ENTRAINMENT OF FREE-RUNNING CIRCADIAN RHYTHMS BY MELATONIN IN BLIND PEOPLE

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Abstract

Background Most totally blind people have circadian rhythms that are "free-running" (i.e., that are not synchronized to environmental time cues and that oscillate on a cycle slightly longer than 24 hours). This condition causes recurrent insomnia and daytime sleepiness when the rhythms drift out of phase with the normal 24-hour cycle. We investigated whether a daily dose of melatonin could entrain their circadian rhythms to a normal 24-hour cycle.

Methods We performed a crossover study involving seven totally blind subjects who had free-running circadian rhythms. The subjects were given 10 mg of melatonin or placebo daily, one hour before their preferred bedtime, for three to nine weeks. They were then given the other treatment. The timing of the production of endogenous melatonin was measured as a marker of the circadian time (phase), and sleep was monitored by polysomnography.

Results At base line, the subjects had free-running circadian rhythms with distinct and predictable cycles averaging 24.5 hours (range, 24.2 to 24.9). These rhythms were unaffected by the administration of placebo. In six of the seven subjects the rhythm was entrained to a 24.0-hour cycle during melatonin treatment (P<0.001). After entrainment, the subjects spent less time awake after the initial onset of sleep (P=0.05) and the efficiency of sleep was higher (P=0.06). Three subjects subsequently participated in a trial in which a 10-mg dose of melatonin was given daily until entrainment was achieved. The dose was then reduced to 0.5 mg per day over a period of three months; the entrainment persisted, even at the lowest dose.

Conclusions Administration of melatonin can entrain circadian rhythms in most blind people who have free-running rhythms. (N Engl J Med 2000;343:1070-7.)

THE endogenous circadian pacemaker oscillates with a period that is slightly longer than 24 hours and that therefore requires synchronization, or entrainment, to the 24-hour day. Entrainment involves regular adjustments of the circadian pacemaker, known as phase shifts, that depend on exposure to environmental time cues, particularly the daily light–dark cycle.[1] Light cues necessary for entrainment are conveyed from the retina to the suprachiasmatic nucleus (the locus of the mammalian circadian pacemaker) by way of the retinohypothalamic tract, a neural pathway that is separate from the visual and oculomotor pathways.[2] In totally blind people, light cues are unavailable, and disturbances of circadian rhythms are common.[3-9]

Among these disturbances are "free-running" rhythms, which reflect the intrinsic oscillation of the circadian pacemaker when it is not influenced by environmental time cues. Free-running rhythms are characterized by a consistent delay in the timing of the circadian cycle by as much as 60 to 70 minutes per day and can be detected by measurement at regular intervals of a marker rhythm, such as the daily rise in the plasma melatonin concentration. In blind people who have free-running rhythms, periodic symptoms of insomnia and daytime sleepiness commonly occur when the circadian pacemaker and, therefore, the circadian rhythm of sleepiness drift out of phase with the desired time for sleeping.[8] These symptoms vary considerably but can be among the most burdensome aspects of blindness. We evaluated the daily administration of melatonin as a method of entraining the circadian rhythms of totally blind people with free-running rhythms.

METHODS

Study Design

We studied seven subjects who were totally blind, as determined by ophthalmologic examination. They had free-running circadian rhythms, indicated by a predictable shift in the time of the cyclic rise in the plasma melatonin concentration, measured on three occasions about two weeks apart. At the time of a screening assessment, the subjects were in good general health and were not taking any medications that might affect plasma melatonin concentrations or sleep. Information about the study was provided to the subjects in print, in Braille, and on an audiotape; all the subjects gave written informed consent. The institutional review board of the Oregon Health Sciences University approved the protocol and the consent forms.

This study had a crossover design, balanced according to the order of treatment (melatonin first or placebo first). The subjects took 10 mg of oral melatonin or placebo nightly, approximately one hour before their preferred bedtime. We selected the 10-mg dose of melatonin because we were not able to document unequivocally the occurrence of entrainment in a previous, three-week trial of 5 mg.[10] The timing of the circadian cycle was assessed near the beginning, middle, and end of each trial by determining the time of day at which the endogenous melatonin concentration rose above 10 pg per milliliter (43 pmol per liter). This event has been found to be a reliable marker of the phase of the endogenous circadian cycle.[11]

The optimal timing of melatonin administration was determined with use of the melatonin phase-response curve, which describes the relation between the time in the circadian cycle that melatonin is given and its effects on the circadian rhythm. Treatment was initiated when the subject's free-running rhythm was approaching a normal phase (defined as a cycle in which the rise in the plasma

melatonin concentration to >10 pg per milliliter occurred at about 9 p.m.[12]) and was continued until this rise was projected to occur at about 9 a.m. — that is, about 12 hours out of phase (assuming that treatment had no effect on the phase). Consequently, the planned duration of treatment varied among the subjects from three to nine weeks according to each subject's free-running circadian period. The subjects were asked to maintain consistent sleep schedules according to their preferred times for sleeping. Only the principal investigator and the project manager, and not the subjects, nurses, or research assistants, were aware of the treatment being given.

