Bromocriptine alone or associated with L-dopa plus benserazide in Parkinson's disease

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SUMMARY Twenty-six patients affected by Parkinson's disease were treated with a 2-Br- α -ergocriptine (CB 154): 14 cases were given CB 154 alone, and 12 were given CB 154 along with L-dopa plus benserazide (Madopar). Both CB 154 and combined therapy (CB 154+Madopar) induced a significant improvement in total disability score, tremor, rigidity, akinesia, self-sufficiency, and some motor performance tests (dynamic tests). No significant difference was found between results obtained with CB 154 therapy and with Madopar treatment, while the improvement induced by combined therapy (CB 154+Madopar) was significantly higher than that obtained by Madopar alone. The adverse reactions caused by CB 154 alone or associated with Madopar are similar to those observed during other dopaminergic treatment. CB 154 alone or combined with Madopar appears to be a useful advance in the management of Parkinson's disease.

2-bromo- α -ergocriptine (CB 154) is an ergot alkaloid which has been proved effective in suppressing lactation and inhibiting prolactin secretion (Flückiger and Wagner, 1968; Billiter and Flückiger, 1971). As several experimental studies on animals (Corrodi *et al.*, 1973; Miyamoto *et al.*, 1974; Goldstein *et al.*, 1975) showed that CB 154 has a dopamine stimulating effect both at presynaptic and postsynaptic levels, bromocriptine has been used in the treatment of Parkinson's disease (Calne *et al.*, 1974; Lieberman *et al.*, 1976a; Gerlach, 1976; Parkes *et al.*, 1976; Gautier and Durand, 1977).

Another ergoline derivate (lergotriple), which reduces plasma prolactin concentration has been tried in the treatment of Parkinson's disease with not very satisfactory results (Lieberman *et al.*, 1975). The results obtained with CB 154 in the treatment of Parkinson's disease are certainly valid although with different effects observed by different authors. According to Kartzinel *et al.* (1976a) CB 154 is more effective than L-dopa plus carbidopa (Sinemet), while Gerlach (1976) notes that CB 154 is less effective than L-dopa plus benserazide (Madopar). Lieberman *et al.* (1976b) claim that CB 154 would be useful in patients no

longer responding to L-dopa. The addition of caffeine did not enhance the antiparkinsonism potency of ergocriptine (Kartzinel *et al.*, 1976b).

Taking this diversity of opinions regarding the therapeutic effectiveness of 2-bromo- α -ergocriptine into account, it seemed interesting to compare the results obtained with the various therapies as follows: (1) CB 154 versus no specific treatment; (2) CB 154 versus Madopar; and (3) CB 154 plus Madopar versus Madopar alone.

Subjects and methods

Twenty-six subjects (Table 1), 14 females and 12 males, with a mean age of 59.5 years (maximum 68 years and minimum 46 years) consented to participate in this trial after being informed of the possible risks and benefits. All the subjects were affected by Parkinson's disease; in three cases the disease was just beginning and slight, seven patients were grade 2, 12 were grade 3, and four were grade 4 (according to the Webster scale). The clinical pattern in most patients consisted of rigidity and akinesia; tremor was actually evident in only seven cases.

The mean duration of the illness was 5.4 years (range five months to 13 years). The patients, with the exception of the three in the first stage of the disease, had been under treatment for a mean of three years (range six months to six years)

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with various antiparkinsonism substances: L-dopa and decarboxylase inhibitor (Madopar) 18, L-dopa six; piribedil four; and benztropine six. One patient underwent stereotactic surgery (unilateral thalamotomy).

The on-off phenomenon was present in two patients, abnormal involuntary movements were present in two others, and hallucinations and dementia in one case. Before beginning the pharmacological trials the previous drug therapies (L-dopa, benztropine) were suspended and all patients, with the exception of the three without treatment, were given or continued Madopar therapy. Our patients were divided into two groups.

The first group consisted of 14 patients, of whom 11 received Madopar treatment (mean dosage of 625 mg daily) and three, in the first stage of the disease, did not receive any antiparkinsonism therapy before entering the trial. The Madopar treatment was withdrawn for at least five days, and then the CB 154 treatment was begun in the same subjects. In all 14 patients treatment was begun with a daily dosage of 5 mg, increasing this by 5 mg every third day until optimum efficacy was reached. The treatment was carried out for a minimum of seven weeks. The maximum dose administered was 90 mg/day and the minimum 30 mg/day, with a mean dose of 60 mg/day in six-hourly doses. In one subject the treatment was suspended because of an evident depressive state.

Thus 13 patients in the first group were involved in the CB 154 trial, of whom 10 had also received Madopar treatment previously. Evaluation of the illness was done in the patients on Madopar therapy, in the patients without therapy, and in the patients on CB 154 treatment, so that it was possible to compare the test scores of CB 154 versus no treatment, of Madopar versus no treatment, and of CB 154 versus Madopar.

