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Melatonin Replacement Therapy of Elderly Insomniacs

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Summary: Changes in sleep–wake patterns are among the hallmarks of biological aging. Previously, we reported that impaired melatonin secretion is associated with sleep disorders in old age. In this study we investigated the effects of melatonin replacement therapy on melatonin-deficient elderly insomniacs. The study comprised a running-in, no-treatment period and four experimental periods. During the second, third and fourth periods, subjects were administered tablets for 7 consecutive days, 2 hours before desired bedtime. The tablets were either 2 mg melatonin administered as sustained-release or fast-release formulations, or an identical-looking placebo. The fifth period, which concluded the study, was a 2-month period of daily administration of 1 mg sustained-release melatonin 2 hours before desired bedtime. During each of these five experimental periods, sleep–wake patterns were monitored by wrist-worn actigraphs. Analysis of the first three 1-week periods revealed that a 1-week treatment with 2 mg sustained-release melatonin was effective for sleep maintenance (i.e. sleep efficiency and activity level) of elderly insomniacs, while sleep initiation was improved by the fast-release melatonin treatment. Sleep maintenance and initiation were further improved following the 2-month 1-mg sustained-release melatonin treatment, indicating that tolerance had not developed. After cessation of treatment, sleep quality deteriorated. Our findings suggest that for melatonin-deficient elderly insomniacs, melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep. **Key Words:** Melatonin administration—Elderly—Actigraph—Sustained-release—Fast-release.

Melatonin, an indoleamine secreted by the pineal gland at night, has been implicated in the regulation of the sleep–wake cycle (1,2). Early studies suggested sedative effects of melatonin administered to humans in pharmacological and supraphysiological dosages (3 and references cited therein). Exogenous melatonin was also shown to exert synchronizing effects on circadian rhythms: it phase-advanced sleep of patients suffering from a delayed sleep phase syndrome (4,5), facilitated the post-flight adaptation to jet-lag (6) and synchronized the sleep–wake cycles of blind patients to the environmental light/dark cycles (7–9). Nocturnal rise in the secretion of endogenous melatonin was correlated with the timing of the sleep gate in normals (10) and in a free-running blind man (9). The sedative hypnotic effects of melatonin were consistently observed for daytime administration, i.e. when circulating plasma melatonin levels are low (11–16). However, at nighttime, when endogenous melatonin levels are higher, additional sedative hypnotic effects were not observed (17,18).

Previously, we reported that impaired melatonin secretion is associated with sleep disorders in old age. Circulating melatonin levels have been found to be significantly lower in elderly insomniacs than in age-matched controls, and their onset and peak times delayed (19).

In the present study we investigated the effect of melatonin treatment on melatonin-deficient insomnia in the elderly. In view of our findings, we hypothesized that these elderly insomniacs could benefit from melatonin replacement therapy.

Previous studies investigating the effects of melatonin treatment have used gelatine capsules containing melatonin, allowing the fast release of the hormone into circulation. However, melatonin has an estimated half-life between 35 and 50 minutes and is rapidly eliminated (20), while in a human study of the plasma

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TABLE 1. *Number of subjects participating in each part of the study*

Experimental period	Elderly population (n)		
	Without sleep disorders	Independently living insomniacs	Institutionalized insomniacs
Baseline 1 week	25	8	18
Placebo 1 week		8	18
2 mg melatonin fast-release 1 week		8	18
2 mg melatonin sustained-release 1 week		8	18
1 mg melatonin sustained-release 2 months		5	12
Withdrawn for 3 months			9

pharmacokinetics of melatonin it was shown that slow-release preparation (2 mg) is able to extend high plasma melatonin for 5–7 hours (21). Thus, we used a sustained-release melatonin in order to restore melatonin levels in the elderly throughout the night. We report here on the effects of fast- and sustained-release melatonin administered nightly on sleep in the elderly insomniacs.

