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Drew Dawson,* Naomi L. Rogers,*[,1] Cameron J. van den Heuvel,[†]
David J. Kennaway,[†] and Kurt Lushington*

*Centre for Sleep Research, Faculty of Humanities and Social Sciences, University of South Australia, Queen Elizabeth Hospital, Woodville Road, Woodville SA 5011, Australia; [†]Department of Obstetrics and Gynecology, University of Adelaide, North Terrace, Adelaide SA 5005, Australia

Abstract Previous research has suggested a role for the pineal hormone melatonin in the control of the body's sleep-wake and thermoregulatory systems. In the elderly population, there have been reports of decreased nighttime secretion of melatonin and suggestions that this may, in turn, be responsible for the increased incidence of sleep disorders reported by this age group. On this basis, it has been suggested that augmented nocturnal melatonin levels may improve sleep quality in age-related sleep disorders. Following screening assessments, 12 elderly (> 55 years) subjects with sleep maintenance insomnia were treated with either 0.5 mg transbuccal melatonin or a placebo for two sessions of 4 consecutive nights, at least 3 days apart. Subjects self-selected lights-out times, and sleep was assessed using standard polysomnographic (PSG) measures. Body temperature was measured continually from 2100 to 0700 h, and sleep quality was assessed from PSG variables measured. Nightly urine samples were assayed for the melatonin metabolite 6-sulfatoxy-melatonin (aMT.6S). Compared to the placebo, transbuccal melatonin administration significantly increased mean nocturnal aMT.6S excretion (mean ± *SEM*: 194.2 ± 16.5 vs. 42.5 ± 7.7 nmol). In addition, there was a significant reduction in core body temperature relative to the placebo condition ($p < .05$). However, sustained transbuccal melatonin treatment had no positive significant effect on any PSG measure of sleep quality. The results from the present study suggest that sustained nocturnal administration of melatonin, in the low pharmacological range, might be of limited clinical benefit in this subject population.

Key words transbuccal melatonin administration, elderly insomniacs, sleep, core temperature

INTRODUCTION

Commonly reported sleep problems in those older than 55 years of age include an increased number of awakenings across the night (Zepelin et al., 1984) and an increased time to return to sleep (Webb and Campbell, 1980; Dement et al., 1982) resulting in decreased sleep quality. Consequently, an increased incidence of

1. To whom all correspondence should be addressed.

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insomnia typically is reported for this age group. The underlying cause(s) of this age-related insomnia have yet to be identified. It has been suggested, however, that the pineal hormone, melatonin, might play a causal role in age-related insomnia.

Previous research has suggested a role for melatonin in the control of the body's sleep-wake and thermoregulatory systems (Dawson and Encel, 1993; Myers and Badia, 1995). The timing of the nightly increase in melatonin secretion has been reported to coincide with the nocturnal decline in core body temperature (Cagnacci et al., 1992) and increase in sleep propensity (Tzischinsky et al., 1993). Furthermore, exogenous melatonin has been widely reported to produce both soporific (for a review, see Wirz-Justice and Armstrong, 1996) and hypothermic (for a review, see Cagnacci, 1996) effects following administration.

Several authors have suggested that as we age, nocturnal levels of melatonin are reduced (Iguchi et al., 1982; Sack et al., 1986; Waldhauser et al., 1988). Furthermore, there have been suggestions that as we age, there is a decrease in our ability to respond to melatonin. Specifically, an attenuated hypothermic response to melatonin with increased age has been reported (Cagnacci et al., 1995). From these findings, it has been hypothesized that the age-related decrease in sleep duration and quality may result from decreased levels of endogenous melatonin and consequent attenuation of the nocturnal drop in core temperature (Zepelin and McDonald, 1987; Campbell et al., 1989; Garfinkel et al., 1995).

According to this hypothesis, exogenous replacement of nocturnal melatonin may lower nocturnal core temperature and, consequently, improve sleep quality. Although intuitively appealing, there are not yet good clinical data to support this hypothesis. Some recent studies have suggested that evening administration of oral melatonin might increase the quality and duration of nocturnal sleep in older insomniacs (MacFarlane et al., 1991; Garfinkel et al., 1995; Haimov et al., 1995; Wurtman and Zhdanova, 1995; Zhdanova et al., 1995). By contrast, other studies have reported little or no improvement following evening administration of melatonin (James et al., 1990; Singer et al., 1995; Ellis et al., 1996; Hughes et al., 1998).

