The Effect of Rotigotine on Cognitive Function and Sleep Problems in Parkinson's Disease: an Open-Label Pilot Study

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Abstract

Background: We hypothesized that rotigotine may have a positive effect on cognitive function in patients with Parkinson's disease (PD) by improving daytime motor function and nighttime sleep status due to its 24-hour sustained properties.

Methods: We evaluated the effect of rotigotine on motor symptoms, cognitive function, daytime sleepiness, sleep disturbances, and motor symptoms in 10 PD patients with sleep disturbances, defined as a PD Sleep Scale (PDSS)-2 score of ≥ 15 , in a single-center, 3-month open-label study. Participants received 24 mg/24 h (patch content: 4.5-9 mg) rotigotine for a 3-month period. At baseline and 3 months, patients were evaluated on the Movement Disorder Society Revision of the Unified PD Rating Scale (MDS-UPDRS) parts III and IV and cognitive assessments, such as the Mini-Mental State Examination (MMSE), frontal assessment battery (FAB) and Montreal Cognitive Assessment (MoCA). The Epworth Sleepiness Scale (ESS) and PDSS-2 were administered at baseline and at 1 month, 2 months and 3 months.

Results: At 3 months, MDS-UPDRS part III (-10.7, $p < 0.001$) and MDS-UPDRS part IV (-1.0, $p = 0.023$) scores significantly decreased, MoCA scores (1.7, $p = 0.0095$) significantly increased, and off time significantly decreased (-43.0 min; $p = 0.029$) from baseline. PDSS-2 scores significantly decreased from baseline at 2 months (-14.5, $p < 0.05$) and 3 months (-20.0, $p < 0.001$). ESS, MMSE or FAB scores did not significantly change after rotigotine treatment.

Conclusion: Our preliminary findings suggest that low-dose rotigotine could improve motor symptoms, sleep disturbance, and cognitive function without worsening daytime sleepiness in patients with PD.

Introduction

Parkinson's disease (PD) is characterized not only by classic motor signs due to degeneration of nigrostriatal dopaminergic neurons but also by high rates of nonmotor symptoms, including sleep disorders, cognitive impairment, depression and autonomic symptoms, due to impairments in nondopaminergic systems such as noradrenergic, serotonergic and cholinergic systems [1]. At the onset of motor symptoms, dopaminergic neurons in the midbrain substantia nigra are decreased by 60%, and dopamine content in the striatum is reduced by 80% [2]. Therefore, dopamine replacement treatment with dopamine receptor agonists and levodopa is the mainstay of treatment for motor symptoms of PD. On the other hand, there is still insufficient evidence for treating nonmotor symptoms such as sleep disturbances and cognitive impairment.

Rotigotine is a 24-hour long-acting transdermal dopamine agonist that is effective in improving motor symptoms and wearing-off phenomena. It is commonly used in combination with levodopa and has been reported to be effective in PD patients younger than 70 years of age [3] as well as in advanced-stage PD [4]. In a double-blind, placebo-controlled trial (dose titration period of 1–8 weeks and maintenance period of 4 weeks), rotigotine improved motor symptoms as well as nocturnal motor symptoms and sleep disturbances as evaluated by the PD Sleep Scale (PDSS)-2 [5], and improvements in sleep disturbances

lasted for 43 weeks following the long-term open trial [6]. In a study using axial inertial sensors, rotigotine improved nocturnal immobility and difficulty turning in bed in PD patients [7]. In addition, rotigotine has been reported to be effective for pain [8], restless legs syndrome, and nocturia [6]. A multicenter, observational, retrospective study using nonmotor symptom questionnaires reported that rotigotine treatment improved sleep and mood/cognition domains after 6 months [9]. However, no studies have evaluated cognitive function in detail before and after the administration of rotigotine.

We hypothesized that rotigotine would have a positive effect on cognitive function by improving daytime motor function and nighttime sleep status due to its 24-hour sustained properties, and we designed a study to assess cognitive function and sleep status before and after rotigotine treatment in PD patients who suffered from sleep disturbances.