METHOD AND DESIGN

Subjects

The study population comprised three groups: i) independently living insomniacs (eight patients: four male, four female; aged 73.1 ± 3.9 years); ii) institutionalized insomniacs (18 patients: six male, 12 female; aged 81.1 ± 8.9 years) living a minimum of 6 months in a nursing home; iii) elderly without sleep disorders (25 patients: 19 male, six female; aged 71.4 ± 5.2 years) living independently in the community. The purpose of recording the elderly group without sleep disorders was to validate the subjective complaints of insomnia. This group was not included in the treatment part of the study. These subjects overlap with those in our previous report of sleep disorders and melatonin rhythm in the elderly (19). The insomnia patients (the independently living insomniacs and the institutionalized insomniacs) were considered "melatonin-deficient" because they had significantly lower peaks of secretion than did the elderly without sleep disorders [1.8 ± 0.2 μg/hour, 0.6 ± 0.1 μg/hour and 3.3 ± 0.4 μg/hour, respectively (analysis of variance [ANOVA]), $F(2,48) = 15.47$, $p < 0.0001$]. All subjects were in good clinical condition, and none met any criteria for dementia or depression according to the Mini-Mental State Examination (MMSE) (22) or the Hamilton rating scale (23). Subjects were personally interviewed by an experienced physician to rule out significant sleep apnea syndromes which could be related to physiologically based insomnia, or any medical illness that might interfere with sleep. None of the subjects used any medication that could affect sleep or the noradrenergic system for at least 1 month prior to the study. Because in the International Classification of Sleep Disorders (ICSD) (24) there is no diagnosis of insomnia in the elderly, we accepted volunteers if they reported sleeping poorly on at least 3 nights per week and if their insomnia had lasted for a minimum of 6 months. Volunteers also had to report that their insomnia clearly affected their daytime functioning, that it was not caused by chronic pain or any known medical disease and that the volunteer did not use either alcohol or drugs that might affect sleep. Volunteers were then sent a number of questionnaires, including a one-week sleep log, a mini-sleep questionnaire (MSQ) (25) and the Technion Sleep Questionnaire.

Experimental paradigm

The study comprised one 7-day, running-in, no-treatment period, followed by three 7-day experimental periods, during which subjects were administered tablets 2 hours before desired bedtime. The tablets were either 2 mg melatonin administered as sustained-release (S-1w) or fast-release (F-1w) or an identical-looking placebo (PL). These treatments were randomly assigned and conducted in a double-blind procedure. Between each experimental period there was a washout period of at least 2 weeks to exclude the possibility of carryover effects. During the fifth period a long-term, low dosage of sustained-release melatonin was administered in order to determine whether any tolerance or side effects to this replacement therapy exist. During this period, 17 out of the 26 insomnia patients were administered 1 mg sustained-release melatonin (S-2m) for 2 months, 2 hours before desired bedtime. During this treatment, patients were unaware of whether they received placebo or melatonin. In nine institutionalized insomniacs, sleep–wake patterns were monitored for 3 months after melatonin treatment was withdrawn (Table 1). During each of these six experimental periods, a subject's sleep was continuously monitored for 1 week by miniature actigraphs worn on the wrist which enabled monitoring of sleep under natural circumstances, with minimal distortions. In the 2-month treatment period, sleep–wake patterns were monitored during the last week of the treatment period.

The actigraph measures wrist activity utilizing a piezoelectric element, and translates wrist movements into an electrical signal which is digitized and memorized. Recordings were analyzed by an automatic algorithm as previously described (26) to determine sleep duration (total number of minutes defined as sleep),

sleep efficiency index (% of sleep duration out of total bedtime), sleep latency (time to fall asleep from bedtime) and mean activity level (the mean sum of actigraphic movements recorded during sleep divided by sleep duration). Activity level during sleep can be viewed as an index of the restfulness of the sleep period.

Data analysis

The statistical analysis of the subjects' sleep was based on the actigraphic parameters from the continuous 1-week monitoring in each experimental period. In order to eliminate night-to-night variability, the actigraphic parameters were averaged across the 7 consecutive nights for each subject, in each experimental period.

The actigraphic parameters were analyzed by repeated measures ANOVA and by t test (two-tailed). Post hoc Duncan tests were used to determine treatment differences.

