

Nocturia: a blinded, randomized, parallel placebo-controlled self-study of the effect of 5 different sedatives and analgesics

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Abstract

Background: In a previous study I noted that, when taken occasionally as a nighttime sedative, the benzodiazepine (BZD) oxazepam decreased nocturia. The objective of the present study was, using placebo and other sedatives and analgesics, to assess whether oxazepam decreases nocturia and, if so, how?

Methods: I conducted a prospective, randomized, placebo-controlled self-study over a period of 10 months using oxazepam, zopiclone and trazodone as sedatives, and naproxen and oxycodone as analgesics. I assessed each medication 10 times, for a total of 60 tests. Each test included assessment of sleep adequacy, number and volume of overnight voidings and chemistries. Every test was a "first-time" or "naive" event.

Results: All medications differed in several parameters from placebo, but nocturia only showed a significant reduction with naproxen and oxazepam. Nocturia occurred a mean (standard deviation [SD]) of 1.6 (0.84) times nightly with placebo and fell to 0.6 (0.5) with oxazepam, which was a 63% decrease without any change in urine volume. Naproxen reduced nocturia to a mean (SD) of 0.7 (0.8) times nightly by reducing water, salt and potassium excretion. Compared with placebo, all medications had less urine sodium loss and decreased fractional sodium excretion (FENa), suggesting increased renal tubular sodium reabsorption. This effect was most marked with naproxen. Neither improved sleep quality with zopiclone nor pain relief with oxycodone resulted in reduced nocturia.

Conclusion: The effect of naproxen was probably a direct one on the kidney. The reduction of electrolyte excretion produced by the other medications is possibly a central effect on sympathetic activity, and the effect was too small to change urine volume. The effect of oxazepam was to make the bladder less irritable and could not be attributed to a decrease in urine volume, electrolyte change, sedation or analgesia. A central γ -aminobutyric acid-mediated effect in the cord or brain could explain the results observed with oxazepam.

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Introduction

Nocturia, defined as awakening 1 or more times at night owing to the urge to void,¹ is more common in older men and women, and the night urine contains a greater fraction of the 24-hour sodium excretion compared with that of younger adults.^{2,3} Usually there are no structural abnormalities in the urinary tract, or if some, such as prostatic hypertrophy, are present they are not responsible for the symptom.⁴

By chance, I noted that when the functionally short-acting benzodiazepine (BZD) oxazepam (the *N*-demethylated 3 hydroxylated

metabolic product of diazepam),⁵ was occasionally taken for nighttime sedation, nocturia was reduced. In a previous study (unpublished data, 2003), this effect was tested in an open setting without placebo. Nocturia decreased from a mean (standard deviation [SD]) of 1.2 (0.6) to 0.4 (0.5) times nightly ($n = 9$, $p < 0.010$) and was associated with decreased sodium excretion. Subsequently, we became aware of a previous study⁶ where diazepam had been used to decrease nocturia. The authors believed it acted by improving quality of sleep.

I designed the present study to examine this effect more carefully and to compare oxazepam with the closely related non-BZD sedative zopiclone, which also acts by binding to the γ -aminobutyric acid type A, (GABA_A) receptor.⁷ In addition, I included 2 analgesics, naproxen (a nonsteroidal anti-inflammatory) and oxycodone (an opioid), which is twice as potent as morphine on a weight basis.⁸ Finally, I added the sedative/antidepressant trazodone,⁹ which binds to 5-hydroxytryptamine and adrenergic receptors, and conducted a blinded, randomized self-study. This methodology has been validated previously.¹⁰

Methods

I am a white man whose laboratory and behavioural characteristics were established in several studies¹¹ during the 2 years preceding the present study. At the time of study, I was 77 years old, weight was stable at 65 kg, body mass index was 22.8 kg/m² and medications had been unchanged for several years. Medications included 5 mg/d of finasteride, 12.5 mg/d of chlorthalidone, 40 mg of sotalol twice daily and 100 mg/d of losartan. History included

prostatic hypertrophy and hypertension, both controlled with treatment. Prostate size was 30 g, as estimated by a senior urologist, and blood pressure was between 110/65 and 120/70 mm Hg. Symptoms were nocturia once or twice nightly, urgency and, rarely, urge incontinence.

To ensure blinding, a pharmacist provided pills for the study in brown opaque sealed #1 coin envelopes measuring 2.2 × 3.5 inches. Thirty minutes before reclining for sleep, the top was cut off and the envelope placed in the mouth so that the single pill inside fell on the tongue and was washed down with several sips of water without having been seen or identified. Placebo was coated sugar, and medications were 15 mg of oxazepam; 5 mg of zopiclone; 500 mg of naproxen; 5 mg of oxycodone, immediate release; and 50 mg of trazodone. The bladder was emptied before retiring and the urine discarded. I measured and saved subsequent urine until rising the following morning; the bladder was emptied again to complete the night collection. I coded sleep quality as bad (1), indifferent (2) or good (3).

