Beneficial Effects of Ramelteon on Rapid Eye Movement Sleep Behavior Disorder Associated with Parkinson’s Disease - Results of a Multicenter Open Trial

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Abstract

Objective Melatonin is effective for treating patients with rapid eye movement sleep behavior disorder (RBD). Ramelteon, a novel hypnotic, acts as a melatonin receptor agonist. In the current study, we investigated the effects of ramelteon on sleep disorders, including RBD, in patients with Parkinson’s disease (PD).

Methods We evaluated 35 patients from multiple centers with idiopathic PD accompanied by sleep disturbances (age: 69.1±11.1 years; 17 men, 18 women; PD morbidity: 6.9±5.7 years; Hoehn & Yahr stage: 2.5±0.8; levodopa dose equivalent: 561±401 mg/day). The patients received 8 mg of ramelteon before sleep once daily for 12 weeks. Motor and sleep symptoms were evaluated both before and after ramelteon administration.

Results Of the 35 patients enrolled in this study, 24 (68.6%) were diagnosed with probable RBD (pRBD) using the Japanese version of the RBD screening questionnaire. Ramelteon administration reduced the severity of sleep disturbances in patients with PD. It also lowered scores on the Japanese version of the RBD questionnaire in patients with PD and pRBD.

Conclusion Ramelteon may have beneficial effects on sleep disturbances, especially on RBD in patients with PD.

Key words: ramelteon, REM sleep behavior disorder, RBD, sleep disturbance, clinical trial, Parkinson’s disease


Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by vigorous, injurious behaviors related to vivid, action-filled, violent dreams during nocturnal REM sleep (1). RBD has been frequently described during the course of synucleinopathies, including Parkinson’s disease (PD) and multiple system atrophy (MSA) (2). In terms of treatment, clonazepam is the standard first-line therapeutically used for RBD. Moreover, guidelines for the treatment of idiopathic RBD recommend a combination of clonazepam and melatonin as a level B treatment (3). However, patients with synucleinopathies experience adverse effects of clonazepam such as falls, drowsiness and aggravation of obstructive sleep apnea; thus, effective therapeutics with fewer adverse effects are needed.

Ramelteon is a melatonin receptor agonist that has been approved in Japan as a hypnotic to treat insomnia (4). Because melatonin and ramelteon have relatively few adverse side effects, they have both proven useful in the elderly population, especially in patients with neurological disorders (5). To date, only one randomized controlled trial has reported beneficial effects of melatonin on RBD (6). Several
open and retrospective trials (7-11) have also suggested that melatonin has beneficial effects on idiopathic and/or secondary RBD. Moreover, Nomura et al. (12) reported that ramelteon was effective in treating patients with secondary RBD complicated by PD or MSA. Therefore, melatonin agonists may prove beneficial in treating RBD in patients with PD with fewer adverse effects. In order to confirm this hypothesis, we conducted an open trial across multiple institutes where we administered ramelteon to patients with PD and sleep disorders including RBD.

Materials and Methods

Patients

This study was performed at the department or division of neurology of four institutes: Okayama Kyokuto Hospital, Tottori University, the Research Institute for Brain and Blood Vessels-Akita and Fukuoka University. The ethics committee of each institute provided approval for this study. We enrolled patients with idiopathic PD accompanied by any sleep disturbance between July 1, 2013, and June 30, 2014. The diagnosis of PD was made according to the criteria of the UK Brain Bank (13). The exclusion criteria were as follows: patients who were 85 years or older or 50 years or younger, patients who might be pregnant or breastfeeding, and patients who had severe complications. Written informed consent was obtained from each patient prior to the study.

Participants were started on once-daily oral treatment of 8 mg of ramelteon, which was administered before sleep for 12 weeks. The dosing and timing of its administration were determined following the reported usage and therapeutic equivalent of ramelteon approved by the Ministry of Health, Labour and Welfare, Japan. Participants were required to maintain the same dosage of all medications, except ramelteon, that they had been taking at the time of their entry into the study.