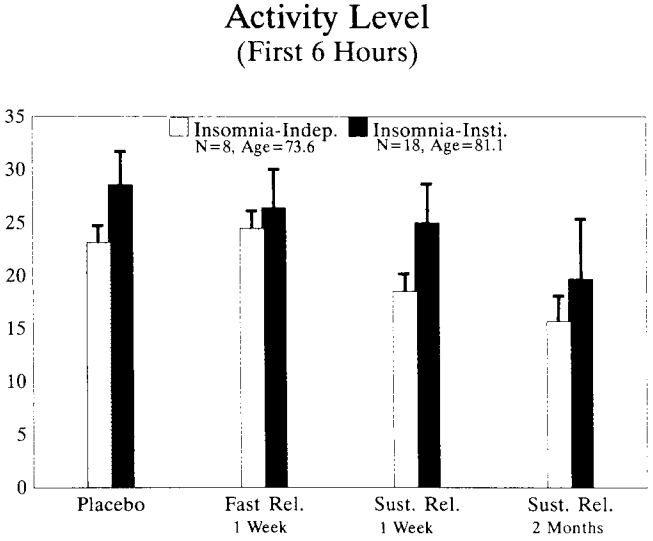

FIG. 1. Activity level of the two insomniac groups in the four experimental periods. There were significant differences between sustained-release melatonin for 2 months and all other treatments.

RESULTS

Actigraphic sleep parameters

In order to validate the subjective sleep quality, we compared the sleep maintenance (sleep efficiency and activity level during sleep) of those who complained of sleep disorders with that of those who did not, during the 1-week, running-in, no-treatment period, by actigraphic measurements. Two-sample t test (two-tailed analysis) revealed statistically significant differences in sleep efficiency and in activity level between the group of elderly without sleep disorders and the combined insomniac group [88.16 ± 1.12 ($\bar{x}$ ± SE) vs. 77.3 ± 1.96, $t_{49} = 4.32$, $p < 0.0001$; 13.05 ± 1.19 vs. 26.9 ± 2.67, $t_{49} = 4.40$, $p < 0.0001$, respectively]. Insomniacs had lower sleep efficiency and increased activity during sleep. There were no significant differences in sleep efficiency and activity level between the institutionalized insomniacs and the independently living insomniacs (76.7 ± 2.66 vs. 79.03 ± 3.39, $t_{24} = 0.31$, $p < 0.58$; 28.6 ± 3.62 vs. 23.16 ± 2.79, $t_{24} = 0.81$, $p < 0.42$).

For the two insomniac groups, there were between-group differences in sleep duration because institutionalized insomniacs had earlier bedtimes than did independently living insomniacs (2123 ± 0015 hours vs. 2414 ± 0009 hours; $t_{24} = 4.40$, $p < 0.001$). Therefore, to assess the efficacy of melatonin on sleep quality, the effects of melatonin treatment were studied during the first 6 hours after sleep onset. Repeated measures ANOVA showed that sleep duration was not influenced by melatonin treatment within each group ($F = 0.19$, df = 3,63, $p > 0.91$).

Repeated measures ANOVA of the first 6 hours in the first three 1-week periods (PL, F-1w, S-1w) revealed significant differences in activity level ($F = 3.78$, df = 2,48, $p < 0.03$), and in sleep efficiency ($F = 3.95$, df = 2,48, $p < 0.05$) (Fig. 1). Post hoc Duncan tests revealed significant differences in sleep efficiency and in activity level between S-1w and PL groups (80.4 ± 1.82 vs. 77.4 ± 1.96, 23.0 ± 2.53 vs. 26.9 ± 2.67, respectively). There were no significant differences between the F-1w (78.8 ± 1.75, 25.8 ± 3.77) and S-1w groups nor between the F-1w and PL groups.

Repeated measures ANOVA of the same variables with the addition of the S-2m treatment revealed significant improvement in sleep efficiency and activity level ($F = 6.27$, df = 3,63, $p < 0.0008$; $F = 6.66$, df = 3,63, $p < 0.0006$, respectively). Post hoc Duncan tests revealed significantly higher sleep efficiency (84.3 ± 2.26) and lower activity level (18.6 ± 3.03) after 2 months of 1-mg sustained-release melatonin treatment compared with the respective parameters after 1-week treatment (Table 2 and Fig. 1). For a demonstrative case see Fig. 2.

