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MELATONIN PHARMACOTHERAPY FOR NOCTURIA IN MEN WITH BENIGN PROSTATIC ENLARGEMENT

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ABSTRACT

Purpose: Nocturia is a common condition often attributed in aging men to benign prostatic enlargement. Older adults are prone to nocturnal sleep disturbance, of which disturbed circadian rhythm may be a component since it improves with nighttime administration of melatonin. This study was designed to investigate melatonin as a potential treatment for nocturia associated with bladder outflow obstruction in older men.

Materials and Methods: A total of 20 men with urodynamically confirmed bladder outflow obstruction and nocturia were entered into a randomized, double blind, placebo controlled crossover study assessing the effect of 2 mg controlled release melatonin at night on nocturia. Symptoms were assessed at baseline and after each 4-week treatment period using a frequency volume chart, the International Prostate Symptom Score and symptom problem index. Maximum urinary flow rate and post-void residual urine volume were also assessed.

Results: Baseline frequency of nocturia was 3.1 episodes per night. There were 7 men (35%) with detrusor overactivity and 10 (50%) had nocturnal polyuria. Melatonin and placebo caused a decrease in nocturia of 0.32 and 0.05 episodes per night ($p = 0.07$) and a decrease in the nocturia bother score of 0.51 and 0.05, respectively ($p = 0.008$). Nocturia responder rates (a reduction from baseline of at least -0.5 episodes per night) differed between the active medication and placebo groups ($p = 0.04$). Daytime urinary frequency, International Prostate Symptom Score, relative nocturnal urine volume, maximum urinary flow rate and post-void residual were unaffected by melatonin treatment.

Conclusions: Melatonin treatment is associated with a significant nocturia response rate, improvement in nocturia related bother and a good adverse effect profile. However, it is uncertain whether the observed changes in this study are clinically significant.

KEY WORDS: urination disorders, melatonin, prostatic hyperplasia

Nocturia is the complaint of having to wake at night to void.[1] It is experienced by men and women, and is especially prevalent in older adults.[2] Prevalence of benign prostatic enlargement (BPE) in men also increases with aging. Nocturia is often attributed to BPE in men, but although they may be associated in older individuals a causal relationship is uncertain. Thus, nocturia is often found to respond less satisfactorily than other lower urinary tract symptoms after medical or surgical treatment of BPE.[3] Overall the pathophysiology of nocturia is complex and nocturnal polyuria may be implicated in a significant number of cases.[4]

Sleep disturbance is a common experience of older adults, many of whom depend on prescribed sedatives. Loss of normal circadian rhythms may be responsible in many who find it difficult to sleep at night and hormonal factors are often involved. Hormonal changes may also have significant effects on upper and lower urinary tract function, some of which vary in a circadian manner.

Melatonin (N-acetyl-5-methoxytryptamine) is a pineal gland hormone secreted predominantly at night. It is a prime physiological determinant of circadian rhythms and, therefore, could influence the physiological decrease in urine output and frequency at night seen in healthy individuals, either directly or indirectly through effects on other hormones. Nocturnal production of melatonin is impaired in older adults and several clinical trials have demonstrated that exogenous administration of melatonin to this group improves sleep.[5,6] Impaired melatonin production could also be involved in the disruption of the normal circadian pattern of micturition that leads to nocturia in older adults, including men with associated BPE. The aim of the current study was to determine whether administration of melatonin at night to these patients would improve the symptoms of nocturia either by an effect on circadian control or by improvement of sleep quality.

MATERIALS AND METHODS

Male patients with self-reported nocturia on average 3 or more times per night (from International Prostate Symptom Score [IPSS] question 7) were entered into the study. This group was chosen based on substantial symptom bother and optimizing detection of treatment response. All men had palpable benign prostate enlargement on digital rectal examination. All patients underwent videourodynamic study with bladder outflow obstruction confirmed in each case. Transabdominal ultrasound for estimation of prostate volume and post-void residual (PVR) were undertaken at baseline. Exclusion criteria were evidence of alternative lower urinary tract pathology (eg urinary tract infection, abnormal urinary cytology, suspicion or evidence of prostate cancer, chronic retention of urine, bladder stone), renal or hepatic impairment,

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history of surgical treatment for bladder outflow obstruction and use within the preceding month of diuretics, α-adrenergic antagonists, 5-α-reductase inhibitors, anti-depressants or sedatives.