The medications were randomized in blocks of 6 (5 active drugs plus placebo), the envelopes were labelled 1–60 and adjusted so that the same medication could not be taken at the end of one block and the beginning of the next. There was a minimum of 72 hours between tests and, because the same drug was not taken consecutively, there would usually be 1 week or more before the drug was repeated. The aim was to have the equivalent of a first-time exposure for every test. Each medication was taken 10 times for a total of 60 tests

between October 2004 and June 2005. Only the test number was known and the code was not broken until the study was completed.

Following each night's collection, the urine was mixed and a 5 mL aliquot was frozen. After completion of the study, all collections were analyzed as a single batch in September 2005 at the Montreal General Hospital Clinical Chemistry Laboratories using a Hitachi 9.7 analyzer. Osmolality was measured in duplicate on a Fiske osmometer. I provided 5 blood samples at intervals between September 2005 and May 2006. Each was analyzed the same day. The results were all in the normal range and within experimental error. Before the study, blood had been analyzed at 9 am and 9 pm on 2 consecutive days,¹¹ yielding similar values. Therefore, mean values for serum creatinine, sodium and osmolality from the samples obtained during the study period were used to calculate the derived values of fractional sodium excretion (FENa), creatinine and osmolar clearances according to standard formulae.¹²

I entered the data in Excel (Microsoft Corp.) spreadsheets and analyzed them using the statistical routines. Results are shown as mean (SD). I evaluated the differences between medications using multivariate regression with $p < 0.05$ as the threshold of statistical significance.¹³

Results

Perfect sleep scores (3 for every night) were achieved with oxazepam and zopiclone only

Table 1. Summary of findings from self-study, by treatment type*

Characteristic	Treatment, mean (SD)†					
	Placebo	Oxazepam	Zopiclone	Naproxen	Oxycodone	Trazodone
Sleep score	2.5 (0.9)	3.0 (0.0)	3.0 (0.0)	2.7 (0.7)	2.7 (0.5)	2.2 (0.8)
Hours in bed	8.4 (0.6)	8.7 (0.6)	8.3 (0.6)	8.2 (0.4)	8.6 (0.5)	8.6 (0.8)
Urine volume, mL	666 (261)	590 (170)	641 (176)	358 (202)¶	520 (139)	504 (192)
Nocturia	1.6 (0.8)	0.6 (0.5)¶	1.3 (0.5)	0.7 (0.8)¶	1.1 (0.7)	1.1 (0.6)
Nocturia-free nights‡	1	4	0	5	2	1
Max void volume,§ mL	425	450	450	400	400	425

*Ten tests were performed with each treatment, for a total of 60 tests.

†Unless otherwise indicated.

‡Nocturia-free nights out of a possible maximum of 10.

§Max void volume is the maximum nocturnal volume of any voiding for this drug.

¶ $p < 0.05$ when compared with placebo.

(Table 1); however, the differences between the medications were small and nonsignificant. Total urine volume was highest with placebo, but the difference in volume with the other medications was significant with naproxen only. However, when expressed in millilitres per minute, the volumes with both naproxen and trazodone were different from that with placebo (Table 2).

With all drugs there was less nocturia than with placebo, but only for oxazepam and naproxen was the effect marked enough to achieve significance. Maximum void volume did not differ among medications and was usually less than the total night volume.

Urine chemistries were most changed for naproxen (Table 2). It differs from the other drugs in the intensity of the effect, yet findings with all medications show less electrolyte loss than with placebo, particularly in sodium excretion and the percentage of filtered sodium that appears in the urine (FENa%). Potassium loss was reduced with oxazepam, naproxen and oxycodone. Glomerular filtration, as approximated by creatinine clearance, was similar among all medications and placebo, and osmolalities varied considerably but were not significantly different from one another. The osmolar clearance (the number of osmotically active particles excreted per minute divided by the plasma osmolality) was decreased with naproxen and, to a lesser extent, with oxycodone and trazodone because of the decrease in sodium and its accompanying anions and, in some instances, reduced urea loss (data not shown).

Discussion

Nocturia is caused either by the delivery of too large a volume of urine for the capacity of the bladder or by the decreased storage ability of the organ. In most elderly people with nocturia, both of these abnormalities exist, and this is illustrated in the present study.

Only 2 medications reduced nocturia: naproxen and oxazepam. Naproxen reduced the volume of urine by 46% mainly through reduced sodium excretion. As creatinine clearance was unchanged, tubular sodium reabsorption would have to increase, which is shown by the 54% decrease in the percentage of FENa, less total urine solute and higher osmolality. This effect was similar in magnitude to that described previously in normal volunteers who were given the same dose of naproxen.¹⁴ With oxazepam, urine volume was unchanged and urine composition was similar to that seen with the other medications. Decreased nocturia could only be the result of improved storage. Because no effect on nocturia was observed with sedatives (zopiclone or trazodone) or analgesics (oxycodone), these cannot be causative in the oxazepam effect. Similarly, both oxazepam and zopiclone yielded perfect sleep scores, yet nocturia with oxazepam was half that with zopiclone. The change in capacity could be a direct effect on the bladder or its nerve supply.