We were able to determine sleep latency only for the independent elderly groups. Repeated measures ANOVA of the independent elderly insomniacs revealed borderline statistically significant differences in sleep latency in the three 1-week experimental periods ($F = 3.37$, df = 2,14, $p < 0.06$) (Fig. 3). Post hoc Duncan tests revealed shorter sleep latency in the F-1w group than in the PL group (32 ± 7 minutes vs. 54 ± 13 minutes), and no difference in sleep latency between the F-1w and S-1w (37 ± 11 minutes) groups, nor between the slow-release and PL groups. Repeated

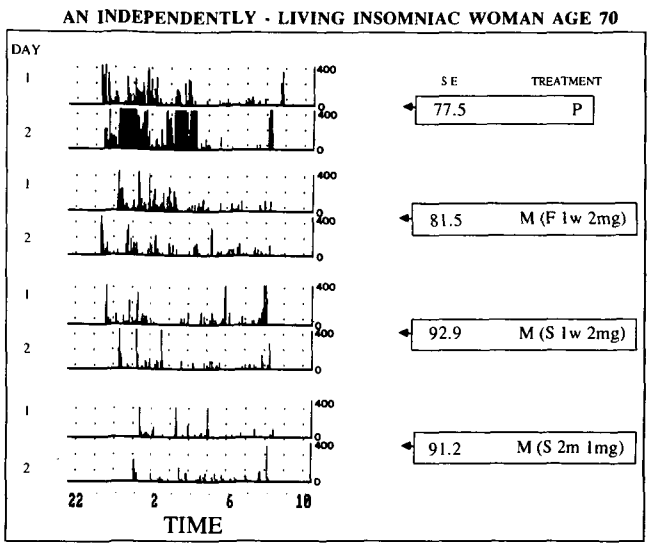

FIG. 2. Coresponding data of actigraphic recordings of an independently living insomniac woman, from lights-off until lights-on during the four experimental periods: three 7-day experimental periods during which subjects were administered 2 mg sustained-release (S-1w) or fast-release (F-1w) melatonin, or an identical-looking placebo (PL), followed by a 2-month period of 1 mg sustained-release melatonin (S-2m).

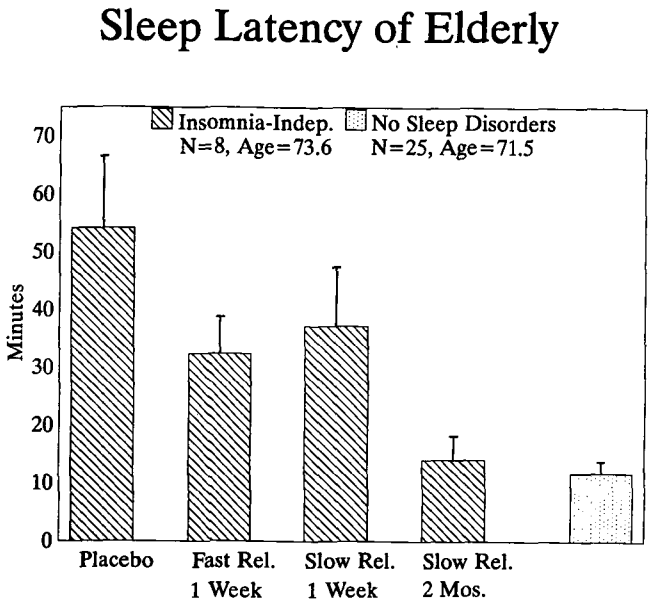

FIG. 3. Sleep latency of the insomniac elderly in the four experimental periods. For significant differences see text.

measures ANOVA with the addition of the 2-month treatment revealed a significant difference in sleep latency ($F = 3.02$, df = 3,18, $p < 0.05$). Post hoc Duncan tests revealed that sleep latency after 1 week's treatment with fast-release was equivalent to 2 months' treatment with sustained-release (14 ± 5 min) (Table 2 and Fig. 3). Two-sample t test (two-tailed) revealed no significant differences in sleep latency between the insomnia patients after 2 months of melatonin treatment and the elderly without sleep disorders (12 ± 2 minutes; $t_{29} = 0.23$, $p > 0.81$) (Fig. 3).

The sleep disorders reappeared after melatonin treatment was withdrawn for 3 months in the nine patients who were examined. Paired t test (two-tailed) revealed a borderline statistically significant difference in sleep efficiency between subjects undergoing 2 months of 1-mg sustained-release melatonin treatment and subjects in the withdrawal period (76.02 ± 1.47; $t_8 = 2.05$, $p < 0.07$), while there was no statistical difference in sleep efficiency between the placebo group and subjects in the withdrawal period ($t_8 = 0.04$, $p > 0.97$).