Study design. The study had a double blind, crossover design. Patients were randomized to receive 2 mg controlled release melatonin tablets (Neurim Pharmaceuticals, Tel Aviv, Israel) or placebo for 4 weeks. Crossover followed a 7-day washout. Double blind treatment was taken 1 hour before bedtime. Frequency volume (FV) charts were completed by patients for 7 days before the baseline visit and for 7 days at the end of each 1-month treatment period. IPSS and American Urological Association symptom problem indexes (SPI) with questions on degree of bother corresponding to items in the American Urological Association symptom index[7] were assessed at baseline and at the end of each treatment period. Maximum urinary flow rate (Qmax) and PVR were also assessed at baseline and at the end of each treatment period. Nocturia (mean number of nocturnal awakenings to urinate, not including the first morning void after rising from bed) and mean daytime urinary frequency were calculated from the FV charts. Total urine volume for 24 hours and nocturnal urine volume (the volume passed between bedtime and rising in the morning, including the first void after rising) were measured during each week in which the FV chart was completed. Relative nocturnal urine volume (nocturnal urine volume as a percentage of the 24-hour urine) was calculated and nocturnal polyuria was diagnosed if this value was greater than 33%.[8]

End points and data analysis. The primary end point was mean change from baseline in nocturia episodes per night. Nocturia responder rates for different changes from baseline (-0.5, -1.0 and -2.0 episodes per night) were calculated from the FV chart data. The sample size was calculated to provide 80% power to detect a mean difference between treatment groups of 0.5 episodes per night, with $\alpha = 0.05$. Secondary end points were mean changes in daytime urinary frequency, relative nocturnal urine volume, total IPSS, IPSS question 7 (Q7) (nocturia score), nocturia bother score (from SPI), Qmax and PVR. Paired t tests were used for analysis of mean changes from baseline and the chi-square test was used for analysis of responder rates. Data were analyzed on an intent to treat basis. Results are presented as mean $\pm$ SD. Inquiries were made regarding adverse events at each visit and treatment was discontinued if appropriate. Methods, definitions and units conform to the standards recommended by the International Continence Society.[9] The study was approved by the Central Oxford Research Ethics Committee and informed consent was obtained from each subject.

RESULTS

A total of 20 male patients with a mean age of 72.2 years (range 60 to 81) were randomized. One man did not complete the study due to withdrawal of consent. Baseline characteristics are shown in table 1. Mean prostatic diameter measured on transabdominal ultrasound was 3.25 cm (range 2.6 to 4.2) corresponding to an approximate prostate volume from 41 to 50 ml.[10] On urodynamic assessment 7 men (35%) had detrusor overactivity. Ten men (50%) had nocturnal polyuria as calculated from FV chart.

TABLE 1. *Baseline characteristics*

	Mean $\pm$ SD
Nocturia episodes/night from FV chart	3.1 $\pm$ 0.8
Nocturia episodes/night from IPSS question 7	3.2 $\pm$ 0.9
Nocturia bother score from SPI	3.7 $\pm$ 1.2
Daily urinary frequency from FV chart	7.9 $\pm$ 2.5
% Relative nocturnal urine vol	31.7 $\pm$ 7.2
Total IPSS	19.7 $\pm$ 5.4
Ml/sec Qmax	9.7 $\pm$ 2.5
Ml PVR vol	28.3 $\pm$ 47.7

