Rasagiline does not exacerbate autonomic blood pressure dysregulation in early or mild Parkinson's disease

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ABSTRACT

Introduction: Orthostatic hypotension (OH) and abnormal blood pressure (BP) fluctuations occur mainly due to noradrenergic dysfunction and are clinically important in patients with Parkinson's disease (PD). They lead to impairments of cognition function, daily activities, and quality of life. Some monoamine oxidase (MAO)-B inhibitors have a sympathomimetic amine, which can be attributed to OH. Therefore, we determined whether rasagiline, a common MAO-B inhibitor used in PD treatment, can contribute to cardiovascular autonomic BP dysregulation in patients with early or mild PD.
Methods: Nineteen patients with early or mild PD were recruited, and tilt test and 24-h ambulatory BP monitoring (ABPM) were performed before and after rasagiline administration. Early or mild PD was defined as patients with de novo (n = 4), levodopa (n = 10), dopamine agonist (n = 1), levodopa and one dopamine agonist (n = 2), levodopa and droxidopa (n = 1), and levodopa and istradefylline (n = 1). Furthermore, patients with motor fluctuation and multiple dopamine agonists were excluded from our study.
Results: OH and BP frequency were not significantly exacerbated before or after rasagiline administration. No significant differences of type in BP fluctuation on ABPM and the degree of nocturnal BP falls were found before and after rasagiline administration. The Unified Parkinson's Disease Rating Scale motor score in patients (post-rasagiline administration) was significantly improved compared with before.
Conclusion: Rasagiline seems to be a suitable medication for Parkinsonian symptoms in patients with early and mild PD. It does not exacerbate cardiovascular autonomic responses, circadian rhythm of BP, or both.

1. Introduction

Parkinson's disease (PD) is a heterogeneous syndrome characterized by a combination of motor and non-motor symptoms, including depressive or anxious states, hyposomnia, sleep disturbance, or autonomic dysfunction. Also, autonomic dysfunction associated with PD is characterized by constipation, urinary dysfunction, decreased or impaired sweating, and cardiovascular events, such as orthostatic hypotension (OH), postprandial hypotension (PPH), supine hypertension, and nocturnal hypertension even in the earliest stages of PD [1]. Cardiovascular autonomic impairment is a severe sign of disease prognosis, and patients with PD and OH are at a greater risk of death than other patients with PD [2]. OH occurs mainly due to sympathetic noradrenergic dysfunction and is clinically relevant in about 50% of patients with PD, including de novo cases. Furthermore, cognition impairment, daily activities, and quality of life are affected by OH [3]. Abnormal blood pressure (BP) fluctuations common in OH frequently occur in PD, and cognitive impairment is associated with abnormal BP fluctuation [4], particularly the failure of nocturnal BP falls in PD [5].

Irreversible MAO-B inhibitors have been used as anti-Parkinson's agents in patients with PD. They are widely employed as a monotherapy and an adjunct to levodopa with peripheral decarboxylase inhibitors [6]. One of these MAO-B inhibitors has a sympathomimetic amine derived from L-methamphetamine, which can increase BP and heart rate. This effect has been attributed to its sympathomimetic activity. In addition, OH may occur as a side effect of selegiline and levodopa and is an independent risk factor for mortality in patients with PD [7]. Rasagiline is a potent and specific MAO-B inhibitor and is approved as an antiparkinsonian drug in many countries. However, rasagiline is not metabolized to amphetamine or amphetamine-like derivatives. Its major

metabolite is aminoindan, which has no sympathomimetic activity; therefore, it seems to have less sympathetic impairment than other MOA-B inhibitors [8]. This study clarifies whether rasagiline could be responsible for cardiovascular autonomic dysfunction in patients with early or mild-stage PD.

2. Materials and Methods

2.1. Study participants

Forty-three patients with PD meeting the diagnostic criteria for PD proposed by the UK Parkinson's Disease Society Brain Bank who received rasagiline were entered into a research database at Daisan Hospital, The Jikei University School of Medicine, between September 2018 and April 2021. Nineteen patients with early or mild PD were recruited, and tilt test of BP and 24-h ambulatory BP monitoring (ABPM) were performed before and after rasagiline administration.

Early or mild-stage PD in our study was defined as patients with de novo, only levodopa, one dopamine agonist, and no motor fluctuation despite receiving other Parkinsonian medications, such as droxidopa or istradefylline. The Hoehn and Yahr average score of the patients is 2.2, and the mean total levodopa equivalent dose is 234 mg, which was calculated according to Tomlinson et al [9].

Our study comprised four cases of de novo PD, eleven cases with only levodopa, one case with a dopamine agonist, two cases with levodopa and dopamine agonist, one case with levodopa and istradefylline, and one case with levodopa and droxidopa. No patient had signs of motor fluctuation, including the "wearing-off" phenomenon, orthostatic faintness, or dizziness.

