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ORIGINAL ARTICLE

Effect of Rivastigmine on Behavioral and Psychiatric Symptoms of Parkinson's Disease Dementia

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ABSTRACT

Objective A recent study showed that rivastigmine and memantin improved behavioral and psychiatric symptoms of dementia (BPSD) in Alzheimer's dementia. Furthermore, according to recent guidelines presented by the Movement Disorder Society, rivastigmine is efficacious for the treatment of dementia in Parkinson's disease (PD). We investigated the efficacy of rivastigmine for BPSD in patients with Parkinson's disease dementia (PDD).

Methods Twenty-three patients in whom cognitive impairment occurred at least one year after a diagnosis of PD participated in this open-label trial. Cognitive, psychiatric, and motor symptoms were assessed before and after 24 weeks of treatment with rivastigmine using unstructured clinical assessments and rating scales including the Unified Parkinson's Disease Rating Scale, Mini-Mental State Examination (MMSE), and the Neuropsychiatric Inventory.

Results Age (± standard deviation) was 74.7 ± 5.9 years, average duration of PD was 3.5 ± 3.7 years, Hoehn and Yahr scores were 2.2 ± 0.8, and baseline MMSE scores were 19.1 ± 4.2. Improvements in global mental symptoms and neuropsychiatric symptoms were significant; among them, hallucination, depression and appetite changes improved. Caregiver distress significantly decreased, including distress resulting from hallucinations, depression, apathy, and appetite changes.

Conclusions Although controlled trials are required, the findings suggest that rivastigmine is useful for control of several neuropsychiatric symptoms and beneficial for caregiver distress in patients with PDD.

Key Words Parkinson disease; Dementia; Rivastigmine; Neuropsychiatry; Symptoms.

A variety of behavioral and psychological symptoms of dementia (BPSD) commonly occur in patients with Parkinson's disease (PD) and Parkinson's disease dementia (PDD).[1-3] Approximately 90% of patients exhibit at least one neuropsychiatric symptom, and over 70% present with two or more symptoms.[3] These neuropsychiatric disturbances are associated with reduced quality of life,[4,5] increased caregiver burden and stress,[2,6,7] disabilities in daily living,[8] increased risk of admission to a nursing home,[9] and increased mortality in nursing home patients.[10]

Atypical antipsychotic drugs are widely used to treat delusions, hallucinations, aggression, and agitation, although adverse effects are frequent and severe;[11] gait abnormalities, somnolence, cerebrovascular adverse events, edema, extrapyramidal symptoms, urinary tract infections, and mortality have been reported.[12] These adverse effects are important causes of antipsychotic drug discontinuation.

Cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists have been used to treat cognitive impairment in dementia. A recent study showed that rivastigmine and memantin improved BPSD in Alzheimer's dementia.[13] Furthermore, ac-

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cording to recent guidelines presented by the Movement Disorder Society, rivastigmine is efficacious for the treatment of dementia in PD.[14]

Therefore, we aimed to investigate the efficacy of rivastigmine for BPSD in PDD. The effect of rivastigmine on caregiver distress was also assessed.

MATERIALS & METHODS

Patients

Twenty-three patients diagnosed with PDD at the movement disorder outpatient clinic of Seoul St. Mary's Hospital, Seoul were enrolled. The diagnosis was based on UK PD Society Brain Bank clinical diagnostic criteria and clinical diagnostic criteria for probable PDD.[15,16] Clinical information included age, gender, disease duration, a history of hypertension, diabetes mellitus, heart disease, or dyslipidemia, and current medication. Data from complete physical and neurological examinations, laboratory tests, and brain magnetic resonance imaging were obtained. Patients 1) with a history of stroke, or other neurological and psychiatric disorders, 2) atypical PD or secondary Parkinsonism, or 3) secondary causes of dementia were excluded. Patients who were undergoing other clinical research or were taking the study medication for other metabolic disorders, or were pregnant were also excluded.

All patients were on antiparkinsonian medications. The equivalent daily dose of levodopa was calculated as follows: dose of levodopa plus dose of dopamine agonists multiplied by equivalents (= 1 × levodopa dose + 0.75 × controlled release dose + 0.33 × entacapone + 20 × ropinirole dose + 100 × pramipexole + 10 × selegiline + 1 × amantadine).[17] All patients were diagnosed as having dementia for the first time upon enrollment in this study. No PD patients had ever taken anti-dementia drugs prior to this study.

