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Istradefylline improves daytime sleepiness in patients with Parkinson's disease: An open-label, 3-month study

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ABSTRACT

Background: Istradefylline, a selective adenosine A2A receptor antagonist, has been reported to improve daily "off time" and motor symptoms in patients with Parkinson's disease (PD). However, the effect of istradefylline on sleep problems has not been thoroughly investigated.
Methods: We evaluated the effect of istradefylline on daytime sleepiness, sleep disturbances, and motor symptoms in 22 PD patients who were affected by the wearing off phenomenon in an open-label, 3-month study. Participants received 20–40 mg/day istradefylline once daily (morning) over a 3-month period. The Epworth Sleepiness Scale (ESS), PD sleep scale (PDSS)-2 and PD Questionnaire (PDQ-8) were administered at baseline, 2 weeks, 1 month, 2 months and 3 months. 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.
Results: Twenty-one patients (95.5%) completed the study. At 3 months, MDS-UPDRS part III (-5.3, $p = 0.0002$) and part IV (-2.5, $p = 0.001$) scores improved and off time decreased significantly (-50.1 min, $p = 0.0004$). PDQ-8 scores were unchanged at 3 months. ESS scores decreased significantly at 2 months and 3 months (-2.4 and -3.3, respectively, $p < 0.0001$), but the total PDSS-2 scores did not change.
Conclusion: Istradefylline improved daytime sleepiness in PD patients, possibly through its effect on enhancing alertness. In addition, the lack of significant changes in the total PDSS-2 scores over the study period suggests istradefylline had no negative impact on sleep.

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1. Introduction

Non-motor symptoms such as sleep problems, depression and cognitive impairment are frequently observed in patients with Parkinson's disease (PD), and their negative impacts on patient quality of life have been recognized [1]. Compared to motor symptoms in PD, several non-motor symptoms are refractory to dopaminergic treatment, because non-motor symptoms are attributable not only to the degeneration of dopaminergic neurons in the substantia nigra but also to serotoninergic, noradrenergic and cholinergic involvement in the brain. Among non-motor symptoms, sleep disturbances and excessive daytime sleepiness are frequent in PD patients and are difficult to manage in clinical practice. Therefore, further studies to find effective approaches to treating sleep problems are warranted.

Istradefylline, a selective adenosine A2A receptor (A2AR) antagonist, improves motor symptoms and reduces daily "off time" in patients with PD through nondopaminergic mechanisms [2]. Istradefylline acts on A2ARs located on the GABAergic cell bodies and terminals of the indirect striatopallidal pathway, causing inhibition through a nondopaminergic mechanism [3]. The blockade of A2ARs on striatopallidal neurons by istradefylline is estimated to inhibit excessive striatopallidal neuronal activity in PD, thus improving Parkinsonism [4]. In addition to its effect on motor symptoms, istradefylline may improve non-motor symptoms in PD based on the distribution of adenosine A2ARs within the basal ganglia and in the cerebral cortex and thalamus [5]. However, the effect of istradefylline on non-motor symptoms, including sleep/wake problems, has not been carefully investigated. A1 and A2AR antagonists such as caffeine have been reported to induce wakefulness by blocking the action of adenosine on A2ARs [6]. This finding suggests that istradefylline may

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have beneficial effects on daytime sleepiness. We therefore evaluated the effect of istradefylline on daytime sleepiness, sleep disturbances and motor symptoms in patients with PD in an open-label, 3-month study.

2. Methods

This single-center, 3-month open-label study was conducted between October 2015 and December 2016. The inclusion criteria were levodopa-treated PD patients who suffered from the wearing off phenomenon and whose dopaminergic treatment was unchanged for at least one month. PD patients with psychosis or dementia, defined as scores of 23 or lower on the Mini-Mental State Examination (MMSE), were excluded. Twenty-two PD patients (9 M/13 F, age 70.7 ± 4.6 y) were finally enrolled in this study. Participants received 20–40 mg/day istradefylline once daily (morning) over a 3-month period. Patients were suggested to increase the dose from 20 mg to 40 mg one month after the initiation of istradefylline treatment. Questionnaires on sleep and habits (smoking, alcohol and caffeine intake) were administered to the participants. The amount of caffeine in different types of beverages was defined according to the Standard Tables of Food Composition in Japan in the Fifth Revised and Enlarged Edition, published by the Ministry of Education, Culture, Sports, Science and Technology (http://www.mext.go.jp/). Briefly, the estimated caffeine content per serving was 90 mg per cup of coffee (150 ml), 20 mg per cup of green tea (100 ml) and 30 mg per cup of black tea (100 ml). The consumption of decaffeinated coffee or tea was not assessed. During the study period, patients were instructed to continue the same dosage of other medications for PD and to maintain habitual intake of caffeine, tobacco and alcohol.

