Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels

Jaime Kulisevsky, 1 Asunción Avila, 1 Manel Barbanoj, 2 Rosa Antonijoan, 2 Marcelo L. Berthier 3 and Alexandre Gironell 1

1 Department of Neurology, and 2 Clinical Pharmacology Unit, Pharmacological Research Area, Sant Pau Hospital, Autonomous University of Barcelona, and 3 Service of Neurology, Virgen de la Victoria University Hospital, Málaga, Spain

Correspondence to: Jaime Kulisevsky, MD, Department of Neurology, Sant Pau Hospital, Sant Antoni M. Claret 167, 08025 Barcelona, Spain

Summary

The contribution of dopaminergic systems to cognitive defects in Parkinson's disease and the cognitive effects of levodopa remain controversial. The levodopa plasma levels and the neuropsychological performance of 10 parkinsonian patients with a stable motor response to the drug, and 10 matched parkinsonian patients with a 'wearing-off' phenomenon were studied 12 h after levodopa was withdrawn (time zero), and at 1 h and 4 h after an oral dose of levodopa (i.e. at '+1H' and '+4H'), to investigate whether discrete cognitive domains are more sensitive to levodopa in parkinsonian patients with the wearing-off phenomenon. Considering the 20 patients as a whole, levodopa significantly diminished the response time in verbal and visuospatial memory tests, the extradimensional matching test and the Wisconsin card sorting test (WCST), without significantly improving or worsening the patient's accuracy. A significant group-by-time effect was only evident in the WCST; while in stable patients levodopa produced no changes, wearing-off patients significantly reduced the number of categories achieved and had more perseverative errors at '+1H', recovering at '+4H'. These results confirm previous findings of selective adverse effects of levodopa on highly demanding executive tasks in Parkinson's disease and additionally suggest that some previous discrepancies between studies may be accounted for by lack of differentiation between stable and wearing-off conditions. 'Frontal' disturbances on neuropsychological tests with levodopa may become evident only after massive degeneration of the dopamine systems has occurred.

Keywords: levodopa; Parkinson's disease; cognition; executive functions; motor fluctuations

Abbreviations: UPDRS = unified Parkinson's disease rating scale; WCST = Wisconsin card sorting test

Introduction

Parkinson's disease is associated with relatively subtle cognitive impairment (for a review, see Brown and Marsden, 1990). Poor performance on neuropsychological tests may occur even in unmedicated patients in the early stages of the disease and may become part of fluctuating cycles in more advanced phases (Lees and Smith, 1983; Huber et al., 1987; Cooper et al., 1991). Deficits have been reported in different cognitive domains such as memory (Warburton, 1967; Wilson et al., 1980), visuospatial processing (Boller et al., 1984), attention (Downes et al., 1989) and concept formation and executive functions (Cools et al., 1984; Flowers and Robertson, 1985).

The pathophysiological basis of the cognitive impairment in Parkinson's disease remains unclear. The similarity of some cognitive deficits with those reported following focal lesions of the prefrontal cortex (Taylor et al., 1986), together with the role of dopamine in the modulation of complex circuits linking the basal ganglia with prefrontal cortex (Alexander et al., 1986), have supported the idea that changes in the levels of dopamine stimulation may modify cognitive performance (Taylor et al., 1986; Gotham et al., 1988). However, despite a considerable body of research, there is no consensus with regard to the effects of levodopa on cognitive functions in Parkinson's disease. Indeed, in
parkinsonian patients, levodopa has been reported to either improve (Bowen et al., 1975; Downes et al., 1989; Lange et al., 1992), impair (Gotham et al., 1988) or not affect (Pillon et al., 1989) frontal cognitive performance, and to improve (Meier and Martin, 1970; Arbit et al., 1970; Halgin et al., 1977; Rogers et al., 1987; Mohr et al., 1987; Cooper et al., 1992), impair (Huber et al., 1987, 1989; Poewe et al., 1991) or not affect (Rafal et al., 1984; Lange et al., 1992) memory functions.

Many studies dealing with the role of dopamine on parkinsonian cognition have examined patients before levodopa treatment and at various stages thereafter (Riklan et al., 1976; Portin and Rinne, 1980, 1987), or have studied the 'on' and 'off' states in the same patient (Brown et al., 1984; Rafal et al., 1984; Girotti et al., 1986; Gotham et al., 1988) but, to our knowledge, there have been no studies that compared the acute effects of levodopa on the cognitive performance between appropriately matched groups of stable and fluctuating patients at different levels of plasma levodopa concentrations.

