A dopamine agonist, pramipexole, and cognitive functions in Parkinson's disease

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A NON-ERGOT DOPAMINE AGONIST, PRAMIPEXOLE, AND COGNITIVE FUNCTION IN PARKINSON'S DISEASE

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PD – Parkinson’s disease

DA – Dopamine

Abstract

Cognitive decline in Parkinson's disease (PD) has been observed in the domains of visuospatial capacity, memory and frontal lobe functions. The contributions of dopaminergic system to cognitive dysfunction in PD and the cognitive effect of dopamine agonist receptor remain controversial. The aim of this study was evaluate the influence on a non-ergot dopamine receptor agonist pramipexole on cognitive functions in PD patients. Two groups of patients with idiopathic PD (8 patients in each group) were investigated during one year of treatment. The patients involved in the study were selected according to dopamine agonist medication. While all patients were on levodopa and selegiline treatment only one group of patients (8 patients) received dopamine agonist pramipexole (as Mirapexin) 3-4 mg/day. Two groups did not differ for the gender ratio, age, disease duration and years of education. Cognitive testing was performed in all patients using Verbal Fluency Test (VFT, category and letter fluency) and Hooper Visual Organization Test (HVOT) to assess frontal lobe functions, including attention and integrate function. Both groups of PD patients demonstrated significant cognitive decline compared to controls ($p<0.05$) according to visuospatial capacity and executive function. Semantic fluency was slightly better in pramipexole group but did not reach significance ($p<0.05$). In conclusion we can say the further studies are needed with bigger number of patients included to explore the influence of dopaminergic medication on cognitive function in Parkinson's disease.

Key words: Parkinson's disease, cognitive functions, dopamine agonists, pramipexole, verbal and category fluency, The Hooper Visual Organization Test

Introduction

Parkinson's disease (PD) has long been conceived to be mainly a motor disorder. In the last few decades it has been increasingly more recognized that many patients with PD will experience cognitive decline in the course of their illness (1). Cognitive impairment in PD patients typically involves executive functions (defined as planning and performance of goal-directed behaviour and measured by tests assessing abilities such as planning, set shifting, set maintenance), attention and visuo-spatial functions (2). The mechanisms underlying cognitive impairment in PD probably involve impaired activity in fronto-striatal pathways subserving cognitive functions (3). Current age, age of onset and disease duration exert important effects on cognitive functions in PD patients (4). The effect of antiparkinsonian medication on cognitive performance is another confounding factor. Dopamine (DA) agonists have shown beneficial therapeutic effects on motor symptoms in PD, but their influence on cognitive functions is still controversial. Some studies suggest that DA ameliorates a certain frontal lobe function, such as focused attention (5), but other failed to demonstrate cognitive improving in patients treated with a DA agonist (6). In fact, the effects of levodopa and DA on cognitive functions have been reported as beneficial as well as deleterious (7). Pramipexole is a novel non-ergoline dopamine agonist with high binding specificity for the dopamine D2 receptor family and with preferential affinity to the dopamine D3 receptor subgroup (8). Clinical trials with pramipexole as monotherapy and as an adjunct to levodopa have shown the compound to be safe, well tolerated, and efficacious (9). However the recent study form Brusa et al (10) indicates that pramipexole slightly worsens cognitive function in PD patients compared to an off-treatment condition. The negative influence on cognition was explained by unbalanced stimulation of D2-receptor subtypes alone by pramipexole. The aim of this study is to evaluate the influence of the DA agonist pramipexole on cognitive functions in PD patients already treated with levodopa.

Material and Methods

Subjects

Sixteen patients referred to the Movement Disorders and Clinical Neuropharmacological Centre, Neurological Department, Zagreb School of Medicine, was investigated during one year of treatment. All subjects fulfilled the UK Parkinson's Disease Society Brain Bank clinical criteria for PD (11). An exclusion criterion was clinical evidence of possible dementia assessed using the mini mental state examination (MMS). Only patients scoring above 24 on the MMS were included in the study. The patients with idiopathic PD were divided into two groups of 8 patients each, according to DA agonist medication. While all the patients received levodopa and selegiline, one group (8 patients) has been additionally treated with the DA agonist pramipexole (Table 1). Eight control subjects (four female and four male), matched for age (mean age 56.3 ± 9.3, range 40-66) and educational level (mean years 12.5 ± 2.8, range 8-17), with no history of central nervous system disorders, were examined. Controls were also given the MMS with the same inclusion threshold as the patients (>24). The two groups of PD patients and controls did not differ for the gender ratio, age and years of education (Table 1).

All the subjects gave their informed consent to participation in the study and the local research ethics committee approved the study.

Neuropsychological assessment

Neuropsychological testing was performed to assess the frontal lobe functions, including attention and integrated functions. Cognitive tests included the Verbal Fluency Test (semantic and letter fluency) and the Hooper Visual Organization Test (12,13). Semantic fluency was evaluated by asking subjects to generate in one-minute periods as many different items as possible from the category of animals. Subjects were provided superordinate categories. In letter fluency, subjects

were instructed to generate words starting with a specific letter of the alphabet (FAS). They were instructed that proper nouns and words with the same stem but different endings would not be counted. The score was the number of different words produced in one minute.

On the Hooper Visual Organization Test subjects recognized cut up and rearranged pictures of 30 common objects.

Statistical analysis

The effect of levodopa alone, levodopa and DA agonist pramipexole on cognitive functions was assessed by means of one-way ANOVA. Post hoc comparisons were performed by Scheffe test. Accepted significance level was $p<0.05$.

The software package Statistica v. 5.5 was used for statistical analysis.