Stable doses of levodopa, dopamine agonists, monoamine oxidase B inhibitors, amantadine, and catechol-O-methyltransferase inhibitors were administered from one month before the clinical trial to the end of the trial. Anticholinergic drugs that had adverse effects on cognition[18] and antipsychotics, antidepressants, anxiolytics, and sedatives that had effects on BPSD were not permitted.

Each patient gave informed consent for participation before entry. The Institutional Review Board of Seoul St. Mary's Hospital, Catholic University of Korea, Seoul approved the study protocol. All procedures complied with ethical standards for human investigations and the principles of the Declaration of Helsinki.

Study design

This was a prospective, longitudinal, open-label, observational, single center, 6-month clinical trial on the effect of rivastigmine for improving BPSD and reducing caregiver burden in PDD patients. Baseline data were obtained 15 days before starting rivastigmine. At the second visit, a rivastigmine was administered and titrated to all patients for four weeks. Adverse effects were examined on the third visit. All subjects were administered a maintenance dose of rivastigmine for 20 weeks. After twenty weeks, final assessments were performed on patients and their caregivers.

Clinical evaluations

General cognitive status and dementia severity were evaluated using the Korean version of the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Global Deterioration Scale (GDS). Parkinsonian motor symptoms were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) part III, and the modified Hoehn and Yahr scale when medicated.

To assess neuropsychiatric symptoms, the Neuropsychiatric Inventory (NPI) was used.[19] The NPI is composed of questions in 12 different categories covering four major neuropsychiatric symptom domains: mood, apathy, agitation, and psychosis. Symptom frequency was rated on a scale of 1 to 4 (1 = less than once a week; 2 = once a week; 3 = several times a week; 4 = everyday), and severity was rated on a scale of 1 to 3 (1 = mild; 2 = moderate; 3 = severe). A composite score ranging from 1 to 12, defined as the product of frequency and severity, was calculated. The important aspect of caregiver distress was also recorded and scored for each neuropsychiatric symptom complex. The caregiver was asked to rate their own emotional or psychological distress caused by each symptom on a scale of 0 to 5 (0 = no distress; 1 = minimal; 2 = mild; 3 = moderate; 4 = moderately severe; 5 = very severe). A total caregiver distress score was obtained by summing the individual scores on the 12 items.

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Statistical analysis

Statistical analyses were performed with SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). All demographics were reported using the mean, standard deviation, number, and percentage. Because of the relative small number of cohorts and the non-normal distribution of NPI data, nonparametric Wilcoxon signed ranks test (two-tailed) was used to compare neuropsychiatric symptoms and caregiver distress between baseline and 6 months after rivastigmine treatment. A p value < 0.05 was considered significant.

Table 1. Clinical and demographic characteristics of patients at baseline and 6 months after rivastigmine treatment

Variables	Baseline	6 months	*p* value
Age (years)	74.7 ± 5.9	-	
Sex, male (%)	11 (47.8)	-	
Hypertension (%)	10 (43.5)	-	
Diabetes mellitus (%)	3 (13.0)	-	
Heart disease (%)	3 (13.0)	-	
Dyslipidemia (%)	2 (8.7)	-	
Current or ex-smoker (%)	3 (13.0)	-	
Disease duration (years)	3.5 ± 3.7	-	
UPDRS part III	24.7 ± 14.8	24.7 ± 14.9	1.000
Hoehn and Yahr stage	2.2 ± 0.8	2.1 ± 0.7	0.665
MMSE	19.1 ± 4.2	19.7 ± 3.9	0.012*
CDR	1.1 ± 0.6	1.0 ± 0.5	0.063
GDS	3.7 ± 0.8	3.8 ± 0.8	0.083
Levodopa equivalent dose (mg)	574.2 ± 415.3	-	

Data represent mean ± standard deviation or numbers of patients (percentage). Analyses were performed by Wilcoxon signed ranks test. *p < 0.05. UPDRS: Unified Parkinson's Disease Rating Scale, MMSE: Mini-Mental Status Examination, CDR: Clinical Dementia Rating, GDS: Global Deterioration Scale.

