EFFECTS OF FAST- AND CONTROLLED-RELEASE MELATONIN FORMULATIONS ON DAYTIME SLEEP AND MOOD

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Abstract

The effects of controlled- (CR) and fast-release (FR) melatonin (2 mg) formulations on induction and quality of a 3 hour daytime nap were compared in a placebo controlled double-blind crossover study. Fatigue and mood before and after sleep were also compared. FR melatonin significantly increased sleepiness and hostility and the actigraph assessed sleep efficacy and total sleep time. The effects of CR melatonin on sleep did not significantly differ from those of the FR melatonin or placebo. Self-assessed alertness after the nap was lower after the CR melatonin compared to placebo. Sleep quality in the night following the treatment with either FR- or CR melatonin did not differ from that following placebo. These results indicate that the acute effects of melatonin on nap sleep and mood, depend on the mode of administration. They also imply that melatonin treatment at noon does not significantly suppress sleep in the following night.

Introduction

Melatonin (5-methoxy N-acetyltryptamine) secreted by the pineal gland at night has acute hypnotic effects when taken at daytime, i.e., when endogenous
melatonin levels are low (Cramer, Rudolph et al., 1974; Arendt, Borbely et al., 1984; Lieberman, Waldhauser et al., 1984; Dollins, Zhdanova et al., 1994). A recent study (Dawson, Encel et al., 1995) has shown that melatonin given 3 times daily improved daytime sleep and may permit shift workers to override the circadian system for short periods. Melatonin is short-lived in humans (Waldhauser, Waldhauser et al., 1984). Thus, it must be repeatedly administered to maintain effective doses in the blood for several hours, as indeed done by Dawson, Encel et al. (1995). We have developed a novel, controlled release melatonin formulation, which maintains effective melatonin concentrations in the blood for 5-8 hours. Here we compared its effects to those of fast-release melatonin (2 mg) or placebo on sleep quality and mood in the afternoon nap and the following night.

Methods

Ten young male volunteers (age 28 ± 2 years), healthy in body and mind who signed an informed consent participated. Study protocol was approved by the ethics committee. On a double-blind crossover basis each subject received one fast-(FR) or controlled-release (CR) tablet containing 2 mg melatonin (Circadin™, Neurim Pharmaceuticals), or placebo with identical appearance. Tablets were given at 11:00 hr on three non-consecutive days with 1 day washout period between treatments. Subjects had a nap between 12:00-15:00 hr. and night sleep from 23:30 until 07:00 the next morning.

Sleep quality during the naps and nights was estimated from activity data recorded by actigraphs (Somnitron™, Neurim Pharmaceuticals, Israel) worn on the wrist of the non-dominant hand. The amount of activity, defined as the number of zero crossings per 30-second epoch, was used to calculate the total sleep time (time from sleep onset to offset), sleep onset latency (time spent awake from bedtime to sleep onset) and sleep efficiency (% time scored as sleep from total sleep time). The Stanford Sleepiness Scale (SSS; Hoddes, Dement et al., 1973) was used to quantify the progressive stages of the sleep-alertness continuum and the Lader-Bond visual analog scales (5 cm) questionnaire was used for emotional ratings. Sleep quality during napping and night was subjectively assessed by sleep logs. After the results of the questionnaires and actigraphs were summarized, the experiment code for tablet identification was revealed. Data were analyzed separately by means of analysis of variance (ANOVA) for repeated measures with a factor of group (placebo and the two melatonin formulations) followed by t-
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tests for dependent samples. Treatment main effect for each of the reported contrasts is significant at the P<0.05 level.

Results

Nap sleep: Actigraphic recordings indicated that melatonin treatment significantly increased the nap sleep efficiency from a mean of 82% with placebo to 85% with either the FR or CR melatonin (Figure 1). Total sleep time also increased from a mean of 147 min. with placebo to 152 min. with either the FR or CR melatonin (Figure 1). These effects were significant with the FR formulation only (t(9) = 3.04, p = 0.014 and t(9) = 2.94, p = 0.016, respectively). Nap sleep latency after FR and CR melatonin (14±7 and 14±13 min. respectively) did not significantly differ from that after placebo (17±11 min.).

