The Sydney Multicentre Study of Parkinson's disease: a report on the first 3 years

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SUMMARY One hundred and twenty nine de novo patients with idiopathic Parkinson's disease are being followed over a 5 year period in a double-blind multicentre study comparing low-dose bromocriptine (< 30 mg/day) with low-dose levodopa-carbidopa (< 600/150 mg/day). Sixty six patients have been randomised to bromocriptine and 63 patients to levodopa-carbidopa. Improvement has been greater in the levodopa-carbidopa group than in the bromocriptine group. Involuntary movements have so far only occurred in patients on levodopa-carbidopa, the incidence being much lower than is usually described with conventional doses. Mild, end-of-dose failure has occurred in both treatment groups; however, no patient has developed the "on-off" phenomenon. Low-dose levodopa-carbidopa appears to be a more effective anti-Parkinsonian treatment than low-dose bromocriptine but more prone to cause dyskinesia.

The value of levodopa in the long-term treatment of Parkinson's disease is limited by the emergence of dyskinesia and the "on-off" phenomenon.¹⁻³ Attempts to reduce the incidence of these problems by giving levodopa in low dosage have met with limited success.^{4,5} Dyskinesia has rarely been observed and the "on-off" phenomenon has not been described in patients treated with bromocriptine alone.⁶⁻⁸ Nausea, postural hypotension and confusion limit the use of bromocriptine in up to 35% of patients using conventional doses.⁹⁻¹¹ Several studies have shown that these side-effects can be minimised by giving bromocriptine in low dosage.^{7,12,13}

The aim of this study is to compare the efficacy and side-effects of low dose bromocriptine (< 30 mg/day) with low-dose levodopa-carbidopa (< 600/150 mg/day) over a 5 year period in de novo patients. We report the results of the first 3 years of the study during which patients were recruited.

Methods

One hundred and forty nine patients with idiopathic Parkinson's disease were recruited over a 3 year period from neurologists and general practitioners in the Sydney area.

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neurologists and general practitioners in the Sydney area. Although the target population was de novo patients, 15 patients who had received levodopa for less than 3 months were accepted into the study. This medication was ceased one month prior to the patient entering the trial. Four Sydney hospitals are participating in the study. At each hospital clinic a participating neurologist confirmed the diagnosis of idiopathic Parkinson's disease and the need to commence treatment. Patients were then stratified according to age and previous treatment (18 patients had been taking anticholinergics, 11 patients levodopa-carbidopa alone and 4 patients anticholinergics and levodopa-carbidopa). They were then randomised to receive either bromocriptine or levodopa-carbidopa. Informed consent was obtained.

Patients were given a placebo preparation for 1 month during which time two baseline assessments were made. They were then given either 1 mg/day of bromocriptine or 20/5 mg/day of levodopa-carbidopa in identical looking capsules. The dose was increased gradually at weekly, then monthly intervals until the patient reported a satisfactory response. If the patient was receiving anticholinergics or amantadine, these were continued unchanged during the trial. Only the hospital pharmacist knew which drug the patient was taking. The code was broken only if: (1) the response was unsatisfactory, (2) unacceptable side-effects occurred, (3) a greater than maximum trial dose was required, (4) one of the trial end-points occurred. The main end-points listed in the trial protocol were dyskinesia and the "on-off" phenomenon. If the response was inadequate, wherever possible the original trial drug was continued and the dose increased above the "low-dose" maximum of 30 mg/day of bromocriptine and 600/150 mg/day of levodopa-carbidopa. Patients continue to

be followed even if they are no longer on the therapy initially allocated.

The patients were seen monthly for about 6 months during which time the hospital neurologists titrated the dose (Phase I). Thereafter, the patients returned to their referring neurologists for the major part of their care but continue to be assessed in the hospital clinics at six monthly intervals for four and a half years (Phase II).

One neurologist attends all clinics in addition to the four hospital neurologists and examines all patients at baseline, end of titration phase and yearly thereafter. At regular intervals a comparison is made between the scores of this neurologist and the hospital neurologists, following simultaneous independent examinations of patients, with the aim of achieving uniformity between the four participating hospitals.

