Melatonin Treatment for Insomnia in Parkinson’s Disease: A Pilot Study

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Complaints of insomnia are common in patients with Parkinson’s disease (PD). Melatonin has been shown to improve insomnia in some populations but has not been well studied in patients with PD. The primary aims of this pilot study were to assess endogenous melatonin secretion in PD patients by determining the time of dim-light melatonin onset (DLMO), and to compare the effect of exogenous melatonin (5 mg) therapy with placebo on nocturnal sleep in patients who complained of insomnia. A double-blind, placebo-controlled, cross-over trial was employed. Subjects (n=8) with PD and no evidence of depression, cognitive impairment, or primary sleep disorders participated in the 4-week protocol. During a 1-week treatment period, subjects took melatonin (5 mg) or placebo capsules (administered in random order) 30 minutes before bedtime, with a 1-week washout between treatments. DLMO was determined by RIA of blood samples. Nocturnal sleep was assessed by actigraphy. Subjective sleep quality was assessed with daily diaries and a weekly questionnaire. The mean DLMO was 21:05. During the melatonin treatment week there was a nonsignificant decrease in nocturnal wake time (20 minutes) and an increase in sleep efficiency (3%). Six subjects (75%) reported that they slept better during the melatonin treatment week. Results of this pilot study do not indicate that melatonin administration improves objective sleep in PD patients who complain of insomnia.

CURRENT CLAIM: Melatonin did not significantly improve quality of sleep in people with Parkinson’s disease.

METHODS

Subjects

Eight men diagnosed with PD, mean age 65.6 years (SD=7.1, range 56-74), and mean disease duration since diagnosis of 5.5 years (SD=3.2, range 0.3-10.4) participated in this double-blind, placebo-controlled, cross-over design study. Only men were enrolled due to the small nature of this pilot study and the effect of gender on sleep (Bliwise, 2000). The extent of disability was graded on the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). This instrument is widely used both clinically and in research to evaluate PD patients.
assess the overall functional status of patients with PD. Subjects had an average score of 8.5 (range 0-18) on the UPDRS Activities of Daily Living Scale (Part 2) and a score of 30.3 (range 16-45) on the Motor Scale (Part 3). The average Hoehn and Yahr Scale score was 2.3 (SD=0.7, range 1-3) with an average Schwab and England Activities of Daily Living Scale score of 86% (SD=12%, range 70-100%). All subjects were maintained on stable doses of antiparkinsonian medications during the course of the study and had taken levodopa for an average of 4.3 years (SD=3.5, range 0-10). Specific daily medications and dosages for each subject are described in Table 1.

Subjects were screened for depression, since this aspect of PD can contribute to sleep disturbance (Aldrich, 2000). All Geriatric Depression Scale scores (long form; Yesavage et al., 1983) were within the normal range with a mean of 3.5 (SD=2.3, range 1-7). A self-rating questionnaire for measuring subjective sleep quality during the preceding 1-month period, the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), was used at enrollment. Global scores >5 indicate severe sleep problems. The mean PSQI global score for this sample was 12.5 (SD=4.1, range 6-17). While the PSQI scores for all subjects indicated severe sleep problems, none of the subjects responded positively to the questions about snoring, being unable to breathe comfortably, or long pauses between breaths. Two subjects did report leg twitching or jerking while they slept one or more times per week. The study protocol had prior approval of our institution’s Committee on Human Research, and written informed consent was obtained from all subjects.

