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LOW, BUT NOT HIGH, DOSES OF MELATONIN ENTRAINED A FREE-RUNNING BLIND PERSON WITH A LONG CIRCADIAN PERIOD

Alfred J. Lewy,* Jonathan S. Emens, Robert L. Sack, Brant P. Hasler, and Rebecca A. Bernert

Sleep and Mood Disorders Laboratory, Departments of Psychiatry, Ophthalmology and Physiology/Pharmacology, Oregon Health & Science University, Portland, Oregon

ABSTRACT

In a previous report, we were unable to entrain one out of seven totally blind people with free-running endogenous melatonin rhythms to 10 mg of exogenous melatonin. This person had the longest circadian period (24.9 h) of the group. We now find that this person can be entrained to 0.5 mg of melatonin, but not to 20 mg. These results are consistent with the idea that too much melatonin may spill over onto the wrong zone of the melatonin phase–response curve. (*Chronobiology International, 19(3), 649–658, 2002*)

Key Words: Circadian rhythms; Free-running totally blind people; Melatonin; Melatonin phase–response curve

INTRODUCTION

Since 1987, there have been several reports on giving melatonin to blind people (1–10). We recently showed that a nightly 10-mg dose of melatonin could synchronize free-running totally blind people, thus correcting a burdensome sleep disorder—short, fragmented nighttime sleep with daytime naps—that recurred when their circadian rhythms, drifting later each day, became out of phase (11).

*Corresponding author.

However, one of the seven treated subjects failed to entrain, and we speculated that a higher dose might be needed because this subject had the longest circadian period (24.9 h) of this group, and because it is well known in animal studies that the entraining agent must be proportionately stronger the more the circadian period differs from 24 h (12). We now report that a higher dose of melatonin (20 mg) was ineffective, whereas a lower dose (0.5 mg) successfully entrained this subject.

Since blind people usually make every attempt to sleep at the normal time, their sleep–wake cycles while living in society do not typically free-run. Indeed, there are more published reports of "non-24h sleep–wake disorder" or "hypernycthemeral" syndrome in sighted people (13–22) than in blind individuals (4,6,23,24), even though it is well documented that blind people sleep poorly when their endogenous circadian rhythms are not in their normal phase (3,25,26). The endogenous melatonin rhythm used in the present study is a marker for all of the circadian rhythms tightly coupled to the circadian pacemaker and is the best way to determine whether or not a person is entrained or free-running (11,27). Melatonin is relatively free of masking effects, especially in totally blind people. If the melatonin circadian rhythm is determined to be free-running, the endogenous circadian period and therefore the individual is considered to be free-running, even if the constrained and masked other circadian rhythms do not clearly show a classical free-running pattern. Preliminary analysis of the subject's sleep diary and actigraphy data suggests that an out-of-phase circadian melatonin rhythm is associated with poorer, fragmented nighttime sleep and an increase in daytime napping, which will be reported on when the analysis is completed.

METHODS

The subject was a 46-yr-old, male, married, and master's level counselor who worked on a regular schedule until July 2000 (approximately day 980 in Fig. 1). He was unemployed thereafter but attempted to maintain a normal sleep schedule. He lost his sight at age 12 as a result of an accident in which a canister of flash powder exploded, spraying glass fragments into his eyes. Initial attempts to preserve vision in one of his eyes failed, and he was eventually given prosthetic shells bilaterally. The subject was aware of his first difficulties with sleep beginning in late high school and college during which he would often be awake at night and would periodically fall asleep in class. After graduating from college, he worked as a counselor at a telephone crisis service and continued to be symptomatic. During the time of study, his typical bedtimes were between 21:00h and 23:00h and his waketimes were between 05:00h and 07:00h. He reported insomnia characterized by difficulty initiating sleep, as well as by awakening for 1–3 h after 2–3 h. He did not report a history consistent with parasomnias such as sleep walking, sleep talking, teeth grinding, or nightmares. He had no problems with significant nocturnal pain or loud snoring. Polysomnography confirmed the absence of any other primary sleep disorders.