In a study of 'frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa, Gotham et al. (1988), when confronted with some intriguing results (performance improving on some tests with levodopa and deteriorating in others) recommended studies in which patients were classified on an a priori basis according to their levels of dopamine depletion. The appearance of fluctuations in motor disability in response to levodopa can be viewed as evidence of disease progression as they probably indicate further dopamine cell loss and the deficiency of compensatory mechanisms, such as the capacity of the residual dopaminergic terminals to store the dopamine newly synthesized from a dose of levodopa (Chase et al., 1993). The advanced parkinsonism of many of these patients is associated with enhanced sensitivity to small changes of plasma levodopa concentrations and their peripheral pharmacokinetics of levodopa are highly correlated with the 'on' and 'off' states (Shoulson et al., 1975). If discrete cognitive deficits in Parkinson's disease arise, at least in part, from dysfunction of dopaminergic neuronal systems, either from dopamine deficiency in the caudate nucleus (Taylor et al., 1986) or from loss of mesocortical dopaminergic afferents to the prefrontal cortex (Javoy-Agid and Agid, 1980; Cooper et al., 1992), the cognitive status of the more denervated fluctuating patients should be more sensitive to acute changes of levodopa plasma levels. To investigate this hypothesis, we studied two groups of parkinsonian patients, 10 with stable and 10 with fluctuating motor responses. In order to plot the dose–response curves relating levodopa to cognitive function more accurately, we gave the patients, at three different plasma levodopa levels, a neuropsychological battery chosen to tap major aspects of cognitive functions known to be affected in Parkinson's disease.

Patients and methods

Subjects

Twenty non-demented patients regularly attending the neurology department of Sant Pau Hospital (Barcelona, Spain) with idiopathic Parkinson's disease (nine women and 11 men; mean age 63.3±7.4 years, range 45–77 years) participated in the study. Informed consent was obtained from all patients. Patients with a Mini-Mental State Examination (Folstein et al., 1975) score <25 were excluded. The patients either had a stable motor response to levodopa (n = 10) or a 'wearing-off' response (n = 10), but none of them had complex motor fluctuations (on-off phenomena). These stable and wearing-off patients were otherwise unselected (e.g. for the severity of the disease or the presence or absence of tremor). Fifteen of the 20 patients (seven stable and eight wearing-off) were also taking dopamine agonists. None of the patients had undergone neurosurgical procedures or were taking anticholinergic drugs. Table 1 shows the demographic and clinical data of the two groups of patients studied.

Procedure

Each patient was examined the day before the study and underwent a full experimental block in order to be familiarized with the test protocol. The antiparkinsonian medication was withdrawn overnight, resulting in a drug free interval of at least 12 h before the test dose. Patients arrived at the laboratory at 08.00. On the morning of the study patients were seated in a room adjacent to the examiner and given as much time as needed to complete two psychiatric rating scales: (i) the 21-item Beck depression inventory (Beck et al., 1961), a self-report scale for measuring the intensity of depressive symptomatology; (ii) the 20-item self-report scale for measuring state of anxiety of the STAI (Spielberger state–trait anxiety inventory) questionnaire (Spielberger et al., 1970). Medication was given at 10.00 and consisted of a single oral dose of levodopa (plus carbidopa or benzerazide) roughly equal to half of each patient's usual total daily dosage of levodopa (overall mean of 243.7±78.1 mg, range 100–375 mg; stable patients received 220.0±63.2 mg, range 100–250 mg; wearing-off patients received 267.5±87.4 mg, range 100–375 mg; t test, P = 0.183). No other antiparkinsonian medications were given. The assessments of motor symptoms were made using the motor subscale of the unified Parkinson's disease rating scale (UPDRS) (Fahn et al., 1987) and were obtained by the same examiner in the basal condition, just prior to levodopa ingestion, and when the patient determined that levodopa had achieved its usual beneficial effect (which in every case occurred in <1 h).

Plasma levodopa levels

Neuropsychological tests were carried out before ingestion of levodopa (basal level) and at 1 h and 4 h afterwards (i.e. at +1H and +4H). In all cases, blood was drawn at regular
Neuropsychological testing

Neuropsychological tests were administered always using the following fixed sequence.

(1) Motor performance, finger tapping test
Patients were asked to press a key on a recording device, repeatedly and as quickly as possible with the index finger. Each subject completed 12 trials of 10 s each. They were always asked to begin with the right index finger. Once the subjects completed the first trial they were instructed to continue with the left index finger and then to alternate left and right. The first six trials allowed no visual feedback apart from the actual finger movement during execution of the task. The next six trials were done with reinforcement of the behaviour, i.e. with direct visual feedback by presenting the performance on a screen as a rising coloured bar, whose position corresponded to the number of taps executed. The score for each hand was the average for each set of three trials of 10 s duration. The two averages were then combined.

(2) Verbal memory
This was examined using a word-list learning test. The subject was requested to learn 10 words appearing successively for 2 s each on a computer screen. A yes/no recognition of words from a subsequent 20-word list, with each word appearing for 2 s on the screen, was requested 1 min thereafter. Ten of the 20 recognition test words were drawn from the learned list whereas the other 10 words had not been presented earlier. The patient was asked to remain attentive to the screen and to indicate by pressing a key, as quickly as possible, whether each presented word had (‘yes’ key) or had not (‘no’ key) appeared in the learned list. The task was repeated with the same learning list in three successive trials. Three testing time points were chosen: zero time, +1 h, +4 h, and, in order to prevent a learning effect, different lists were given at each time point, making a total of 60 words (positive or negative). The word lists had been tested previously on healthy volunteers in our laboratory. Reaction time was also recorded. A time window of 2000 ms was applied in order to include delayed responses.

