The effect of dopamine agonists on cognitive functions in non-demented early-mild Parkinson's disease patients

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Summary

The effect of dopamine agonists (DAs) on cognition in Parkinson's disease (PD) is not yet completely established. Previous papers reported a worsening effect on some cognitive functions with some DAs, but not with others, suggesting that DAs may differently affect cognition in PD patients according to their pharmacological characteristics.
We set out to test the effect of rotigotine and cabergoline on cognitive functions in a group of forty non-demented early-mild PD patients (H &Y <2). Subjects were randomly divided into two groups and evaluated in a randomized cross-over study using neuropsychological tests; at the same time, motor function was monitored under three different treatment conditions: DA (rotigotine or cabergoline), L-dopa, and off therapy. Rotigotine and cabergoline were chosen because while they share a mixed D1 and D2 receptor profile, the former is non-ergolinic and the latter ergolinic.
No significant differences were found in cognitive function between the basal condition and the DA treatments. On the basis of the present data, which we compare with previous findings regarding pramipexole IR and pergolide, we hypothesize that combined stimulation of both dopamine receptor families, as occurs with rotigotine, cabergoline, L-dopa and pergolide, may preserve cognitive functions more than pure D2 family stimulation.

KEY WORDS: cabergoline, cognition, pharmacokinetic, rotigotine

Introduction

As well as providing relief from many of the motor symptoms of Parkinson's disease (PD), the use of levodopa (L-dopa) might exert an effect on certain aspects of cognition involving flexibility and working memory, which tap into frontostriatal dopamine pathways (Kehagia, et al., 2010). Conversely, the cognitive effect of dopamine agonist (DA) treatment in these patients is still controversial and, to date, a topic dealt with in very few clinical studies.
A previous study in a population of non-demented mild PD patients aged about 55 years (Brusa et al., 2005) showed that pergolide, an ergot-derived DA, does not affect cognition; conversely, another study in a similar population (non-demented patients aged around 55, affected by early-mild PD) showed that pramipexole, a non-ergot DA, may slightly impair short-term verbal memory and attention and executive functions (Brusa et al., 2003). It is worth noting that both drugs stimulate D2 receptors. However, unlike pergolide, pramipexole does not stimulate D1 receptors, but preferentially binds to D2, D3 and D4 receptors (Perachon et al., 1999). Thus, it was proposed that the pramipexole-induced cognitive deficits in the studied mild PD patients may reflect this drug's different receptor affinity.
Against this background, we set out to investigate the possible cognitive effect of rotigotine and cabergoline, two DAs with a broad spectrum of action across the D1-D5 receptors. In addition to their D3 activity, rotigotine and cabergoline have considerable affinity for D1 receptors, unlike other non-ergot DAs, such as pramipexole and ropirinole (Naidu and Chaudhuri, 2007; Gerlach et al., 2003). A population of non-demented early-mild PD patients was divided into two arms and tested under three treatment modalities: DA treatment (rotigotine or cabergoline in two arms), L-dopa, and off-treatment condition.
Moreover, since a comparison with previous studies was necessary, we conducted the study exploring the same cognitive functions (through the administration of a similar test battery) and utilizing the same study protocol used in the previous studies on pramipexole and pergolide (Brusa et al., 2003, 2005) in homogeneous populations of PD patients.

Materials and methods

Forty right-handed patients (18 women and 22 men) diagnosed with PD according to the London Brain Bank Criteria (Daniel and Lees, 1993) were selected for our study. The clinical characteristics of the patients and their Unified Parkinson's Disease Rating Scale (UPDRS section III) scores are reported in table I (over). All the patients were under DA treatment and were investigated in order to establish whether their DA dose should be increased or L-dopa introduced into their treatment. The aim of our study was to compare the different neuropsychological effects of L-dopa and DA (rotigotine or cabergoline) treatment, independently of the possible influ-

ence of motor condition; therefore, in each patient, drug regimens were adjusted to obtain similar motor performances with DA and with L-dopa. Since, in advanced stages of PD, L-dopa is known to induce a greater motor improvement than DAs, patients with a Hoehn and Yahr (Fahn and Elton, 1987) score higher than 2.5 were excluded from the study. Other exclusion criteria were detection, at screening evaluation, of: mental decline (MMSE <27/30), major psychiatric disorders, psychoactive drug intake, alcoholism, strokes or previous neurosurgical operations.