Approximately three months after the initial treatment, three of the subjects were treated a second time with melatonin at a dose of 10 mg per day. After their circadian rhythms were again entrained, the dose was gradually reduced to 0.5 mg per day, with the aim of determining the minimal effective dose of melatonin. In two of these three subjects, after treatment was discontinued, the time at which the plasma melatonin concentration rose above 10 pg per milliliter was determined every day or every other day for one week to explore the possibility that melatonin treatment might produce effects on the circadian pacemaker that persist after discontinuation of treatment (aftereffects).[13]

Analytic-grade melatonin (administered under Investigational New Drug application 26,318) was obtained from Regis Chemical (Morton Grove, Ill.) and was formulated under a pharmacist's supervision in gelatin capsules with a lactose filler. The placebo capsules contained only lactose. The pill containers were coded and were labeled for the subjects in both print and Braille.

Outcome Measures

The timing of the increase in endogenous melatonin production was determined as a marker of the circadian phase. To measure plasma melatonin on a given day, the subjects were admitted to the General Clinical Research Center of Oregon Health Sciences University, and blood samples were obtained every hour for 24 hours. To ensure that there was no interference from exogenous melatonin, no study capsules were taken on the day of sampling or on the preceding one or two days. Plasma melatonin concentrations were measured in the core laboratory by radioimmunoassay with an antibody raised in the laboratory of Kennaway et al.[14] and with reagents supplied by American Laboratory Products (Windham, N.H.). The lower limit of sensitivity of this assay is 1.0 pg per milliliter (4.3 pmol per liter); the interassay coefficient of vari-

ation is 10.2 percent at a concentration of 15 pg per milliliter (64 pmol per liter). This assay has been validated by gas chromatography–mass spectrometry.[11] Each 24-hour set of plasma melatonin measurements generated the time of day at which the plasma melatonin concentration exceeded the threshold of 10 pg per milliliter. The circadian period was then determined at base line and for the melatonin and placebo trials by fitting a linear regression line to the times of this increase on successive days.

The effects of treatment on total time asleep, sleep latency (the interval between the beginning of the opportunity for sleep and the onset of sleep), sleep efficiency (the total time asleep divided by the time allowed as an opportunity for sleep), and time spent awake after the onset of sleep were assessed by polysomnography performed in a sleep laboratory. The subjects were allowed to sleep from 10 p.m. until 6 a.m. Seven polysomnograms were recorded for each subject; the first (obtained during the screening assessment) was used to rule out any primary sleep disorders and to accustom the subject to the sleep laboratory. Polysomnograms were also recorded at the beginning, middle, and end of the melatonin and placebo trials, within several days before or after each assessment of circadian phase. The time at which the plasma melatonin concentration was predicted to reach the threshold of 10 pg per milliliter on a specific night of polysomnographic recording was extrapolated from the linear regression line fitted to the measured time points.

Statistical Analysis

Unless otherwise stated, data are expressed as means ±SD. Differences in circadian period were tested for statistical significance by two-sided t-tests for repeated measures. Differences in polysomnographic variables according to treatment (melatonin or placebo), the stage of the trial (beginning, middle, or end), and interaction (a differential effect of treatment depending on the stage of the trial) were tested for statistical significance by analysis of variance and by post hoc two-sided t-tests for repeated measures.
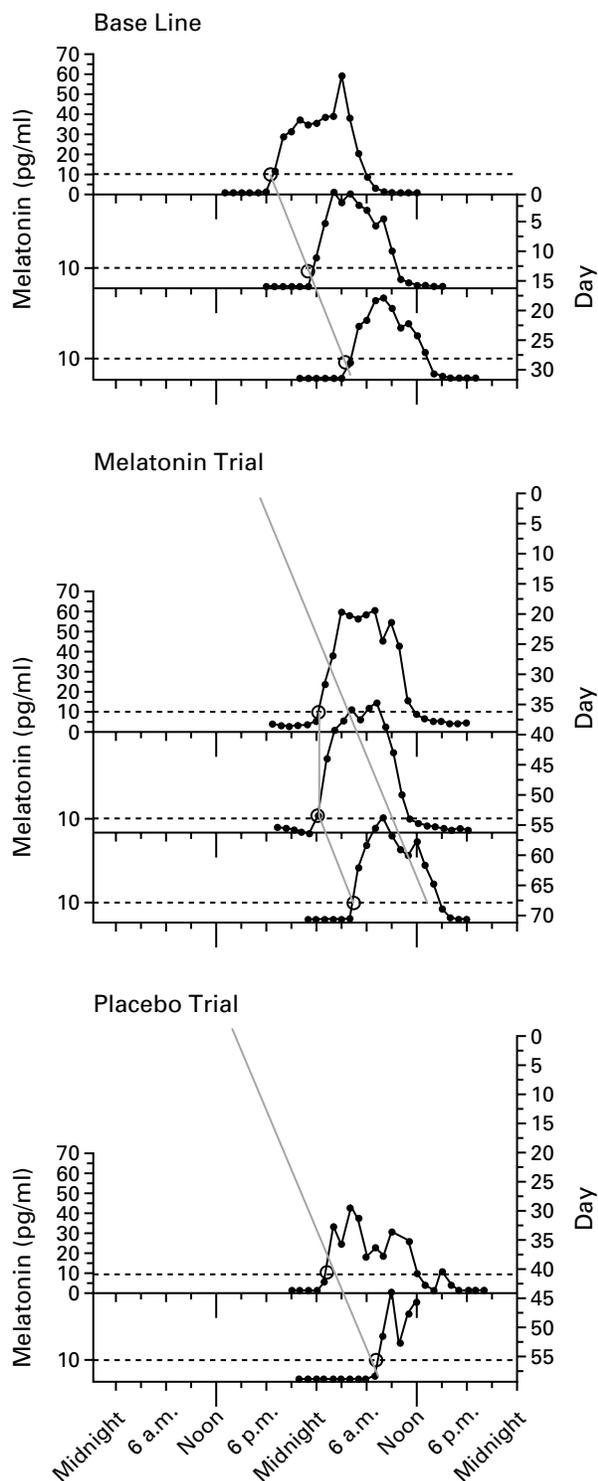
RESULTS

