Does Exogenous Melatonin Improve Adaptation to Night Shift Work in Residents?

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A. Study Purpose and Rationale

The purpose of this study is to determine whether 3 mg of melatonin ingested 30 minuntes before day sleep is effective in helping medical residents adapt to night shift work.

At least twice a year during the three years of residency training in Internal Medicine at Columbia Presbyterian Medical Center interns and residents work nights for two consecutive weeks. This abrupt shift from day to night work is usually associated with an increase in sleepiness and fatigue during work hours, and a decrease in mood and quality of sleep during the day. In humans, the circadian rhythm for the release of melatonin from the pineal gland is closely synchronized with the habitual hours of sleep. Alterations in synchronization due to phase shifts (resulting from transmeridian airline flights across time zones or unusual working hours) or blindness are correlated with sleep disturbance (1). Many of the health and safety problems reported by shift workers result from the sleep deprivation associated with shorter, fragmented day sleep (2). Circadian adaptation to jet travel across many time zones or to night shift work requires that circadian rhythms phase shift to reentrain to the new light-dark and sleep-wake cycle (3). In addition to the sleep-promoting effects of exogenous melatonin, ingestion of melatonin can produce phase shifts in its own circadian rhythm. Lewy and colleagues generated a phase-response curve to melatonin in humans that demonstrated circadian phase advances with melatonin administration in the late afternoon and evening and circadian phase delays with administration in the later hours of sleep and morning (4).

Melatonin has been administered to treat the symptoms associated with night shift work and jet lag, (but the reports on this effect are inconsistent) on the presumption of its ability to reset the circadian clock and promote sleep onset. Many field studies have claimed a benefit of melatonin over placebo (5-7). In one large sample (melatonin, N=474; placebo, N=112), pooled across many studies, use of melatonin led to a 50% reduction in self-rated jet lag (8). Other studies report no benefit of melatonin over placebo in alleviating jet lag symptoms (3). Adaptation to night shift work has been studied in simulated models of night shift work and in the field. Sharkey and Eastman showed that melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study (9). Melatonin produced larger phase advances than placebo in the circadian rhythms of melatonin and temperature. Although, differences in subjective ratings of sleepiness and mood, and recorded sleep durations were not statistically significant. In a second study on the affect of melatonin in adapting to a simulated night shift, sleep quality, but not psychomotor performance was improved in the melatonin group compared to placebo group (10). In a double-blinded, randomized, crossover study looking at emergency medical services personnel working night shifts, the only improvement in sleep quality was a decrease in interim awakenings (11). There was no significant difference between the two treatments with respect to mean sleep latency, duration, and efficiency, and subjectively rated sleep quality. Similarly, no significant benefits were noted between the scores for daily posttreatment mood or workload ratings. In a second double-blinded, placebo-controlled crossover trial, the effectiveness of melatonin to improve night alertness and day sleep was assessed (12). Melatonin improved gestalt day sleep (P= .3) and gestalt night alertness (P= .03) but in neither case was the improvement statistically significant. Of 13 secondary comparisons, 8 showed a benefit of melatonin over placebo; none showed a benefit of placebo over melatonin (although only one comparison was statistically significant– improved alertness at the end of a night shift over placebo.) Of note, sleep routines in the two above studies were not assessed, including if study subjects were going to sleep at the same time each morning. Variation in daytime sleep routines in

an individual may limit the effectiveness of melatonin in phase shifting their circadian rhythm. Theses studies were also assessing adaptation after short periods of time i.e. 2-6 nights.

Although previous studies have not shown statistically significant differences between placebo and melatonin in adapting medical personnel to night shift work, there were trends towards improved adaptation. In addition, melatonin's hypnotic and circadian effects, short biological half-life, minimal cost, and low toxicity make it an attractive treatment strategy to improve shift workers' tolerance to night shift.