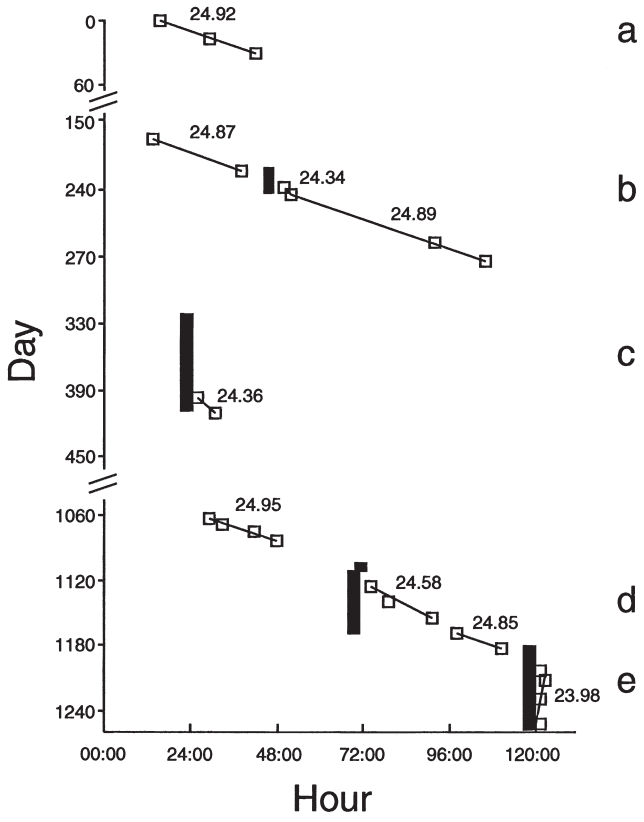

Figure 1. A totally blind subject with free-running circadian rhythms during four trials of oral melatonin administration. Each data point represents an assessment of circadian phase as determined by successive measurements of the time that endogenous plasma melatonin concentrations rose above the 10 pg/mL threshold. Vertical lines represent the timing and duration of exogenous melatonin administration. The slopes of the fitted regression lines indicate circadian period (shown in h beside the regression lines) during a given treatment. The calculated circadian periods represent mean determinations between d of assessment; fluctuation of circadian period probably occurs as the melatonin dose stimulates different parts of the shifting PRC. (a). Baseline free-running circadian rhythm of 24.92 h. (b). Administration of 10 mg melatonin for 17 d beginning at CT 20.5 led to a shortened period of 24.34 h without entrainment. (c) Administration of 9–10 mg of melatonin over 83 d again failed to entrain this subject but shortened circadian period to 24.36 h. (d) Administration of 20 mg initially at CT 14.6 shortened the subject's circadian period to 24.58 h after 60 d. (e) Administration of 0.5 mg, initially at CT 20.6 caused entrainment (circadian period of 23.98 h) after 47 d. In the absence of melatonin treatment, circadian periods were 24.92 h, 24.87 h, 24.89 h, 24.95 h, and 24.85 h.

The subject was totally without light perception as demonstrated by ophthalmologic examination, which revealed phthisis bulbi, retained intraocular foreign bodies, and total retinal detachments. With the exception of a history of ulcerative colitis, his health was otherwise good as demonstrated by physical examination, electrocardiogram, and routine chemistries. He took no medications

that interfered with the production or measurement of endogenous plasma melatonin levels. Information about the study was provided to the subject in print, Braille, and on an audio tape; the subject gave written informed consent. The Institutional Review Board of Oregon Health & Science University approved the protocol and the consent forms.

The phase of the circadian pacemaker was determined by measuring plasma melatonin levels in order to determine the melatonin onset (MO). The operational definition of the MO is the time when endogenous levels continuously rise above 10 pg/mL. This has been found to be a reliable marker of the phase of the endogenous circadian pacemaker (27). We define the MO as occurring at circadian time (CT) 14 in most entrained sighted people, (the MO usually occurs 14 h after waketime, which is by convention designated CT 0) (37). The subject's free-running circadian period was assessed by MO determinations spaced 2–4 wk apart. The CT of melatonin administration on any particular day was predicted by adding the expected phase drift per day (e.g., 0.5 h per day in a subject with a period of 24.5 h) to the most recent MO determination. If, for example, the MO onset was predicted to occur at 19:00h on a given day that exogenous melatonin was given at 18:00h, then the CT of melatonin administration would be CT 13 (1 h earlier than CT 14, the designated CT of the MO, no matter the clock time of its occurrence). These calculations were confirmed retrospectively as well.

The subject was admitted to the General Clinical Research Center for each MO determination, obtaining blood samples every hour for 24 h. No melatonin capsules were taken on the day of admission, and the dose was reduced to 0.5 mg the day before admission as well, so that exogenous melatonin levels were not present during the day of blood sampling. Plasma melatonin concentrations were measured in the core laboratory by radioimmunoassay with an antibody raised in the laboratory of Kennaway et al. (29,30) and reagents supplied by American Laboratory Products (Windham, NH). The lower limit of sensitivity of this assay is 0.3 pg/m; the interassay coefficient of variation is 7.2% at a concentration of 18.8 pg/mL. The assay was validated by gas chromatography—mass spectrometry (GCMS) (28,31). Immediate-release melatonin in dosages of 10, 20, and 0.5 mg were administered orally 1 h before the subject's preferred bedtime. Analytic-grade melatonin (administered under Investigational New Drug application 26,318) was obtained from Regis Chemical (Morton Grove, IL) and was formulated under a pharmacist's supervision in gelatin capsules with a lactose filler. The pill containers were coded and were labeled for the subject in both print and Braille. Pharmacokinetic data for the 0.5-mg dose were also obtained in this subject.