The characteristics of the seven subjects are shown in Table 1. The plasma melatonin concentrations in a representative subject (Subject 2) are shown in Figure 1. A regression line fitted to the three time points at

TABLE 1. CHARACTERISTICS OF SEVEN BLIND SUBJECTS WITH FREE-RUNNING CIRCADIAN RHYTHMS AT BASE LINE AND DURING THE ADMINISTRATION OF PLACEBO OR MELATONIN.

SUBJECT NO.	SEX	AGE	CAUSE OF BLINDNESS	AGE AT ONSET OF TOTAL BLINDNESS	STATUS OF EYES	CIRCADIAN PERIOD		
						BASE LINE	PLACEBO	MELATONIN
		yr		yr			hr	
1	F	42	Congenital glaucoma	6	Bilateral enucleation	24.2	24.2	24.0
2	M	46	Trauma	31	Eyes present	24.3	24.3	24.0
3	M	47	Congenital glaucoma	36	Unilateral enucleation	24.4	24.3	24.0
4*	F	50	Retinopathy of prematurity	Birth	Eyes present	24.5	—	24.0
5	F	45	Retinopathy of prematurity	Birth	Bilateral enucleation	24.4	24.3	24.0
6	M	57	Trauma	26	Bilateral enucleation	24.6	24.5	24.0
7	M	44	Trauma	12	Partial bilateral enucleation (prostheses)	24.9	24.8	24.3
Mean ±SD		48±5				24.5±0.2	24.4±0.2	24.0±0.1

*Complete data for the placebo trial were not obtained for Subject 4, and hence this subject was excluded from the statistical analysis.
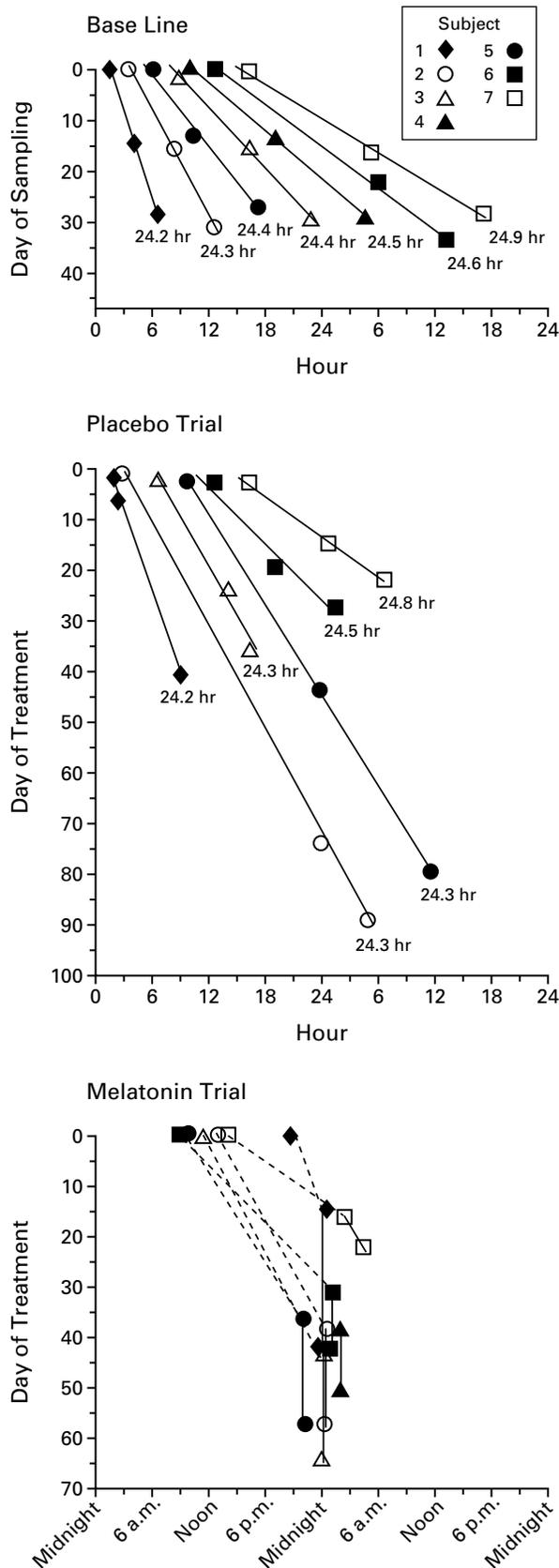
Figure 1. Plasma Melatonin Profiles in Subject 2 at Base Line and during the Placebo and Melatonin Trials.

