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Melatonin Fails To Improve Sleep Or Agitation In A Double-Blind Randomized Placebo-Controlled Trial Of Institutionalized Patients With Alzheimer's Disease

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Abstract

Objectives—Patients with Alzheimer's dementia often display both agitated behavior and poor sleep. Given that the disease is often associated with low endogenous levels of melatonin, exogenous melatonin administration may lead to improvements in sleep and agitation.

Design—Randomized, placebo-controlled study.

Setting—Nursing homes in San Diego metropolitan area.

Participants—Subjects were patients with probable Alzheimer's disease.

Intervention—Melatonin (8.5 mg immediate release and 1.5 mg sustained release) (n=24) or placebo (n=17) administered at 10:00 PM for 10 consecutive nights. The protocol consisted of baseline (3 days), treatment (10 days), and post-treatment (5 days) phases.

Measurements—Sleep was measured continuously using actigraphy. Agitation was rated using both the Agitated Behavior Rating Scale and the Cohen-Mansfield Agitation Inventory. Treatment effects were examined both across the 24-hour day and separately by nursing shift.

Results—There were no significant effects of melatonin, compared to placebo, on sleep, circadian rhythms, or agitation.

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Conclusion—This study failed to find a beneficial effect of exogenous melatonin, consistent with a number of other studies. The lack of efficacy may be related to the absence of a true treatment effect or to the super-physiological dose of melatonin used.

Keywords

Alzheimer's; sleep; agitation; melatonin; dementia

INTRODUCTION

Sleep disruption and agitated behavior are common in patients with Alzheimer's disease (AD).⁽¹⁾ One treatment for sleep disturbance is melatonin (N-acetyl-5-methoxytryptamine), which plays a major role in the regulation of sleep and circadian rhythms. Melatonin secretion may drop as much as 80% in the elderly, with even further dysregulation in patients with dementia. (2) It has been hypothesized that the decrease in melatonin may play a major role in the disturbed sleep patterns of patients with AD, and may thereby increase agitated behaviors.

In 2005, the NIH State of the Science conference on insomnia concluded that although melatonin appears to be effective for the treatment of circadian rhythm disorders, little evidence exists for efficacy in the treatment of insomnia.⁽³⁾ However, there were insufficient data on elderly with few studies in patients with dementia, and all with mixed results.^(ex. 4, 5)

This study compared the effect of melatonin vs. placebo on sleep and agitation in a double-blind placebo-controlled trial of nursing home AD patients. We hypothesized that AD patients randomly assigned to receive melatonin would show improved nighttime sleep (ex: increased sleep efficiency) and stronger circadian rhythms as assessed by actigraphy, and reduced agitation compared to those randomized to placebo.

METHODS

Subjects

Forty-one nursing home patients (68.3% women) with probable AD participated (mean(SD) duration at nursing home = 18.9(16.6) months, range= 5 – 70 months; mean(SD) age was 82.9 (7.0) years, range=61–95 years; mean(SD) level of education was 14.2(2.5) years; mean(SD) Mini Mental State Examination score of 5.8(5.6), range 0 – 18).

Procedure

Written consent was obtained from the patient's legal guardian. Verbal assent was obtained from the patient's physician, and when possible, from the patient. A neurologist conducted a brief examination and reviewed medical records to confirm the diagnosis of probable AD, using NINCDS-ADRDA diagnostic criteria.⁽⁶⁾

The protocol consisted of 3 days baseline (no treatment), 10 days treatment (melatonin or placebo), and 5 days follow-up (no treatment). Subjects were randomized to receive either placebo or melatonin. Melatonin consisted of a combined dosing formulation containing 8.5 mg immediate release (Regis Technologies) and 1.5 mg time release (PAR Pharmaceuticals). The goal of this supra-physiologic dose was to provide both an initial soporific effect plus a longer-lasting dose to entrain circadian rhythms and reduce early morning awakenings. Patients in the placebo group received capsules containing inactive compound that were identical in appearance to the melatonin capsules. Capsules were administered by nursing staff at 10:00 PM each night during the treatment period. Timing of administration was documented by on-site research staff.