Signs of Parkinson's disease are recorded on a modified Columbia Scale,¹⁴ giving a maximum score of 102. Disability is recorded on a 5 point modified North Western University Disability Scale¹⁵ and symptoms and side-effects in standard questionnaires. The severity of the disease is graded on the Hoehn and Yahr Scale.¹⁶ Once a year, fluctuations are assessed by means of a pegboard test and standardised walking test performed at hourly intervals throughout the day. A neuropsychological assessment is made at baseline and after 3 and 5 years.

For the purposes of this communication, the Columbia scores at 1 and 2 years have been compared with baseline scores. The results of patients in the double blind aspect of the study have been analysed by the study statistician, the participating neurologists remaining blind to the drug being administered to individual patients.

Results

Exclusions

Of the 149 patients referred into the study, 10 have been excluded because they had the following: cystic lesion of the basal ganglia on CT (1), essential tremor (2), undetermined congenital disorder (2), progressive supranuclear palsy (1), Shy-Drager syndrome (1), suspected striato-nigral degeneration (1), pinealoma and hydrocephalus (1), life-long non-progressive bradykinesia (1). Ten further patients failed to complete Phase I: four moved elsewhere, five were non-compliant and one died from myocardial infarction.

Patient cohorts

One hundred and twenty nine patients have completed the titration phase; 63 were randomised to levodopa-carbidopa and 66 to bromocriptine. The characteristics of these patients are shown in table 1.

Table 1 Characteristics of 129 patients completing phase I of trial

Medication	n	Mean age years (range)	Mean duration of disease prior to entry into trial months (range)	Mean Hoehn & Yahr Stage (range)	Mean Modified Columbia score (range)
Levodopa-carbidopa	63	63.0 (41-79)	24.6 (3-144)	2.2 (1-3)	15.0 (5-33)
Bromocriptine	66	61.8 (42-76)	21.8 (1-96)	2.3 (1-3)	18 (3-33)

Fig D(1y): levodopa-carbidopa group at 1 year; B(1y): bromocriptine group at 1 year; Total: total number of patients originally allocated the drug; Same drug: number of patients still taking the drug originally allocated; Other drug: number of patients switched to the other drug being tested in this study; Combined: number of patients taking levodopa-carbidopa and bromocriptine.

The figure shows the number of patients who have completed 1, 2 and 3 years of treatment to date. It is clear that far fewer patients in the bromocriptine group remain on their original treatment as sole therapy than in the levodopa-carbidopa group.

Doses

The mean, daily doses of the two drugs in patients remaining on their initial therapy at 1, 2 and 3 years are shown in table 2. The daily dose for both drugs is rising progressively as the trial proceeds and it has been necessary to exceed the low-dose range in a small number of patients.

Breaking the treatment code

The reasons for breaking the drug code in the two groups of patients are shown in tables 3 and 4. For bromocriptine, the major reason was lack of efficacy. In 12 patients the code was broken within 1 year. All but two of these patients had moderately severe disease (Hoehn and Yahr Stage III) and in some the disease was rapidly progressive. Of 10 patients in

Table 2 Doses of levodopa-carbidopa and bromocriptine at 1, 2 and 3 years in patients remaining on original therapy

	Mean dose (mg/day)	Range	Patients exceeding low dose maximum
One Year			
Levodopa-carbidopa group (n = 46)	335/83.75	150-750	2
Bromocriptine group (n = 29)	18	5-45	1
Two years			
Levodopa-carbidopa group (n = 26)	363/91	150-600	0
Bromocriptine group (n = 14)	22	6-35	1
Three Years			
Levodopa-carbidopa group (n = 10)	380/45	250-500	0
Bromocriptine group (n = 1)	35	—	1

whom confusion occurred with bromocriptine, five had evidence of dementia at baseline.

Involuntary movements were the main reason for breaking the treatment code in patients receiving levodopa-carbidopa. Dyskinesia (choreo-athetoid movements often occurring at peak-dose times) began at a mean of 16 months (range 7-24 months) after commencing medication. The mean duration of disease prior to the onset of dyskinesia was 44 months (range 14-60 months). Nineteen percent of patients (six out of 32) had developed dyskinesia after 2 years on levodopa-carbidopa. Foot dystonia (sustained inversion of the foot, clawing of the toes or dorsiflexion of the large toe) appeared at a mean of 21 months (range 12-30 months) after treatment and after a mean duration of disease of 44 months (range 25-78 months). Sixteen percent of patients (five out of 32) had developed foot dystonia after 2 years.