Patients were randomly assigned to two different groups to separately test the effect of the two DAs, in comparison with L-dopa, in each group. All the subjects were included in our study after a fifteen-day wash-out period. At the end of the wash-out, a first neuropsychological assessment was performed. Patients were then randomly divided into two treatment arms: half of them received L-dopa first, and the other half received rotigotine or cabergoline first.

After three months of treatment with the first drug (L-dopa or rotigotine/cabergoline), the patients were assessed with neuropsychological tests.

The patients were then crossed over to the second drug. Three months later they were re-assessed with the same neuropsychological battery.

The treatments consisted of one daily dose of rotigotine (mean final dose 8±1.19 mg, mean ± SD) or cabergoline (mean final dose, 6±1.5 mg daily), or three daily doses of L-dopa (mean daily dose 357.5±138.46 mg).

Motor score, assessed by UPDRS, was identical under the different treatments.

Cognitive functions were assessed using the following tests:

– MMSE (Mini-Mental State Examination)

– Memory: Rey Auditory Verbal Learning Test (RAVLT) (Carlesimo et al., 1996) (cut-off for immediate recall: 28.52; cut-off for delayed recall: 4.68); Digit Span test (cut-off forward: 3.75; backward: 2) (Brusa et al., 2005).

– Attention and executive functions: Trail Making Test (TMT) (cut-off: A:93; B:282; B-A:186) [Brusa et al., 2005]; Stroop Color-Word Naming Task (cut-off W: 75; C: 58; CW: 25) (Brusa et al., 2005); Tower of London (cut-off 28.3) (Krikorian et al., 1994);

– Deductive intelligence: Raven Matrices Test (cut-off:17.5) (Brusa et al., 2005);

– Verbal and semantic fluency: FAS (cut-off: 17); semantic fluency (cut-off: 9) (Brusa et al., 2005).

These tests were always administered in the morning one hour after the first morning dose of L-dopa and one hour after the patch was applied, or when the ergolinic DA (cabergoline) assumed was at study state. When possible (RAVLT), re-tests were performed using parallel test forms, to avoid learning-related phenomena. Moreover, the order of presentation of the parallel forms was counterbalanced appropriately.

The UPDRS section III was administered at every neuropsychological assessment to verify similarity of motor functions (within ±10%) under L-dopa and rotigotine/cabergoline (Table I).

Statistical analysis

For both groups, the effect of L-dopa, DAs and the off-treatment condition on cognitive functions was assessed by means of a two-way ANOVA utilizing two within factors, first “treatment” with three levels (off-treatment vs L-dopa vs DA), and second, “tests”, which included, separately, attention and function tests, memory function tests, and verbal and semantic fluency tests. Post hoc comparisons were performed by Tukey test when possible, according to the significance of the main factors or their interaction. Results were corrected with Greenhouse Gaisser correction when necessary. The accepted significance level was $p<0.05$.

In the two groups, UPDRS section III scores in the different treatment conditions were evaluated by means of non-parametric one-way Friedman ANOVA for repeated measures (off-treatment vs L-dopa vs DA), followed by the Wilcoxon test.

The comparison of the present data with previous neuropsychological data obtained in patients tested while on pramipexole and pergolide is reported in the discussion, together with comparison of the clinical characteristics (age, disease duration, mean education) and UPDRS scores between the populations. A double-tailed Student’s t-test was used to compare the clinical data, while the Mann-Whitney test was used to compare the mean UPDRS score between populations in different treatment conditions: off-treatment, L-dopa treatment, DA treatment. The significance of neuropsychological data was studied only within each population and no direct comparison was performed between the DAs.

Table I - Patients’ clinical characteristics

	Rotigotine group (n=20)			Cabergoline group (n=20)		
Mean age	56±5.63 years			57±2.13 years		
Mean disease duration	2.3±1.4 years			3.1±0.5 years		
Mean education	10.2±2.7 years			10.5±3.4		
UPDRS (section III) score	Rotigotine phase 17.23±2.8	L-dopa phase 18.12±4.63	Wash-out phase 29.02±3.1	Cabergoline phase 19.23±1.4	L-dopa phase 17.12±2.14	Wash-out phase 28.11±4.2

However, the effect of each agonist was compared to that of L-dopa in each population.