B. Study Design and Statistical Analysis

This will be a double-blinded, randomized, crossover study. Subjects will be volunteers from the intern class. Assuming 100% participation the number of subjects will be 52. Over the course of intern year, each subject will do two separate night-float rotations. Each night-float shift lasts for 14 days during which interns work from 6:30 pm to 7:00 am every night except Friday nights. Subjects will be asked to attempt to keep to the night-float wake-sleep schedule during their day off. There is approximately a six month period of time between the night-float shifts. The randomization procedure will ensure that equal numbers of subjects take melatonin or placebo first. Subjects will be asked to avoid alcohol or sedative medications during the study and to record caffeine intake. Subjects will fill out a standardized life events scale before and after each set of 14 days of night shift work. Subjects will be given 3 mg of melatonin the morning after each night shift during one block of night-float and an identically appearing placebo the other block of night-float. Subjects will be instructed to take one capsule orally 30 minutes before each consecutive day sleep. They will also be instructed to start each sleep period at the same time each day. The exact time will be left up to the individual subject secondary to differences in travel time home from work and pre-sleep routines. It will be suggested that subjects avoid exposure to excessive sunlight before sleep periods secondary to its ability to circadian phase shift (10). Dark sunglasses will be provided for subjects if subjects do not have their own. Subjects will be asked to record any side effects experienced while taking the capsules.

Cognitive performance will be measured using a computer-based digit symbol substitution task to measure working memory. This subject-paced task involves the matching of digits (0-9) to symbols (circle, triangle, etc.). The number of correct responses in 1.5 min is counted to measure working memory performance (13). A serial addition/subtraction task will also be performed. The serial addition/subtraction task is a subject-paced task requiring the completion of 50 mental arithmetic trials. The average number of correct responses per min is used as an assay of cognitive throughput performance (14). The tests will be performed at the beginning of each shift and at the end of each shift. The performance data will be averaged across the shift and analyzed using the paired t-test. Sample size will be determined by the number of interns who volunteer for the study. Assuming that there is 100% participation, the sample size will be 52. The effect that can be detected for a sample size of 52 and a standard deviation for the above tests of 15, at a power of 80% and significance level of 0.05 is 5.9.

During each night shift, starting with the second night shift, subjects will record their alertness on the Stanford Sleepiness Scale (SSS), the results of which correlate with the results of objective skill tests (15). The SSS score will be recorded two times each shift: just before the subject starts the shift and at the end of the shift.

To assess mood, subjects will complete the Profile of Mood States (POMS), a 65-item adjective checklist, two times each shift: just before the subject starts the shift and at the end of the shift (16). The POMS forms will be analyzed to produce scores for six factors: tension-anxiety, fatigue-inertia, depression-dejection, vigor-activity, anger-hostility, and confusion-bewilderment.

Sleep quality will be assessed with a daily sleep log. Sleep variables will include latency (time between bedtime and sleep onset), reported awakenings during sleep, sleep efficiency (total time asleep as a percentage of total time in bed), and total sleep time.

C. Study Procedure

Study questionnaires and cognitive testing will be performed as described in Section B. The questionnaires and testing should be of minimal inconvenience to study participants. The duration of the entire study will be one year and each participant will spend a total of 4 weeks participating in the study.

D. Study Drugs

Melatonin is currently marketed as a dietary supplement. Melatonin will be administered orally in the form of a 3 mg capsule. Data from previous studies in which exogenous melatonin was given and melatonin levels were measured serially indicate that melatonin's half-life is 2-3 hours. Melatonin has a large first-pass metabolism, and oral administration results in as much as a 300-fold variation in individual peak levels. In normal young adults, the average daytime and peak nighttime values are 10 and 60 pg/mL, respectively. An oral dose of 10 mg results in levels that average more than 5,000 pg/mL. As little as 0.3 mg orally can produce physiologic peak levels in some individuals (12). A dose of 3 mg was chosen based on its ability to phase shift human circadian rhythms (9). Pure melatonin appears to be safe when given for limited periods. Subjects taking doses as high as 3 to 6 gm/day for 1 month noted only some abdominal cramping (12). Side effects were rare in studies in which 3-10 mg of melatonin were used. Side effects include headache and drowsiness. The purity of the melatonin used in this study will be evaluated with the use of high-performance liquid chromatography.

E. Medical Device

N/A

F. Study Questionnaires

Please see Section B for a description of the Stanford Sleepiness Scale and Profile of Mood States questionnaires.

G. Study Subjects

The study participants will be interns in the Internal Medicine training program at Columbia Presbyterian Medical Center. Exclusion criteria will include the current use of any minor tranquilizers, narcotics, antidepressants, or sleeping pills during the study; pregnancy, or any medical history of underlying endocrine, cardiac or neurological condition.