Table 2. Changes in neuropsychiatric inventory between baseline and 6-month rivastigmine treatment

Neuropsychiatric inventory	Baseline	6 months	*p* value
Total score	19.7 ± 19.1	14.3 ± 21.6	0.049*
Delusions	1.1 ± 2.0	1.0 ± 2.8	0.674
Hallucinations	1.3 ± 2.8	0.3 ± 0.9	0.048*
Agitation and aggression	1.2 ± 2.4	1.1 ± 2.8	0.592
Depression and dysphoria	3.2 ± 3.7	1.4 ± 2.7	0.001†
Anxiety	3.5 ± 4.3	3.1 ± 4.9	0.529
Euphoria	0.4 ± 0.2	0.0 ± 0.0	0.317
Apathy	2.8 ± 3.8	1.4 ± 3.1	0.131
Disinhibition	0.8 ± 2.1	1.0 ± 3.1	0.588
Irritability and lability	1.3 ± 2.7	2.1 ± 3.8	0.292
Aberrant motor behavior	1.1 ± 2.1	1.6 ± 3.7	0.598
Sleep disturbance	1.8 ± 3.1	1.3 ± 3.5	0.475
Appetite changes	1.5 ± 2.5	0.2 ± 0.7	0.024*

Data represent mean ± standard deviation. Analyses were performed by Wilcoxon signed ranks test. *p < 0.05, †p < 0.001.

RESULTS

Of the 23 patients in total, 11 were men. The mean age was 74.7 ± 5.9 years and mean PD duration was 3.5 ± 3.7 years. Ten patients had hypertension, 9 had diabetes, 2 had dyslipidemia, and 3 had heart disease. Three patients were current smokers and 20 patients were non-smokers. The mean UPDRS part III score was 24.7 ± 14.8 and mean Hoehn and Yahr score was 2.2 ± 0.8. As for cognitive status, the mean MMSE score was 19.1 ± 4.2, mean CDR score was 1.1 ± 0.6, and mean GDS score was 3.7 ± 0.8. Patients were administered levodopa (all patients) and a dopamine agonist (10 patients), entacapone (15 patients), or amantadine (1 patient). The mean levodopa equivalent dose was 574.2 ± 415.3 mg (Table 1).

All except one patient exhibited one or more neuropsychiatric symptoms. Depression (82.6%) was the most frequent neuropsychiatric symptom, followed by anxiety (73.9%), apathy (56.5%), and sleep disturbance (47.8%). Delusions, hallucinations, agitation, and aggression, disinhibition, irritability and lability, aberrant motor behavior, and appetite changes occurred in 17–35% of patients. Euphoria was observed in only one patient.

The mean total NPI composite score at baseline was 19.7 ± 19.1 and total caregiver distress score was 8.1 ± 6.4. NPI composite scores and caregiver distress scores were highest in the anxiety domain with 3.5 ± 4.3 and 1.4 ± 1.3, respectively, whereas those of depression were 3.2 ± 3.7 and 1.3 ± 0.9, respectively, and those of apathy were 2.8 ± 3.8 and 1.0 ± 1.3, respectively (Table 2 and 3).

Of the enrolled patients, 20 were administered a transdermal rivastigmine patch and 3 were administered an oral agent. The mean dose of transdermal rivastigmine was 6.1 ± 2.3 mg and that of oral rivastigmine was 8.0 ± 1.7 mg. After 24 weeks of rivastigmine treatment, general cognitive functions measured by MMSE, CDR, and GDS tended to improve (Table 1) and neuropsychiatric symptoms were significantly improved (p = 0.049). Patients reported improvements in the domains of hallucination, depression, and appetite after rivastigmine treatment (Table 2). Caregiver distress scores decreased from 8.1 ± 6.4 to 5.4 ± 7.4 (p = 0.020). Caregivers were less distressed by hallucinations (p = 0.026), depression (p = 0.003), apathy (p = 0.009),

and appetite changes (p = 0.023) after rivastigmine treatment (Table 3). All patients were well controlled during rivastigmine treatment and no serious adverse events occurred.

