state of health (6), and in those who void three or more times nightly, a greater mortality rate from all causes (7), presumably because of its association with several chronic medical illnesses. Epidemiologic data suggest that nocturia is more prevalent among adults with type 2 diabetes, cardiac disease, hypertension, and among those using diuretics (2-5) probably because these medical conditions are associated with alterations in general fluid status and urinary excretion patterns.

The need to arise from sleep in order to urinate occurs when nocturnal bladder capacity is exceeded by nocturnal urine production. Common sense dictates that nocturia will be present when bladder capacity is unusually small; this can occur either when the physical capacity of the bladder is reduced (e.g. by prior irradiation or by the presence of tumor) or alternatively when the functional capacity of the bladder is reduced (e.g. by detrusor overactivity or by painful bladder disorders). Patients with small bladder capacity suffer from both daytime and nighttime urinary frequency and treatment can be usefully directed at the lower urinary tract disorder. In practice, many patients with troublesome nocturia have normal bladder capacity but become symptomatic because there is an increased nocturnal urine production rate. In such patients, treatment is logically directed at reducing the rate of nocturnal urine production. For example, pathophysiological considerations and clinical experience suggest that increased nocturnal urine output and nocturia are to be expected in patients with obstructive sleep apnea, hyperosmolar states, congestive heart failure, peripheral edema, and chronic kidney disease (8). These conditions are thought to cause nocturia because they result in nocturnal polyuria (NP), or an increase in the proportion of urine output that occurs during the night. In clinical practice, patients are usually considered to demonstrate NP if more than 33% of their 24-hour fluid output occurs at night (9). In its nocturia evaluation guidelines, the International Continence Society recommends that in patients seeking help for troublesome nocturia, initial evaluation should be focused on determining whether or not NP is present – with attribution to a lower urinary tract cause if NP is not present, and attribution to a cause outside the lower urinary tract if NP is present (Figure 1). This approach is based only on pathophysiologic considerations and there have been no clinical reports about the utility and practicality of this approach.

At our Medical Center, women with nocturia are first evaluated by the urogynecology service. When contributory lower urinary tract causes have been excluded and/or maximally treated and troublesome nocturia persists, patients are referred to the Nephrology service for further evaluation. As part of routine evaluation by the Nephrology service, we determine whether NP is present and extend that NP evaluation to determine the pattern of solute and water diuresis that is present with the aim of matching a treatment to the underlying pathophysiology. This report describes the results of that innovative evaluation in a clinical sample of nocturia patients who were found to have NP during their nocturia evaluation.

Materials and Methods

After Institutional Review Board approval, we conducted a retrospective chart review of all patients referred to the Nephrology Clinic for evaluation of troublesome nocturia between January 2007 and July 2009. At our medical center, women with nocturia are referred to us for evaluation only after they have undergone initial evaluation by the urogynecology team and have been found to have nocturia that either cannot be explained by lower urinary tract abnormalities, or in whom contributory lower urinary tract

abnormalities have already been maximally treated but nocturia persists as a troublesome symptom. As part of the routine evaluation by the Nephrology service, patients perform a 24-hour urine collection while on their usual diet and fluid intake. The 24-hour collection is split into two containers, one of which is filled with urine that is collected during the daytime, and the second of which is filled with urine collected during the nighttime. Patients discard their first morning void as they begin their daytime collection (since that urine was produced during the nighttime) and thereafter to collect all voided urine until they retire that night to sleep. All urine voided during the night and the first voided urine of the next morning is collected in a second container. Patients note the time that they rise from sleep and the time they retire to sleep during the urine collection period. The morning following collection of these daytime and nighttime specimens, patients have blood drawn for a basic metabolic panel.

Lab results included plasma sodium (mmol/L), potassium (mmol/L), chloride (mmol/L), carbon dioxide content (mmol/L), blood urea nitrogen (mg/dL), creatinine (mg/dL), and glucose (mg/dL). Urine collections were analyzed separately as day and night samples. For each, we determined total volume (mL), sodium (mmol/total volume), potassium (mmol/total volume), chloride (mmol/total volume), urea nitrogen (mg/dl), creatinine (mg/dl), glucose (mg/dl), and osmolality (mmol/L), and time of collection (hrs). Nocturnal polyuria is considered to be present when patients produce more than one-third of their total (daytime plus nighttime) urine output at night (9).