Six patients on levodopa-carbidopa, three on bromocriptine and one on combined therapy have reported mild, end-of-dose deterioration. All three patients on bromocriptine had moderately severe disease, with Columbia scores of about 30. In no case was the end-of-dose deterioration sufficiently severe to require an increased frequency of dosage of bromocriptine. Four of the six patients with this problem in the levodopa-carbidopa group are now taking the drug four or more times daily.

Changes in the Columbia scores

Changes in the Columbia scores at 1 and 2 years of all

Table 3 Reasons for breaking the drug code in patients randomised to bromocriptine

Problem	No	Mean dose (range) mg/day
Lack of efficacy < 30 mg/day	8	17 (7.5-25)
Lack of efficacy > 30 mg/day	14	42.7 (30-75)
Confusion	10	13 (1-30)
Postural hypotension	3	13 (10-15)
Nausea	2	14 (12.5-15)
Lack of compliance	2	11.5 (3-20)
Other	1	17.5
	40	

patients remaining on their initial therapy, regardless of whether the treatment code had been broken, are shown in tables 5 and 6. More patients improved and these to a greater degree on levodopa-carbidopa than on bromocriptine. At 1 year, 59% of patients on levodopa-carbidopa and 31% of patients on bromocriptine had a 20% reduction in the Columbia score. At 2 years, 58% of patients on levodopa-carbidopa and 7% of patients on bromocriptine had improved by 20% or more. Patients who improved on low-dose bromocriptine tended to have mild disease with tremor. The number of patients who have been in the trial for 3 years is not sufficient for a meaningful analysis.

Follow-up of patients no longer on initial therapy alone

Twenty two patients did not improve on bromocriptine and had sufficient disability to warrant breaking the treatment code. Of these, 12 out of 13 improved when levodopa-carbidopa was added to the bromocriptine and six out of seven improved when bromocriptine was replaced by levodopa-carbidopa. Six out of 10 patients who became confused on bromocriptine also developed confusion on levodopa-carbidopa.

Three patients, in whom levodopa has replaced bromocriptine, have developed dyskinesia after a mean of 15 months (range 4-31 months) on levodopa, while two other patients have developed dystonia of the foot after 2 and 12 months respectively on levodopa. The mean period of treatment with

Table 4 Reasons for breaking the drug code in Levodopa-carbidopa group

Problem	No	Mean dose (range) mg/day
Dyskinesia	7	386 (300-500)
Dystonia of foot	7	357 (250-550)
Lack of efficacy		
< 600 mg/day	3	400 (300-500)
> 600 mg/day	1	750
Confusion	2	325 (300-350)
	20	

Table 5 Mean (%) change in modified Columbia score for patients still on initial randomised therapy after one year

Medication	Levodopa-carbidopa	Bromocriptine
Number of patients in each group	50	54
Patients still on initial therapy	46	29
Number of patients who have improved	30	15
% improvement: mean	35	25
range	7-79	5-46
Number of patients who have deteriorated	15	9
% deterioration: mean	18	37
range	8-45	5-120
Number of patients who are unchanged	1	5

bromocriptine for these five patients was 16 months (range 5-33 months) prior to its cessation.

All four patients who had an inadequate response to low-dose levodopa responded to higher doses (mean 900 mg/day).