H. Recruitment of Subjects

The study will be announced in a letter sent to all incoming interns. The letter will clearly state that the study is voluntary and that there will not be a penalty by not participating.

I. Confidentiality of Study Data

Each study volunteer will be assigned a unique numerical code that will be used to label questionnaires, cognitive studies and sleep diaries. Investigators will be blinded to code identities until after the analysis of data. Study medications will be packaged, coded, and distributed by third-party participants.

J. Potential Conflict of Interest

N/A

K. Location of the Study

The study questionnaires and cognitive testing will be done in the residents' lounge in Milstein Hospital. Although this is not a "clinical care area" the study involves minimal risk to subjects.

L. Potential Risks

The subjects will experience minimal risk or discomfort during this study. There is no established treatment for adapting to night shift work. Study participants will be receiving the study drug for half of the study period and a placebo for the other half. There is no reason to suspect that during the placebo portion of the study the subject's condition will worsen.

M. Potential Benefits

Possible benefits from participating in this study include improvements in the quality of sleep, mood, energy level and cognitive performance during night shift work. The subjects may or may not benefit as a result of participation in this study.

N. Alternative Therapies

One alternative therapy is timed exposure to bright light. Studies have shown that timed exposure to bright light improves sleep and alertness during simulated night shifts (10). This therapy is currently not available at Columbia Presbyterian Medical Center.

O. Compensation to Subjects

There will be no compensation to subjects.

P. Costs to Subjects

The subject will not incur any additional costs as a result of participating in this study.

Q. Minors as Research Studies

N/A

R. Radiation of Radioactive Substance

N/A

S. References

1. Brzezinski A: Melatonin in Humans. NEJM 1997; 336:186-195.

2. Beaton RD, Murphy SA: Sources of occupational stress among firefighter/EMTs and firefighters/paramedics and correlations with job-related outcomes. Prehosp Disaster Med 1993; 8:140-149.
3. Spitzer RL, Terman M, Williams JB, Terman JS, Malt UF, Singer F, and Lewy AJ: Jet lag: clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized, double-blind trial. Am J Psychiatry 1999; 156:1392-1396.
4. Lewy AJ, Ahmed S, Jackson JML, and Sack RL: Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int 1992; 9:380-392.
5. Arendt J, Aldhous ME, Marks V, Arendt JH: Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. BMJ 1986; 292:1170.
6. Petrie K, Dawson AG, Thompson L, Brook R: A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. Biol Psychiatry 1993; 33:526-530.
7. Claustrat B, Brun J, David M, Sassolas G, Chazot G: Melatonin and jet lag: confirmatory results using a simplified protocol. Biol Psychiatry 1992; 32:705-711.
8. Arendt J, Skene DJ, Middleton B, Lockley SW, Deacon S. Efficacy of melatonin treatment in jet lag, shift work and blindness. J Biol Rhythms 1997; 12:604-617.
9. Sharkey KM, Eastman CI. Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. Am J Physiol Regulatory Integrative Comp Physiol 2002; 282:R454-R463.
10. Dawson D, Encel N, and Luchington K. Improving adaptation to simulated night shift: timed exposure to bright light versus daytime melatonin administration. Sleep 1995; 18:11-21.
11. James M, Tremea MO, Jones JS, and Krohmer JR. Can melatonin improve adaptation to night shift? Am J Emerg Med 1998; 16:367-370.
12. Jorgensen KM and Witting MD. Does exogenous melatonin improve day sleep or night alertness in emergency physicians working night shifts? Ann Emerg Med 1998; 31:699-704.
13. Wechsler D. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp., 1981.
14. Thorne DR, Genser SG, Sing HC, Hegge FW. The Walter Reed performance assessment battery. Neurobehav Toxicol Teratol 1985; 7:431-436.
15. Hoddes E, Zarcone V, Smythe H, Phillips R, and Dement WC. Quantification of sleepiness: a new approach. Psychopharmacology 1973; 10:431-436.
16. McNair DM, Lorr M, and Droppleman LF. Manual for the Profile of Mood States. San Diego, CA: Educational and Industrial Testing Service, 1971.