The times of day at which the plasma melatonin concentration rose above a threshold of 10 pg per milliliter are shown as open circles on the dashed lines. The slopes of the regression lines drawn between these circles are an indication of the circadian rhythm: a slanting line indicates a free-running rhythm and a vertical line an entrained rhythm. The assessment at base line showed that this subject had a free-running rhythm (circadian period, 24.3 hours). During treatment with melatonin (10 mg taken daily at 11 p.m.), the rhythm was entrained (circadian period, 24.0 hours); it reverted to a free-running rhythm (circadian period, 24.3 hours) after melatonin treatment was stopped (on day 57). The rhythm was not affected by placebo taken daily at 11 p.m. (circadian period, 24.3 hours). All the regression lines have the same slope, indicating a circadian period of 24.3 hours, except for that during melatonin treatment, which indicated a circadian period of 24.0 hours. To convert the values for plasma melatonin to picomoles per liter, multiply by 4.3.

which the plasma melatonin concentration rose above 10 pg per milliliter before treatment (at base line) indicates a free-running circadian period of 24.3 hours (i.e., a delay in the rise in the plasma melatonin concentration to >10 pg per milliliter by 0.3 hour per day). The rhythm was regular, as indicated by a standard error in the slope of the regression line of 0.005 hour; consequently, the rise in this subject's plasma melatonin concentration could be accurately projected (for example, the standard error of prediction three weeks after the last measurement of plasma melatonin was 14 minutes). During the trial of melatonin, Subject 2 took melatonin daily at 11 p.m., except on days 38 and 57, when his endogenous melatonin profiles were assessed. On day 38, the plasma melatonin concentration rose above 10 pg per milliliter 3.6 hours earlier than the time predicted for a free-running rhythm with a period of 24.3 hours, and on day 57 it was 9.4 hours earlier (Fig. 1). Furthermore, the time of the rise in plasma melatonin was similar on days 38 and 57, indicating that the rhythm was effectively entrained to a 24-hour cycle. During the placebo trial, the circadian period was 24.3 hours, indistinguishable from that at base line.

The times of day at which the plasma melatonin concentration rose above 10 pg per milliliter in each of the seven subjects are shown in Figure 2. Complete data for the placebo trial were not obtained for Subject 4, and she was consequently excluded from the statistical analysis. The circadian periods at base line and during the placebo trial were highly correlated (r=0.95, P=0.003 for the correlation). The mean circadian period during the trial of melatonin was significantly different from the mean circadian period during the placebo trial (24.0±0.1 hours [95 percent confidence interval, 23.9 to 24.1] vs. 24.4± 0.2 hours [95 percent confidence interval, 24.2 to 24.6]; P<0.001), but it was not significantly different from 24.0 hours (P=0.12).

In Subject 7, there was a cumulative phase advance of 3 hours during the trial of melatonin, but the rhythm clearly failed to entrain to a 24-hour cycle. Subject 7 had the longest circadian period at base line (24.9 hours) of any of the subjects. Because the short duration of melatonin administration in this subject (18 days) may have accounted for the lack of entrainment, he was subsequently given melatonin on an open-label basis (10 mg daily at bedtime) for approximately 3 months. His plasma melatonin concentration rose above 10 pg per milliliter at 1:30 a.m. on day 45 of this treatment and at 7:30 a.m. on day 86, indicating lack of entrainment.