Results

Neuropsychological and clinical data

Table I shows the mean rating scores on UPDRS section III, administered at the time of the neuropsychological evaluations. As stated in the methods, no significant changes were found in the UPDRS evaluation between L-dopa and DA treatment. On the contrary, all treatments significantly lowered the UPDRS score in comparison with the off-treatment condition ($p<0.01$). Tables II and III show the neuropsychological scores and ANOVA analysis results. All the studied patients reported scores at the high end of normal when tested in the wash-out condition. No significant difference was found between the off-treatment condition and L-dopa or rotigotine/cabergoline treatment.

Table II - Neuropsychological results in the three explored conditions - rotigotine group.

Tests		Rotigotine	L-dopa	Off condition	Performance change
Memory function					
RAVLT					
Total words trials 1-5		43.81±8.68	48.82±9.44	41.94±10.20	⇑
Long Delay Free Recall		9.77±2.42	10.49±2.76	9.26±2.56	⇑
Digit Span forward		5.86±1.41	5.88±1.10	5.75±1.11	⇑
backward		4.11±1.16	4.28+ 0.70	3.9±0.99	⇑
Verbal and semantic fluency					
Verbal fluency		35.00±7.82	36.71±12.40	30±11.37	⇑
Semantic fluency		18.83±5.33	17.38±6.00	16.85±5.68	⇑
ANOVA					
Drug effect		n.s.			
Test effect		F= 79.27 p>0.001			
Interaction		n.s.			
Attentional tests					
Trail Making	A	47.14±17.84	40.42±14.52	42.57±22.87	⇓
	B	86±29.44	75.42±10.81	98.42±25.56	⇓
	B-A	39.7±21.80	35±14.39	55.42±31.64	⇓
ANOVA					
Drug effect		n.s.			
Test effect		F=60.68 p>0.001			
Interaction		n.s.			
Stroop Test	W	98.44±14.11	109.71±14.98	98.8±25.0	⇑
	C	81.88±12.7	91.28±3.92	86.0±19.88	⇑
	CW	54.44±14.50	60.71±12.51	54.5±18.82	⇑
ANOVA					
Drug effect		n.s.			
Test effect		F=221.96 p>0.001			
Interaction		n.s.			
Tower of London		28.88±3.68	31.42±1.87	29.61±3.33	⇑
ANOVA					
Drug effect		n.s.			
Test effect		F=14.3 p>0.001			
Interaction		n.s.			
Deductive intelligence in the three explored conditions					
Raven Matrices		30±6.02	33.57±5.43	30.45±5.48	⇑
ANOVA					
Drug effect		n.s.			

Abbreviations: RAVLT=Rey Auditory Verbal Learning Test; n.s.=not significant.

Comparison with previous clinical and cognitive data

The comparison of clinical (UPDRS score, disease severity and disease duration, amount of drug intake) and demographic (age, sex) data between the present and previous populations did not demonstrate any significant differences. The motor score, compared in the off-treatment condition, or under L-dopa or DA treatment, did not differ significantly between the different populations. These findings showed that the subjects were homogeneous in terms of age, disease duration, and motor response to the drugs.

Table III - Neuropsychological results - cabergoline group.

Tests		Cabergoline	L-dopa	Wash out	Performance change
Memory function					
RAVLT					
Total words trials 1-5		44.67±7.35	47.02±10.33	45.11±11.02	⇑
Long Delay Free Recall		8.45±2.33	9.03±2.48	8.78±2.16	⇑
Digit Span forward		5.1±1.22	5.2±1.61	5.0±1.11	⇑
backward		3.6±1.72	3.5±1.21	3.3±0.62	⇑
ANOVA					
Drug effect		n.s.			
Test effect		p>0.001			
Interaction		n.s.			
Verbal and semantic fluency					
Verbal fluency		28.12±8.22	30.54±9.74	27.43±9.63	⇑
Semantic fluency		14.54±2.58	15.11±4.79	14.32±3.56	⇑
ANOVA					
Drug effect		n.s.			
Test effect		p>0.001			
Interaction		n.s.			
Attentional tests					
Trail Making	A	64.31±23.34	64.45±27.52	66.66±30.11	⇓
	B	144.5±77.11	150.6±79.83	156.9±81.13	⇓
	B-A	74.5±58.33	76.2±51.64	83.1±52.33	⇓
ANOVA					
Drug effect		n.s.			
Test effect		p>0.001			
Interaction		n.s.			
Stroop Test	W	98.5±21.32	98.9±20.65	94.5±19.11	⇑
	C	70.2±17.84	69.23±13.21	66.96±11.52	⇑
	CW	41.62±8.74	45.44±7.57	38.6±6.61	⇑
ANOVA					
Drug effect		n.s.			
Test effect		p>0.001			
Interaction		n.s.			
Tower of London		25.83±2.34	28.12±6.88	27.99±1.53	⇑
ANOVA					
Drug effect		n.s.			
Test effect		p>0.001			
Interaction		n.s.			
Deductive intelligence					
Raven Matrices		31.36±6.34	32.67±2.56	30.34±5.23	⇑
ANOVA					
Drug effect		n.s.			