(3) Spatial memory
This was examined using a visual retention test. Recall of visuospatial material was assessed on a computer screen divided into 20 rectangles by six horizontal and five vertical lines. The patient was asked to learn this pattern of division. Afterwards, the lines disappeared from the screen and 10 white blocks appeared successively, one every 2 s. Each block appeared randomly occupying 10 of the previously delineated rectangles. The delineated rectangles reappeared on the screen 1 min later. The patient was asked to replace the 10 blocks on the corresponding rectangles with a cursor without taking into account the order in which they had appeared. The task was repeated in three successive trials with the same sequence of stimuli. As in the verbal memory tasks, the test was carried out at three different time points with a different sequence of stimuli presented at each time, so that the patient was required to locate correctly a total of 30 elements.

(4) Executive function

(4A) The Wisconsin card sorting test. This test (see Heaton, 1981) was administered in the original format (128 cards) by means of a computer program presenting the cards on the screen. This test requires the matching of cards to stimulus categories whose predetermined order is unknown to the subject. These categories change without warning according to an internal sequence. Correct responses depend...
solely on the use of error feedback. Performances were scored for categories completed and perseverative errors (Millner, 1963). Reaction time was also measured for each response.

(4B) Extra-dimensional matching, complex reaction time. This modification of the Stroop test (Stroop, 1935) consisted of 60 coloured stimuli that were the actual names of four colours (blue, green, red or yellow) presented randomly on a computer screen. Each colour name was printed either in the corresponding colour or in a different one from that written. The patient was required to press the 'yes' key when both the name and the colour coincided and the 'no' key when the name and colour did not match. The parameters recorded were: the number of correct, incorrect and delayed responses, and reaction time for each stimulus (time window 2000 ms).

Statistical analysis
Statistical analysis was performed using a two-way ANOVA including the between the factor ‘motor condition’ (patients with stable responses and patients with wearing-off responses to oral levodopa) and the factor ‘time’ (time point in relation with levodopa intake: basal, +1H, +4H) to all variables derived from the neuropsychological analysis. One-way ANOVA (factor time) was applied to the total sample. The UPDRS data were analysed by nonparametric two-tailed Wilcoxon or Mann–Whitney U test where appropriate. Statistical significance was set at $P < 0.05$.

Results
Plasma levodopa levels
No significant differences were found between stable and wearing-off patients in basal levels of plasma levodopa. However, although there were no significant differences in peak levodopa levels (in wearing-off patients, $1036.3 \pm 211.9$ ng ml$^{-1}$ and stable patients, $972.8 \pm 259.7$ ng ml$^{-1}$) there was a significant delay in the time to the peak levodopa level in stable patients (Fig. 1) (wearing-off, $45.0 \pm 29.4$ min; stable, $87.0 \pm 30.0$ min; Mann–Whitney U test, $P = 0.007$).

Motor findings
There were no significant basal differences in the total scores of the UPDRS motor subscale between wearing-off (57.2$ \pm $19.6 points) and stable (41.8$ \pm $12.4 points) patients. After levodopa intake, every patient improved their score and the patient group as a whole showed a marked improvement of the total UPDRS motor subscale (wearing-off, changed to $29.6 \pm 19.1$ points, $P = 0.009$; stable, changed to $32.7 \pm 13.0$ points, $P = 0.005$). Again, no significant differences were found between groups for the total UPDRS motor subscale.

Neuropsychological findings
Finger tapping test
Results of the finger tapping test are shown in Table 2. No significant differences between groups were observed in basal conditions either when the simple task was executed or when the behaviour was reinforced with visual feedback. Although levodopa intake increased the number of taps in the simple and reinforced tasks, this effect did not reach statistical significance either when considering the total sample or when stable and wearing-off patients were separately considered. However, when analysing the results of three trials of the test separately, the observed increment reached statistical significance at the third trial in the reinforced condition, both when the total sample was considered [$F(2,38) = 4.10$, $P = 0.024$] changing from $6.47 \pm 2.10$ taps in basal conditions to $7.19 \pm 2.10$ taps at $+1H$ and to $7.15 \pm 2.29$ taps at $+4H$, or when both subgroups were taken into account [factor time $F(2,36) = 4.08$, $P = 0.025$].

Verbal memory
Results of the verbal learning test are shown in Table 3. Three aspects of verbal memory functioning were analysed.

(i) Correct responses. There were no significant differences between groups in basal conditions in the number of correctly recognized words. No significant effects of levodopa intake were observed for the total sample or when each subgroup was separately considered. The same profile was obtained when correct positive and negative recognition were analysed separately (from all subjects in basal evaluation, positive: $23.65 \pm 5.23$; negative: $21.75 \pm 7.74$).

