ELSEVIER

Sleep Medicine 2 (2001) 167–168

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Search and commentary

Article reviewed: Entrainment of free-running circadian rhythms by melatonin in blind people ☆

Richard P. Allen

Johns Hopkins University School of Medicine, Neurology and Sleep Medicine, Baltimore, MD, USA

Accepted 13 December 2000

Objectives

Determine whether or not a totally blind person can be entrained to a normal 24-h cycle by a daily dose of melatonin.

Study design

Partially blinded, placebo-controlled, crossover study balanced for treatment order.

Study population

Seven totally blind subjects (three females, four males, ages 42–57, age at onset of blindness birth – 36) with free-running circadian cycles documented by melatonin onset times.

Methods

Treatment was either placebo or 10 mg melatonin taken orally each night of the treatment phases about one hour before the subject's preferred bedtime. Circadian phase was determined by the first time plasma melatonin concentration exceeded 10 pg/ml (43 pmol/liter). Circadian period before treatment was determined by linear regression of phase for three determinations taken about 2 weeks apart. Treatment was initiated when phase was determined to have melatonin onset at about 21:00. The treatment was continued until the subject's previously determined free-running cycle length would be 12 h out of phase (expected melatonin onset at about 09:00), a length determined for each subject by the subject's previously measured circadian period length. The repeat treatment occurred when the phase cycled back to the 21:00 melatonin onset. Polysomnograms were obtained at baseline and at the beginning, middle and end of each treatment cycle (timing depended on the subject's period length). Evaluation was made for phase, period length, total sleep time, sleep latency, sleep efficiency, and time spent awake after sleep onset (WASO). Only the project director and the principal investigator knew the placebo vs. treatment condition. The patients and all other staff were blind to treatment condition.

About 3 months later three of the subjects that had been successfully entrained by melatonin were again treated with nightly doses of 10 mg melatonin in an open-phase of treatment. After being re-entrained to the 24-h cycle the dose of melatonin was gradually reduced to 0.5 mg each night to determine an estimate of the minimally effective dose to maintain entrainment.

☆ Robert L. Sack, Richard W. Brandes, Adam R. Kendall, Alfred J. Lewy, (New Engl J Med 2000; 343:1070–1077).

PII: S1389-9457(01)00076-4

Results

Baseline period lengths ranged from 24.2 to 24.9 h and were unchanged by placebo treatment. Six of the seven subjects were entrained to a 24-h period during melatonin treatment. Subjects showed on melatonin compared to placebo significantly ($P < 0.05$) reduced WASO (decreased by about 25–75 min) and improved sleep efficiency (increased by about 8–17%).

The fading dose study found stable entrainment lasting up to 120 days for all three subjects on the lowest dose of 0.05 mg. These three subjects returned to free-running condition within a few days to 1 month after stopping melatonin.

Conclusions

Nightly use of 10 mg melatonin suffices to entrain to a 24-h cycle most blind people who have free-running circadian cycles. Once entrained the 24-h rhythm may be maintained by a dose as low as 0.5 mg.

Comment

Totally blind people lacking access to light from the retina are deprived of the primary external cue needed to entrain the circadian cycle to the 24 h day. Many blind people, consequently, show circadian rhythm disturbances including free-running cycles expressing the endogenous circadian period length, which for man is slightly longer than 24 h. It has long been argued that appropriately timed melatonin could be used to provide the external cue needed for entrainment to a 24 h day. While case studies have been presented documenting this benefit, prior controlled studies failed to show entrainment. This study provides the first data confirming entrainment from melatonin. This study differed from the prior negative studies in both using a higher dose of melatonin and also starting treatment when the subject's phase matched social demands. It is not clear if both of these are needed but at this point both should be considered when treating a blind person. The success in maintaining entrainment at the very low dose of 0.5 mg is very encouraging. It is unclear if a smaller dose would also provide entrainment, but it may take a larger dose to establish than maintain entrainment.

Given this study's very small sample size and its failure to have a complete blind, clinical application of these findings needs to be done cautiously. It appears, however, that if melatonin is to be used for entrainment of a blind person then its use should generally follow the procedures in this study. Thus initially the nocturnal dose may need to be high (e.g. 10 mg) and after entrainment has been established may be gradually reduced, possibly to as low as about 0.5 mg. The problem for the clinician is determining whether or not the patient is free running and knowing when to start treatment. Melatonin measurements, particularly the repeated ones needed for determining onset times are expensive and not readily available to the clinician. The next best thing is the use of sleep-wake logs with free-running indicated by gradually developing delay in sleep phase and treatment starting time based on when the subject's phase seems fairly normal. This last is indicated by both normal sleep latency and less awakening during sleep. While not ideal, this may suffice for clinical practice. Hopefully, future studies will increase the sample size and include some assessment of clinically useful tools for deciding when to treat. Until there are more studies, application to clinical practice should be done with caution. The clinician planning to use melatonin to treat a blind person. needs to consider the three issues of: circadian phase timing, dose and determining that the patient is free running.