

Comparison of the effects of bromocriptine and levodopa in Parkinson's disease

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SUMMARY The effects of bromocriptine and levodopa were compared in a blind trial in 18 patients with Parkinson's disease. Optimal doses of the two drugs were given in identical capsules: there was no significant difference between the therapeutic effects. There were wide individual differences in response to the two drugs. Side effects were more common with bromocriptine, but were similar to those caused by levodopa. Four patients were unable to take bromocriptine because of side effects.

Bromocriptine, which is a dopamine agonist, has been shown to have a therapeutic effect in Parkinson's disease when given in association with levodopa (Calne *et al.*, 1974; Parkes *et al.*, 1976). Both bromocriptine and levodopa (after conversion to dopamine) are thought to have their therapeutic effect by an action on dopamine receptors in the striatum, but the relative clinical efficacy of the two substances has not so far been assessed. It is known that the pharmacokinetics of bromocriptine differ from those of levodopa (Flückiger, 1976 personal communication). Levodopa depends on conversion to dopamine for its action whereas bromocriptine has a direct action. There is also the possibility of differential effects at the receptor site to different agonists. Finally, metabolic products may modify the effect of these compounds and cause side effects.

We have made a comparative study of the effects of bromocriptine and levodopa in a group of patients with Parkinson's disease. Double-blind assessment was carried out on patients taking optimal dosage of either bromocriptine or levodopa, the therapeutic effects were measured, and the side effects of the two regimens recorded.

Methods

Patients with idiopathic Parkinson's disease attending the outpatient department of the Derbyshire Royal Infirmary were asked to take part in a therapeutic trial of bromocriptine. Twenty-four patients entered the preliminary phase of the trial. Their ages ranged

from 50 to 73 years, and the degree of disability varied from mild to severe. Four of the younger men were still at work, while five patients were almost housebound. All except one had previously been treated with either levodopa or a combination of levodopa and decarboxylase inhibitor (Sinemet), in optimal dosage for up to five years. At the start of the trial those patients who were on Sinemet were given instead an optimal dose of levodopa. Twenty patients were also taking an anticholinergic drug (either benzhexol or orphenadrine), and three patients were taking amantadine. These drugs were continued throughout the trial in unchanged dosage.

During an initial period bromocriptine was introduced at a dose of 2.5 mg three times daily, and increased at weekly intervals. At the same time the levodopa was gradually withdrawn. The final dose of bromocriptine was the minimum judged to give optimal therapeutic effect.

The blind phase of the trial began once the optimal dose of levodopa and bromocriptine had been established for that patient. Patients were supplied with identical capsules containing either bromocriptine 2.5 mg or levodopa 250 mg according to a predetermined schedule. There were four treatment phases—two on bromocriptine and two on levodopa, with each drug alternating with the other. During a three month trial period the drugs were switched twice at random intervals so that neither drug was taken continuously for more than six weeks or for less than two weeks. Patients were seen at intervals of two weeks, and their response was assessed on each occasion by one of two observers. The assessment was performed using a standard pro forma similar to that used in previous investigations (Godwin-Austen

et al., 1969). Side effects, both symptomatic and on examination, were recorded at each attendance.

Patients were asked to return any unused capsules at the end of each two week phase. We believe that all our patients took their capsules as instructed, but we did not carry out estimations of blood level of bromocriptine or levodopa, nor any analysis of urinary metabolites.

Results

Twenty-three patients started taking bromocriptine. During the initial period four patients were unable to tolerate the drug and were withdrawn from the trial; the side effects are discussed later. One patient required operation for an ovarian tumour and was excluded from the trial. Thus 19 patients entered the blind phase.

The optimal dose of bromocriptine was between 7.5 mg and 40 mg, and the dose of levodopa was between 1 g and 4.5 g. Two patients needed adjustment of the doses of one or both drugs, and this was achieved without breaking the trial code.

THERAPEUTIC EFFECTS

When the total disability scores from the trial group were considered (Figure), seven patients showed greater benefit from bromocriptine while eleven were better on levodopa (Table 1). Statistical analysis (Wilcoxon two sample ranking test) demonstrated that there was no significant difference ($p = <0.1$) in this patient group between the therapeutic effects of these two drugs.