PD-associated motor severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score [10] in 15/19 patients after receiving rasagiline. Between the two sessions of the tilt test and 24-h BP monitoring, no patient had taken any medication that could influence cardiovascular function. The clinical characteristics of the patients are summarized in Table 1.

2.2. Tilt test

Patients were tilted to an upright position for 3 min after resting for 3 min in the supine position. Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a sphygmomanometer after 3 min of rest in the supine position. After their BP stabilized, SBP and DBP were measured immediately after standing and every minute after subjects were tilted for about 3 min. The maximum decrease in SBP during tilt was evaluated as orthostatic BP decline. Additionally, OH was defined as a fall in SBP by $\geq$ 20 mmHg. The test was performed at least 2 h after mealtime to exclude any potential effects of PPH. Finally, we performed the tests at the same time of day before and after drug administration.

2.3. Twenty-four-hour ABPM

Twenty-four-hour ABPM of hospitalized patients or outpatients was performed using a noninvasive automated portable recorder. BP was measured every 30 min during the daytime (7:00–21:00) and every hour during the nighttime (22:00–6:00). Furthermore, SBP was used as an indicator of BP. Nocturnal falls in BP were calculated using the formula: SBP day − SBP night/SBP day × 100 (%). "SBP day" refers to the mean SBP during the daytime, and "SBP night" refers to the mean SBP during the nighttime. Cases with nocturnal falls in BP of $\geq$ 10%, <10%, and no falls were defined as dipper, non-dipper, and riser types, respectively, as described in previous studies [4].

Evaluations using the UPDRS-approved motor, tilt test, and 24-h BP monitoring were performed at an interval of 70 $\pm$ 27 d (minimum 32 d, maximum 170 d) in patients who were receiving rasagiline.

2.4. Cardiac 123I-MIBG scintigraphy

Patients were given an intravenous injection of 111 MBq 123I-MIBG (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan). The relative organ uptake of 123I-MIBG was determined using scintigraphy by region-of-interest analysis in the anterior view. In addition, the ratio of the average pixel count in the heart (H) to that in the mediastinum (M) was calculated (H/M ratio) after 3 h.

Deidentified data from a database of patients were used in this retrospective study. The study was approved by the Ethics Committee of The Jikei University School of Medicine (approval number: 28–261 [8504]).

2.5. Statistical analysis

Statistical analyses were performed using a statistical data analysis system (Esumi Co., Ltd., Tokyo, Japan). The differences in UPDRS motor, BP change on tilt test, and nocturnal BP falls on ABPM were analyzed for pre- and post-rasagiline administration using the Wilcoxon rank-sum test. P values for differences in the tilt test or BP fluctuation types on ABPM for pre- and post-rasagiline administration were calculated using Chi-square ($\chi2$) tests for binary variables. P < 0.05 was considered statistically significant.

3. Results

There was no difference in OH frequency before and after rasagiline administration. BP change in the tilt test was not significantly exacerbated before and after rasagiline administration. Although the difference was not statistically significant, the riser type in BP fluctuation type on ABPM increased to five cases (from three cases) after rasagiline administration. Additionally, the non-dipper type decreased to four cases (from seven cases), whereas there was no significant change in dipper type after rasagiline administration. No significant difference was found in nocturnal BP falls on AMPB before and after rasagiline administration. Finally, the UPDRS motor score in patients after rasagiline administration was significantly improved compared with before (Table 2).

4. Discussion

Our study demonstrated that rasagiline administration did not exacerbate OH or nocturnal BP falls on ABPM in early- or mild-stage PD. There was no resultant "wearing-off" phenomenon or other signs of motor fluctuation. A previously published systematic review and *meta*-analysis of OH incidence in PD and atypical Parkinsonism showed that the estimated prevalence of OH was approximately 30% in PD. Furthermore, patients with PD with symptomatic OH tend to be older and have a longer disease duration and more severe Parkinson staging. Furthermore, 52% of patients with early-stage PD with no prior medical treatment have OH [5]. OH is considered a vital nonmotor symptom in early-stage PD as patients with OH have poor mobility and mortality [2].

Nocturnal BP falls in ABPM, typically found in healthy persons, are

Table 1
Clinical characteristics of PD patients.

	PD patients
Number of patients	19
Age (years)	72.2 $\pm$ 8.8 (55–84)
Gender (female/male)	6/13
Duration of disease (years)	3.4 $\pm$ 1.9 (0.5–8)
Hoehn-Yahr stage	2.2 $\pm$ 0.5 (1–3)
H/M ratio on MIBG scintigraphy	1.44 $\pm$ 0.38 (0.99–2.31)
Levodopa equivalent dose (mg)	234 $\pm$ 138 (0–430)

Mean $\pm$ standard deviation (min–max).
H/M: heart/ mediastinum.