This variability in results to date may, in part, reflect the pharmacology of melatonin. With a half-life less than 1 h (Vakkuri et al., 1985; Lushington et al., 1997), plasma melatonin profiles following oral administration will be significantly greater than those observed endogenously. Furthermore, low oral doses of melatonin may be rapidly cleared and no longer present during the second half of the sleep period (Vakkuri et al., 1985). Conversely, higher doses are likely to produce plasma levels far exceeding those observed endogenously and, therefore, may reflect pharmacological rather than physiological effects.

Recent developments in transbuccal delivery systems permit the administration of melatonin in a sustained manner that more closely mimics the endogenous physiological profile. Transbuccal administration of melatonin has been reported to produce sustained levels of melatonin that closely mimic the endogenous profile (Bènës et al., 1997). Furthermore, it has been reported that following transbuccal administration of melatonin, there is reduced interindividual variation in plasma levels achieved and the pharmacokinetic profiles relative to oral administration of melatonin (Bènës et al., 1997).

In the present study, transbuccal melatonin patches were administered in a double-blind placebo crossover design to elderly subjects reporting insomnia. The aim of the present study was to determine whether nocturnal melatonin replacement, using a transbuccal delivery system, would lower core temperature and improve sleep in these subjects.

METHODS

Subjects

Subjects were recruited from media advertising and selected according to the criteria for *International Classification of Sleep Disorders* (American Sleep Disorders Association, 1990) for moderate to severe psychophysiological insomnia and Waters et al. (1993) criteria for sleep maintenance insomnia. Potential subjects were those who had been suffering from sleep maintenance insomnia for at least 6 months and who reported an average of 30 min or more wake after sleep onset, with an average total sleep time of less than 6 h duration and a sleep efficiency of less than 85%. In addition, subjects had to be free of medication known to affect sleep, melatonin production, or thermoregulation. Furthermore, subjects with a habitual sleep onset time earlier than 2100 h or a final wake time earlier than 0400 h were excluded.

A total of 12 subjects older than 55 years of age (mean = 65.67 years, *SEM* = 1.68) gave informed consent to participate in the present study, which was approved by the Queen Elizabeth Hospital Committee

on Ethics of Human Research. Subjects were screened for medical and psychiatric illness and sleep disorders using questionnaires, clinical interviews, sleep diaries, actigraphy, and overnight polysomnography (PSG). None of the subjects was suffering from any concurrent medical or psychiatric illness or occult sleep disorder.

Experimental Protocol

Subjects were required to abstain from caffeine, alcohol, and medications for 24 h prior to and during the experimental procedure. Subjects participated in two experimental sessions of 4 nights each, at least 3 days apart, from 1900 to 0700 h. Between 1900 and 2100 h, subjects had electrodes attached to their faces and scalp (EEG [C3-A2, O2-A1], EMG, EOG) and had rectal probes inserted. At 1900 h, a patch containing either 0.5 mg melatonin or placebo was placed on the gums of subjects, such that melatonin and placebo were administered for 4 consecutive nights in a randomized, double-blind crossover design. Subjects retired to bed at 2100 h and participated in quiet activities until they chose to go to sleep. Subjects' self-selected times of lights out in the laboratory were not significantly different from their lights-out times at home.

Sleep Measures

EEG, EMG, and EOG were continuously recorded across the sleep period. Electrographic data were sampled at a rate of 500 Hz and stored at a rate of 250 Hz using a Medilog SAC-847 paperless EEG system (Oxford Medical, Oxford, UK). EEG data were obtained within a 70-Hz bandwidth, with a low-filter cutoff of 0.33 Hz. PSG recordings were scored manually, in 30-sec epochs, according to standard criteria (Rechtaschaffen and Kales, 1968) modified according to Webb and Dreblow (1982).

The following PSG variables were used in analysis:

Total sleep time: The amount of sleep that occurs between the time of sleep onset and sleep termination, that is, the amount of time spent asleep minus the amount of time spent awake (Stage 0), in minutes.

Sleep onset latency: The elapsed time between the recording start time (subject's self-selected sleep time) and sleep onset (3 consecutive epochs of sleep), in minutes.

REM onset latency: The elapsed time between sleep onset and the first epoch of the first REM period, in minutes.

Early morning awake: The elapsed time between sleep termination and the time the subject arose from bed.

Percentage time awake: The percentage of time spent awake (Stage 0) during the sleep period.

Sleep efficiency: The percentage of time that the subject was in bed following sleep onset that was spent asleep.