(ii) Time employed to produce the correct responses. There were no significant differences between groups in basal conditions. Although levodopa induced a decrease of this time at $+1H$, it did not reach statistical significance. However, when positive and negative responses were
Table 2  Finger tapping test

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>+1H</th>
<th>+4H</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without feedback on the screen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>19.87±6.3</td>
<td>21.20±6.2</td>
<td>20.91±7.1</td>
<td>P = 0.372</td>
</tr>
<tr>
<td>Stable</td>
<td>19.32±5.8</td>
<td>19.59±4.8</td>
<td>20.21±5.6</td>
<td>M: 0.498; T: 0.379</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>20.42±7.1</td>
<td>22.81±7.4</td>
<td>21.60±8.6</td>
<td>M×T: 0.518</td>
</tr>
</tbody>
</table>

| **With feedback on the screen** |            |            |            |             |
| Total sample         | 20.18±6.2  | 21.50±6.3  | 21.08±6.8  | P = 0.330   |
| Stable               | 19.77±5.8  | 19.96±5.8  | 20.76±5.1  | M: 0.589; T: 0.328 |
| Wearing-off          | 20.58±6.9  | 23.04±6.8  | 21.41±8.5  | M×T: 0.326  |

All data shown as mean±standard deviation. +1H/+4H = 1/4 h after levodopa; M = for motor condition; T = for time; M×T = interaction.

Table 3 Verbal learning test

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>+1H</th>
<th>+4H</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total of correct responses (positive+negative)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>45.40±11.8</td>
<td>46.25±9.5</td>
<td>45.90±9.8</td>
<td>P = 0.822</td>
</tr>
<tr>
<td>Stable</td>
<td>43.70±11.1</td>
<td>41.90±11.9</td>
<td>42.60±11.5</td>
<td>M: 0.161; T: 0.813</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>47.10±12.1</td>
<td>50.60±5.2</td>
<td>49.20±6.7</td>
<td>M×T: 0.146</td>
</tr>
</tbody>
</table>

| **Mean reaction time of correct responses (ms)** |            |            |            |             |
| Total sample         | 1.10±0.3   | 1.20±0.2   | 1.15±0.6   | P = 0.119   |
| Stable               | 1.12±0.1   | 1.11±0.1   | 1.15±0.6   | M: 0.510; T: 0.127 |
| Wearing-off          | 1.10±0.3   | 1.05±0.2   | 1.09±0.5   | M×T: 0.576  |

| **Total delayed recognized words (positive+negative)** |            |            |            |             |
| Total sample         | 6.55±10.3  | 5.85±9.7   | 4.70±9.6   | P = 0.032   |
| Stable               | 6.30±10.6  | 8.20±13.0  | 6.20±13.6  | M: 0.574; T: 0.038 |
| Wearing-off          | 6.80±10.5  | 3.50±3.9   | 3.20±3.2   | M×T: 0.351  |

All data shown as mean±standard deviation. M = for motor condition; T = for time; M×T = interaction.

analysed separately, the time to produce positive responses diminished significantly [F(2,34) = 8.08, P = 0.01] changing from 1060±140 ms in basal conditions to 980±150 ms at +1H. This also held true when both subgroups of patients were taken into account in the analysis [factor time: F(2,32) = 7.70, P = 0.002].

(iii) Non-correct responses. Non-correct responses were outright errors (8.00±5.14) and delayed responses (6.55±10.26). There were no significant differences between groups in non-correct responses in basal conditions. No significant changes were observed in the number of errors after levodopa intake. However, levodopa was associated with a significant reduction in the number of delayed responses, when the total sample was considered. Although the two-way ANOVA also showed a significant time effect, this was not observed when the time analysis was applied to the two groups separately.

Spatial memory
Results of the spatial memory test are shown in Table 4. Again, no significant differences between groups were observed in basal conditions, and levodopa intake produced no significant effects either in the entire sample of patients or when both subgroups were separately considered.

Executive function: Wisconsin card sorting test

Number of categories. As is shown in Table 5, there were no significant differences in the number of categories achieved by stable and wearing-off patients in basal conditions. No significant effects of levodopa were observed when the total sample of patients was considered. However, when the motor condition was taken into account, a significant interaction effect was obtained, indicating that levodopa did not produce significant changes in the stable group, while the wearing-off patients significantly reduced the number of categories achieved at +1H after drug intake, recovering thereafter (Fig. 2).

Number of perseverative errors. Although no significant results could be observed, the wearing-off patients exhibited more perseverative errors than stable patients at +1H after drug intake.

Mean reaction time after each stimulus. The mean reaction time did not show significant differences between groups in basal conditions. Considering the total sample of patients, a significant reduction of the mean reaction time was observed after levodopa intake. Moreover, the two-way ANOVA showed a significant time effect, although when
Table 4  Spatial memory test: number of correctly located elements

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>+1H</th>
<th>+4H</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>17.65±3.1</td>
<td>17.45±3.1</td>
<td>17.60±2.6</td>
<td>P = 0.944</td>
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<tr>
<td>Stable</td>
<td>16.60±2.6</td>
<td>17.50±3.6</td>
<td>17.50±3.1</td>
<td>M, 0.517; T, 0.942</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>18.70±3.3</td>
<td>17.40±2.6</td>
<td>17.70±2.1</td>
<td>M×T, 0.155</td>
</tr>
</tbody>
</table>

All data shown as mean±standard deviation. M = for motor condition; T = for time; M×T = interaction.