Measures

The Actillum (Ambulatory Monitoring, Inc, Ardsley, NY), a wrist-mounted device which records activity level and light exposure, was used to estimate sleep/wake. The Actillum has been previously validated against EEG in the nursing home population.⁽⁷⁾ Nighttime variables computed included total sleep time (TST; hours of sleep per night), %SLEEP (the percentage of the time in bed spent asleep), wake after sleep onset (WASO; minutes of wakefulness during the night), %WAKE, number and mean duration of sleep bouts. Daytime variables included total daytime sleep time (dTST; hours of sleep per day), percent sleep (%daysleep; the percentage of the time spent asleep during the day), number and mean duration of sleep episodes.

Agitation was assessed with the Agitated Behavior Rating Scale (ABRS)⁽⁸⁾ and the Cohen-Mansfield Agitation Inventory (CMAI).⁽⁹⁾ Agitation was rated on the ABRS by trained study staff observing patients for 20 seconds every 15 minutes for 24 hours every other day and from 0730 to 2000 on the alternating days. At each observation, five categories of agitated behavior were rated on a scale of 0 (no agitation present) to 3 (high intensity agitation): manual manipulation, searching and wandering, escape behaviors, tapping and banging, and verbal agitation. The first four categories were combined to create a Physical Agitation score. Over the course of the 5-year study a total of 88,077 ratings were completed by 67 observers, each of whom was initially trained to meet a minimum standard of 90% agreement with a “gold standard” rater. Raters were blind to treatment condition.

The CMAI requires caregivers to rate the frequency of agitated behavior over the previous two weeks. Aggressive behavior, physically non-aggressive behavior, verbal agitation, and total agitation scores are computed. Nursing staff most familiar with the patient from each of the three staffing shifts (day, evening, night) completed the CMAI immediately prior to and immediately after completion of the ten day treatment period. For each patient and within each shift, the same nurse completed the ratings.

Data Analysis

Activity rhythm analyses were conducted by fitting an extended cosine model to the data⁽¹⁰⁾ that provided estimates of amplitude, acrophase, minimum and the steepness of the curve. In order to examine the effects of melatonin on sleep, activity rhythms, and agitation, a series of ANOVAs were performed. Effects were examined both across the 24-hour day and within predefined time periods of: morning (wake-up time to 1100 hours), afternoon (1100–1600 hours), evening (1600 hours to bedtime), and night (bedtime to wake-up time). Agitation outcome measures were the ABRS Physical and Verbal Agitation subscales and total scores on the CMAI. Blom normal score transformations were conducted to normalize all agitation variables.

Each ANOVA model included treatment (melatonin vs. placebo) and phase of study (baseline, treatment days 1–5, treatment days 6–10, posttreatment) as factors. For agitation analyses, time of day (morning, afternoon, evening, night for the ABRS and day, afternoon, night shift for the CMAI) served as additional within-subjects factors. Omnibus tests of the full model were followed by a priori contrasts. A treatment response contrast was computed as the change from baseline to treatment days 6–10 and a relapse effect contrast was computed as the change from treatment days 6–10 to posttreatment. All analyses were performed using SAS Version 8.1 (SAS Institute Inc, 1999).

RESULTS

Actigraph Sleep Results

As shown in Table 1, there were no significant differences in treatment effects of melatonin vs. placebo on any actigraphic sleep parameters or circadian rhythms parameters either during the day or night. There was also no change from the treatment to follow-up phases.

Agitation

There were no significant differences in treatment effects between the melatonin and placebo treated groups in any of the analyses of observed the ABRs physical or verbal agitation (all $p > 0.05$). There were no significant changes in CMAI ratings between groups or as the result of treatment. There were small but significant differences in agitation ratings across nursing shifts on the CMAI, regardless of treatment group ($F(8,142)=2.6$, $p=.011$) such that agitation was highest during the day (31.6(10.3)) compared to the evening (29.8(9.3)) or night (27.4 (10.2)) shifts.

DISCUSSION

This study failed to find any effect of exogenous melatonin on sleep, activity rhythms or agitation compared to placebo in institutionalized patients with severe Alzheimer's disease. These data are consistent with a growing body of research that has failed to find evidence supporting the efficacy of melatonin on sleep in this or other populations.(4) The only significant finding was that, independent of treatment, agitation ratings were higher during the day compared to nighttime.

