Nocturnal 6-Sulfatoxymelatonin Excretion in Insomnia and Its Relation to the Response to Melatonin Replacement Therapy

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PURPOSE: Melatonin, which is produced by the pineal gland at night, is an endogenous sleep regulator. Both sleep disorders and impaired melatonin production are common among the elderly. We examined the excretion of the major melatonin metabolite 6-sulfatoxymelatonin in insomnia patients aged ≥55 years and its relation with the subsequent response to melatonin therapy.

METHODS: We studied 517 insomnia patients, along with 29 age-matched and 30 younger healthy volunteers. Nocturnal urinary 6-sulfatoxymelatonin excretion was assessed between 10 pm and 10 am. Three hundred and ninety-six of the insomnia patients were treated for 2 weeks with placebo and for 3 weeks with 2 mg per night of controlled-release melatonin, of which 372 provided complete datasets. Clinical response, assessed with the Leeds Sleep Evaluation Questionnaire, was defined as an improvement of 10 mm or more on the visual analog scales.

RESULTS: Mean (± SD) 6-sulfatoxymelatonin excretion was lower in the insomnia patients (9.0 ± 8.3 μg per night) than in volunteers of the same age (18.1 ± 12.7 μg per night, $P < 0.05$) and in younger volunteers (24.2 ± 11.9 μg per night, $P < 0.05$). About 30% of patients (112/372) excreted ≤3.5 μg of sulfatoxymelatonin per night, which is considered to be lower than normal for this age group. These "low excretors" had a significantly higher response to melatonin replacement therapy (58% [65/112] vs. 47% [122/260], $P < 0.05$).

CONCLUSION: Low nocturnal melatonin production is associated with insomnia in patients aged 55 years or older, and identifies patients who are somewhat more likely to respond to melatonin replacement. **Am J Med. 2004;116:91–95.** ©2004 by Excerpta Medica Inc.

Primary insomnia is characterized by difficulty initiating or maintaining sleep for at least 1 month that distresses the patient or impairs daytime functioning. About 30% of persons aged 65 years or older have insomnia (1–6). Because complaints about poor sleep do not correlate well with objective findings (7,8), the diagnosis of insomnia and the clinical assessment of treatment effects are based on self-report.

Melatonin (N-acetyl-5-methoxytryptamine) is produced and secreted by the pineal gland at night, and promotes sleep in humans (9). It is metabolized rapidly in the liver. Urinary excretion of its major metabolite—6-sulfatoxymelatonin—is a useful measure of the total amount of melatonin produced (10). Peak serum levels of melatonin at night, as well as 6-sulfatoxymelatonin excretion, decrease significantly with advancing age (11–15), although these age-related declines are less pronounced in healthy subjects (16,17). Several studies have suggested a possible association between age-related disturbances in the sleep-wake cycle and this decrease in melatonin output (16,18–21), but other studies have found similar age-related decline in melatonin production in good and in poor sleepers (22,23).

If melatonin deficiency is a cause of insomnia, patients with low melatonin levels should be more likely to benefit from melatonin therapy than those with normal levels. Some (24–29) but not all (30–32) studies have demonstrated beneficial effects of melatonin on sleep in insomnia patients aged 55 years or over and in patients who presumably had low production of melatonin. These studies varied in their inclusion criteria and most had only a relatively small number of subjects. We therefore assessed 6-sulfatoxymelatonin levels in a large cohort of well-characterized insomnia patients aged 55 years or over, and determined the relation between 6-sulfatoxymelatonin excretion and subsequent improvement in sleep after melatonin replacement therapy.

METHODS

Subjects

Patients (330 men, 187 women) aged 55 years or over (mean [± SD] age, 68 ± 8 years; range, 55 to 93 years) with primary insomnia according to standard criteria (33) were recruited from general medical clinics in France, Israel, and The Netherlands from 1995 to 1998. Patients were excluded if they had symptoms of anxiety (Covi scale [34]), depression (Raskin scale [35]), or senile dementia (MINI [36]), or had a history of a severe psychiatric disorder. Of these patients, 172 (age, 65 ± 6

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years) were healthy and 345 (age, 69 ± 9 years) had one or more chronic medical problems.