For both daytime and nighttime urine samples, we calculated urine flow rate (mL/hour), urine osmolar excretion rate (mosmoles/hour), urine sodium excretion rate (mmol/hour), ratio of urine osmolarity to serum osmolarity, free water reabsorption rate (mL/hour), and creatinine clearance rate (micromoles/hour) (see Table 1 for calculations).

Statistics

SPSS Version 15.0 (SPSS Inc, Chicago, IL) was used for data management and statistical analysis. Statistical analysis was primarily descriptive. Where appropriate, Mann-Whitney and Kruskall-Wallis nonparametric tests were used to compare sample medians, with a 5% significance level used.

Table 1. Analyses and calculations performed on all urine collections

Variable	How variable was calculated
Urine flow rate (Uvol)	Total urine volume divided by time (hours) over which urine was collected (mL/hour)
Solute excretion rate	Total urine osmoles (Uosm) divided by time over which urine was collected (mmol/hour)
Urine sodium excretion rate	Total urine sodium (UNa) divided by time over which urine was collected (mmol/hour)
Uosm/Posm	Total urine osmoles divided by calculated plasma osmolarity
Free water reabsorption	(Uvol-[(Uosm*Uvol)/Posm]) divided by time over which urine was collected (mL/hour)
Creatinine Clearance	[(Total urine creatinine multiplied by total urine volume)/ plasma creatinine)] divided by time over which urine was collected (mL/minute)

Uosm/Posm, Ratio of Urine osmolarity to plasma osmolarity

Results

Of 31 female patients referred for nocturia evaluation during the study time period, 29 patients with mean age 74 years (range 56-92) demonstrated NP and are included in this analysis. The two patients

that were excluded did not excrete greater than one-third of their total urine output at night compared to day. Comorbid chronic medical conditions included hypertension in 14 (51%) patients, known coronary artery disease in 3 (10%), diabetes mellitus Type 2 in 7 (24%), and obstructive sleep apnea in 6 (21%).

Overall, as detailed in Table 2, the group demonstrated remarkably abnormal patterns of solute and water excretion. As expected in this group of patients with NP, the rate of urine production was dramatically greater at night (mean 118 mL/hr) than during the day (mean 56 mL/hr; $p<0.001$); solute excretion was markedly increased at night (mean 41 mmol/hr) compared to during the day (mean 27 mmol/hr; $p=0.001$), and free water absorption was marginally decreased at night (mean 18mL/hr) compared to during the day (mean 33mL/hr; $p=0.053$).

Within this broad pattern of abnormality, we were able to categorize patients further into three broad classifications, according to their patterns of daytime and nighttime solute and water diuresis. Specifically, we found that patients fell into one of three categories, with statistically significant differences in study variable values as detailed in Table 2:

1) Those with increased nocturnal solute diuresis but without decreased nocturnal free water reabsorption, i.e. whose osmolar excretion rate was greater at night than during the day but whose rate of free water reabsorption was not diminished during the night. Usually, this nocturnal solute diuresis was due to an increased nocturnal sodium diuresis rate.

2) Those with decreased nocturnal free water reabsorption but without increased nocturnal solute diuresis, i.e. who demonstrated a decreased rate of free water reabsorption during the night (as compared to during the day) but whose rate of solute diuresis was not increased at night.

Table 2. Results of evaluation in 29 patients demonstrating nocturnal polyuria

Parameter	All nocturnal polyuria patients (n=29)		Increased nocturnal solute diuresis (n=9)		Decreased nocturnal free water reabsorption (n=8)		Nocturnal Mixed diuresis (n=12)	
	Day	Night	Day	Night	Day	Night	Day	Night
Urine flow rate (ml/hr)	56.3 ± 29.5†	117.8 ± 70.7	38.6 ± 18.1	88.5 ± 51.3	75.0±16.8*	94.9 ± 24.1	57.1 ± 35.9*	155.1 ± 88.5*
Uosm rate (mmol/hr)	26.8 ±11.3‡	40.8 ± 20.2	21.3 ± 7.8	44.2 ± 19.8	32.9 ± 8.0*	28.1 ± 6.7*	26.8 ± 13.7	46.6 ± 23.6*
UNa rate (mmol/hr)	4.0 ± 1.9	8.5 ± 5.5	3.1 ± 1.4	9.9 ± 5.9	5.8 ± 2.0*	4.9 ± 1.5*	3.5 ± 1.4	9.9 ± 6.1
Uosm/Posm	1.7± 0.5	1.3 ± 0.5	2.1 ± 0.7	1.8 ± 0.5	1.4 ± 0.3*	1.0 ± 0.2*	1.6 ± 0.4	1.1 ± 0.2
Free H_20 reabs (ml/hr)	33.1 ± 23.1§	18.4 ± 40	32.8 ± 30.5	59.9 ± 33.1	34.1 ± 23.4	-1.8 ± 24.1*	32.6 ± 18.1	0.7 ± 29.2*
Creatinine Clearance (ml/min)	80±34.4	90.9±42	62.8 ± 25.8	86.2±32.2	94.7±21.9*	81.5±29.6	83±42.6	100.7±54.6

*significantly differs at the 5% level from variable values in the 'nocturnal solute diuresis' group (Kruskal-Wallis testing).