Figure 1: Effects of CR or FR melatonin or placebo (PLC), on mean (± SD) actigraph-derived nap sleep efficiency (a, left panel), and total sleep time (b, right panel). *p<0.05 compared to PLC (n=10).

Actigraph-assessed as well as subjects' self reported sleep quality in the night following the nap, were not significantly affected by either melatonin treatments.

Mood: No main effect was found in SSS responses to either FR or CR melatonin. The Lader-Bond questionnaire indicated that hostility and sleepiness were higher after FR melatonin than placebo (t(9) = 3.34, p = 0.009 and t(9) = 2.67, p = 0.026 respectively). The CR formulation did not have such effects. Hostility and sleepiness after CR did not significantly differ from those after placebo and were significantly lower than those after the FR melatonin (t(9) = 2.85, p = 0.019 and t(9) = 2.55, p = 0.031, respectively).

Immediately after napping subjects felt sleepier after CR melatonin than after placebo (t(9) = 3.62, p = 0.006) (Figure 3). The effect of FR did not significantly differ from that of the CR or placebo. No other effects on mood,
before or after the nap and night sleep, were found. All treatment by order interactions were non-significant.

Figure 2: (Left Panel). Effects CR or FR melatonin or placebo (PLC) on mean scores of sleepiness (a) and hostility (b) before the nap (Lader-Bond questionnaire).* p<0.05 compared to PLC (n = 10).

Figure 3: (Right Panel). Effects of CR or FR melatonin or placebo (PLC) on mean scores of alertness after nap (Lader-Bond questionnaire).* p<0.05 compared to PLC (n = 10).

Discussion
The data indicate, in agreement with previous reports on hypnotic activity of melatonin (Dollins, Zhdanova et al., 1994; Hughes, Badia et al., 1994), that acute ingestion of FR melatonin (2 mg) increases feelings of sleepiness and hostility compared to placebo. Surprisingly, the CR melatonin did not affect mood. This apparent discrepancy could be a dose-related phenomenon, since the CR induces lower melatonin levels for longer periods of time than the FR formulation. However, much lower doses (0.1–0.5 mg) of melatonin given at noon have been shown to effect mood (Dollins, Zhdanova et al., 1994; Terlo, Laudon et al., 1997). This suggests that the mood responses to melatonin may critically depend on the profile of the melatonin peak generated in the blood.

The objective measures indicated improvement in nap sleep after FR compared to placebo. The effects of CR melatonin on nap sleep did not differ statistically from those of the FR formulation, despite differences in their effects on mood. We have recently shown that in melatonin-deficient elderly people with...
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insomnia, CR melatonin improved sleep maintenance but did not significantly improve sleep latency, whereas FR melatonin shortened sleep latency but did not significantly improve sleep maintenance (Haimov, Lavie et al., 1995; Garfinkel, Laudon et al., 1995). As the same subjects took both formulations the difference in significance of the effects generated might be due to a greater variability in the effects of the CR formulation on sleep. This could be due to the different increment in the serum melatonin generated by the two formulations. Namely, peak melatonin concentrations in blood would be generated within a shorter time after administration of FR melatonin and its level would be higher than that of CR melatonin. Taken together, these data imply that the effects of the two formulations differ, although both produce blood levels sufficient to affect mood and sleep.

After the forced wake-up, the degree of alertness reported by the subjects was lower with both melatonin formulations than placebo. These effects could result from the forced wake-up before blood melatonin returned to baseline levels and from the increased nap sleep efficiency. The somewhat greater effect of the CR formulation might be the outcome of its sustained action. Interestingly, sleep quality during the night following the treatment with both melatonin formulations was not significantly poorer than after placebo. Hence, under the conditions of our experiment, there is no indication for a decline in sleep demand during a night-shift following melatonin treatment. In a recent study (Terlo, Laudon et al., 1997), we have found that induction of a 4 hour nap in the late afternoon by 1 mg FR melatonin resulted in a somewhat lower sleep efficiency in the following night. Therefore, the beneficial effect of melatonin treatment on night shift performance may be an outcome of the decrease in sleep demand. We assume that such decrease may become more pronounced if a longer nap is allowed and if the nap is delayed to the late afternoon, close to the night-shift. This possibility is currently being investigated.

References