We also enrolled two groups of healthy volunteers without sleep complaints: a younger group comprising subjects aged 20 to 35 years (n = 30; all men; mean age, 27 ± 2 years) and an older group comprising subjects aged ≥55 years (n = 29; 13 men and 16 women; mean age, 67 ± 6 years). These patients had been recruited for pharmacokinetic and drug interaction studies. The number of healthy volunteers was small compared with the number of patients because the excretion of 6-sulfatoxymelatonin in healthy subjects has been studied extensively (15,22,23,37–40) and our results were compatible with the published data.

All subjects could not have used any psychoactive medication for at least 1 month before the study. The study protocols had been approved by the local ethics or human subjects committees; and all subjects were informed in detail about the investigation and gave written informed consent.

Measurements

Urine was collected at night (10 PM to 10 AM) and during the day (10 AM to 10 PM) while at home. To enhance compliance, no specific instructions were given about lighting conditions while sleeping. Urinary 6-sulfatoxymelatonin levels were determined by radioimmunoassay (41). Patients and their physicians were not provided the results of these tests.

Of the 446 insomnia patients who were recruited in France, 396 were treated with placebo tablets for 2 weeks (once daily, between 9 and 11 PM), followed by tablets of identical composition and appearance containing 2 mg of melatonin (Circadin, controlled-release formulation; Neurim Pharmaceuticals, Tel Aviv, Israel) for 3 weeks. A controlled-release formulation was used to provide sufficient melatonin levels throughout the night; this formulation has been shown, in double-blind placebo-controlled studies, to be superior to placebo in improving sleep (26,27). Each patient served as his or her own control for comparisons of the effects of melatonin versus placebo.

On each of the last three mornings of the placebo and treatment periods, patients reported their sleep the night before and their behavior in the morning using the Leeds Sleep Evaluation Questionnaire (42). This questionnaire includes 10 questions that measure four domains of sleep and morning behavior: ease of getting to sleep (mean of questions 1, 2, and 3); quality of sleep (mean of questions 4 and 5); hangover on awakening from sleep (mean of questions 6 and 7); and alertness and behavioral integrity the following morning (mean of questions 8, 9, and 10). Answers are provided on a 0- to 100-mm analog scale. The mean changes in the four domains at the end of the treatment period (as compared with the placebo period) were calculated for each patient. In accordance with other visual analog scale variables (43–45), clinical response was defined as a mean improvement of 10 mm or more.

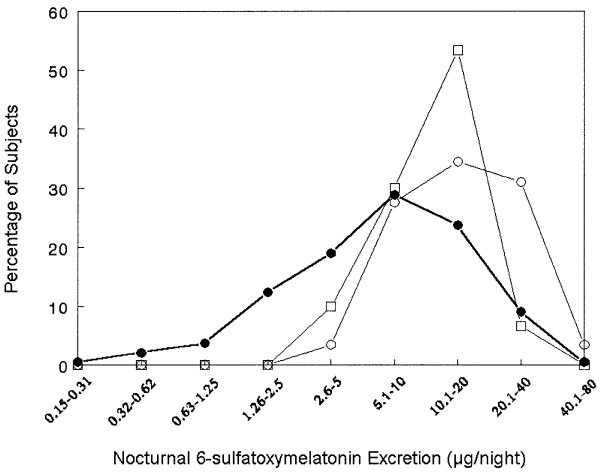

Figure. Frequency distribution of nocturnal 6-sulfatoxymelatonin excretion in healthy volunteers (n = 30 [open squares], ages 20 to 35 years; n = 29 [open circles], ages ≥55 years) and in patients with insomnia aged ≥55 years (n = 517 [closed circles]).