The effects of 2 mg melatonin and placebo on primary and secondary end points are shown in tables 2 and 3. Mean frequency of nocturia per night (from the FV chart) decreased from 3.1 at baseline to 2.8 with melatonin and 3.0 with placebo ($p = 0.07$). A statistically significant difference in the number showing a decrease in the mean number of nocturia episodes per night of at least 0.5 was identified ($p = 0.04$, table 3). Three patients (15%) receiving melatonin achieved a mean decrease of at least 1 episode of nocturia per night, compared with no patients receiving placebo ($p = 0.07$). Similarly, melatonin was associated with a nonsignificant decrease in the response to the IPSS nocturia question 7 from 3.3 to 2.8 ($p = 0.10$). There was a reduction in the response to the nocturia bother score question from the SPI with melatonin from 3.7 to 3.1, while placebo caused a reduction in the response from 3.7 to 3.6, giving an overall improvement in the nocturia bother score with melatonin of 0.5 relative to placebo ($p = 0.008$). A more substantial improvement in the nocturia bother score was seen in those men showing a decrease in number of episodes of nocturia per night (table 3), principally in the 3 individuals showing a mean decrease of at least 1 episode per night in whom the mean decrease in nocturia bother score was 1.7. For the 3 individuals showing a mean reduction of 0.5 to 0.9 episodes of nocturia per night the mean decrease in nocturia bother score was only marginally larger than the study cohort overall at 0.3.

No statistically significant effect of melatonin on relative nocturnal urine production, daytime urinary frequency, total IPSS, Qmax or PVR was demonstrated. Subgroup analysis for patients with detrusor overactivity compared to those without detrusor overactivity, and those with nocturnal polyuria compared to those without showed no difference among groups in response to active medication. No adverse events for melatonin or placebo were reported and there were no clinically significant changes in blood hematological or biochemical indexes.

DISCUSSION

In this study men with nocturia reported fewer episodes of nocturia and an improvement in bother scores related to nocturia. Several thresholds for decrease of nocturia episodes were tested as potential definitions for clinical response (reductions of -0.5, -1.0 and -2.0 episodes per night). Melatonin therapy resulted in significant improvement in clinical responder rate when defined as a reduction of -0.5 episodes per night. However, while the change in nocturia related bother after melatonin treatment was significantly better than after placebo treatment, the actual decrease in the incidence of nocturia (measured on FV chart and IPSS) did not reach statistical significance. Furthermore, the magnitude of effect was relatively small. The clinical significance of a mean decrease in nocturia of 0.5 episodes per night is uncertain. Three individuals (15%) showed a more substantial decrease of at least 1.0 episode per night. Since these individuals also showed a greater decrease in nocturia bother score than the cohort overall, which was not the case for a reduction of 0.5 to 0.9 episodes of nocturia per night, at least 1.0 fewer episodes of nocturia per night from the FV chart could signify a threshold above which response could be described as clinically useful.

Some aspects of the study design should be considered in interpretation and design of future studies. The possibility of a greater clinical response with longer study duration cannot be excluded since nocturia has a strong behavioral component (eg preventive voiding[11]), improvement of which is unlikely to be immediate. A parallel group design may be appropriate, although this design would demand a larger sample size. Furthermore, studies are required to define the clinical significance of particular decrease in incidence of

TABLE 2. *Effects of melatonin and placebo on primary and secondary end points*

	Mean (SD)			
	Baseline	Melatonin	Placebo	p Value (paired t test)
Nocturia episodes/night from FV chart	3.1 (0.8)	2.8 (0.7)	3.0 (0.8)	0.07
Nocturia episodes/night from IPSS question 7	3.3 (0.9)	2.8 (1.2)	3.3 (1.3)	0.10
Nocturia bother score from SPI	3.7 (1.2)	3.1 (1.1)	3.6 (1.1)	0.008
Daily urinary frequency from FV chart	7.9 (2.5)	8.0 (2.5)	8.0 (2.2)	0.83
% Relative nocturnal urine vol	31.7 (7.2)	31.8 (9.1)	31.9 (7.4)	0.91
Total IPSS	19.7 (5.4)	19.4 (5.6)	19.7 (5.6)	0.37
Ml/sec Qmax	9.7 (2.5)	9.9 (2.2)	9.9 (2.4)	0.83
Ml PVR vol	28.3 (47.7)	27.8 (52.8)	31.7 (45.7)	0.55