Experimental Paradigm

A double-blind, placebo-controlled, cross-over trial was employed. Subjects were admitted to the General Clinical Research Center approximately five hours before their usual bedtime for the DLMO assessment. Blood sampling began four hours before usual bedtime and continued at 30-minute intervals until awakening the next morning. A special blood drawing system was used with a double stopcock and long tubing that was placed behind a curtain so that subjects were not disturbed during the nighttime blood draws. To minimize masking, subjects were maintained in dim light conditions (<50 lux) beginning four hours before bedtime and throughout the night. The remainder of the protocol was carried out in subjects’ own homes. During the 4-week protocol, Week One served as a run-in period and provided baseline data and information about the ability of the subject to adhere to the experimental protocol. Subjects who successfully completed Week One were randomized to continue in Week Two, during which they took either melatonin or placebo tablets 30 minutes before bedtime. Week Three served as a washout, and during Week Four subjects received either melatonin or placebo tablets (whichever they did not receive in Week Two). Sleep-activity data were collected by wrist actigraphy (Ambulatory Monitoring, Inc., Ardsley, NY). Subjects also kept daily diaries to provide additional subjective data (e.g., sleep satisfaction, subjective estimates of sleep duration and quality, nap times) and completed the General Sleep Disturbance Scale (GSDS) weekly (Lee, 1992).

Data Analysis

The statistical analyses of subjects’ sleep were based on actigraphic data from the continuous one-week monitoring in each experimental period. Recordings were analyzed using the Action III™ and Action W™ software. Data were averaged across the seven consecutive days for each subject to minimize night-to-night variability. DLMO was operationally defined as the clocktime when the evening onset of plasma melatonin reached 25% of its nighttime peak (Hughes et al., 1998).

RESULTS

Radioimmunoassay (Melatonin direct 125I RIA; Elias USA, Inc.) of blood samples revealed an average DLMO of 21:05 (range 18:40-24:00), an average peak endogenous melatonin concentration of 48 pg/ml (SD=31, range 12-101) and an acrophase of 02:41 (SD=2:23, range 23:30-07:30). Subjects’ average habitual bedtime was 23:15 (range 21:45-01:30) with the average DLMO occurring 2 hours and 20 minutes prior

<table>
<thead>
<tr>
<th>Antiparkinsonian Medication</th>
<th>Subject Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Dose</td>
<td>1</td>
</tr>
<tr>
<td>Levodopa (regular)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Levodopa (controlled release)</td>
<td>800 mg</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>–</td>
</tr>
<tr>
<td>Perigolide</td>
<td>–</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>–</td>
</tr>
<tr>
<td>Selegiline</td>
<td>10 mg</td>
</tr>
<tr>
<td>Symmetrel</td>
<td>200 mg</td>
</tr>
</tbody>
</table>
The level of melatonin production decreases with advancing age (e.g., Sack et al., 1986), beginning in the second or third decade (e.g., Kennaway et al., 1999; Touitou, 2001). Hughes et al. (1997) characterized people with levels of <15 pg/ml as "low" producers in a group of older subjects (mean age 67 years) with sleep maintenance insomnia; one of our subjects met this criteria (12 pg/ml) but the remaining seven subjects fell within the defined "normal" producer range (25-101 pg/ml). However, seven of our subjects fell well below the normal nocturnal range of 112.6±13.5 pg/ml reported for younger subjects (Zhdanova et al., 1996). Given the variability in literature reports, it is difficult to speculate as to whether this group of patients with PD and complaints of insomnia are similar to or different from similarly aged subjects with insomnia but not PD.

A one-week treatment period in this sample of patients with PD did not significantly improve sleep efficiency (3%). The small sample size (n=8) in our study may have contributed, in part, to the small effects. The principal criteria for inclusion in this pilot study was subjective perception of a sleep disturbance and diagnosis of PD, but disease duration and severity, duration and amount of treatment, age, and severity of sleep disruption varied between subjects.