Table 2

Frequency of OH and BP change on tilt test, type in BP fluctuation, the degree of nocturnal BP falls on ABPM, UPDRS motor score between before and after receiving rasagiline.

	before rasagiline	after rasagiline	P value
Number of patients	19	19	–
Tilt test OH (−/+)	10/9	10/9	ns
BP change on tilt test (mmHg)	15.3 ± 27.5 (−31–64)	17.7 ± 19.0 (−18–51)	ns
BP fluctuation type on ABPM dipper/non-dipper/riser	9/7/3	10/4/5	ns
Nocturnal BP falls on AMPB (%)	5.1 ± 8.3 (−14–17)	7.8 ± 11.8 (−12–31)	ns
UPDRS motor score (n = 15)	28.9 ± 9.7 (9–45)	20.6 ± 9.0 (9–34)	<0.01

OH: orthostatic hypotension, BP: blood pressure, ABPM: ambulatory blood pressure monitoring, UPDSR: Unified Parkinson's Disease Rating Scale.

frequently reduced or reversed in PD [21]. Abnormal daily BP fluctuation in PD has been associated with cardiovascular autonomic dysfunction. Thus, it is important to assess BP fluctuation because such disruption in typical BP patterns is associated with cognitive dysfunction in PD [5].

Medications, such as levodopa, dopamine agonists, MAO-B inhibitors, and other anti-Parkinson drugs are often used as frontline treatments for PD-associated motor disability. However, many anti-Parkinson drugs affect the cardiovascular system, sometimes exacerbating OH. For example, a previous study reported SBP reduction in the orthostatic test from 8.1 mmHg to 20 mmHg with levodopa and from 16.1 mmHg and 12.5 mmHg to 19 mmHg with an MOA-B inhibitor [11].

Proactive prevention and treatment of BP in PD abnormalities are important for enhancing activities of daily living and quality of life and reducing mortality and cognitive dysfunction. Furthermore, using anti-Parkinson drugs that have fewer effects on BP circulatory dysregulation may be significant to PD's overall prognosis and progression.

The first MAO-B inhibitor, selegiline, is a selective and irreversible propargylamine-based compound that has been used for treating PD for more than 40 years. MAO-B inhibits the degradation of dopa by monoamine oxidase, thereby increasing the concentration of dopa in the striatum. MAO-B inhibitors, such as selegiline, are recommended as first-line treatments for mild PD because long-term use of levodopa alone is associated with motor fluctuations [12].

Selegiline is metabolized to its major metabolites, methamphetamine and amphetamine, in the liver [13]. Amphetamine can induce OH by impairing sympathetic functions [13]. Amphetamine metabolization could cause the false neurotransmitter hydroxyephedrine, which depletes norepinephrine nerve terminals [14]. Additionally, previous research has attributed cardiovascular autonomic function and clinically occurring OH to selegiline administration [14].

Another irreversible selective MAO-B inhibitor, rasagiline, became available about a decade ago [8]. Rasagiline has a major advantage compared with selegiline, as its metabolites do not include potentially toxic amphetamines [8]. However, it has not been clarified in practice whether rasagiline induces OH or abnormal BP fluctuation in PD.

Our study shows that rasagiline administration does not affect OH, degree of decrease in SBP on tilt test, BP fluctuation type, or nocturnal BP falls on AMPB in early and mild PD. Furthermore, the mean of the patients' UPDRS motor score decreased from 28.9 to 20.6 points before and after rasagiline administration, indicating improved motor function.

There are limitations to this study. First, the number of cases is relatively small. Second, the study was conducted on patients with early-stage and mild PD, but not on moderate or severe cases that involve the "wearing-off" phenomenon. Third, the short rest period of three minutes in the supine position before tilt test is different from the standard method of five minutes.

Future research should include a greater number of patients,

advanced PD cases, or both. However, the key finding of this study—that rasagiline can be used in early or mild PD without the fear of circulatory dysregulation of the autonomic system—is of great importance to the field of clinical PD research.

5. Conclusion

Rasagiline is presumed not to influence OH and daily BP fluctuations as it does not metabolize to amphetamines attributed to the potentially sympathomimetic activity or OH. Rasagiline can be a suitable therapy for Parkinsonian symptoms because it does not exacerbate cardiovascular autonomic responses or alter the circadian rhythm of BP in patients with early and mild PD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

Hisayoshi Oka: drafting/revising the manuscript for content, including medical writing; study concept and design; acquisition of data; analysis and interpretation of data. Renpei Sengoku: study concept and design; acquisition of data; analysis and interpretation of data; review and critique. Atuso Nakahara: study concept and design; acquisition of data; review. Mikihiro Yamazaki: study concept and design; acquisition of data; review. All authors have read and approved the final manuscript.

Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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