RESULTS

Several attempts at entraining the subject were made (Fig. 1). His pre-treatment (baseline) period was 24.9 h (Fig. 1a). As reported previously (11), a dose of 10 mg administered initially at CT 20.5 (4.5 h after the predicted MO)

failed to entrain the subject after 17 d of treatment. However, the circadian period of the subject was decreased to 24.3 h, before reverting to the pre-treatment period of 24.9 h after the 10-mg melatonin treatment was discontinued (Fig. 1b).

Since this dose decreased the subject's period without actual entrainment, treatment was subsequently initiated for a much longer period of time. After taking 9–10 mg of melatonin for 83 d, the subject still failed to entrain. However, his period again shortened this time to 24.4 h (Fig. 1c).

A higher dose of melatonin (20 mg) was then begun at CT 14.6 (0.6 h after the predicted MO) and was continued for 60 d. The subject again failed to entrain. However, his period shortened to 24.6 h (Fig. 1d).

When melatonin at a dosage of 0.5 mg was administered initially at CT 20.6 (4.6 h after the predicted MO), the subject's rhythms entrained with a period of 24.0 h by 47 d of treatment. Entrainment at this dosage was maintained for 161 d, and he continued to be entrained by this melatonin dose (Fig. 1e). A detectable effect was demonstrated relatively quickly: within the first 20 d, the subject's period was decreased to 24.5 h, and after 29 d it was 24.1 h before entrainment occurred (circadian period = 24.0 h).

DISCUSSION

Our explanation for why the lower dose worked better than the higher dose requires an understanding of the melatonin phase–response curve (PRC) (32,33,39). Exogenous melatonin causes phase advances (shifts to an earlier time) when it is administered between 8 h before and 4 h after the MO and causes phase delays (shifts to a later time) when it is administered between 4 h after and 8 h before the MO (Fig. 2). Another way to describe the relationship between the phase of the melatonin PRC and the MO [which is, as far as we know, unchanging, since these two circadian rhythms (unlike the sleep–wake cycle) appear to be tightly coupled to the endogenous pacemaker] is as follows: the MO is always CT 14; advance responses occur when exogenous melatonin is given between CT 6 and 18; delay response occurs when exogenous melatonin is given between CT 18 and 6. The melatonin PRC also suggests that the duration of the exogenous melatonin pulse may affect the magnitude of the resulting melatonin-induced phase shift, in that, stimulating as much of the appropriate (12-h) zone of the PRC as possible might produce a greater phase shift (34). A corollary is that the balance of stimulating the advance vs. the delay zones (or—if melatonin is an "on/off" signal—the balance between extending the combined exogenous–endogenous elevation of melatonin levels earlier vs. later) might affect the magnitude of the resulting phase shift. In other words, the larger the melatonin dose, the more likely it will "spill over" onto the "wrong" zone of the PRC. After the treatment failures with high doses (10- and 20-mg) of melatonin, we became concerned about spillover and elected to use a low dose that proved to be successful. As previously reported (11), the 10-mg dose can entrain blind free-runners with circadian periods shorter than 24.9 h, probably because they require less of a daily phase advance for entrainment if they have a period closer to 24 h than the subject we describe herein.