Stage changes in sleep period: The number of times the sleep stage changes during the sleep period.

Time of sleep onset: The clock time at which sleep onset occurred.

Wake after sleep onset: Summation of all the time spent in Stage 0 during the sleep period when the duration of the awakening was 5 min or greater.

Investigation of the following frequencies using spectral analysis also was performed: 0 to 4 Hz (delta waves), 4 to 8 Hz (theta waves), 8 to 12 Hz (alpha waves), 13 to 15 Hz (sigma waves), and 16 to 32 Hz (beta waves).

Body Temperature

Core body temperature was monitored continuously from 2100 to 0700 h in both experimental sessions. Temperature was sampled at 2-min intervals using a Steri-Probe 491B rectal thermistor (YSI, Yellow Springs, OH) and 4499E skin surface thermistors (YSI) attached to hands and feet, connected to a Mini-Logger ambulatory recording system (Mini-Mitter, Sunriver, OR).

Urinary Melatonin

All urine produced between 2100 and 0700 h was collected, and an aliquot was assayed to determine concentrations of the urinary melatonin metabolite 6-sulfatoxy melatonin (aMT.6S). The concentration of aMT.6S in the urine samples was determined by an adapted method using the Bhulmann Melatonin radioimmunoassay (RIA) kit, which measures melatonin by a double-antibody RIA based on the Kennaway G280 anti-melatonin antibody (Aldous and Arendt, 1988).

Statistical Analysis

Differences in nightly aMT.6S levels between the melatonin treatment and placebo conditions were compared using repeated-measures analysis of variance (ANOVA) and planned comparisons. Comparison of sleep on Nights 3 and 4 within and between each condition were compared using repeated-measures ANOVA. Differences in body temperature on Nights 3 and 4 between conditions were compared using repeated-measures ANOVA.

RESULTS

Melatonin Levels

Transbuccal melatonin administration significantly increased mean (± *SEM*) aMT.6S levels from 42.5 ± 7.7 nmol in the placebo condition to 194.2 ± 16.5 nmol in the melatonin condition ($p < .0001$) (see Fig. 1).

Sleep Measures

There was a significant night by condition effect of melatonin administration on early morning awake time ($p < .05$). There was a significant effect of melatonin administration on wake after sleep onset (WASO) ($p < .05$), where melatonin administration resulted in increased WASO in the first half of the night relative to the second half of the night, compared to placebo, on Night 4 ($p < .05$). When comparing the amount of WASO across the whole night, melatonin administration significantly increased WASO on Night 3 relative to placebo ($p < .05$); however, on Night 4, both melatonin and placebo produced comparable amounts of WASO across the whole night.

There was no significant difference between the melatonin condition and placebo condition for any other PSG sleep variable measured (see Table 1).

Investigation using spectral analysis revealed no significant effect of transbuccal melatonin administration on any waveform.

Body Temperature

There was a significant decrease in core body temperature during the melatonin condition relative to the placebo condition, $F = 6.1$, $p < .05$. In addition, there was a significant effect of time on core body temperature, $F = 2.6$, $p < .05$, which is likely to reflect the circadian variation in core body temperature (Fig. 2). It would appear that in the melatonin condition, core body temperature had started to rise and to approach the levels recorded in the placebo condition at around 0400 h.

Subjective Detection of Melatonin Administration

When questioned at the completion of the study, subjects were unable to discern when they had been administered melatonin and placebo at a rate greater than what would be expected by chance.

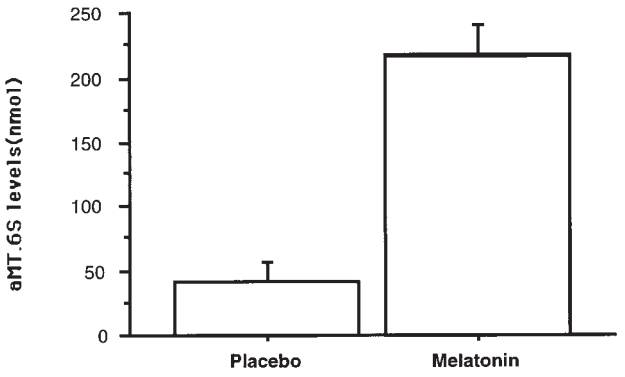

Figure 1. Difference in nocturnal urinary 6-sulfatoxy melatonin levels between the placebo and melatonin conditions. aMT.6S = 6-sulfatoxy-melatonin.