Results

The scores on the tasks are reported in Table 2. A one-way ANOVA showed a significant effect for group regarding verbal fluency ($F=13.64$, $p<0.001$), semantic fluency ($F=3.92$, $p<0.05$) and the Hooper Visual Organization Test ($F=18.98$, $p<0.001$). Post hoc analysis (Scheffe test) demonstrated that PD patients performed worse on verbal fluency, semantic fluency and the Hooper Visual Organization Test ($p<0.05$) compared to age and educational matched controls. However there was no difference between PD patients treated with levodopa alone or levodopa combined with pramipexole (Scheffe test, $p<0.05$).

In semantic categories tasks provided with superordinate categories there was no difference in cognitive performance of PD patients compared to the controls (Table 2). Semantic fluency was slightly better in pramipexole group, but did not reach statistical significance (post hoc analysis, Scheffe test, $p>0.05$).

Discussion

Executive function deficits are among the most prominent cognitive deficits in PD, and may be one of the earliest signs of cognitive deterioration in the disorder (14). Regarding these fact we wonted to explore the influence of DA agonist pramipexole on executive function in PD patients.

Letter and category fluency tests were originally developed to assess fluency in aphasic patients, but impaired verbal fluency could be also a sign of executive dysfunction. To generate words in these tasks, subject must plan and initiate a systematic search of memory (15). Performance in letter fluency test is reported both as intact (16) and impaired in PD patients (17). Compared to controls, our PD patients showed significantly inferior performance in this task. In trials calling for semantic category, the patients did not differ from controls. They were provided with superordinate categories to assist retrieval, and maybe this is the reason for the intact category fluency in PD patients. More explicit instructions could have beneficial effect, because PD patients have difficulty in initiating cognitive strategies for retrieving stored information. Some studies reported impairment in category fluency tasks in PD patients and their normalization when more explicit instructions were provided (18).

Our patients were worse in the Hooper Visual Organization Test compared to the controls. The Hooper Visual Organization Test is a measure of visuospatial processing commonly employed in neuropsychological assessment. Huntington's disease patients demonstrate early in the course of the disease impairment on The Hooper Visual Organization Test, and actually their performance was highly discriminative of early symptomatic patients from asymptomatic gene carriers (19). Huntington's disease is characterised by striatal pathology and patients early in the course of the disease demonstrate specifically cognitive impairment caused by frontostriatal dysfunction (20). On the other hand The Hooper Visual Organization Test is a measure of visual integration ability, but also requires elementary vocabulary skills and the ability to label common objects. Diminished

performance in this test may be due to difficulty to name the objects or to impaired visual organization. Verbal disturbances, primarily associated with word finding, are common in PD patients (21).

Although PD patients treated with pramipexole had a higher Hoehn and Yahr stage than those treated with levodopa, there was no difference in cognitive performance. The benefit of levodopa treatment on cognition is usually less pronounced than that on motor symptoms (22). Some specific cognitive deficits may recover whereas others remain unimproved (23). Our results indicate dissociation of specific cognitive functions and motor symptoms in PD. This is consistent with the view that most cognitive functions in PD are more dependent on nondopaminergic mechanisms than the motor symptoms (24).

There was no significant effect of the DA agonist pramipexole on cognitive test performance in PD patients compared to levodopa, despite their different mode and site of therapeutic actions. Recent study from Brusa et al (25) demonstrates that pramipexole slightly worsens cognitive function in PD patients compared to an off-treatment, contrary to effect exerted by levodopa and DA agonist pergolide. These results were explained by D1 and D2-receptors stimulation produced by levodopa and pergolide, contrary to stimulation of D2 and D3 exerted by pramipexole. These findings suggest that D1-receptor stimulation is necessary to spare or recover cognitive function in PD patients. Other reason for cognitive decline in patients treated by pramipexole was explained as D3-receptors stimulation, which is thought to produce attentional deficit. Our results did not show cognitive differences between PD patients treated with pramipexole or levodopa alone. However we did not compare a treatment effect regarding the wash out condition or monotherapy with pramipexole on cognitive functions. Our results suggest that pramipexole in combination with levodopa does not produce cognitive dysfunction in mild/moderate PD patients. A limitation of our study is a small sample of control and PD patients. Subjects took pramipexole for no more than

one year. This duration is a relatively short period of treatment, and chronic treatment with the DA agonists is needed to further elicit the influence of DA pramipexole and levodopa on cognitive function in PD patients.

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Table 1. Patient data

	PARKINSON'S DISEASE		CONTROLS
	LEVODOPA TREATMENT	PRAMIPEXOLE TREATMENT	
Number of patients	8	8	8
Female/Male	4/4	3/5	4/4
Mean age (SD), range	56.1 (7.5), 43-63 years	55.8 (6.7), 41-63 years	56.3 (9.3), 40-66 years
Years of education (SD), range	11.9 (4.3), 7-15 years	12.3 (4.4), 8-17 years	12.5 (2.8), 8-17 years
Hoehn and Yahr stage	2.5	3	

Table 2. Neuropsychological performance of the patients with Parkinson's disease treated with levodopa or DA agonist pramipexole and of the control group

	PARKINSON'S DISEASE		CONTROLS
	LEVODOPA TREATMENT	PRAMIPEXOLE TREATMENT	
Letter fluency, mean (SD)	26.1 (5.9)*	27.4 (5.5)*	31.4 (5.3)
Semantic fluency, mean (SD)	17.1* (4.7)	18.2 *(9)	20.5 (5.4)
Hooper Visual Organization Test, mean (SD)	17.1(3.8)*	17.8 (7.1)*	22.6 (6.2)
Semantic fluency provided with superordinate categories, mean (SD)	15.5 (5.9)	16.1 (5.5)	16.7(5.3)

* One-way ANOVA, post hoc Scheffe Test, $p<0.05$