We are aware of only a few studies where a direct effect of BZDs on the human bladder have been examined. In vitro, there was no effect on

Table 2. Urine chemistries, by treatment type*

Urine chemistry	Treatment, mean (SD)†					
	Placebo	Oxazepam	Zopiclone	Naproxen	Oxycodone	Trazodone
Vol‡, mL/min	1.3 (0.6)	1.1 (0.4)	1.3 (0.4)	0.7 (0.4)§	1.0 (0.3)	1.0 (0.3)§
Na, mmol/Vol	57.3 (7.9)	48.3 (12.1)§	47.3 (10.7)§	25.6 (4.7)§	45.0 (8.0)§	38.0 (10.0)§
Na, µmol/min	113.7 (18.3)	93.3 (26.5)§	94.5 (24.0)§	51.4 (8.2)§	87.5 (14.7)§	72.7 (17.4)§
FENa, %	1.1 (0.2)	0.9 (0.2)§	0.9 (0.2)§	0.5 (0.1)§	0.9 (0.1)§	0.7 (0.2)§
K, µmol/min	52.4 (10.6)	42.6 (6.2)§	54.4 (12.0)	43.3 (10.6)§	39.9 (7.0)§	49.5 (10.0)
Cl, µmol/min	71.1 (11.7)	61.8 (22.1)	62.0 (18.7)	28.6 (6.4)§	59.6 (11.4)	55.2 (12.3)§
Ccr, mL/min	71.6 (11.7)	71.7 (4.8)	74.4 (4.3)	71.3 (6.5)	69.8 (6.1)	69.3 (4.3)
Osmolality, mOsm/kg	538 (195)	538 (148)	497 (160)	678 (210)	574 (141)	579 (142)
Cosm, mL/min	2.1 (0.2)	1.9 (0.3)	1.9 (0.3)	1.4 (0.2)§	1.8 (0.2)§	1.7 (0.3)§

Ccr = creatinine clearance; Cl = chlorine; Cosm = osmolar clearance; FENa = fractional sodium excretion; K = potassium; Na = sodium; Vol = volume.

*Ten tests were performed with each treatment, for a total of 60 tests.

†Unless otherwise indicated.

‡Volume of urine excreted during the night.

§ $p < 0.05$ when compared with placebo.

isolated detrusor strips when contractions were induced with and without diazepam, although an inhibitory effect was observed in the bladders of rats.¹⁵ In adults or children there was no effect on bladder parameters when diazepam was administered intramuscularly,¹⁶ or when the less lipophilic midazolam was administered as a nasal spray.¹⁷ In comparison to these negative reports, there is extensive animal literature on spinal and supraspinal effects of BZDs, mostly mediated through GABA_A receptors.¹⁸⁻²⁰ Based on this evidence, we would speculatively favour a central effect of oxazepam. Zopiclone also binds to GABA_A receptors but differs slightly in its effects and profile of receptor subtype binding.^{7,21}

The decrease in urine sodium and percentage of FENa, as compared with placebo, was significant for all drugs. In addition, there were similar but less consistent changes for potassium, chloride and osmolar clearance. For naproxen, this is probably a direct effect on the kidney. Opioids are also known to have a renal and a central effect (via μ receptors) on sodium reabsorption.^{22,23} However, we are unaware of any previous reports relating BZDs, zopiclone or trazodone to electrolyte changes. This effect is therefore either an artifact, which is not in agreement with the data, or more likely a central effect causing antinatriuresis. A decrease in sympathetic output from the forebrain to the kidney, changing tubuloglomerular balance through the juxtaglomerular apparatus, could explain these findings.^{24,25}

The strengths of this study are the design and the comparison of multiple drugs. The main weakness is that only 1 person was studied. However, given that the sample is representative of nocturic elderly people,¹¹ there is reason to believe that the results are generalizable in a larger population. In addition the use of a single subject has been validated in several previous studies.¹⁰

Finally, it may be possible to find among the 1000 or more BZDs that have been synthesized some that have no sedative effect but retain the antinocturic action.

Conclusion

Nocturia was reduced only by naproxen and oxazepam. The marked sodium retention and decrease in urine output with naproxen and the similarity to previous studies suggests that this result

was a direct renal tubular effect. Urine volume was unchanged with oxazepam, and because the other sedatives and analgesics had no effect on nocturia this could not explain the findings with oxazepam. It is suggested that oxazepam was acting through central pathways, either in the spinal cord or higher, causing bladder relaxation, most likely involving GABAergic mechanisms. Aside from naproxen, the other drugs had a small but definite effect in decreasing sodium excretion and reducing the FENa%. This may be a central effect mediated through the sympathetic nervous system, as suggested previously in a study of circadian weight and sodium excretion in older people.¹¹

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