Table 5  Wisconsin card sorting test

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>+1H</th>
<th>+4H</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>4.95±1.5</td>
<td>4.70±1.7</td>
<td>4.90±1.4</td>
<td>*P = 0.471</td>
</tr>
<tr>
<td>Stable</td>
<td>4.50±1.7</td>
<td>4.60±1.7</td>
<td>4.20±1.4</td>
<td>*M, 0.203; T, 0.407</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>5.40±0.8</td>
<td>4.80±1.40</td>
<td>5.60±0.9</td>
<td>M×T, 0.014</td>
</tr>
<tr>
<td>Number of perseverence errors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>8.60±5.7</td>
<td>9.05±6.7</td>
<td>9.02±6.4</td>
<td>P = 0.749</td>
</tr>
<tr>
<td>Stable</td>
<td>8.80±5.2</td>
<td>8.50±5.7</td>
<td>10.60±5.7</td>
<td>M, 0.379; T, 0.737</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>8.40±7.8</td>
<td>9.60±6.8</td>
<td>7.44±6.3</td>
<td>M×T, 0.131</td>
</tr>
<tr>
<td>Mean reaction time (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>4.50±2.6</td>
<td>3.81±2.05</td>
<td>4.10±2.5</td>
<td>P = 0.050</td>
</tr>
<tr>
<td>Stable</td>
<td>5.27±2.4</td>
<td>4.34±3.0</td>
<td>4.71±3.3</td>
<td>**M, 0.229; T, 0.052</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>3.74±1.4</td>
<td>3.29±1.6</td>
<td>3.48±1.6</td>
<td>M×T, 0.633</td>
</tr>
</tbody>
</table>

All data shown as mean±SD. M = for motor condition; T = for time; M×T = interaction. *P < 0.05, **P < 0.01 (ANOVA factor time).

Fig. 2  Relationship between individual levodopa plasma levels and differences from pre-drug performance in the number of categories achieved in the Wisconsin card sorting test executed 1 h after drug-intake. Filled squares = stable patients; + = wearing-off patients. Disregarding individual levodopa plasma levels, stable patients obtained the same or better test scores, while wearing-off patients obtained the same or worse test scores, relative to their pre-drug performances.

Both groups were separately analysed, the mean reaction time reduction only reached statistical significance in stable patients [F(2,18) = 4.0, P = 0.036].

Executive function: extra-dimensional matching test

Results of this test are shown in Table 6.

Number of correct responses. In basal conditions, there were no significant differences between stable and wearing-off patients in the number of correct responses (congruents plus incongruents) achieved. No significant effects of levodopa intake were observed when considering the total sample of patients or when stable and wearing-off patients were separately analysed. The same profile was obtained when congruent and incongruent responses were separately analysed (from all subjects in pre-treatment evaluation: congruents, 22.90±9.27; incongruents, 22.70±9.03).

Mean time employed to produce the correct responses. There were no significant basal differences between groups. The levodopa produced a significant reduction of this time, an effect observed in the total sample of patients and when both subgroups were considered separately [stable, F(2,14) = 5.80, P = 0.015; wearing-off, F(2,14) = 8.76, P = 0.003]. The same profile was also observed when congruents' and incongruents' responses were separately analysed (from all subjects in basal evaluation: congruents, 841.1±130.9 ms; incongruents, 915.2±157.8 ms).

Number of non-correct responses. We observed that it mainly corresponded to delayed reactions (10.50±16.72), the rest (3.90±3.39) being outright errors. There were no significant differences between groups in non-correct responses in basal conditions. No significant changes were observed in the number of errors after levodopa intake. However, regarding the number of delayed responses, levodopa showed a tendency to decrease them at +1H (t = 2.05, P = 0.055) when the total sample was considered, an effect that reached statistical significance when both subgroups were considered separately.
Continuous i.v. levodopa infusion rates. However, they found that choice reaction time became prolonged as plasma levodopa decreased (Pullman et al., 1988), thus supporting the notion that dopamine replacement is essential when the required task increases in complexity. Accordingly, in a more recent study (Malapani et al., 1994), a group of parkinsonian patients did not vary their performance on a non-competitive choice reaction time task between 'on' and 'off' states, but when the choice reaction time test comprised two simultaneous cognitive tasks they showed a significant increase in the inter-response interval in the 'off' state, compared with their own performance in the 'on' state. Overall, the results of the present study are in agreement with these data. Finger tapping test results, an index of motor speed, were only slightly improved by levodopa in our parkinsonian patients. In contrast, an improvement in response time was consistently observed in other tests requiring more complex central neural processing. Thus, levodopa significantly reduced: (i) positive response times and the number of delayed responses in the verbal memory test; (ii) correct response times and the delayed responses in complex reaction time (extra-dimensional matching test); and (iii) response times in the WCST. Keeping in mind the difficulties of measuring bradyphrenia in Parkinson's disease (Saint-Cyr et al., 1993), an levodopa-related improvement in the speed of central neural processing can be inferred from these data. Nevertheless, our patients' improvements in response initiation time at high-levodopa plasma levels (+1H) was not accompanied by a significantly more accurate performance in any of the tests, relative to the basal condition (0H) or to the low levodopa-plasma level state (+4H). As a whole, these patients continued to produce a similar number of errors and incorrect responses, and their performance on the spatial memory test was also unaffected by levodopa.