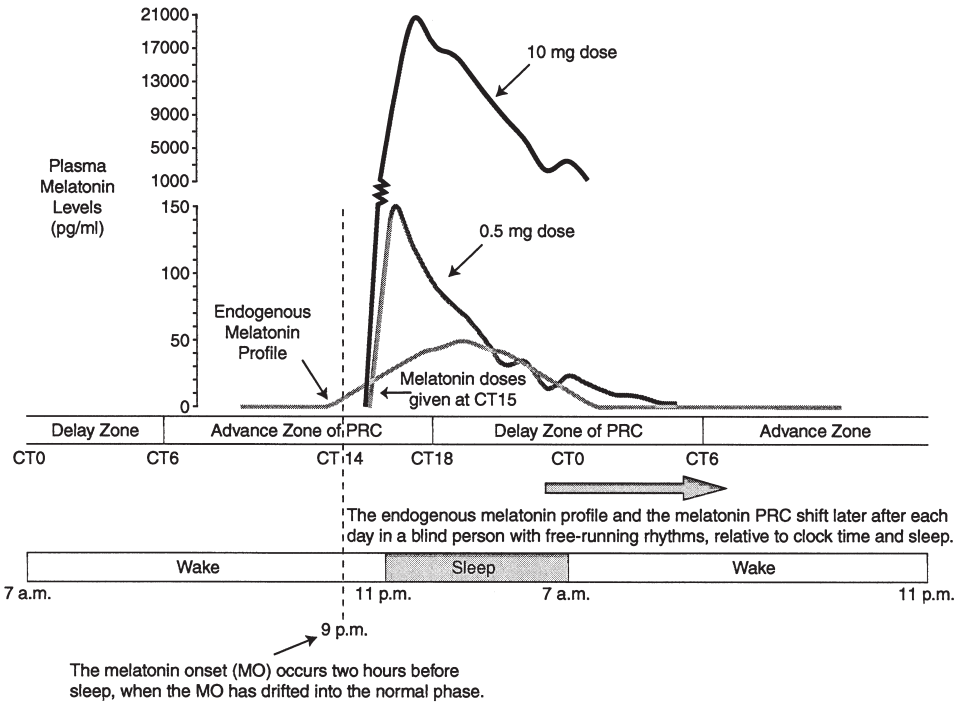

Figure 2. Pharmacokinetic data from two different melatonin doses (0.5 and 10 mg) in relation to the endogenous melatonin profile and the melatonin phase response curve (PRC). The 0.5-mg dose and the endogenous melatonin profile are data from the subject in this study. The 10-mg data were from another subject and were not collected beyond 10 h; it is clear that they cause more stimulation of the delay zone of the melatonin phase response curve than the 0.5-mg dose. By convention, CT 14 is the endogenous MO. In free-running subjects, the endogenous melatonin profile and the melatonin phase response curve (which are phase-locked) drift later each day with respect to the sleep–wake cycle. Normal phase is when the MO occurs 2 h before sleep onset (14 h after waketime). Exogenous melatonin causes phase advances when it is given between CT 6 and 18 and causes phase delays when it is given between CT 18 and 6; however, the concentrations and duration of exogenous melatonin levels as they spill over onto the wrong zone of the melatonin phase response curve may also affect the phase-shifting effect of exogenous melatonin.

Entrainment of this blind subject using a lower dose of melatonin has potentially important ramifications. We no longer assume that blind people with free-running rhythms who have long circadian periods will be unentrainable or would necessarily need very high doses of melatonin; we now assume that these people are potentially entrainable, although lower doses may be required. Higher doses of melatonin may be unnecessary and even detrimental in some people: we have recently shown that the 0.5-mg dose is also effective as a de novo treatment in three individuals (with circadian periods of 24.2–24.5 h) (35). As mentioned above, the present case report also suggests that apparently due to spillover, higher doses may be less effective in some individuals than lower doses—particularly in blind people with even longer circadian periods who require a greater daily phase

advance for entrainment and in those people who are slow metabolizers of melatonin.

The success of lower doses indicates that melatonin can be given on a long-term basis with more assurance that it will be safe. Since lower doses are less often associated with sleepiness, melatonin can be confidently given during the early evening (36), which would more likely result in the MO occurring 2 h before bedtime, which is the normal phase relationship between the sleep–wake cycle and the endogenous circadian pacemaker (37). When using nonsoporific doses that can be given well before bedtime, selection of the clock time of administration can be made as a first approximation, by referring to the published relationship (36) between phase angle of entrainment and pre-treatment free-running circadian period with the goal of having the endogenous MO entrain at a phase, which is 2 h before sleep onset (the normal phase relationship); if the melatonin dose is sufficiently low treatment should be initiated on the day when the MO is predicted to occur a few hours before the selected clock time of melatonin administration, because this will ensure that the entrainment point on the melatonin PRC will not be missed and will also ensure that before contact between exogenous melatonin and the entrainment point is made, the number of days of stimulating the advance zone of the melatonin PRC will be maximized. After steady-state entrainment has occurred, the administration time can be adjusted to "fine tune" the time of MO, so that it occurs 2 h before sleep onset, although this must be done very gradually. Stimulating the advance zone before entrainment occurs may be helpful in shortening the circadian period [due to an aftereffect, or "during effect," Fig. 3 of Ref. (11)]. The reason why the subject did not entrain to the 10-mg dose in the previous study may have been that he had an unusually long circadian period and therefore required the greatest daily phase-advance shift to maintain entrainment. Although undoubtedly the 10-mg dose overlapped the delay zone of the melatonin PRC in all of the subjects, our other subjects who displayed circadian periods of 24.6 h or less were still able to be sufficiently phase-advanced daily to be able to entrain.

Clearly, at least in some people, optimizing the magnitude of the phase-shifting effects does not follow a log-linear dose–response curve that has been previously reported (38). Finally, the efficacy of exogenous doses that increase melatonin levels to the same order of magnitude as that produced by the pineal provides support for a circadian function of endogenous melatonin production. Endogenous melatonin in sighted people may help the light–dark cycle augment entrainment of the endogenous circadian pacemaker (32,33,39).

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