Methods

We performed a single-center, 3-month open-label study between July 2018 and December 2020. The participants received 2 mg-4 mg/24 h (patch content 4.5 mg-9 mg) rotigotine for a 3-month period. The dose of rotigotine was increased from 2 mg to 4 mg/24 h after 1 month of treatment according to the physician's judgment. The inclusion criteria were PD patients who suffered from sleep disturbances. PD was diagnosed by board-certified neurologists according to the Movement Disorder Society (MDS) clinical diagnostic criteria for PD [10]. Excluded patients included those with atypical Parkinsonian syndrome, vascular parkinsonism or drug-induced parkinsonism who were carefully differentiated by brain magnetic resonance imaging and neurological examination in combination with clinical markers such as olfactory testing, dopamine transporter scan and cardiac metaiodobenzylguanidine scintigraphy. Patients with psychosis or dementia, defined as scores of 20 or lower on the Mini-Mental State Examination (MMSE), were excluded. Disease severity was evaluated by Hoehn and Yahr (HY) staging [11]. At baseline and 3 months, patients were assessed by the Japanese version of the MDS revision of the Unified PD Rating Scale (MDS-UPDRS) parts III (motor examination) and IV (motor complication) [12], and cognitive functions were assessed by the MMSE, frontal assessment battery (FAB) and the Montreal Cognitive Assessment (MoCA) [13]. The PDSS-2 was used to evaluate PD-related sleep disturbances [14]. All patients included in this study had sleep disturbance, defined as a PDSS-2 score of 15 or greater [15]. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [16]. The ESS and PDSS-2 were administered to the patients at baseline and at 1 month, 2 months and 3 months.

Statistical analysis

Paired t-tests were used to compare MDS-UPDRS III and IV scores, off time and cognitive assessments (MMSE, FAB and MoCA) at baseline and at 3 months. Repeated measures ANOVA followed by Dunnett's multiple comparison test was employed to analyze differences in PDSS-2 and ESS scores at baseline and at 1 month, 2 months and 3 months. Two-tailed p values < 0.05 were considered to be statistically significant. GraphPad Prism for Mac (Version 8; GraphPad Software, San Diego, USA) was used for statistical analyses and figure creation.

Results

Ten PD patients with sleep disturbances (6 M/4 F; age, 72.2 ± 5.6 y; disease duration, 4.3 ± 4.0 y) were enrolled, and all completed the study (Table 1). The Hoehn and Yahr stages in the on and off states were 2.7 ± 0.5 and 3.7 ± 0.5 , respectively. Six (60.0%) patients received 2 mg/24 h rotigotine, and four received 4 mg/24 h rotigotine. One was drug naïve, seven (70%) were being treated with levodopa and one (10%) was on another dopamine agonist. Mean levodopa dose was 215.0 ± 150.9 mg/day. At 3 months, MDS-UPDRS part III (-10.7 , $p < 0.001$) and part IV (-1.0 , $p = 0.023$) scores were significantly decreased, MoCA scores (1.7 , $p = 0.0095$) were increased, and off time was significantly reduced (-43.0 min; $p = 0.029$) from baseline (Fig. 1). PDSS-2 scores significantly decreased at 2 months (-14.5 , $p < 0.05$) and 3 months (-20.0 , $p < 0.001$) from baseline. ESS (-3.1 , $p = 0.24$), MMSE (0.5 , $p = 0.27$) and FAB (-0.4 , $p = 0.44$) scores did not significantly change after rotigotine treatment.

Table 1
Patient background at baseline

	Patients with PD
Sex (M/F)	6/4
Age (years)	72.2 ± 5.6
Disease duration (years)	4.3 ± 4.0
Hoehn and Yahr stage on state	2.7 ± 0.5
Hoehn and Yahr stage off state	3.7 ± 0.5
MMSE	26.3 ± 3.0
FAB	14.0 ± 2.2
MoCA	19.6 ± 2.7
MDS-UPDRS part III	38.7 ± 12.0
MDS-UPDRS part IV	2.5 ± 2.2
Off time (min)	120.1 ± 146.9
PDSS-2	20.7 ± 9.6
ESS	12.4 ± 2.4
Levodopa (mg/day)	215.0 ± 159.9
Data are expressed as the mean $\pm$ SD (range)	
ESS = Epworth Sleepiness Scale; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; MDS-UPDRS = Movement Disorder Society revision of the Unified PD Rating Scale; MoCA = Montreal Cognitive Assessment; PD = Parkinson's disease; PDSS-2 = PD Sleep Scale-2	