The assessment scores were also analysed for differences in symptoms, functional disability, bradykinesia, tremor, and rigidity. There was no statistically significant difference in patient response to these two drugs in any of these subscores.

The two patients who were much better on levodopa showed a particular deterioration in their rigidity and functional capacity subtest scores while on bromocriptine, whereas the two patients who were better on bromocriptine had particular improvement in bradykinesia. It is noteworthy that the patients who were better on levodopa tended to be those who showed greatest disability.

SIDE EFFECTS

The side effects experienced during the blind phase of the trial are summarised in Table 2. The most common side effect produced by bromocriptine was nausea, which affected eight patients. In only one patient was the nausea and associated vomiting so severe as to contribute to withdrawal from the trial in the initial stage. Other patients were able to prevent nausea by taking their tablets after food, but in two

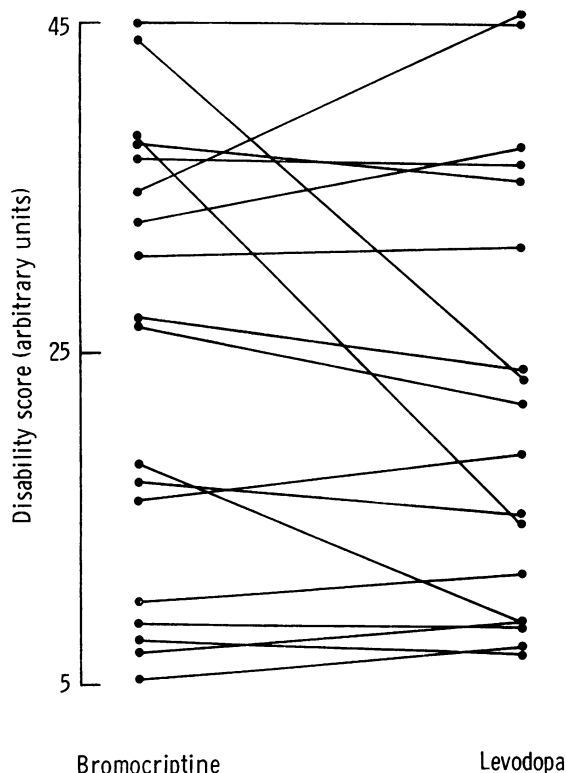


Figure Relative disability scores in 18 patients on either bromocriptine alone or levodopa.

Table 1 Comparative therapeutic effects of bromocriptine and levodopa in 18 patients

Outcome	Totals	All symptoms	All signs	Functional capacity	Tremor	Rigidity	Bradykinesia
Same	0	2	0	3	9*	0	1
Bromocriptine better	7	7	10	6	6	6	9
Levodopa better	11	9	8	9	3	12	8

*Eight patients had no tremor on either drug.

cases this was effective only after a reduction in dose of bromocriptine, followed by a more gradual increase.

Two patients suffered colicky abdominal pain soon after starting on bromocriptine. This necessitated their withdrawal from the trial, and the pain settled after stopping bromocriptine. One of these patients also became constipated: two other patients became constipated with taking bromocriptine but had no

Table 2 Side effects experienced by 18 patients on bromocriptine and levodopa during the blind phase* of the trial

Side effect	Bromocriptine	Levodopa
Abnormal movements	2	2
'On-off' attacks	1	1
Confusion, hallucinations, nightmares	3	3
Episodes of disturbed behaviour	2	0
Blurred vision	3	1
Drowsiness	2	0
Nausea and vomiting	7	1
Constipation	2	1
Postural hypotension	1	0
Flushing	2	0

*The four patients withdrawn from the initial stage had the following side effects: abdominal pain (2), nausea and vomiting (1), constipation (1) dysarthria and paraesthesiae (1).

abdominal pain. Their constipation responded to an increase of fruit and roughage in the diet.