Statistical Analysis

Normality of the distributions of 6-sulfatoxymelatonin values was examined with the Kolmogorov-Smirnov test. Because the nocturnal excretion of 6-sulfatoxymelatonin in patients with insomnia aged 55 years or older showed significant dispersions from normality, comparisons were performed using log-transformed values, with one-way analysis of variance and the Duncan post-hoc test. The normal range of 6-sulfatoxymelatonin was defined as the 2.5 to 97.5 percentiles for the log-transformed values in the healthy volunteers. Rates of response to melatonin treatment among patients by levels of 6-sulfatoxymelatonin excretion were analyzed with the chi-squared test for trend. Patients were also dichotomized into those excreting high and low 6-sulfatoxymelatonin levels; the rates of response to melatonin treatment between these two groups were compared using the chi-squared test. A P value <0.05 was considered significant. Statistical analyses were performed with SAS software, version 7 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Mean (± SD) nocturnal 6-sulfatoxymelatonin excretion was lower in the patients with insomnia (9 ± 8 µg per night) than in the older (18 ± 13 µg per night) or the younger healthy volunteers (24 ± 12 µg per night; Figure; $P<0.001$). Insomnia patients with chronic medical problems (specifically coronary heart disease) excreted signif-

Table 1. Nocturnal 6-Sulfatoxymelatonin Excretion in Insomnia Patients Aged ≤55 Years

Group of Patients	No. of Patients	6-Sulfatoxymelatonin Excretion (μg per night)	*P* Value
		Mean ± SD	
Without chronic medical problems	172	10.4 ± 7.9	
With chronic medical problems	345	8.3 ± 8.4	<0.05*
Coronary heart disease	59	6.5 ± 4.7	<0.01*
Hypertension	162	8.2 ± 7.5	0.3*
Diabetes	24	7.5 ± 6.0	0.4*
Country of origin			
The Netherlands	20	7.6 ± 4.6	
Israel	51	8.9 ± 7.5	
France	446	8.9 ± 7.6	

* Compared with patients who did not have chronic medical problems.

icantly lower amounts of 6-sulfatoxymelatonin than those without these problems (Table 1).

The normal range of 6-sulfatoxymelatonin excretion was defined as 8 to 56 μg per night for healthy adults aged 20 to 35 years and 4 to 55 μg per night for healthy adults aged 55 years or older. The median 6-sulfatoxymelatonin excretion in the patients with insomnia was 6.7 μg per night. More than half (56% [289/517]) of the insomnia patients excreted less 6-sulfatoxymelatonin than the amount considered to be normal for the healthy volunteers aged 20 to 35 years (≥8 μg per night), and 30% (155/517) excreted less than the amount considered to be normal for the older healthy adults (≥4 μg per night). Among the 172 insomnia patients without medical problems, 43% (n = 74) excreted less than 7 μg of 6-sulfatoxymelatonin per night and 16% (n = 28) excreted less than 3.5 mg of 6-sulfatoxymelatonin per night.

Response to Melatonin Treatment

Of the 396 insomnia patients who were treated with placebo and melatonin (mean baseline excretion, 8.9 ± 7.8 μg per night), data on sleep quality were missing for one or both treatment periods in 24 patients. The remaining 372 were divided into six groups, based on their baseline 6-sulfatoxymelatonin excretion (Table 2). Lower baseline levels of excretion were associated with a significantly higher response to melatonin replacement therapy for three of the four outcome measures: ease of getting to sleep, quality of sleep, and alertness and behavioral integrity the following morning (Table 2).

The percentage of responders to melatonin replacement therapy, as measured by improvement in quality of sleep, was significantly higher among the 112 low excretors of 6-sulfatoxymelatonin (≤3.5 μg per night) than among the remaining 260 patients (58% [n = 65] vs. 47% (n = 122), $P < 0.05$). Similar results were seen for improvement in alertness and behavioral integrity (43% [n = 48] vs. 29% [n = 75], $P < 0.05$), but not for ease of getting to sleep (51% [n = 57] vs. 42% [n = 109], $P = 0.1$) or hangover on awakening (36% [n = 40] vs. 30% [n = 78], $P = 0.3$).