Discussion

In this study we used a within-subject design to examine the effects of levodopa challenge on selected cognitive domains in Parkinson's disease. The main question addressed was: does dopaminergic stimulation produce differing effects on different cognitive domains, and do patients with stable and wearing-off motor responses to oral levodopa respond differently in particular domains? We have shown that high plasma levels of levodopa (i) improved response initiation time in all tests in both groups, (ii) did not modify the patient's accuracy in verbal memory, spatial memory or in the extra-dimensional matching tests, and (iii) produced a selective adverse effect on a highly-demanding executive task (WCST), but only in the wearing-off group. This latter effect remained hidden from the statistical point of view when the total sample of patients was considered, without taking into account their type of motor response to oral levodopa. In the following sections, we will discuss two aspects of our data: first, the effects of levodopa on the total sample of patients, second, its effects on the stable and the fluctuating groups taken separately.

Motor speed and speed of cognitive processing

Several studies of the relationship between dopaminergic stimulation and response initiation time in patients with Parkinson's disease before and at varying times after the beginning of levodopa treatment have shown that clinical changes in bradykinesia did not always accompany changes in reaction time and cognitive performance (Evarts et al., 1981; Rafal et al., 1984; Girotti et al., 1986; Hietanen and Teräväinen, 1986; Bloxham et al., 1987; Mayeux et al., 1987; Dubois et al., 1988; Pillon et al., 1989; Starksteine et al., 1989). For example, Pullman et al. (1988), found no significant improvement in simple reaction time at three different continuous i.v. levodopa infusion rates. However, they found that choice reaction time became prolonged as plasma levodopa decreased (Pullman et al., 1988), thus supporting the notion that dopamine replacement is essential when the

Dopamine and memory function

The lack of effects of levodopa on accuracy of performance in memory tests in our patients is in agreement with other studies on Parkinson's disease that report no significant effect of dopaminergic therapy or withdrawal on traditional memory tests, such as the Wechsler Memory Scale (Wechsler, 1945) or the Brown–Peterson distractor task (Cooper et al., 1992).

Table 6 Extra-dimensional matching test (complex reaction time)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>+1H</th>
<th>+4H</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total correct responses</td>
<td>45.60±17.7</td>
<td>50.05±13.8</td>
<td>47.9±13.6</td>
<td>0.174</td>
</tr>
<tr>
<td>Total sample</td>
<td>44.4±18.1</td>
<td>45.4±15.8</td>
<td>45.3±19.3</td>
<td>0.020</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>46.8±16.9</td>
<td>54.7±5.4</td>
<td>50.5±11</td>
<td>0.205</td>
</tr>
<tr>
<td>Mean reaction time (ms)</td>
<td>794.19±120.5</td>
<td>796.83±128.1</td>
<td>P = &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>898.86±159.2</td>
<td>824.48±139.6</td>
<td>*M, 0.402; T, 0.000</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>857.42±115.8</td>
<td>763.90±97.62</td>
<td>**M×T, 0.846</td>
<td></td>
</tr>
<tr>
<td>Fluctuating</td>
<td>10.50±16.7</td>
<td>5.60±10.7</td>
<td>6.50±10.2</td>
<td>0.101</td>
</tr>
<tr>
<td>Total sample</td>
<td>11.80±18.6</td>
<td>8.20±14.4</td>
<td>8.80±13.1</td>
<td>0.455; T, 0.032</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>9.20±15.4</td>
<td>3.00±4.5</td>
<td>4.20±6.0</td>
<td>0.830</td>
</tr>
</tbody>
</table>
| All data shown as mean±SD. M = for motor condition; T = for time; M×T = interaction. *P < 0.05, **P < 0.01 (ANOVA factor time).
We also found that levodopa failed to improve the accuracy of performance in various tests of visual memory and learning including pattern and spatial recognition memory, delayed matching to sample and visuospatial associative learning (Lange et al., 1992) or incidental and intentional recall (Cooper and Sagar, 1993). On the other hand, two other studies which examined memory using a different methodology (Huber et al., 1987, 1989) suggested that dopamine replacement influence memory in Parkinson’s disease. Using a day before test recall test, Huber et al. (1987, 1989) found that variation of plasma dopamine levels between the time of original learning and subsequent memory retrieval resulted in a loss of retrieval efficiency by conditioning a 'state-dependent' memory impairment. In other words, these authors concluded that the information learned in one state, regardless of whether dopamine levels were high or low, was recalled more efficiently if the patient was in the same high or low plasma-dopamine state. However, as in our study, Huber et al. (1987) also found that memory performance was not influenced by the absolute level of dopamine, either high or low, in spite of a significantly slower memory acquisition rate when dopamine levels were low.