Additionally, although a 5 mg dose of melatonin administered over one week minimally improved sleep, a longer duration of treatment or a higher dose might produce a more robust effect. For example, three weeks of treatment with a 2 mg controlled release melatonin preparation (Garfinkle et al., 1995) resulted in a 7% increase in sleep efficiency and a 24-minute decrease in wake after sleep onset in elderly subjects. Haimov et al. (1995) also reported higher sleep efficiency and lower nighttime activity in elderly insomniacs after a two-month treatment course. Singer et al. (1995a) found a 6% increase in sleep efficiency and a 19-minute decrease in waketime after sleep onset in PSG-monitored sleep in eight healthy elderly persons after nightly treatment with 50 mg melatonin for 16 nights. No effect was obtained from a low physiologic melatonin dose (0.2 mg sustained release) under identical conditions (Singer et al., 1995b). A study by Hughes et al. (1998) also showed that low doses of melatonin (0.5 mg) shorten sleep latency but do not affect measures of sleep maintenance in elderly people with sleep-maintenance insomnia. Dawson and et al. (1998) found similar results for sustained transbuccal melatonin treatment. Although these studies were small, they suggest that melatonin is unlikely to increase sleep continuity measures unless given in doses of at least 2 mg, and that even at very high doses, the effect on sleep maintenance is modest in older adults.

The results of this pilot work did not provide support for the contention that melatonin treatment improves sleep. However, there was a 20 minute nonsignificant decrease in nocturnal waketime with a concomitant increase in sleep efficiency; and 75% of subjects reported sleeping better during the melatonin treatment week. Expanding upon these findings, we are currently employing more stringent inclusion/exclusion criteria.

**DISCUSSION**

The results of this pilot work did not provide support for the contention that melatonin treatment improves sleep. However, there was a 20 minute nonsignificant decrease in nocturnal waketime with a concomitant increase in sleep efficiency; and 75% of subjects reported sleeping better during the melatonin treatment week. Expanding upon these findings, we are currently employing more stringent inclusion/exclusion criteria.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Melatonin</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep-onset Latency (in minutes)</strong></td>
<td>9±13 (0-36)</td>
<td>9±2 (0-7)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Total Sleep Time (in minutes)</strong></td>
<td>325±92 (186-476)</td>
<td>337±107 (184-489)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset (in minutes)</strong></td>
<td>120±73 (17-199)</td>
<td>101±50 (19-176)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Number of Night-time Awakenings</strong></td>
<td>13±7 (3-20)</td>
<td>13±5 (6-20)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Duration of Each Awakenings (in minutes)</strong></td>
<td>10±4 (4-16)</td>
<td>8±4 (3-16)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Sleep Efficiency</strong></td>
<td>73±17% (48-97%)</td>
<td>76±14% (51-96%)</td>
<td>0.25</td>
</tr>
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</table>

Paired *t*-test analyses of actigraphy data (Table 2) revealed a nonsignificant decrease in nocturnal waketime during the melatonin treatment of approximately 20 minutes. Mean sleep efficiency (SE) (minutes sleep/total minutes nocturnal sleep episode) increased 3% (ns) with 63% of subjects experiencing increases ranging from 3-16%. Mean sleep-onset latency decreased from 9 minutes on placebo to 2 minutes on melatonin (ns) with 63% of subjects experiencing decreases ranging from 2 to 32 minutes. Of particular interest was the decrease in sleep-onset latency variability during the melatonin treatment so that no subject took longer than 7 minutes to fall asleep (SD=13, range 0-36 placebo; SD=2 range 0-7 melatonin). There was no significant change in the number of nighttime awakenings or the duration of each awakening during the melatonin treatment week.

Subjective data analysis revealed that GSDS scores were not significantly different during the placebo (47.4±18.2, range 23-81) and melatonin (49.0±20.4, range 24-80) weeks. The most commonly reported reason for awakening was a "full bladder." The majority of subjects (75%) reported that they "slept better" during the melatonin week. That is to say, the majority of patients could discriminate between placebo and melatonin. Thus, despite a lack of statistical significance, the observed differences in sleep were clinically significant as judged by the subjects. Subjects reported no adverse events during the experimental protocol.
(e.g., sleep efficiency <80% at baseline) to ensure a more homogeneous sample, testing a higher pharmacologic dose (e.g., 50 mg in addition to 5 mg) and longer duration of treatment in a larger sample. This should facilitate better assessment of the clinical efficacy and tolerability of melatonin as a therapeutic agent to treat sleep disruption in patients with PD.

ACKNOWLEDGMENTS

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REFERENCES


