Short report

A randomised controlled study of bromocriptine versus levodopa in previously untreated Parkinsonian patients: a 3 year follow-up

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SUMMARY The long term effects of a de novo treatment with levodopa versus bromocriptine were compared in respectively 13 and 15 previously untreated patients with Parkinson’s disease in a prospective randomised trial. Thirteen patients were treated with levodopa alone (mean dose 444, SEM 63 mg daily) whereas 15 others received bromocriptine alone (mean dose 50, SEM 6 mg daily) during 37, SEM 4 and 32, SEM 4 months respectively. For a similar decrease in the Columbia rating scale, the nature of long term side effects was different in the two groups: three patients on levodopa developed peak-dose dyskinesias and one other dystonia. With bromocriptine, one patient developed a severe psychosis whereas 3 others suffered from primary lack of efficacy (1 case) or late decrease in efficacy (2 cases). These results demonstrate the potential of D2 dopamine agonists (like bromocriptine) in the de novo treatment of Parkinson’s disease; however, their use is limited by their lack of efficacy and/or the occurrence of neuropsychiatric side effects.

The limitations of long-term levodopa therapy have led to attempts to develop new therapeutic strategies. Among them, the use of dopamine receptor agonists like bromocriptine as the first treatment of the disease has been proposed (for review see1). In 1979, we reported the lack of motor side effects (such as dyskinesias, dystonias and on-off effects) after several years of treatment with bromocriptine alone in previously untreated Parkinsonian patients.2 Several reports3-10 have confirmed these preliminary observations. However, most of these studies5-9 were retrospective and uncontrolled trials. We report here the first results of a prospective randomised controlled study of bromocriptine versus levodopa in previously untreated patients with Parkinson’s disease, with a 3 year follow up.

Patients and methods

This study included 28 patients with idiopathic Parkinson’s disease whose main clinical data (age, sex, duration of the disease, clinical stage at the entry into the protocol according to Hoehn and Yahr’s scale11) are presented in the table. Most of these patients were mildly disabled. None of them had previously been treated with levodopa. Ten (six in the bromocriptine group and four in the levodopa group) received an anticholinergic drug (trihexphenidyle: 4 to 10 mg daily), in a constant dose during the whole study. These 28 patients were assigned randomly to the two treatment groups. Patient’s characteristics were not statistically different between the two groups. Bromocriptine or levodopa (with dopa-decarboxylase inhibitor) were introduced at low doses (2.5 mg and 50 mg respectively) and gradually increased over a 3 week period according to their effectiveness and the patient’s tolerance. Nausea, vomiting or orthostatic hypotension were treated if necessary with domperidone (30 to 60 mg daily). Each of the 28 patients was treated and followed by the same physician who assessed the motor status at each consultation (twice a year) using the Columbia University Scale12 and adapted the dosage according to the clinical status. Side effects of medications were spontan-
Table  
Main characteristics of the patients at the beginning of the study

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Males</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Females</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Mean age</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>SEM (years)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stage I</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>(H &amp; Y) II</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>±5</td>
<td>±5</td>
</tr>
<tr>
<td>Range</td>
<td>7–72</td>
<td>6–60</td>
</tr>
</tbody>
</table>

Stages according to Hoehn and Yahr's scale11 (H & Y). Duration = duration of the disease when the patients entered into the trial.

Results

The mean prescribed doses were 444 mg, SEM 63 mg (range: 150 to 1000 mg) and 50 mg, SEM 60 mg (range 30 to 100 mg) for levodopa and bromocriptine respectively. The figure shows the results assessed before the beginning of the study (time 0) and after 0.5, 1, 2 and 3 years of treatment. There was no statistical difference in the values of Columbia University Scale between the two groups of patients either at the beginning of the study or at any moment of the trial. However, bromocriptine or levodopa induced a significant decrease (p < 0.05) in scale at times 0.5, 1, 2 and 3 years when compared with pretreatment values.

In contrast, the nature of late side effects elicited by the two drugs was different. Four out of the 13 patients with levodopa developed abnormal movements: three had peak-dose dyskinesia after 14, 36 and 40 months of treatment with 300, 650 and 1000 mg respectively, whereas one other patient had foot dystonia after 18 months of treatment with 500 mg levodopa. These abnormal movements led to drop-out from the study and were successfully treated with decreasing doses of levodopa and adding low doses of bromocriptine. Bromocriptine alone induced different side effects: one patient presented an acute psychosis after 24 months of treatment with 40 mg bromocriptine, whereas three other Parkinsonians suffered from primary lack of efficacy (one patient with 90 mg for 3 months) or secondary decrease in efficacy (two patients with 30 and 40 mg after 20 and 36 months respectively) leading us to add levodopa which significantly improved the Parkinsonian symptoms.

Discussion

The purpose of the present prospective and randomised study was to compare bromocriptine and levodopa in terms of both efficacy and late side effects in previously untreated Parkinson’s disease. The data first indicate that relatively high doses of bromocriptine (50 mg) were as effective as moderate doses (444 mg) of levodopa in improving neurological and functional disabilities in Parkinson’s disease. These observations agree with previous reports showing a dose ratio of 1 to 10 between bromocriptine and levodopa.13-15

However, the most important objective of this clinical trial was to compare the long term side effects of the two antiparkinsonian drugs. Previous studies with bromocriptine in new patients were not prospective and/or controlled trials and the recent results from Libman’s group10 did not report long term side effects; that study was only performed over a 21 week period. Moreover, except for the previous studies of Rinne4...
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