

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 bromocriptine¹ as the first treatment of the disease has been proposed (for review see²). 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.³ Several reports⁴⁻¹⁰ have confirmed these preliminary observations. However, most of these studies³⁻⁹ 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.

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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 (trihexiphenidyle: 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

	Levodopa	Bromocriptine
Patients	13	15
Males	11	8
Females	2	7
Mean age	62	60
SEM (years)	2	2
Stage I	2	4
(H & Y) II	6	8
III	5	3
Duration (months)	23	31
Range	±5 7-72	±5 6-60

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

ously reported by the patient at every visit. Testing began in October 1983 and all the patients presently continuing the treatment were reviewed in March 1988. The mean follow-up was 37.4, SEM 3.6 months (range: 24 to 50) and 32.4, SEM 3.7 months (range: 24 to 46) for levodopa and bromocriptine respectively. Comparisons between the two groups was performed using a one-way analysis of variance followed by a Student's *t* test. Data are presented as mean values, SEM.

Results

The mean prescribed doses were 444.2, SEM 63.0 (range: 150 to 1000) mg and 50.0, SEM 6.0 (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

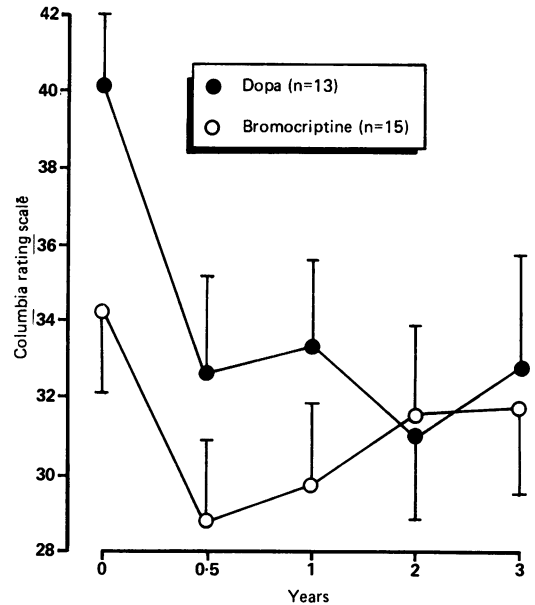


Fig Effects of bromocriptine alone (50, SEM 6 mg daily; open triangles) and levodopa alone (+ dopa decarboxylase inhibitor) 444, SEM 63 mg daily; closed circles) on the Parkinsonian disability (evaluated using Columbia Rating Scale) during the 3 years of the trial. There was no statistical difference at any time of the study between the two treated groups.

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 Rinne⁷

(duration 36 months) and Grimes and Delgado⁸ (30 months), the duration of these trials did not exceed 24 months. Although the number of patients was relatively small, the present work clearly demonstrates that the late side effects induced by the two antiparkinsonian drugs are quite different. Only levodopa induced abnormal movements (4/13 patients), whereas the use of bromocriptine was limited by lack of efficacy (1/15 patients), secondary decrease in efficacy (2/15 patients) or neuropsychiatric side effects (1/15 patients). These results agree with those of the previous uncontrolled studies.³⁻⁹ The absence of abnormal movements and "on-off" phenomena after long term treatment with bromocriptine appears to be the main advantage of the management of new cases of Parkinson's disease with dopamine agonists. We therefore emphasise the potential importance of high doses (40 to 90 mg) of bromocriptine in the early treatment of Parkinson's disease until such time that progressive clinical disability requires the addition of levodopa. However, this therapeutic strategy is not of value in some patients who develop severe neuropsychiatric side effects or do not respond to bromocriptine. The percentage of primary and secondary inefficacy varies in different studies: 77% in Grimes and Delgado's study,⁸ 82% in Lees and Stern's work,⁴ 35% in our preliminary open study⁶ and 27% in the present trial. We believed that the differences between the present results and other studies can be explained by the relatively high doses of bromocriptine used by our group: 56.5 mg in our first uncontrolled trial,⁶ 50 mg in the present work versus 13.2, 14, 28 and 40 mg for the four other studies respectively.^{4,7-9}

From a pharmacological point of view, the lack of abnormal movements or fluctuations after bromocriptine alone have been explained by different hypotheses: the D2 specificity of bromocriptine, its lack of toxic metabolites (like 6 hydroxydopamine for levodopa),¹ its half life longer than levodopa and its mixed "agonist-antagonist" properties at D2 receptors. Moreover, unlike other dopamine agonists, bromocriptine does not differentiate between the low and high affinity D2 receptor binding states.¹ It is also interesting to compare our clinical results with the experimental data of Bedard *et al*¹⁶ who found that chronic treatment with levodopa, but not bromocriptine, induced dyskinesia in monkeys with MPTP-induced Parkinsonism. More recently, the same group found that, in 6 OHDA lesioned rats, chronic treatment with levodopa increased the density of D2 receptors, whereas bromocriptine did not.¹⁷ This unexpected property can perhaps explain why bromocriptine alone does not elicit dyskinesia in previously untreated Parkinsonians.

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