DISCUSSION

In the present study, we investigated the effect of melatonin treatment on melatonin-deficient insomnia

TABLE 2. *Sleep characteristics and ANOVA results of comparisons between the four treatments of the insomniac patients*

		Melatonin treatment			ANOVA		
Variable	Placebo	2 mg fast-release 1 week	2 mg sustained-release 1 week	1 mg sustained-release 2 months	F	p	Difference
Sleep efficiency	77.4 (1.9)	78.8 (1.7)	80.41 (1.8)	84.3 (2.3)	6.27	0.0008	PL = F-1w F-1w = S-1w PL < S-1w < S-2m
Activity level	26.9 (2.6)	25.8 (3.8)	23.0 (2.5)	18.6 (2.5)	6.66	0.0006	PL = F-1w F-1w = S-1w PL > S-1w > S-2m
Sleep latency (min)[a]	54 (13)	32 (7)	37 (11)	14 (5)	3.02	0.05	PL = S-1w F-1w = S-1w F-1w = S-2m < PL

[a] Only for the independently living insomniacs.

Abbreviations used: PL, placebo; S-1w, sustained-release melatonin 1 week; F-1w, fast-release melatonin 1 week; S-2m, sustained-release melatonin 2 months.

SEM in parentheses.

in the elderly. To our knowledge, this is the first report examining the therapeutic effect of melatonin on the elderly population. The experimental paradigm of this study was very long and included multiple trials (Table 1). Our complicated methodology may explain why some patients dropped out during the course of the study.

Our results suggest that melatonin replacement therapy, using a low dosage (1 or 2 mg) of melatonin, has specific effects on sleep initiation and maintenance in these patients.

A 1-week treatment of 2 mg sustained-released melatonin was effective on sleep maintenance (i.e. sleep efficiency and activity level) of elderly insomniacs, while sleep initiation was improved after a 1-week, fast-release melatonin treatment.

Based on these findings, we continued with a long-term, low dosage (1 mg) of sustained-release melatonin. In this preliminary study, sleep efficiency and activity level were improved significantly compared with the 1-week treatment of 2 mg fast- and sustained-release melatonin, while sleep initiation improvement was equivalent to that in the 1-week fast-release treatment. The beneficial effect of fast-release tablets on sleep initiation may come from the high amount of melatonin released immediately after administration, while the benefit of the sustained-release tablets comes from the release of melatonin in small dosages during the entire night. The fact that sleep initiation was improved upon long-term treatment with sustained-release melatonin suggests stabilization of the sleep–wake cycle in melatonin-deficient elderly insomniacs. In addition, these data indicate that, at least during the experimental period, the efficacy of the treatment did not deteriorate.

Because we did not attempt long-term treatment with fast-release tablets, the possibility that long-term treatment with fast-release melatonin may be effective in this respect cannot be refuted at this stage. Another caveat that should be taken into account is the lack of comparable placebo control, which could not be ethically justified. However, as sleep disorders reappeared after melatonin treatment was withdrawn, this strengthens our conclusion that long-term melatonin treatment was effective in initiating and maintaining sleep.

There have been only two reports examining the possible therapeutic benefits of fast-release melatonin in the treatment of insomnia in young subjects. James et al. (27) reported that following acute 1- and 5-mg doses of fast-release melatonin administered to young chronic insomniacs, no changes in either the duration or onset of sleep were observed, while the subjective perception of overall sleep quality was improved. MacFarlane et al. (28) reported that administration of 75 mg melatonin for 7 consecutive days showed a significant increase in subjective assessment of total sleep time but no effect on the subjective feeling of well-being. In neither of these studies was there any evidence of blunted rhythm of melatonin secretion. In a pretreatment study of our elderly insomniacs, we did investigate the rhythm of melatonin secretion and found them to have a deficiency in melatonin secretion during the night (19).

This study suggests two important principles of melatonin replacement therapy of melatonin-deficient, elderly insomniacs: i) melatonin appears to have a beneficial effect when administered in the form of sustained-release tablets and ii) to ensure efficacy, long-term treatment is recommended.

In conclusion, melatonin deficiency seems to be a key variable in the incidence of sleep disorders in the elderly. From the results of the present study, it seems likely that melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep in this population. Further studies employing the chronic administration of melatonin, in varying dosages of different preparations, and the investigation of their effects by segmenting the long-term treatment into intervals must be pursued before determining the most efficient melatonin replacement therapy for elderly insomniacs.

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