DISCUSSION

Neuropsychiatric symptoms were frequently observed in the enrolled PDD patients. All except one patient (95.7%) presented with one or more neuropsychiatric symptoms. The most common symptoms were depression, anxiety, and apathy. Caregiver distress was highest with PDD patients who exhibited anxiety, followed by depression, and apathy. This is consistent with the results of previous studies.[1-3]

In this study, BPSD tended to improve after rivastigmine treatment and caregiver distress was decreased. These findings are consistent with those of previous studies. In an open label trial of rivastigmine that included 15 PDD patients, NPI scores decreased after 14 weeks of treatment but increased after 3 weeks of withdrawal.[20] Another 24-week randomized, multicenter, double-blind, placebo-controlled clinical study of 541 patients showed that NPI-10 scores were reduced from baseline to a greater degree in the rivastigmine group than in the placebo group.[21] In the present study, symptoms of depression improved significantly after 24 weeks treatment. This might be due to stimulation of the 5-HT1A receptor by rivastigmine, which was recently investigated in mice.[22] In addition, rivastigmine treatment improved appetite in patients with PDD. Generally, loss of appetite was reported as one of early side-effects of rivastigmine treatment in patients with PDD.[21] Therefore, this finding is a contradictory, and we can speculate that improvements of depression and apathy following rivastigmine treatment influence appetite change.

The effects of rivastigmine on BPSD in Alzheimer's dementia are variable. In a 6-month study, changes in NPI score were not different between the rivastigmine and placebo groups.[23] In another 12-month study, NPI scores were significantly lower; however, only one domain (agitation and aggression) improved and the remaining 11 domains were not significantly different.[13]

This study has several strengths and weaknesses. The major strength was that PD patients in this study were diagnosed with dementia for the first time upon enrollment and had not previously taken any anxiolytics, antipsychotics, antidepressants, or anti-dementia drugs. Since these drugs improve symptoms, total NPI scores may have been lower in patients using these medications. In addition, we used fixed doses of antiparkinsonian medications for the entire study period because antiparkinsonian medications are associated with behavioral disturbances and neuropsychiatric symptoms.[24] Many neuropsychiatric symptoms in PD were classically considered to be associated with antiparkinsonian medication. This is based on common clinical experience that psychotic symptoms are closely linked with dopaminergic treatment, while dopamine receptor blockers can alleviate these symptoms.[25] Therefore, use of fixed doses of antiparkinsonian drugs can block the important bias associated with worsening neuropsychiatric symptoms in PD.

Several limitations were also identified. Since this study was conducted in a single center, the number of patients was relatively small. In addition, the study was open-labeled and not-blinded and therefore did not include placebo treatment. Therefore, the extent of improvement in neuropsychiatric symptoms could not be precisely compared. Second, the duration between PD onset and dementia diagnosis was relatively short and the baseline global mental functions and neuropsychiatric symptoms were not severe. This study enrolled only mild dementia patients with PD and therefore, the NPI data can be skewed and further studies are needed in advanced patients with PD. Finally, we did not classify the types of dementia.

Table 3. Changes in caregiver distress scores between baseline and 6-month rivastigmine treatment

Caregiver distress score	Baseline	6 months	p value
Total score	8.1 ± 6.4	5.4 ± 7.4	0.020*
Delusions	0.5 ± 0.9	0.3 ± 0.8	0.194
Hallucinations	0.6 ± 0.9	0.1 ± 0.3	0.026*
Agitation and aggression	0.5 ± 0.9	0.6 ± 1.2	0.809
Depression and dysphoria	1.3 ± 0.9	0.6 ± 1.0	0.003†
Anxiety	1.4 ± 1.3	1.3 ± 1.6	0.512
Euphoria	-	-	1.000
Apathy	1.0 ± 1.3	0.3 ± 0.5	0.009†
Disinhibition	0.3 ± 0.8	0.4 ± 1.2	0.854
Irritability and lability	0.6 ± 1.2	0.9 ± 1.3	0.286
Aberrant motor behavior	0.5 ± 0.9	0.5 ± 1.0	1.000
Sleep disturbance	0.8 ± 1.0	0.5 ± 1.2	0.367
Appetite changes	0.7 ± 1.0	0.1 ± 0.3	0.023*

Data represent mean ± standard deviation. Analyses were performed by Wilcoxon signed ranks test. *p < 0.05, †p < 0.001.

In conclusion, the effects of rivastigmine on neuropsychiatric symptoms and caregiver distress in PDD were confirmed in this study. Furthermore, improvements in hallucination, depression and appetite changes were observed, and caregiver distress due to BPSD was significantly reduced. Additional large, randomized, placebo-controlled studies are required.

Conflicts of Interest

The authors have no financial conflicts of interest.

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