DISCUSSION

The present study examined the effects of sustained nocturnal melatonin administration, using a transbuccal patch, on elderly insomniacs. Transbuccal melatonin administration significantly increased nocturnal aMT.6S levels to approximately four times those observed in the placebo condition. In addition, a significant reduction in core body temperature was observed. There was, however, no significantly positive effect of melatonin administration on sleep.

Previous studies examining hypnotic effects of exogenous melatonin typically have administered oral melatonin capsules (James et al., 1990; MacFarlane et al., 1991; Singer et al., 1995; Zhdanova et al., 1995; Ellis et al., 1996; Reid et al., 1996; Hughes et al., 1998). In an attempt to achieve circulating plasma concentrations at, or just above, physiological levels across the sleep period, pharmacological doses have been administered. This approach, however, typically produces a pharmacological profile characterized by high initial levels of melatonin and a subsequent rapid decline. As an alternative, various sustained-release preparations have been developed. However, even sustained-release oral preparations produce high pharmacological levels in the first hours following ingestion (Garfinkel et al., 1995; Haimov et al., 1995; Singer et al., 1995). Thus,

Table 1. Difference between conditions for Nights 3 and 4.

	Placebo		*Melatonin*	
Sleep Variable	*Night 3*	*Night 4*	*Night 3*	*Night 4*
Total sleep time (minutes)	326.1 ± 25.0	218.0 ± 32.2	371.8 ± 18.6	308.5 ± 32.1
Sleep onset latency (minutes)	31.7 ± 8.9	15.3 ± 5.4	14.0 ± 3.7	13.6 ± 5.0
REM onset latency (minutes)	74.8 ± 12.5	83.5 ± 17.1	75.5 ± 23.9	74.3 ± 8.6
Early morning awake (minutes)	52.8 ± 16.8	29.0 ± 8.9	17.6 ± 7.1	36.7 ± 11.6
Percentage time awake	29.8 ± 3.9	29.7 ± 2.6	25.5 ± 3.7	30.6 ± 3.4
Sleep efficiency (percentage)	75.9 ± 3.7	72.4 ± 1.8	75.7 ± 2.7	73.2 ± 2.9
Stage changes in sleep period (number)	113.3 ± 12.1	128.2 ± 13.4	140.7 ± 16.6	115.1 ± 15.3
Time of sleep onset (time [hour] ± minutes)	22:38 ± 12.9	22:20 ± 2.3	22:18 ± 9.6	22:28 ± 7.3

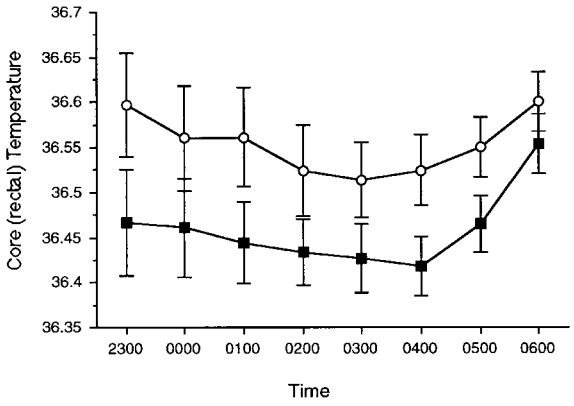

Figure 2. Difference in core (rectal) temperature measures between the two conditions (■ = melatonin, ❍ = placebo) for Nights 3 and 4.

in the majority of these previous studies, melatonin levels in the initial phase typically exceeded physiological levels by several orders of magnitude.

A nighttime profile similar to that observed endogenously can be achieved by administering melatonin via a sustained-release transbuccal patch (Bènës et al., 1997). This would appear to be a preferable approach for melatonin replacement therapies in elderly insomniacs because they typically report more sleep disruption in the second half of the night (for a review, see Bliwise, 1993).

In the present study, the aMT.6S levels in the melatonin condition were closer to physiological levels than in many of the previous studies. The average overnight production of aMT.6S was approximately 200 nmol. This is approximately double the levels reported for young adults (D. Kennaway, unpublished results) and are four to five times the endogenous nocturnal levels produced by this subject group in the placebo condition.

Despite the sustained release of melatonin across the sleep period and achieving significantly elevated aMT.6S levels, the treatment had no significant positive effect on sleep. In contrast to what may have been hypothesized, melatonin administration actually resulted in increased levels of WASO and early morning wakefulness. Whereas these effects of melatonin administration are not desirable, previous research has reported similar effects of sustained exogenous melatonin on sleep (Middleton et al., 1996).