Discussion

Differences in methods of assessment, duration of disease and previous treatment make it difficult to compare the results of this low-dose study with those of studies using conventional doses of levodopa. Comparisons with conventional doses of bromocriptine are rendered even more difficult by the fact that bromocriptine is used as an adjunct to levodopa in most studies. Nevertheless, there can be little doubt that fewer of our patients, both in the levodopa-carbidopa and bromocriptine groups, have improved, and these to a lesser degree than patients treated with high doses of levodopa. After 2 years of treatment with conventional doses of levodopa, 63-77% of patients showed more than 20-25% improvement in three large studies.¹⁷⁻¹⁹ By comparison, 58% of patients originally allocated levodopa-carbidopa and only 7% of patients originally allocated bromocriptine had

Table 6 Mean (%) change in modified Columbia score for patients still on initial randomised therapy after two years

Medication	Levodopa-carbidopa	Bromocriptine
Number of patients in each group	32	27
Patients still on initial therapy	26	14
Number of patients who have improved	18	5
% improvement: mean	42	16
range	6-60	9-33
Number of patients who have deteriorated	6	8
% deterioration: mean	27	31
range	3-57	8-89
Number of patients who are unchanged	2	1

Table 7 Incidence (%) of abnormal involuntary movements (AIMS) in previous studies

Authors	Mean dose of levodopa (mg/day)	% AIMS	Duration of treatment (years)
Lee, Sweet, McDowell 1971 ¹⁸	not stated	85†	2
Shaw, Lees, Stern 1980 ¹⁹	950	60*	1
		67*	3
Boshes 1981 ²⁴	review	70†	2
Rascol 1984 ²⁵	732.9	36.8*	2.5
Hoehn 1985 ²⁶	626.8	52.9*	1-3
Lees, Stern 1983 ²⁷	396	33*	3

*peak dose dyskinesias only
†AIMS not specified

improved more than 20% at 2 years in this study. Moreover, the proportion of patients who had improved at 2 years was lower than at 1 year in the bromocriptine treatment group, suggesting a waning of therapeutic effect with time.

Lest it appear that we are condemning our patients to unnecessary hardship, it should be recalled that the aim of this study was to try to avoid the long-term problems associated with levodopa and bromocriptine therapy by giving the lowest dose which produced a satisfactory response. Our guiding principle was, therefore, to increase the dose of each drug until the patient reported a satisfactory response. This might involve an increase in independence or a return to previously abandoned activities and not be reflected in the Columbia score. Being a de novo study, many of our patients have mild disease (Hoehn and Yahr stage I and II), and a failure to show objective improvement in clinical signs at this stage is of little importance. Patients remaining in the double blind aspect of the study are all satisfied with their progress to date. This is the case after 2 years in 26 out of 32 patients in the levodopa-carbidopa group and in 14 out of 27 patients in the bromocriptine group.

Most published studies include patients with moderate or severe disability. In such patients the main aim of treatment is to produce maximal improvement. A similar approach was followed in 26 patients in this study who did not improve on the low-dose regimen and who had moderately severe or rapidly progressive disease (Hoehn and Yahr stage III and IV). In these patients the low-dose therapy was abandoned and conventional doses of levodopa-carbidopa and bromocriptine were given either singly or in combination.

This study confirms the findings of Poewe, Lees and Stern²⁰ that giving levodopa at low dosage does not prevent some patients from getting involuntary movements. The incidence, however, is considerably lower than with conventional doses (see table 7). None of our patients on bromocriptine has so far developed this side-effect, though five patients who were origin-

ally allocated bromocriptine have since developed involuntary movements on levodopa-carbidopa. These results confirm the view that levodopa has a greater propensity to cause involuntary movements than bromocriptine. The reason for this remains unclear. One possibility is that involuntary movements result from stimulation of both D1 and D2 receptors. Bromocriptine is an agonist only for the latter.²¹ Denervation hypersensitivity, with failure of re-uptake of dopamine by degenerating pre-synaptic neurons, is also regarded as a possible mechanism of dopa-induced involuntary movements.^{19 22 23} Our results show that levodopa is a more effective anti-Parkinsonian agent than bromocriptine but is more prone to produce involuntary movements. This suggests that the beneficial and, as far as involuntary movements are concerned, deleterious effects may be linked.

In conclusion, low dose levodopa-carbidopa appears to be a more effective anti-Parkinsonian treatment than low-dose bromocriptine. Although involuntary movements do occur with low dose levodopa-carbidopa, their incidence is much reduced compared with conventional doses. While no patient on bromocriptine has developed involuntary movements, measurable improvement has occurred in only a minority of patients. It is hoped, however, that this approach will reduce the incidence of long-term side-effects.

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