Polysomnographic data are shown in Table 2. The stage of each trial (beginning, middle, or end) had a significant effect on the efficiency of sleep and on the amount of time spent awake after the onset of sleep, but not on total time asleep or sleep latency. Because the subjects had free-running rhythms during placebo administration, the circadian phase (as reflected by the time of the increase in melatonin production) was progressively later as the trial proceeded. As expected, sleep efficiency was higher ($P=0.05$) and the amount of time spent awake after the onset of sleep was lower ($P=0.02$) at the beginning of the placebo trial (when subjects' rhythms were relatively close to normal phase) than at the end of the placebo trial (when subjects' rhythms were 12 hours out of phase). However, there was no effect on total time asleep or on sleep latency.

At the end of the melatonin trial the average time at which the plasma melatonin concentration rose above 10 pg per milliliter was at 12:18 a.m. (SD, 1.5 hours), close to that for a normal time but delayed as compared with 8:48 p.m. (SD, 1.3 hours), the average time in our study of people with normal sight.[12] The polysomnograms obtained at the end of each trial showed that less time was spent awake after the onset of sleep during the melatonin trial than

Figure 2. Circadian Rhythms in Seven Blind Subjects with Free-Running Circadian Rhythms at Base Line and during the Melatonin and Placebo Trials.

Each data point represents an assessment of circadian phase as determined by the time that endogenous plasma melatonin concentrations rose above the threshold of 10 pg per milliliter. The slopes of the fitted regression lines are indicative of the subjects' circadian period (shown in hours below the regression lines for the base line and placebo conditions). Treatment with melatonin or placebo was begun on day 1. In the top and middle panels, the regression lines are arranged on a relative time scale in ascending order so that they can be easily compared. In the bottom panel, the time scale is absolute and shows the assessments of circadian phase and fitted regression lines for all seven subjects before (dashed lines) and after (solid lines) the melatonin trial. Treatment with melatonin resulted in entrainment (a circadian period of 24.0 hours) in all but one subject (Subject 7); on average, the rise in plasma melatonin after entrainment occurred at 12:18 a.m.

TABLE 2. CIRCADIAN PHASE AND POLYSOMNOGRAPHIC RESULTS IN SEVEN BLIND SUBJECTS AT EACH STAGE
OF THE PLACEBO AND MELATONIN TRIALS.*

VARIABLE	PLACEBO				MELATONIN				P VALUE‡		
	BEGINNING	MIDDLE	END	P VALUE†	BEGINNING	MIDDLE	END	P VALUE§	TREAT-MENT	STAGE OF TRIAL	INTER-ACTION
Time of rise in plasma melatonin to >10 pg/ml											
Mean	9:18 p.m.	2:06 a.m.	5:48 a.m.		8:18 p.m.	11:48 p.m.	12:18 a.m.				
SD (hr)	1.7	2.4	3.4		1.5	0.8	1.5				
Total time asleep (min)	361.0±68.1	370.8±83.0	309.4±91.6		399.8±58.3	404.7±54.1	382.6±60.0		0.12	0.12	0.70
Sleep latency (min)	7.7±6.9	22.2±29.6	13.7±11.0		4.6±3.4	7.3±6.4	10.5±6.6		0.16	0.32	0.48
Sleep efficiency (%)	76.2±15.2	76.3±15.7	62.8±16.7	0.05	87.1±9.3	84.7±10.8	79.5±12.5	0.06	0.06	0.04	0.66
Time spent awake after the onset of sleep (min)	63.0±32.1	87.4±72.5	165.9±71.8	0.02	55.7±43.6	61.9±46.1	88.4±61.2	0.05	0.06	0.003	0.21

*Plus–minus values are means ±SD. Where P values are not shown, the analysis of variance did not indicate significance, and post hoc analyses were not performed.

†P values are for the comparison between the result at the beginning of the placebo trial and the result at the end of the placebo trial.

‡P values were calculated by analysis of variance and are for the comparisons according to treatment (melatonin or placebo), stage of the trial (beginning, middle, or end), and interaction (a differential effect of treatment depending on the stage of the trial).

§P values are for the comparison between the result at the end of the placebo trial and the result at the end of the melatonin trial.

during the placebo trial (P=0.05) and that sleep efficiency was greater with melatonin than with placebo (P=0.06).

During the trial of melatonin taken in gradually reduced doses (step-down protocol), the rise in the plasma melatonin concentration to more than 10 pg per milliliter in the three participating subjects occurred consistently at about midnight (12:47 a.m. [SD, 0.6 hour] in Subject 1, 12:23 a.m. [SD, 0.5 hour] in Subject 2, and 11:50 p.m. [SD, 0.4 hour] in Subject 5), even at the lowest dose (0.5 mg per day), indicating stable entrainment, for approximately 120 days (Fig. 3). In Subject 5, about a month passed after melatonin was discontinued before the circadian rhythm reverted to the base-line period of 24.4 hours. In contrast, in Subject 2, a free-running rhythm resumed and the period returned to base line within several days after melatonin was discontinued (Fig. 3).