Mean daytime 6-sulfatoxymelatonin excretion was 2.8 ± 4.4 μg/d (range, 0 to 67 μg/d) in the insomnia patients. The possibility that responders and nonresponders differed in the timing of melatonin excretion was examined by comparing the proportion of 6-sulfatoxymelatonin excreted during the night among responders and nonre-

Table 2. Relation between Nocturnal 6-Sulfatoxymelatonin Excretion and Subsequent Response to Melatonin Therapy

Category of Response*	6-Sulfatoxymelatonin Excretion Range (μg per night)						*P* for Trend†
	0.15–0.62 (n = 10)	0.63–1.25 (n = 14)	1.26–2.5 (n = 46)	2.6–5 (n = 71)	5.1–10 (n = 107)	10.1–80 (n = 124)	
	Number (%) Responders						
Ease of getting to sleep	8 (80)	11 (79)	22 (48)	34 (48)	41 (38)	53 (43)	0.005
Quality of sleep	9 (90)	8 (57)	28 (61)	33 (46)	48 (45)	62 (50)	0.04
Hangover on awakening from sleep	6 (60)	4 (29)	18 (39)	22 (31)	26 (24)	42 (34)	0.2
Alertness and behavioral integrity the following morning	6 (60)	5 (36)	22 (48)	2 (30)	23 (21)	35 (28)	0.02

* Response was defined as a ≥10-mm improvement (on a 0- to 100-mm scale) compared with placebo.
† Chi-squared test for linear trend.

sponders (for quality of sleep). Mean nocturnal 6-sulfatoxymelatonin excretion was 73% ± 18% of the total amount excreted, and there was no difference between responders and nonresponders ($P = 0.4$).

DISCUSSION

Among patients with insomnia aged 55 years or older, low nocturnal melatonin production—as measured by urinary excretion of 6-sulfatoxymelatonin—is more common than among healthy persons of the same age who do not complain of sleep problems. Mean levels of excretion were especially low in patients with chronic medical problems, consistent with previous studies (24,46–48). Insomnia patients who produce low amounts of melatonin are significantly more likely to benefit from melatonin replacement therapy than those who produce normal amounts.

Our results in healthy subjects aged 55 years or older without sleep problems (excretion of 4 to 55 μg of 6-sulfatoxymelatonin per night) are similar to previous reports (22,23). Of note, low levels of excretion may be more common in the Southern hemisphere in patients aged 50 years or older (49).

Because melatonin replacement therapy was beneficial, particularly in patients with low melatonin production, we conclude that the decline in melatonin production with age (or perhaps with disease) impairs sleep in older patients. However, there is no systematic relation between melatonin production and objectively measured parameters of sleep, as measured in a sleep laboratory (30–32). This may not be surprising, as complaints in patients with insomnia do not correlate well with objective findings (7,8). The partial overlap in 6-sulfatoxymelatonin excretion in patients with and without sleep complaints may explain the lack of a clear-cut correlation between 6-sulfatoxymelatonin excretion and subjective complaints of poor sleep (31,32).

Melatonin might promote sleep via a circadian-entraining effect, rather than a sleep-regulating effect. For example, patients with an abnormal circadian phase should excrete less 6-sulfatoxymelatonin during the night and more during the daytime. We did not find a difference, however, between responders and nonresponders in the amount of 6-sulfatoxymelatonin excreted during the daytime; it therefore appears that an entraining effect of melatonin is not the major determinant of its efficacy. Rather, melatonin replacement therapy may improve sleep quality by treating an underlying deficiency in the endogenous production of this sleep-regulating hormone. It remains to be determined, however, whether the benefits of melatonin replacement therapy are sustained beyond the 3-week period that we studied.

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