TABLE 3. *Nocturia responder rates*

Responder Definition*	Melatonin	Placebo	p Value (chi-square test)	Mean Bother Reduction†
−0.5	6	1	0.04	1.0
−1.0	3	0	0.07	1.7
−2.0	1	0	0.31	2.0

* Change from baseline in mean number of nocturia episodes per night.
† Mean decrease in response to nocturia bother score question from SPI.

nocturia to facilitate definition of clinical response. Clinical significance should also be addressed by evaluation of bother and disease specific quality of life using a questionnaire appropriate to this patient population, for which specifically validated instruments are in development but not yet available. Despite these limitations the trend toward improvement in nocturia with 2 mg controlled release melatonin 2 at night is clear.

Melatonin is short-lived with a half-life of only 40 to 50 minutes. The use of a controlled release melatonin formulation enables maintenance of potentially effective melatonin concentrations throughout the night with a single low dose, which has been shown to be effective in improving sleep in older adults.[5] Even in those patients with well-known medical reasons for nocturia, sleep disorders were still the source of almost all awakenings from sleep which can contribute to habitual rising at night to urinate.[12] Since melatonin is known to improve sleep quality, an improvement in habitual nocturnal voiding may have been part of the subjective benefit of active medication observed in the current study. Lack of decrease in nocturnal urine production, and hence on nocturia due to nocturnal polyuria, suggests the absence of any pharmacological antidiuretic effect directly exerted on the kidneys. The possibility of a direct effect of melatonin on the prostate gland cannot be excluded, mediated by an attenuating effect on androgen receptor function which has been demonstrated in prostate cancer cell lines.[13]

The prevalence of nocturia increases with age, and voiding 1 to 2 times nightly is typical in older adults.[14] Many men with nocturia have additional lower urinary tract symptoms suggestive of bladder outlet obstruction and nocturia is one of the most bothersome symptoms in this group.[15] Despite its prevalence nocturia remains one of the more difficult symptoms to treat, and is the symptom most resistant to conventional therapy for BPE such as α-adrenergic antagonists and transurethral prostatectomy.[3] The effects of several drugs and drug classes on nocturia have been investigated, including desmopressin,[16] anticholinergics,[17] timed diuretics[18] and benzodiazepines.[19] However, therapeutic use of each of these agents may be relatively contraindicated in older adults or men with bladder outlet obstruction. They also convey significant risk of adverse effects, in effect exchanging 1 bothersome symptom for several and leaving the patient no better off.

Melatonin is safe in older adults and reported adverse effects are infrequent, although little is known about long-term use or drug interactions.[20] Documented side effects include decreased body temperature, sedation, headache, depression, tachycardia and pruritis. We did not detect any adverse drug related events with melatonin therapy in the group studied. Therefore, the potential addition of melatonin to the pharmacological armamentarium, either alone or in combination with other agents, may help some patients in whom current options are ineffective or contraindicated. However, further studies are required to establish optimum dose, determine clinical significance of observed changes and address whether a longer study would show a greater effect size as the behavioral component of nocturia is attenuated. It will also be necessary to consider whether melatonin might be effective in a subset of patients with nocturia, such as those without evidence of nocturnal polyuria.

CONCLUSIONS

More men on melatonin had at least a 0.5 decrease in mean number of episodes of nocturia per night versus placebo. No man on placebo achieved decreases of 1.0 or 2.0 in mean number of episodes of nocturia per night as seen in 3 men and 1 man, respectively, on melatonin. However, it is uncertain whether the observed changes in this study are clinically significant. The drug has previously been proven to be well tolerated in older adults and has a better adverse effect profile than drugs currently used for the treatment of nocturia. Therefore it merits consideration for further clinical trials.

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