These findings suggest that the presence of melatonin across the sleep period might not alleviate the repeated awakenings typically suffered by sleep maintenance insomniacs. Furthermore, it would appear that melatonin exacerbated the high levels of early morning wakefulness, also characteristic of this population of insomniacs. It is reasonable to speculate that in the present study, where melatonin administration commenced at 1900 h, the elevated levels of sleep disruption, in addition to the reduced core temperature in the beginning of the sleep period, might be due to a chronobiotic effect of melatonin.

Despite the lack of effect that transbuccal melatonin produced on sleep, there was a significant effect of administration on core body temperature. As can be seen in Fig. 2, there was a significant increase in the magnitude of the nocturnal decline in core body temperature in the melatonin condition.

It is of interest to note that the duration of the decreased core temperature was less than the period of melatonin administration. It is possible that melatonin does not maintain decreased core body temperature across the night but is merely a trigger for this event to occur. Because melatonin administration commenced at 1900 h, it is possible that the melatonin stimulated an earlier decrease in core temperature.

Previous research has suggested that the age-related decline in nocturnal melatonin secretion mediates an attenuated decrease in nocturnal core body temperature (Cagnacci et al., 1995). Although a clearly defined hypothermic effect has been reported for daytime ad-

ministration of melatonin in young subjects (Reid et al., 1996), this effect is less certain in older subjects. Although Cagnacci et al. (1995) reported that daytime melatonin administration (100 mg p.o.) in older subjects failed to lower oral temperature significantly, more recently, Lushington et al. (1997) demonstrated significant hypothermic and hypnotic effects for daytime oral melatonin (5 mg p.o.) in older subjects. In this study, however, the authors observed that these effects were attenuated compared to those reported previously in young subjects. In the present study, low pharmacological levels of melatonin lowered nocturnal core body temperature in these elderly insomniacs less than what typically is reported in younger subjects.

Previous studies have reported hypnotic and hypothermic effects of melatonin at pharmacological levels that are not evident at physiological levels (Dollins et al., 1994; Zhdanova et al., 1995). Therefore, the dose of melatonin administered, and hence the plasma levels achieved, may determine the effect, or at least the magnitude of effect, that is produced. It is possible, therefore, that the 0.5 mg transbuccal melatonin administered in the present study was insufficient for significant hypnotic effects to occur.

Alternatively, the reduced hypothermic effect in the present study might reflect the timing of administration. The studies just cited administered melatonin during the day when endogenous levels are low and core temperature is elevated. The hypothermic effects of melatonin might demonstrate time-of-day variation, whereby temperature may be optimally lowered during the circadian day. Consequently, administration during the circadian night would result in an attenuated decrease in core body temperature.

The period of administration also might be a determining factor. Many of the studies in which melatonin has improved sleep have used dosing periods of between 7 and 60 days (e.g., Garfinkel et al., 1995). Hence, the reported improvement in sleep quality may be mediated by melatonin's phase-shifting properties. On the basis of reported PRCs for melatonin (Lewy et al., 1992), dose durations of 7 or more days are required to achieve even modest phase changes. Furthermore, previous studies have reported that hypnotic effects of melatonin administration may take several days to manifest (MacFarlane et al., 1991; Arendt et al., 1984). Consequently, 4 nights of administration might be insufficient for either hypnotic or chronobiotic effects of melatonin to manifest in these elderly insomniacs.

It is possible that the results in the current study reflect a Type II error, that is, a failure to report a significant difference due to a small sample size. Power analysis of the current study indicates that the effect sizes that would produce a significant difference are comparable to those in other studies.

Although the present study did not find significant hypnotic effects of sustained transbuccal melatonin administration, it would appear that there are a number of factors that need to be taken into consideration when designing melatonin treatment protocols for insomniacs. As mentioned previously, there would appear to be clear differences in the response to melatonin administration between young and elderly subjects as well as in the time of day at which melatonin is administered. In addition, the dose of melatonin administered might be an important determinant of the response achieved. Therefore, future studies should be directed toward investigating the effects of these factors to determine the optimal approach for using melatonin to treat age-related insomnias. In particular, the melatonin levels at which the hypothermic and hypnotic effects emerge would appear to be an extremely critical issue. Furthermore, it would appear to be important to replicate this study using higher doses of melatonin and/or longer administration periods.

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