DISCUSSION

Although melatonin can induce phase advances in circadian rhythms, questions have been raised regarding its potency.[15] Our results indicate that the phase-advancing effects of melatonin are of sufficient magnitude to entrain free-running circadian rhythms in most blind persons who have such rhythms. The average daily phase advance required for entrainment was equal to the circadian period minus 24.0. In all seven subjects in this study, melatonin induced an average daily phase advance of up to 0.6 hour, but this was insufficient to entrain the free-running rhythm in Subject 7, whose base-line circadian period was 24.9 hours. The time of day at which the plasma melatonin concentration rose above 10 pg per milliliter after

entrainment with melatonin was somewhat later than that reported in sighted persons.[12] An abnormally late circadian phase may be corrected by giving melatonin at an earlier time of day, thereby achieving a more normal relation between the rise in the plasma melatonin concentration and the desired sleeping schedule.

Three subjects underwent a second, open-label trial of treatment with melatonin. After entrainment was achieved at a dose of 10 mg of melatonin per day, the dose was gradually reduced. Entrainment was maintained at progressively lower doses for a period of four months, suggesting that a long-term benefit is likely with continuing treatment. The lowest dose tested in this protocol, 0.5 mg daily, resulted in plasma melatonin concentrations that were close to the physiologic range and can therefore be presumed to be very safe. According to these preliminary findings, it appears that treatment with a high dose of melatonin (10 mg per day) may be used to "capture" (initially entrain) a free-running rhythm, but that the dose can be gradually reduced without loss of effect. In some subjects, especially those with a circadian period close to 24.0 hours, a lower dose may be effective as the initial treatment.

Although we studied only seven subjects, the phase-shifting effects of melatonin treatment on circadian rhythms were clear and were consistent with previous data on the resetting of the circadian rhythm in sighted people[16-18] and with findings in case studies in blind people.[6,7,10,19-24] Because of the variability inherent in polysomnographic data, more subjects will need to be studied to document fully the effects of melatonin treatment on sleep. However, previous studies have shown that blind subjects with free-running
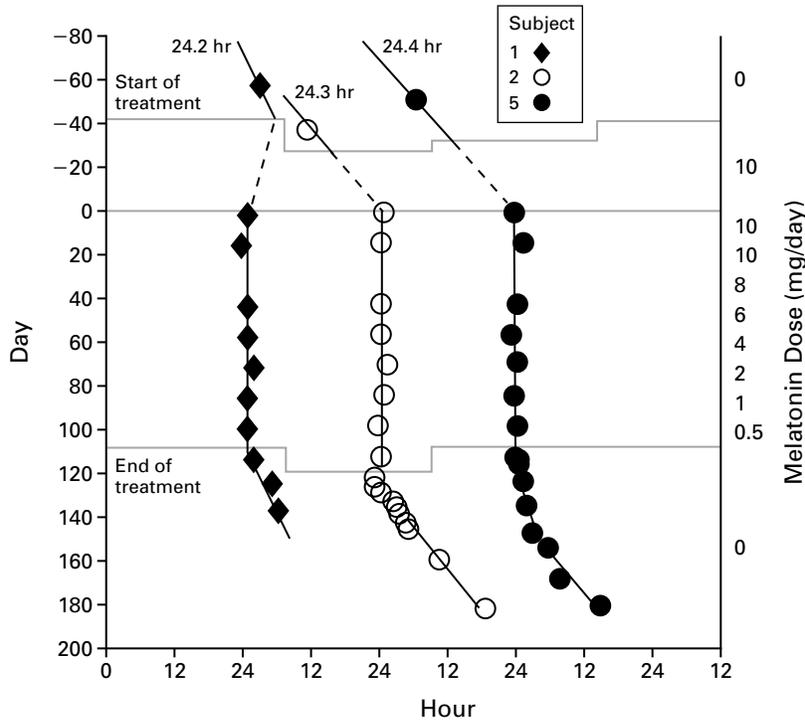
Figure 3. Assessments of Circadian Phase in Three Subjects Who Received Decreasing Doses of Melatonin in an Open-Label Trial.

Each data point represents an assessment of circadian phase as indicated by the time of day that endogenous plasma melatonin concentrations rose above the threshold of 10 pg per milliliter. For clarity, assessments of circadian phase are aligned with the dose-reduction schedule shown on the right. Treatment began (as indicated by the top horizontal line) at 42 days (Subject 1), 28 days (Subject 2), and 33 days (Subject 5) before the assessment of circadian phase on day 0. Free-running circadian periods before the beginning of treatment are shown (in hours) for each subject. After entrainment had been confirmed by a phase assessment on day 28, the dose was reduced every two weeks. The rise in plasma melatonin concentration during treatment occurred consistently at about midnight for 120 days, indicating entrainment, even at a dose as low as 0.5 mg per day. In Subject 1, there was no evidence of aftereffects; however, this subject had only three circadian-phase assessments, at relatively infrequent intervals, after the discontinuation of treatment. In Subject 2, the circadian rhythm became free running within days after treatment was discontinued. In Subject 5, about a month passed after the end of treatment before the circadian period returned to its base-line value, suggesting that entrainment for 120 days had a persistent effect on the circadian pacemaker. Circadian periods before the beginning of treatment are shown (in hours) for each subject.