Evaluation of motor and non-motor symptoms

Motor and non-motor symptoms, including sleep disorders of these patients, were evaluated before (baseline) and at the end of ramelteon therapy (week 12) via an interview by an experienced neurologist. To evaluate these symptoms, we used Hoehn and Yahr staging, the Unified PD Rating Scale (UPDRS) part III (14, 15), Mini-Mental State Examination (MMSE) (16), Frontal Assessment Battery (FAB) (17), Hamilton Rating Scale for Depression (HAM-D) (18), Schwab & England ADL Scale (19), Pittsburgh Sleep Quality Index (PSQI) (20), PD Sleep Scale Version-2 (PDSS-2) (21, 22) and the Japanese Version of the RBD Questionnaire (RBDSQ-JP) (23, 24) to evaluate the severity of RBD. In several patients who gave consent for more frequent measurements, these items were evaluated every four weeks (before and 4, 8 and 12 weeks after starting ramelteon).

For the PSQI, the total score was calculated along with the score for the following seven subcomponents: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction (20). All subcomponents were analyzed separately. The PDSS-2 consists of 15 questionnaires about various sleep and nocturnal disturbances, which are rated by patients using one of five categories: 0 (never) to 4 (very frequent). The total score of the PDSS-2 ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance). We analyzed the significance of ramelteon-induced changes in the total PDSS-2 score and scores for three sub-categories, namely, motor symptoms at night, PD symptoms at night and disturbed sleep (21).

The Japanese version of the RBD screening questionnaire (RBDSQ-J) (25, 26) was used to detect patients with probable RBD (pRBD). Patients with PD and an RBDSQ-J score of 6 or over were diagnosed with pRBD. Aversive events were also simultaneously checked with the evaluation of clinical symptoms.

Statistical analysis

In order to analyze the effects of ramelteon on motor and non-motor symptoms including sleep disorders, we employed a paired type of analysis by using the Friedman test followed by the Wilcoxon signed-rank test. Differences in age, disease duration and levodopa equivalent dose of dopaminergic drugs (LEDD) (27) among patients with PD, both with and without RBD, were calculated using a t-test. Sex differences among the groups were analyzed by a $\chi^2$-test. Differences in motor and sleep disorders among patients with PD with and without RBD were calculated using a Mann-Whitney U-test. A p value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS Statistics, ver. 17.0 for Windows, SPSS Inc., Tokyo, Japan).

Results

Forty-four patients with PD were enrolled in the first investigation. Among them, 35 patients (79.5%) completed this study. Six patients stopped taking ramelteon due to adverse effects, which included excessive daytime sleepiness (one patient), nausea (one patient), lightheadedness (one patient), delirium (one patient) and worsening of constipation (one patient), or due to an unknown adverse effect (one patient). An additional three patients discontinued their participation in the study because they stopped visiting our institutes due to either a traffic accident or relocation (two patients).

Patient characteristics

The characteristics of the 35 patients with PD who completed the present study were as follows: mean age ± SD (range) of 69.1±11.1 years (54-84), 17 men and 18 women,
mean duration ± SD (range) of PD motor symptoms 6.9±5.7 years (1-24), mean ± SD (range) Hoehn & Yahr stage 2.5±0.8 (1-4) and LEDD ± SD of their dopaminergic medication 561±401 mg/day. Among these, 24 patients (68.6%) had pRBD according to the cut-off value of the RBDSQ-J.

Eleven (six men and five women) out of 24 patients with PD and pRBD had accepted evaluation of their motor and sleep symptoms before ramelteon dosing as well as after 4, 8 and 12 weeks of ramelteon dosing.

**Effects of ramelteon on sleep disorders in patients with PD**

Table 1 shows the results of all 35 patients with PD who had completed this study. Ramelteon significantly improved the scores of the UPDRS part III, PDSS-2 and RBDQ-JP, while there was no significant difference in the total score of the PSQI. However, ramelteon significantly improved the “sleep quality” and “sleep latency” subcomponents, and increased the “use of sleep medications” subcomponent score of the PSQI. The total PDSS-2 score was also found to be significantly improved following ramelteon administration. Among the three subcategories of the PDSS-2 scale, ramelteon was found to improve “disturbed sleep” significantly. The RBDQ-JP score was markedly reduced after the initiation of ramelteon treatment in the present study. Furthermore, there was no significant effect on MMSE, FAB, HAMD and Schwab & England ADL scale scores (Table 1).