Contrary to the performance on demanding storage- and recall-memory tasks, performance of parkinsonian patients on working memory tasks (Baddeley and Wilson, 1988; Stuss et al., 1994) has been shown to be sensitive to dopaminergic changes. In this context, Owen et al. (1991) and Lange et al. (1992) showed that spatial working memory deficits in Parkinson’s disease were exacerbated by levodopa withdrawal while impaired performance on other memory tasks was unaffected, and Cooper et al. (1992) showed that dopaminergic medication did not alter deficits found in untreated parkinsonian patients but selectivity improved performance on a task of working memory. However, these studies demonstrating a positive effect of levodopa on working memory tasks (Owen et al., 1991; Cooper et al., 1992; Lange et al., 1992) are in apparent contradiction with the results of a study by Poewe et al. (1991) who, using the Sternberg choice reaction-time paradigm (Sternberg, 1966), observed a significant deterioration in memory scanning speed after a single dose of levodopa (Poewe et al., 1991). Disregarding the differences in test procedures, the tasks used in these latter studies (Owen et al., 1991; Poewe et al., 1991; Cooper et al., 1992) can be considered to rely on frontal-sensitive cognitive procedures (executive tasks) similar to those required to perform the WCST (Lezak, 1983; Taylor et al., 1986; Stuss et al., 1994).

Dopamine and executive function
The magnitude and direction of the effect of dopaminergic medication on tasks related to frontal executive functions reveal differences in statistical outcome among the studies. Some findings have supported the possibility that striatal or frontal dopamine replacement may positively influence executive functions. First, unmedicated patients with Parkinson’s disease are more severely impaired in the WCST than medicated patients (Downes et al., 1989). Second, patients on levodopa achieve more categories in the WCST (Bowen et al., 1975). Last, parkinsonian patients show selectively impaired performance in frontal lobe-dependent spatial working memory following levodopa withdrawal (Owen et al., 1991; Lange et al., 1992). Gotham et al. (1988), however, observed that patients with fluctuating Parkinson’s disease had normal results on certain tests that tap frontal lobe function such as the associative verbal learning and subject-ordered pointing tasks when they were in the ‘off’ state, but deteriorated while in the ‘on’ state.

Interestingly, the Poewe et al. (1991) study showing negative effects of levodopa on parkinsonian patients performance in a frontal lobe-related task (the Sternberg paradigm; Sternberg, 1966), included only patients with fluctuating motor response to oral levodopa. Notably in our study, when the total sample of parkinsonian patients was analysed without taking into account their stable or fluctuating condition, we found that the rise of levodopa plasma levels accelerated completion times for the WCST, and that there were no significant changes in accuracy on the verbal memory test and the extra-dimensional matching test. Hence, if the type of motor response to oral levodopa of our parkinsonian patients had not been taken into account, we would not have been able to observe the negative effect of levodopa on the WCST in the wearing-off group of patients. Thus, it is conceivable that the discrepancies between previous studies examining the relationship between executive functions and dopamine modulation in Parkinson’s disease can be explained, at least in part, on the basis of the different evolution of the patients examined, with de novo and stable responders tending to improve (Bowen et al., 1975), and fluctuating patients (Poewe et al., 1991) tending to deteriorate with levodopa, as in the present study.

Anatomo-functional considerations
The massive projection from the prefrontal cerebral cortex to the head of the caudate nucleus, and the reciprocal striato-pallido-thalamo-cortical projections back to prefrontal cortex via the ‘complex’ basal ganglia circuits emphasize the role of prefrontal-caudate systems in cognition (Alexander et al., 1986, 1990; Cummings, 1993). The dopamine deficit in the caudate nucleus in Parkinson’s disease is well known, and several studies have shown that the dopaminergic projections from the mesocortical dopaminergic system to the frontal cortex also degenerate in Parkinson’s disease, resulting in a frontal dopamine deficit (Javoy-Agid and Agid, 1980; Scatton et al., 1982). However, since in Parkinson’s disease there is a greater dopamine depletion in the motor putamen than in either the caudate or the prefrontal cortex, Gotham et al. (1988) and Poewe et al. (1991) both suggested that the levodopa doses required to remedy the dopamine lack in the putamen may ‘overdose’ any structure where dopamine sites remain relatively intact, namely the prefrontal cortex and...
probably the caudate, thus explaining the negative effect of levodopa on frontal executive tasks.