Four patients had occasional hallucinations, nightmares, and confusion. Two of these patients also had brief episodes of severely disturbed behaviour, when they acted in an abusive and aggressive manner which was entirely out of character. They had only hazy recollection of these episodes, and there was no recurrence in spite of continuing treatment. Three other patients had nightmares and nocturnal confusion while taking levodopa.

Three patients complained of blurred vision while taking bromocriptine. There was no demonstrable impairment of visual acuity or visual field defect. Two patients complained of drowsiness while taking bromocriptine, but this symptom was mild, and they were able to continue taking the drug.

Abnormal movements were observed in two patients while taking bromocriptine. Both patients had dystonic movements of the limbs; the left foot was affected in one patient, and the right arm and leg in the other. The daily doses of bromocriptine in these cases were 10 mg and 20 mg respectively, and the patients had previously taken 1.5 g and 1.0 g of levodopa daily without abnormal movements. In one case the movements were slight and not troublesome. In the other case the movements were more severe and distressing, but were associated with objective improvement in the signs of Parkinsonism. In both cases the abnormal movements disappeared on changing from bromocriptine to levodopa. Two other patients had orofacial dyskinesia while taking levodopa, but no abnormal movements on bromocriptine.

'On-off' attacks were only experienced by one patient while taking bromocriptine 40 mg daily. This patient's symptoms of Parkinsonism were much worse on this dose of bromocriptine than on levodopa

4.5 g daily, and she had no 'on-off' attacks while taking levodopa.

One patient became dysarthric with paraesthesiae after the first dose of bromocriptine. She took no further doses, and her symptoms cleared quickly. She could not be included in the trial.

Discussion

Our results show that, in most patients with idiopathic Parkinson's disease, bromocriptine has therapeutic effects comparable with those of levodopa.

The dose of bromocriptine administered during the trial was established as that dose which, during the introductory phase, was tolerated without side effect, and at the same time produced alleviation of symptoms of Parkinsonism judged by the patient to be optimal and not improved by further dose increase. The average daily dose (22.75 mg) was slightly less than that used by Calne *et al.* (1974) and Parkes *et al.* (1976). We did not increase the dose of bromocriptine to the limit of tolerance. It is, therefore, possible that higher dosage of bromocriptine would have demonstrated a greater therapeutic response.

There was no evidence that bromocriptine had a selective effect on any individual symptom or sign of the disease. Although some patients suffered a deterioration in their symptoms on changing from levodopa to bromocriptine, in only two cases was this deterioration marked. In contrast, two other severely affected patients improved on changing to bromocriptine. These results confirm the therapeutic effects reported by Calne *et al.* (1974), and Parkes *et al.* (1976), but also demonstrate that for most patients who have previously obtained benefit from levodopa, bromocriptine can provide comparable benefit. This was particularly noticeable for mildly affected patients: marked deterioration only occurred in severely affected patients on changing to bromocriptine.

It has been suggested that dopamine agonists might be more effective in severely affected patients because these drugs are not dependent for their action on decarboxylase which may be depleted in the advanced case, and that receptor supersensitivity might increase the therapeutic response to bromocriptine in the patient with severe Parkinsonism (Calne *et al.*, 1974). Our findings, on the contrary, suggest that the more severely affected patient responds less well to bromocriptine.

The side effects of bromocriptine were similar to those of levodopa, except for a greater incidence of intestinal complaints and the occurrence of episodes of severely disturbed behaviour. It is notable that two patients had abnormal movements on bromo-

criptine while levodopa did not cause abnormal movements in these two patients. Similarly, one patient who had no 'on-off' attacks on levodopa did have such attacks on bromocriptine. The abnormal movements were associated with objective improvement in signs of Parkinsonism, whereas the 'on-off' attacks were associated with deterioration. The therapeutic effects of bromocriptine may be denied to some patients because of the severity of the side effects, which in this trial caused the withdrawal of four patients at daily doses of 10 mg or less. However, three patients took 40 mg daily without intolerable side effects.

Bromocriptine offers similar therapeutic effects in Parkinson's disease to those of levodopa, and the side effects of these two drugs are also similar. There are, however, individual variations in response to each drug and, where the use of levodopa is associated with intolerable or dose-limiting side effects, bromocriptine may produce greater benefit.

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