Mann-Whitney test comparing daytime to nighttime values † $p<0.001$; ‡ $p=0.001$; § $p=0.053$.

3) Those with nocturnal mixed diuresis, who displayed features of both increased nocturnal solute diuresis and decreased nocturnal free water reabsorption.

Based on our testing, about a third of patients fell into each category, with 9 (31%) patients demonstrating increased nocturnal solute diuresis, 8 (27%) demonstrating decreased nocturnal free water reabsorption, and 12 (41%) demonstrating nocturnal mixed diuresis. There was no association between concomitant medical conditions and dieresis pattern; there were 5 patients with known hypertension in each group. Both patients that did not have nocturnal polyuria had normal nocturnal excretion patterns (i.e. decreased solute and water excretion at night).

Discussion

Several published review papers describe the evaluation of nocturia patients (8, 10-14), and recommend classifying patients according to whether or not they demonstrate NP: when NP is present, it is recommended that treatment be directed at causes outside the urinary tract. Unfortunately, no published clinical series or clinical trials have documented the utility of this evaluation, and there is no evidence that treatment of comorbid conditions does result in diminution of nocturia in clinical practice though pathophysiologic considerations suggest that such treatment may be efficacious. In our patients we found that nocturia was almost always attributable to the presence of NP. We also found considerable variation in the solute and water diuresis patterns in our patients with NP. This finding is not surprising, given that NP can arise through more than one pathophysiological mechanism. More specifically, we were able to establish 3 specific categories based on mechanism of diuresis: (1) increased nocturnal solute diuresis, (2) decreased nocturnal free water reabsorption, and (3) nocturnal mixed diuresis.

We are not the first to suggest that more than one pathophysiologic process can produce NP; nocturnal water diuresis and solute diuresis have both been noted in other studies of nocturics. For example, Kaye demonstrated that volunteers with nocturia gained significantly more weight during the daytime (mean 0.96kg) and shed more weight at night (mean 1.08 kg) than controls who did not void during the night (mean daytime weight gain 0.66kg, mean nighttime weight loss 0.69kg) (15). Similarly, Torimoto et al demonstrated using bioelectric impedance analysis that men with NP had a significant increase in extracellular fluid in their legs during the day, in contrast to men without NP (16).

Further, Kaye demonstrated that nocturnal sodium, chloride and potassium excretion rates were significantly higher in nocturics than in non-nocturic controls and he suggests that alterations in the renin-angiotensin II system may underlie nocturia in at least some nocturic patients (15). Decreased nocturnal levels of arginine vasopressin have also been implicated in the pathogenesis of nocturia, forming the rationale for treatment of nocturia with desmopressin (8, 10-13, 15, 17). Bodo et al found that men with persistent nocturia after prostate ablation had significantly lower mean ADH levels than controls who had relief of their nocturia (12).

Our study is limited by the fact that we have no information about patients' fluid and/or salt intake while doing their 24-hour urine collection. However, we believe it is reasonable to assume that most fluid and salt intake was during patients' waking hours and that therefore most of their water and salt loads should have been filtered during the daytime, rather than according to the markedly abnormal patterns seen in this group. Further, we believe that our clinical practice of measuring salt and water excretion rates during consumption of patients' usual diets, is clinically relevant, as it likely reflects what is actually happening in our patients' daily lives rather than during a time of artificially imposed fluid and/or salt intake.

Conclusions

We propose that a clinical categorization scheme such as ours, represents an advance that may direct the physician in choosing an appropriate therapy, though this remains to be proven by further study. We postulate that those with increased nocturnal solute diuresis will respond to a low-sodium diet and evening loop diuretic, and those with decreased nocturnal free water reabsorption will respond to evening administration of desmopressin. Further investigation will be directed at using this data in order to guide therapy for these patients.

Conflict of Interest

The authors have no relevant conflicts of interest to report.

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