rhythms sleep better when their circadian rhythms of sleepiness are more in phase with their desired times for sleeping.[9,25,26]

Why was melatonin effective in entraining the circadian rhythms of these subjects, whereas some previous attempts were not reliably successful?[10,27] Perhaps the longer duration of treatment used in the current study was important for successful entrainment. In addition, a 10-mg daily dose of melatonin may be more effective than a 5-mg daily dose, the dose used in our previous study.[10] On the other hand, in three of the subjects in our current study, much lower doses (which mimic endogenous plasma melatonin concentrations and induce a phase shift in sighted people[16-18]) maintained entrainment. Finally, there may

be substantial individual variations in the response of the circadian rhythm to melatonin.

Determination of the optimal timing of melatonin administration requires the use of the melatonin phase–response curve, which describes the relation between the time in the circadian cycle that melatonin is given and its effects on the circadian rhythm. Administration of melatonin during the phase-advance portion of the curve (between 8 hours before and 4 hours after the increase in endogenous plasma melatonin production) results in shifts in the cycle to an earlier time of day; administration during the phase-delay portion of the curve (4 to 16 hours after the increase in endogenous plasma melatonin production) shifts the cycle to a later time of day.[16-18] With-

out knowledge of a person's circadian rhythm, it may be difficult to know what day to begin treatment so that the administration of melatonin at bedtime coincides with the phase-advance portion of the melatonin phase–response curve. This is the timing that was attempted in this study. Consequently, several weeks or even months of treatment may be required for the optimal phase relation to develop so that entrainment can be achieved and recurrent sleep problems can be resolved. We recommend that, if possible, treatment be initiated on a day when the plasma melatonin is predicted to rise above 10 pg per milliliter a few hours before the time the drug would be administered.

The benefits with respect to sleep in these subjects may be related not only to entrainment but also to a direct, sleep-promoting action of melatonin. Exogenous melatonin appears to have direct soporific effects, especially if it is ingested at a time when there is no endogenous production of melatonin (for example, during daytime hours in sighted people who are sleeping at conventional times).[28] We recently reported that a 10-mg dose of melatonin given once daily, at bedtime, to blind persons with free-running circadian rhythms improved sleep (without causing substantial phase shifts) when administered during a period when the circadian rhythm was "inverted" — that is, shifted 12 hours out of the normal phase.[29] Furthermore, we found no significant difference between the effects of melatonin and those of placebo when the subjects were tested on nights when their circadian rhythms were congruent with their preferred, conventional times for sleeping. We have speculated that melatonin does not generate sleep but that it can facilitate expression of the need to sleep that accumulates when one is awake.[30]

Melatonin has been widely used as a nutritional supplement in the United States for several years, with no reports of serious adverse effects. Nevertheless, long-term administration of 10 mg per day should be supervised by a physician. This dose can probably be gradually reduced without loss of efficacy.

There are approximately 1 million blind people in the United States, of whom about 20 percent are totally blind.[31] Extrapolating from our previous series,[9] at least half of this 20 percent (about 100,000 people) probably have free-running circadian rhythms, with a high proportion having circadian sleep–wake disorders. Melatonin may prove to be a safe and effective treatment for many of these people.

The phase-shifting effects of melatonin observed in this study of circadian rhythms in blind people may be relevant to the treatment of sighted people as well. People who fly across multiple time zones or who work nighttime or early-morning shifts routinely have symptoms of disordered sleep as a result of circadian disturbances. Similar pathophysiologic mechanisms have been proposed for advanced and delayed sleep-phase syndromes as well as for winter depression.[32]

Administration should be timed according to the melatonin phase–response curve, since adverse effects may result if melatonin is given at times that would produce an antidromic (contrary) phase shift.[16,18]

In conclusion, free-running circadian rhythms in blind people can be entrained to a 24-hour cycle with a daily dose of melatonin, thereby preventing a burdensome sleep disorder.