In our opinion, the hypothesis of dopamine overdosage over a relatively spared frontocaudate loop does not fully explain our findings. We think it should be complemented with the idea that the dopamine overdosage appears to be more dependent on the denervation of the frontocaudate loop than in its preservation. Based on dissociated performance on frontal lobe tests, Gotham et al. (1988) speculated whether different areas of prefrontal cortex might be involved in the different tasks employed, and whether functional levels of dopamine in separate areas of cortex and caudate may differ crucially in Parkinson’s disease (Gotham et al., 1988). They postulated that the actual pattern of deficits seen ‘on’ and ‘off’ medication will depend upon the levels of dopamine in these areas. Our results can be examined both from a pharmacokinetic and a pharmacodynamic perspective. If one considers first that the disrupted function in frontocaudate neuronal loops (as expressed in our fluctuating patients by their worst performance on the WCST at +1H) was due to an overstimulation of dopamine receptors in less severely denervated neurons of the caudate nucleus with therapeutic doses of levodopa, it might be expected that the supposedly less denervated patients (e.g. the stable group) should show the adverse effects of frontocaudate levodopa overdosage more clearly. This was not the case, however. Second, if the functional state of the frontocaudate dopamine receptors was similarly affected in our two groups, in order to sustain the levodopa ‘overdosage’ hypothesis (Gotham et al., 1988), one would have to consider the possibility that the fluctuating patients had either received higher levodopa doses or attained higher levodopa plasma levels after similar oral levodopa doses. In our study however, the total daily dose of levodopa as well as the levodopa administered during the test condition, and both the peak plasma levodopa dose and the area under the plasma levodopa curve were not significatively different between groups. Thus, as the pharmacokinetic profile of plasma levodopa of stable and fluctuating patients was not different, as was previously demonstrated in other studies (Fabbini et al., 1987; Nutt, 1987), we suggest that central pharmacokinetic and pharmacodynamic changes related to the emergence of the wearing-off phenomenon are more likely to be responsible for the emergence of the adverse effects of levodopa.

Although their exact mechanisms are not fully understood, several lines of evidence suggest that the wearing-off phenomenon relates primarily to the extent of degeneration in the nigrostriatal system (Melamed et al., 1981; Zhang et al., 1988) with a reduction in the vesicular storage and regulated release of dopamine. Intraneuronal dopamine levels ultimately begin to mirror precursor availability rather than the stable requirements of a tonically operating synapse (Fabbini et al., 1987) and levodopa may increase extracellular dopamine concentrations much more than in normal or less degenerated striata (Abercrombie et al., 1990; Van Horne et al., 1992) producing the so-called ‘presynaptic supersensitivity’, which may be responsible for some of the adverse effects of levodopa in parkinsonian patients. Thus, in wearing-off patients the doses of levodopa required for motor benefit progressively approach a threshold beyond which further increases in dopamine may interfere with the processes that are involved in the frontal regulation of attention (Saint-Cyr et al., 1993), thus worsening the performance on tasks that require a high level of central control.

The question remains whether different regions of the frontal cortex and caudate nucleus are involved during the execution of different ‘frontal lobe tasks’ (Gotham et al., 1988), or whether certain neuropsychological tests, such as the WCST, are relatively more sensitive than others to a general imbalance in dopamine levels. Thus in our study, the lack of levodopa influence on the accuracy of performance on the modified version of the Stroop test (assumed to be also a measure of frontal lobe functioning) could be explained on the basis that performance depends on separate frontocaudate areas less sensitive to dopamine manipulation, or that the differences are caused by the diverse requirements of these tests. We cannot solve this question. However, Brown and Marsden (1991) demonstrated that the standard administration of the Stroop test (e.g. reading out the colour of the ink, as was done in the present study) has a relatively low resource requirement so that the presence of distracters (the words) does not unduly increase task difficulty in parkinsonian patients, even when the distracters are highly competitive for attention (Brown and Marsden, 1991). They also observed that the requirement to perform a concurrent task, such as random number generation, disrupted performance on a switch version of the Stroop task in parkinsonian patients, even when the correct response was cued, an aid that has previously been shown to reduce Stroop interference in patients (Brown and Marsden, 1991). A similar deficit in simultaneous information processing tasks was demonstrated in other studies (Cooper and Sagar, 1993; Richards et al., 1993; Dalrymple-Alford et al., 1994; Malapani et al., 1994) suggesting that central dopaminergic alterations in Parkinson’s disease disturb the ability to synchronize simultaneous sensorimotor processing. Thus, in terms of the present study, the apparent dissociation between the performance on the WCST and the modified version of the Stroop test (extra-dimensional matching) in the wearing-off group may stem from the lower attentional requirements of the standard Stroop task (Brown and Marsden, 1991), a task that appears less sensitive to dopamine manipulation.

In conclusion, the main results of the present study were that parkinsonian patients with stable and fluctuating motor response to oral levodopa may perform differently under a levodopa challenge on a given test only when the level of complexity reaches a threshold requiring slow, flexible, directed thinking (e.g. in the WCST), while they perform similarly in other tests requiring lower resources (e.g. the extra-dimensional matching test) and tests of psychomotor speed and verbal and visuospatial memory. These differences
in performance may relate to a 'sensitization' of caudate and prefrontal dopamine receptors that parallels the pharmacodynamic changes related to the fluctuating motor response.

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determination of 3,4-dihydroxyphenylalanine, 5-hydroxytryptophan, dopamine, 4-hydroxy-3-methoxyphenylalanine, norepinephrine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, serotonin, and 5-hydroxyindoleacetic acid in rat cerebrospinal fluid and brain by high-performance liquid chromatography with electrochemical detection. J Neurochem 1982; 38: 1241–54.


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