Given the large role that endogenous melatonin plays in the regulation of sleep in healthy adults, it is surprising that, in most studies, exogenous melatonin has not produced significant effects on sleep. There are several explanations that have been put forth to explain the lack of therapeutic efficacy of melatonin among dementia patients. The first and simplest explanation is that exogenous melatonin does not affect sleep propensity at night in this population. The patients in this study, all of whom had advanced disease, may have suffered from such severe neuroanatomical deterioration that the pathways necessary for melatonin to impact sleep quantity and continuity were no longer viable. Specifically, the extent of their neurological damage may have included brain regions necessary for melatonin to be effective such as the ventral lateral preoptic area, a region of the brain involved in sleep/wake regulation. The goal of this study was not to focus on individuals with severe dementia, but this was a consequence of the nursing homes where the study took place. However, the growing number of studies showing a similar lack of efficacy in non-demented samples argues against this being the primary limitation. Another possibility is that the timing of melatonin administration in this study (10PM) diminished its therapeutic potential. Given the circadian dysregulation often seen in patients with AD, the appropriate timing may need to be tailored to each individual's rhythms. Therefore, despite findings that older adults with dementia have comparatively low endogenous melatonin,(2) exogenous administration may be of limited value at night because the usual nocturnal increase in melatonin production may occur at others times of day.

This study also failed to find a phase-shifting effect of melatonin. One reason might be that the super-physiologic dosage of melatonin used may have been sub-optimal. While we used this high dose of melatonin with the goal of optimizing the soporific effects of the agent, it has been argued that it may linger in the brain for too long, affecting the wrong portion of the endogenous melatonin rhythm. If exogenous melatonin remained in the brain until after the core body temperature minimum, there could have been phase advancing effects. As stated in

the NIH State of the Science conference, there is still a lack of a well-defined effective dose. (3)

Lastly, there were no effects of treatment on agitation levels. It was hypothesized that exogenous melatonin would decrease agitation by way of improved sleep and circadian rhythms. Given that these did not improve, it is not surprising that agitation remained unchanged as well.

In summary, 10mg of melatonin was not effective for improving sleep or agitation in patients with severe dementia. It is possible that there are small effects that were not detected with the sample size in this study, although the lack of efficacy in other studies support these results. More recent studies (4) have brought into question whether this compound can be effective in even mild to moderate dementia, leading to questions if the observed disruption in the endogenous levels/rhythm is indeed a contributing factor related to the sleep and behavioral disturbances seen in this population.

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Table 1
Effect of melatonin vs. placebo on sleep parameters (all $p > 0.05$)

	Melatonin Group (n=24)			Placebo Group (n=17)		
	Baseline	Treatment	Follow-Up	Baseline	Treatment	Follow-Up
Total Sleep Time (hrs)	7.9 (1.7)	7.5 (2.2)	7.5 (2.0)	8.0 (2.3)	8.0 (2.5)	7.9 (2.3)
% Sleep	82.0 (10.3)	80.4 (14.1)	78.6 (14.6)	81.0 (14.2)	81.0 (15.9)	80.7 (18.1)
Wake Time (hrs)	1.7 (1.1)	1.9 (1.4)	2.1 (1.6)	1.8 (1.2)	1.7 (1.4)	2.1 (2.6)
% Wake	18.0 (10.3)	19.6 (14.1)	21.4 (14.6)	19.0 (14.2)	19.0 (15.9)	19.3 (18.1)
Total Day Sleep Time (hrs)	1:20 (1:17)	1:51 (1:56)	2:07 (1:59)	1:21 (1:24)	1:36 (1:32)	1:39 (1:46)
% Day Sleep	9.2 (8.5)	11.9 (10.5)	13.7 (11.4)	10.0 (10.8)	12.1 (12.6)	12.5 (13.0)
# of Day Sleep Episodes	7.9 (5.4)	9.0 (6.4)	8.9 (6.0)	10.2 (8.3)	10.1 (8.9)	11.4 (9.8)
Mean Episode Duration (minutes)	12.8 (19.0)	23.0 (43.7)	25.6 (41.4)	7.3 (3.4)	11.6 (14.8)	7.9 (4.4)
Amplitude	0.4 (0.2)	0.4 (0.3)	0.4 (0.3)	0.5 (0.4)	0.4 (0.2)	0.6 (0.4)
Acrophase	14:41 (3:00)	14:32 (2:13)	14:25 (3:28)	14:43 (4:47)	13:48 (1:37)	15:23 (2:52)
Minimum	0.6 (0.3)	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)	0.5 (0.4)