Abbreviations: RAVLT=Rey Auditory Verbal Learning Test; n.s.=not significant.

Moreover, despite the use of cognitive test batteries that were not completely overlapping, the pre-treatment wash-out mean scores, obtained on neuropsychological assessment in the present population, were compared with those reported in the populations of the previous studies treated with pramipexole and pergolide (Brusa et al., 2003, 2005). No significant difference emerged, confirming that the populations were homogeneous also as regards their neuropsychological performances in basal conditions.

Previous neuropsychological data demonstrated that the improvement produced by L-dopa on verbal fluency (FAS) and on executive functions as evaluated by the Stroop test may not be replicated under treatment with pramipexole. The present data, comparing rotigotine/cabergoline to L-dopa, did not demonstrate any significant difference for the Stroop test and FAS. Moreover the worsening of California Short Term memory test, Trail Making and Matrices tests produced by pramipexole in comparison to the wash-out condition, was not replicated by rotigotine/cabergoline.

Discussion

The current study shows that, compared with the off-treatment condition, neither rotigotine/cabergoline nor L-dopa modify patients' cognitive performance.

The present study, when considered together with earlier reports, conducted with the same design (Brusa et al., 2003, 2005) on homogeneous non-demented PD patients, indicates that rotigotine and cabergoline, like pergolide but unlike pramipexole, do not worsen cognitive function. All of the studied patients reported scores at the high end of normal when tested in the wash-out condition, which possibly means that the lack of improvement observed when testing patients on L-dopa and/or on DAs can be explained by a "ceiling effect".

Moreover, other authors have reported absence of response to L-dopa in the same cognitive domains considered by us (Morrison et al., 2004; Leiva-Santana and Alvarez-Saúco, 2006), which suggests that the dopaminergic deficit is only one of the factors involved in the etiopathogenesis of the cognitive dysfunction in PD.

Although we previously suggested that the negative effect of pramipexole on cognition was possibly due to its affinity for D3 receptors, the results of the current study seem to argue against this hypothesis: rotigotine and cabergoline stimulate D3 (pK= 8-9 for rotigotine; Ki=1.27 nM for cabergoline) receptors with an affinity similar to that of pramipexole (Naidu and Chaudhuri, 2007).

Notably, the most remarkable difference between the drugs is that rotigotine and cabergoline (and pergolide), as opposed to pramipexole, behave as agonists at both dopamine receptor families, as does L-dopa. Thus, our data support the hypothesis that interaction with all the DA receptor subtypes (as shown by L-dopa and some DAs) has no impact at all on cognitive function.

D1 receptor stimulation by oral administration of an agonist in healthy humans has been reported to increase visuospatial working memory possibly through an action exerted on prefrontal D1 receptors (Müller et al., 1998). Moreover, activation of D1 receptors in the prefrontal cortex has been reported to increase the attentional performance of rats while the D1 antagonist reduced it (Granon et al., 2000). Furthermore, in the nucleus accumbens of rats, D1 receptor stimulation exerted more selective effects on attentional accuracy, while D2 receptor stimulation did not (Pezze et al., 2007).

On the contrary cognitive differences observed through our data cannot be attributed to pharmacokinetic differences between pramipexole IR, cabergoline, pergolide and rotigotine. The fact that last two drugs share the same Tmax excludes the hypothesis that the reported different results on cognitive domains may reflect a lower synaptic concentration during peak plasma levels with rotigotine.

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