**Effects of ramelteon on sleep disorders in patients with PD with or without pRBD**

The Ramelteon-induced changes in PSQI, PDSS-2, RBDQ-JP and UPDRS part III scores were analyzed independently in 24 patients with PD and pRBD and 11 patients without pRBD who had completed the trial. There were no significant differences of age (± SD) (with pRBD vs. without pRBD: 69.0±12.9 years old vs. 69.4±5.9; p=0.361), disease duration (7.5±6.3 years vs. 5.5±4.1; p=0.329), sex (M/F 14/10 vs. 3/8; p=0.0878), and disease severity determined by Hoehn and Yahr staging (p=0.662) and UPDRS part III (19.5±12.0 vs. 16.5±13.9; p=0.517) between the two groups.

The results obtained in patients with PD with pRBD were almost the same as those obtained from all patients with PD and the sleep problems reported in section 3.2. That is, ramelteon markedly improved the RBDQ-JP score, as well as the UPDRS part III and PDSS-2 scores, in patients with PD with pRBD (Table 2). This effect was also shown for several subcomponents of the PSQI and PDSS-2. In patients with PD without pRBD, ramelteon also significantly improved RBDQ-JP and UPDRS part III scores, as well as the “disturbed sleep” subcomponents of the PDSS-2.

Finally, temporal changes in the effect of ramelteon on each sleep disorder evaluation (Figure) indicate that it was effective in reducing the RBDQ-JP score four weeks after the start of treatment. Ramelteon also slightly improved the total PDSS-2 score eight weeks after the start of treatment.

**Discussion**

In mammals, two types of receptor mediate the effect of melatonin: MT1 and MT2. The activation of MT1 results in a sedative effect, while MT2 is involved in regulation of the circadian rhythm (4). However, the mechanisms that underlie the beneficial effects of melatonin and ramelteon on RBD remain unclear. Some reports have suggested that melatonin might improve RBD due to direct inhibition of REM with atonia (RWA), inhibition of gamma-aminobutyric acid, stabilization of the circadian rhythm, improvement of sleep efficiency and/or modulation of skeletal muscles that
agomelatine, has also been reported to reduce the frequency of patients with PD (11). Another melatonin agonist, study showed that melatonin could improve RBD in around injury in patients with PD (10). The results of one open pam, melatonin may significantly lessen the risk of falls and increases RWA (6-9). Furthermore, compared with clonaze-polysomnography (PSG) have described that melatonin de-
striatal dopamine circuit also regulates sleep quality (30), in-
been reported that melatonin protects exogenous L-dopa
meters have reported that the evidence for the effi-

Table 2. Effects of Ramelteon on Sleep Disorders in Patients with PD with or without pRBD.

<table>
<thead>
<tr>
<th></th>
<th>PD with pRBD (n = 24)</th>
<th>PD without pRBD (n = 11)</th>
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<tbody>
<tr>
<td></td>
<td>Before ramelteon</td>
<td>After ramelteon</td>
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<tr>
<td>UPDRS part III</td>
<td>19.3±12.0</td>
<td>17.5±10.5</td>
</tr>
<tr>
<td>PSQI (total score)</td>
<td>6.4±3.7</td>
<td>5.8±3.6</td>
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<tr>
<td>Sleep quality</td>
<td>1.7±0.9</td>
<td>1.2±0.8</td>
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<tr>
<td>Sleep latency</td>
<td>1.2±1.1</td>
<td>0.7±1.0</td>
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<tr>
<td>Sleep duration</td>
<td>0.5±0.8</td>
<td>0.4±0.6</td>
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<tr>
<td>Habitual sleep efficiency</td>
<td>0.6±0.8</td>
<td>0.4±0.8</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>0.7±0.7</td>
<td>0.7±0.6</td>
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<tr>
<td>Use of sleep medications</td>
<td>0.7±1.3</td>
<td>1.2±1.5</td>
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<tr>
<td>Daytime dysfunction</td>
<td>1.0±1.1</td>
<td>1.2±1.2</td>
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<tr>
<td>PDSS-2 (total score)</td>
<td>14.4±7.2</td>
<td>10.7±6.3</td>
</tr>
<tr>
<td>Motor problems at night</td>
<td>3.0±3.4</td>
<td>1.5±2.8</td>
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<tr>
<td>PD symptoms at night</td>
<td>1.6±2.5</td>
<td>1.0±1.8</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>9.8±4.2</td>
<td>8.2±4.4</td>
</tr>
<tr>
<td>RBDQ-JP</td>
<td>35.5±15.5</td>
<td>19.0±16.9</td>
</tr>
</tbody>
</table>