REFERENCES

1. Moore-Ede M, Sulzman FM, Fuller CA. The clocks that time us: physiology of the circadian timing system. Cambridge, Mass.: Harvard University Press, 1982.
2. Klein DC, Moore RY, Reppert SM. Suprachiasmatic nucleus: the mind's clock. New York: Oxford University Press, 1991.
3. Miles LEM, Raynal DM, Wilson MA. Blind man living in normal society has circadian rhythms of 24.9 hours. Science 1977;198:421-3.
4. Orth DN, Besser GM, King PH, Nicholson WE. Free-running circadian plasma cortisol rhythm in a blind human subject. Clin Endocrinol (Oxf) 1979;10:603-17.
5. Lewy AJ, Newsome DA. Different types of melatonin circadian secretory rhythms in some blind subjects. J Clin Endocrinol Metab 1983;56:1103-7.
6. Sack RL, Lewy AJ, Hoban TM. Free-running melatonin rhythms in blind people: phase shifts with melatonin and triazolam administration. In: Rensing L, an der Heiden U, Mackey MC, eds. Temporal disorder in human oscillatory systems. Berlin, Germany: Springer-Verlag, 1987:219-24.
7. Sack RL, Stevenson J, Lewy AJ. Entrainment of a previously free-running blind human with melatonin administration. Sleep Res 1990;19:404.
8. Nakagawa H, Sack RL, Lewy AJ. Sleep propensity free-runs with the temperature, melatonin and cortisol rhythms in a totally blind person. Sleep 1992;15:330-6.
9. Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. J Clin Endocrinol Metab 1992;75:127-34.
10. Sack RL, Lewy AJ, Blood ML, Stevenson J, Keith LD. Melatonin administration to blind people: phase advances and entrainment. J Biol Rhythms 1991;6:249-61.
11. Lewy AJ, Sack RL, Boney RS, et al. Assays for measuring the dim light melatonin onset (DLMO) in human plasma. Sleep Res 1997;26:733.
12. Lewy AJ, Bauer VK, Cutler NL, et al. Morning vs evening light treatment of patients with winter depression. Arch Gen Psychiatry 1998;55:890-6.
13. Pittendrigh CS, Daan S. A functional analysis of circadian pacemakers in nocturnal rodents. I. The stability and lability of spontaneous frequency. J Comp Physiol 1976;106:223-52.
14. Kennaway DJ, Frith RG, Phillipou G, Matthews DC, Seamark RF. A specific radioimmunoassay for melatonin in biological tissue and fluids and its validation by gas chromatography-mass spectrometry. Endocrinology 1977;101:119-27.
15. Czeisler CA. Evidence for melatonin as a circadian phase-shifting agent. J Biol Rhythms 1997;12:618-23.
16. Lewy AJ, Ahmed S, Jackson JML, Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int 1992;9:380-92.
17. Zaidan R, Geoffriau M, Brun J, et al. Melatonin is able to influence its secretion in humans: description of a phase-response curve. Neuroendocrinology 1994;60:105-12.
18. Lewy AJ, Bauer VK, Ahmed S, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiol Int 1998;15:71-83.
19. Palm L, Blennow G, Wetterberg L. Correction of non-24-hour sleep/wake cycle by melatonin in a blind retarded boy. Ann Neurol 1991;29:336-9.

20. Lapierre O, Dumont M. Melatonin treatment of a non-24-hour sleep-wake cycle in a blind retarded child. Biol Psychiatry 1995;38:119-22.

21. Sack RL, Brandes R, deJongh L, Pen S, Nordstrom S, Lewy AL. Melatonin entrains free-running circadian rhythms in a totally blind person. Sleep 1999;22:Suppl 1:S138-S139. abstract. (See http://www.websciences.org/cftemplate/APSS99/indiv99.cfm?ID=19999284.)

22. Sack RL, Brandes RW, Lewy AJ. Totally blind people with free-running circadian rhythms can be normally entrained with melatonin. Sleep Res Online 1999;2:Suppl:S624. abstract. (See http://www.sro.org/cftemplate/wfsrscongress/indiv.cfm?ID=19998624.)

23. Skene DJ, Lockley SW, Arendt J. Melatonin entrains the free-running circadian rhythms of some blind subjects. Sleep Res Online 1999;2:Suppl:S725. abstract.

24. Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J. Melatonin administration can entrain the free-running circadian system of blind subjects. J Endocrinol 2000;164:R1-R6.

25. Klein T, Martens H, Dijk DJ, Kronauer RE, Seely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep-wake schedule. Sleep 1993;16:333-43.

26. Lockley SW, Skene DJ, Arendt J. Changes in sleep in relation to circadian phase in the blind. In: Touitou Y, ed. Biological clocks: mechanisms and applications. Amsterdam: Elsevier, 1998:247-52.

27. Folkard S, Arendt J, Aldhous M, Kennett H. Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. Neurosci Lett 1990;113:193-8.

28. Sack RL, Lewy AJ. Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. J Biol Rhythms 1997;12:595-603.

29. Sack RL, Brandes RW, deJongh E, Pen SD, Nordstrom SL, Lewy AJ. The acute effects of melatonin administration on sleep in a blind man whose circadian rhythms were inverted. Sleep 1999;22:Suppl 1:S140. abstract. (See http://www.websciences.org/cftemplate/APSS99/indiv99.cfm?ID=19999490.)

30. Sack RL, Hughes RJ, Edgar DM, Lewy AJ. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? Sleep 1997;20:908-15.

31. Vision research — a national plan: 1999-2003. Executive summary. Bethesda, Md.: National Institutes of Health, 1998. (NIH publication no. 98-4288.)

32. Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a pilot study. Psychiatry Res 1998;77:57-61.