Discussion

Our study showed beneficial effects of rotigotine on motor symptoms and motor fluctuation, as with previous studies [3, 4]. Our study included PD patients with sleep disturbances and showed significant improvements in PDSS-2 scores after rotigotine treatment at 2 months and 3 months. This finding is in agreement with a previous study [5] and a meta-analysis of 21 articles that found efficacy with rotigotine on sleep disturbances, as evaluated by PDSS or PDSS-2 scores [17]. Importantly, ESS scores did not increase after rotigotine treatment. Although daytime sleepiness is a problem associated with dopamine agonists, in an open study, daytime sleepiness did not increase in 13 PD patients who were switched from other dopamine agonists, such as pramipexole, cabergoline, and ropinirole, to equivalent doses of rotigotine, and the overall clinical impression was significantly improved [18]. Furthermore, we observed significant improvement in MoCA scores after rotigotine treatment but not in FAB or MMSE scores. These findings may be related to the possibility that the MoCA is considered a more specific and sensitive test to detect changes in cognitive function in patients with PD. The MoCA is a recommended scale for screening cognitive impairment in clinical trials in patients with PD [19].

Sleep is important in memory consolidation, and changes in sleep quality and architecture can cause cognitive decline [20]. A relationship between cognitive impairment and insomnia in older adults has been reported by epidemiological studies [21]. Increased sleep fragmentation could accelerate neurodegeneration via the accumulation of abnormal proteins such as tau and amyloid beta in the brain, leading to dementia [22]. In older people, better cognitive performance was related to having profiles of sleep metrics observed in younger people [23]. Insomnia is associated with impairments in cognitive performance, and thus, relieving insomnia could potentially improve cognitive outcome [24]. A recent systematic review and meta-analysis showed that obstructive sleep apnea was associated with significantly lower MoCA scores in patients with PD [25]. Increased sleep fragmentation and nocturnal hypoxia are important mechanisms, contributing to impair cognition [22].

In our study, the improvement in MoCA scores was thought to be attributable to the improvement in sleep disturbances without affecting daytime alertness. Rotigotine is described as not only a D3/D2/D1 receptor agonist but also an antagonist of $\alpha 2B$ adrenergic receptors and an agonist of 5-HT_{1A} receptors [26]. In animal models, a selective postsynaptic 5-HT_{1A} receptor agonist improved cognitive function [27]. Therefore, in our study, in addition to the improvements regarding nocturnal sleep disturbance, the modulation of 5HT_{1A} receptors may have had a favorable effect on cognitive function.

Our study has several limitations. First, the sample size was small, which was partly due to the single-center study setting in which limited numbers of patients who scored 15 or higher on the PDSS-2 were available. Due to the COVID-19 pandemic, we decided that further patient recruitment would be difficult. Second, polysomnography was not performed, and sleep disturbances were assessed by questionnaire. However, the PDSS-2 can screen PD-related sleep problems and has been validated and widely used [28]. Further multicenter, large-sample studies are needed to confirm whether rotigotine has beneficial effects on cognition by improving daytime motor symptoms and sleep disturbances.

In conclusion, our preliminary findings suggest that low-dose rotigotine could improve motor symptoms and sleep disturbance as well as cognitive function without worsening daytime sleepiness in patients with PD.

Abbreviations

ESS

Epworth Sleepiness Scale; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MDS-UPDRS = Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale; PD = Parkinson's disease; PDSS = Parkinson's Disease Sleep Scale

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of Dokkyo Medical University Hospital. All participants gave written informed consent to participate in this study.

Consent for publication

Not applicable.

Availability of data and materials

The relevant data are within the paper, but the data sets from this study are available from the corresponding author upon reasonable request.

Competing interests

Keisuke Suzuki is an editorial board member of BMC Neurology. The authors declare no potential conflicts of interest in relation to this article.

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None.

Authors' contributions

All authors have read and approved the final manuscript. KS contributed to the study design, method, data acquisition and statistical analysis and drafted the manuscript. KF and HF were involved in the study design, method and data acquisition. KH contributed to the study design, review and supervision.

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Figures

Figure 1

Changes in MDS-UPDRS III and IV, off time, ESS, PDSS-2 and MoCA scores after rotigotine treatment
 *p<0.05; **p<0.01; ***p<0.001 Error bars represent standard errors of the mean.