Values are depicted as averages ± SD. UPDRS: Unified Parkinson’s Disease Rating Scale; MMSE: Mini-Mental State Examination. PSQI: Pittsburgh Sleep Quality Index, PDSS-2: Parkinson’s Disease Sleep Scale-2; P: Parkinson’s disease. RBDQ-JP: REM Sleep Behavior Severity Scale-Japanese version, pRBD: probable REM sleep behavior disorder. n=24 patients with PD with pRBD and 11 patients without pRBD.

have been inhibited by calmodulin (28). Moreover, it has been reported that melatonin protects exogenous L-dopa from autodestruction in the striatum of rats (29). Because the striatal dopamine circuit also regulates sleep quality (30), increased striatal L-dopa bioavailability by melatonin may modulate sleep in patients with PD.

In terms of clinical studies, four reports of studies using polysomnography (PSG) have described that melatonin decreases RWA (6-9). Furthermore, compared with clonazepam, melatonin may significantly lessen the risk of falls and injury in patients with PD (10). The results of one open study showed that melatonin could improve RBD in around 80% of patients with PD (11). Another melatonin agonist, agomelatine, has also been reported to reduce the frequency and severity of RBD in three patients (31). Taken together, these studies suggest that a melatonin agonist may be effective in improving idiopathic RBD.

The present study demonstrated that ramelteon is effective in improving RBD as well as sleep disturbances in patients with PD. Ramelteon markedly improved the RBDQ-JP scores, and slightly reduced the scores in UPDRS part III, PDSS-2, and several PSQI and PDSS-2 subscales. An increased rating of the “use of sleep medications” subcomponent of PSQI could occur in such an add-on medication trial. In patients with PD without RBD, ramelteon also improved RBDQ-JP and UPDRS part III scores, as well as “disturbed sleep” subcomponents of PDSS-2. We postulated that ramelteon may have improved sleep disturbances in patients with PD by improving the underlying sleep disruptions responsible for RBD, which may consequently improve motor function; however, this finding was not clinically evident.

Importantly, ramelteon did not aggravate cognitive function as determined by the MMSE, FAB and the HAMD depression score, nor did it affect the Schwab & England ADL scale. In terms of motor symptom improvement, the reduced UPDRS part III score may have derived from the improved sleep caused by ramelteon. Indeed, it has been reported that a good night’s sleep can improve motor symptoms in the morning in some patients with PD (32). It should be noted that the International Parkinson and Movement Disorder Society Task Force has reported that the evidence for the efficacy of melatonin is insufficient (33). However, the present study suggests that ramelteon may improve RBD as well as other sleep disturbances in patients with PD.

While adverse events associated with ramelteon are reportedly mild, 6 out of 44 patients in the present study stopped taking this drug. It could be that patients with PD are sensitive to ramelteon-induced emerging daytime sleepiness, lightheadedness, delirium and constipation.

The present study had two major limitations. First, it was not a randomized controlled trial but rather an open trial. Moreover, PSG was not performed for the diagnosis of RBD in patients with PD. However, it is known that the
RBDQ-JP is a useful tool with suitable sensitivity to diagnose RBD; thus, we feel that the method used for the diagnosis of RBD in the current study was both sufficient and accurate.

**Conclusion**

The current study showed that ramelteon might be effective in improving sleep disturbances and RBD in patients with PD. In the future, this finding should be confirmed by a randomized controlled trial with PSG examinations.

**Author’s disclosure of potential Conflicts of Interest (COI).**


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