PD was diagnosed by board-certified neurologists according to the UK Brain Bank Clinical Diagnostic Criteria [7], after excluding atypical Parkinsonian syndrome, vascular Parkinsonism or drug-induced Parkinsonism. Disease severity was evaluated by Hoehn and Yahr (HY) staging [8]. At baseline and 3 months, all patients were assessed by the Japanese version of the Movement Disorder Society Revision of the Unified PD Rating Scale (MDS-UPDRS) parts III (motor examination) and IV (motor complication) [9]. All the patients were interviewed about "off time" using MDS-UPDRS 4.3. To evaluate non-motor symptoms, daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) Japanese version [10,11]. Excessive daytime sleepiness (EDS) was defined as ESS scores of 10 or greater. The PD Sleep Scale-2 (PDSS-2) was used to evaluate PD-related sleep disturbances [12]. PDSS-2 three-domain scores of "disturbed sleep," "motor symptoms at night" and "PD symptoms at night" were also evaluated. Quality of life was measured by PD Questionnaire-8 (PDQ-8) [13]. ESS, PDSS-2 and PDQ-8 were determined at baseline, 2 weeks, 1 month, 2 months and 3 months. The levodopa equivalent dose (LED) was calculated based on a previous review [14].

The study was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of Dokkyo Medical University Hospital, and written informed consent was obtained from all patients enrolled in the study.

3. Statistical analysis

Paired *t*-tests were used to compare MDS-UPDRS III and IV scores at baseline and at 3 months. Repeated measures ANOVA followed by Dunnett's multiple comparison test was employed to analyze differences in PDSS-2, ESS and PDQ8 scores at baseline, 2 weeks, 1 month, 2 months and 3 months. Unpaired Student's *t*-tests and Fisher's exact tests were used to compare continuous and categorical variables, respectively, between PD patients with and without EDS. Spearman's rank correlation was used to assess relationships among changes in ESS and MDS-UPDRS III, MDS-UPDRS IV and off time from baseline to the endpoint. Two-tailed p values < 0.05 were considered statistically significant. IBM SPSS software version 24.0 (IBM SPSS, Inc., Tokyo, Japan) was used for statistical analyses, and GraphPad Prism for Windows (Version 5.01; GraphPad Software, San Diego, USA) was used for statistical analyses and figure creation.

4. Results

Table 1 shows the baseline characteristics of PD patients. Twenty-one PD patients (95.5%) completed the study. One patient discontinued due to dyskinesia. Five patients (23.8%) agreed to increase the dosage to 40 mg of istradefylline as suggested. At baseline, mean daily off time was 127.1 ± 89.0 min. Nineteen patients (90.5%) were treated with dopamine agonists, 7 patients (33.3%) were treated with selegiline, and 3 (14.3%) used hypnotics (1 eszopiclone, 1 zolpidem and 1 brotizolam). At 3 months, the MDS-UPDRS part III (−5.3, p = 0.0002) and part IV (−2.5, p = 0.0001) scores improved and off time decreased significantly (−50.1 min, p = 0.0004) compared with baseline scores (Fig. 1). PDQ-8 scores were unchanged at 3 months(18.9 ± 17.6 at baseline; −1.9, p = 0.58). At 3 months, ESS scores decreased in 15 patients (71.4%) and were unchanged in 2 patients (9.5%) compared with baseline. ESS scores decreased significantly at 2 months and 3 months (8.7 ± 6.1 at baseline; −2.4 and −3.3, respectively, p < 0.0001) (Fig. 2A). No significant correlation was observed between mean changes from baseline to the endpoint in ESS and MDS-UPDRS III (r = 0.34, p = 0.13), MDS-UPDRS IV (r = −0.29, p = 0.21) and off time (r = 0.12, p = 0.62). PDSS-2 total scores (15.5 ± 7.5 at baseline; 0.0, −2.2, p = 0.26) did not change (Fig. 2B) and the PDSS-2 three-domain scores of "disturbed sleep," "motor symptoms at night" and "PD symptoms at night" did not significantly change after istradefylline treatment.

Among patients with EDS (n = 9), defined as an ESS score ≥ 10, the improvement in ESS scores at 2 months and 3 months from baseline was more pronounced (Fig. 2C) than that in total patients (−6.6 and −7.8, respectively, p = 0.0020) (Fig. 2A). However, at 3 months, PDSS-2 total scores (−4.6, p = 0.078) (Fig. 2D) and three-domain scores did not significantly improve. PD patients with EDS had an increased male/female ratio, lower MMSE scores and less daily caffeine intake than did those without EDS (Table 2).

Table 1
Baseline patient characteristics.

	PD (n = 21)
M/F	8/13
Age (y)	70.9 ± 4.5
Caffeine (mg/d)	156.2 ± 89.6
Coffee, n (%)	19 (90.5)
Green tea, n (%)	8 (53.9)
Black tea, n (%)	5 (23.8)
Alcohol, n (%)	5 (22.7)
Smoking, n (%)	0 (0.0)
MMSE	27.0 ± 2.1
Disease duration (y)	7.8 ± 5.0
Hoehn and Yahr stage (On state)	2.5 ± 0.6
Hoehn and Yahr stage (Off state)	3.7 ± 0.8
MDS-UPDRS III	29.1 ± 12.4
MDS-UPDRS IV	5.5 ± 2.6
The use of anti-PD drugs, n (%)	
Levodopa	21 (100.0)
Entacapone	5 (23.8)
Amantadine	2 (9.5)
Selegiline	7 (33.3)
Zonisamide	4 (19.0)
Dopamine agonists	19 (90.5)
Ropinirole	3 (14.3)
Pramipexole	7 (33.3)
Rotigotine	10 (47.6)
Levodopa equivalent dose (mg/d)	693.3 ± 305.6

PD, Parkinson's disease; MMSE, Mini-Mental State Examination; MDS-UPDRS, Movement Disorder Society Revision of the Unified PD Rating Scale.

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