The second group was formed of a further 12 patients with Parkinson's disease who were on Madopar treatment at the mean daily dose of 700 mg. CB 154 was added to the Madopar therapy: for every 10 mg CB 154 given, Madopar was reduced by 125 mg until one half of the effective Madopar dosage was reached, so that these patients were receiving Madopar at the mean dose of 375 mg/day and CB 154 at the mean dose of 25 mg/day. In two cases the addition of CB 154 was suspended because of side effects (postural hypotension) after the first administration. The total number of patients involved in the trial of CB 154 plus Madopar was, therefore, 10. Evaluation of the illness was performed in these

Table 1 Synopsis of cases

Number of patients	Sex	Age (yr)		Duration of illness (yr)		Severity of illness (number of patients)				Duration of previous treatment (yr)		Previous treatment (number of patients)			
		male	female	mean	range	mild	moderate	severe		mean	range	Madopar	L-dopa	Piribedil	Benztropine
26	14	12		59.5	46-68	5.4	0.5-13	10	12	4	3	0.5-6	18	6	4

Table 2 Results of statistical analysis of various test scores with different therapies

Therapy	Number of patients	Total score	Rigidity	Akinesia	Tremor	Self-sufficiency	Dynamic tests
CB 154 versus no treatment	13	$p < 0.001$	< 0.001	< 0.01	< 0.01	< 0.01	< 0.05
Madopar versus no treatment	10	$p < 0.01$	< 0.01	< 0.02	< 0.02	< 0.05	< 0.02
CB 154 versus Madopar	10	$p < ns$	ns	ns	ns	ns	ns
CB 154 + Madopar versus Madopar	10	$p < 0.05$	> 0.05	$= 0.05$	ns	> 0.05	> 0.05

patients during Madopar treatment alone and, during the combined treatment (Madopar plus CB 154).

In evaluating disability we have used the scale proposed by Duvoisin analysing 25 different manifestations of Parkinson's disease, grade 0 being normal and grade 4 characterised by maximum impairment. We evaluated the self-sufficiency of our patients by considering their performance on the following complex daily activities: (1) dressing; (2) buttoning a jacket; (3) tying shoe laces; (4) washing; (5) cutting meat; (6) rising from a chair; (7) movement in bed. These tasks were rated on the scale 0=normal execution to 4=total inability. We also evaluated the time taken (in seconds) to perform the following simple actions (dynamic tests): (1) rising from a chair, turning round, and returning to the sitting position; (2) walking 11 metres as quickly as possible; and (3)

making a 360 degree turn in a supine position in bed. Lastly, all the patients were given an intelligence test (PM38).

These tests were given to the patients once a week for the entire period of the pharmacological trials, and the scores were derived from the mean observation of three different examiners. The best scores of the various tests were used for the statistical evaluation. Statistical analysis was performed using a paired *t* test (Student's *t* test).

Careful attention was directed to possible changes of pulse rate, respiration, and standing and lying blood pressure. Side effects such as constipation, nausea, vomiting, asthenia, mouth dryness, psychic disturbance, dyskinesia, paradoxical akinesia, and on-off phenomenon were taken into consideration. Haematological, hepatic, and renal function tests were done before, during, and after our investigation.

Fig. 1 Graph of the mean score of total disability (T.S.), self-sufficiency (S.), akinesia (AK.), rigidity (R.), and tremor (T.) during different therapies and in basal conditions; — no therapy; . . . Madopar; - - - CB 154; — — — Madopar and CB 154.

Results

In the first group of patients we compared the scores obtained in basal conditions to those on CB 154 therapy, in basal conditions to Madopar therapy, and on Madopar to CB 154 therapy. In the second group we compared the scores obtained in Madopar to CB 154 plus Madopar therapy.

Table 2 and Fig. 1 show that a significant improvement of all parameters (total score, hyper-tonia, akinesia, tremor, self-sufficiency, dynamic tests) was observed after treatment with CB 154 in respect to basal values.

A significant improvement on basal conditions was also evident for Madopar therapy, although the improvement was not as marked as on CB 154 treatment. The impression was that the effect of CB 154 was greater than that of Madopar, but the comparison of the results obtained with CB 154 and those obtained with Madopar was not significant. Comparing CB 154 plus Madopar and Madopar alone, we obtained a much greater improvement on the combined therapy.

Fig. 2 Reduction in total disability score to bromocriptine 30, 60 and 80 mg in 10 patients with Parkinson's disease. Note that the maximal slope of the curve is reached at 30 mg dose level.

We have tried to evaluate the efficacy of CB 154 in respect to dosage. Figure 2 demonstrates that the maximum percentage improvement is reached at the 30 mg dosage level, while higher doses elicit a further improvement but to a lesser degree. The PM 38 psychological test was not significantly modified by the various therapies.

The side effects are shown in Table 3. Gastric disturbances (pain, nausea, vomiting) were most frequent but could be relieved with a simple

Table 3 Side effects

Effect	Treatment	
	CB 154 alone	CB 154 + Madopar
Gastric disturbances	8	5
Depression	5	2
Postural hypotension	2	3
Dyskinesia	—	1
On-off phenomenon	—	1
Confusion	—	1

antacid treatment. A slight and transitory depressive reaction was observed in three patients with CB 154 and in two with combined treatment. Two other patients on CB 154 treatment were irritable and depressed and the treatment was withdrawn. In both of these patients a similar reaction appeared with subsequent treatment with Madopar, and, therefore, the patients were treated with tricyclic antidepressants which also have some antiparkinsonism effect. In one case the depressive reaction was immediate at the 10 mg dose level of CB 154, and in the other the depression began later at the dose of 30 mg CB 154, when an improvement was already evident. Both patients were affected by an early and very slight form of Parkinson's disease and had not received any treatment before. An increase of hyperkinetic movements was observed in one case, a worsening of mental disturbance (confusion and hallucination) in another. A fall of arterial blood pressure was evident in five cases. Livedo reticularis of limbs appeared in one case.

Discussion

These results clearly show the effectiveness of bromocriptine (CB 154) in the treatment of Parkinson's disease and are comparable with those previously reported by Kartzinel *et al.* (1976c) and Parkes *et al.* (1976). Rigidity and akinesia were significantly reduced, whereas tremor was less effectively alleviated. The appearance of tremor was slight in our patients, and we, therefore, suggest that the statistical analysis might change in a larger population. The scores of self-sufficiency and dynamic tests were also significantly improved (Table 2).

The effectiveness of combined therapy (CB 154 plus Madopar) was significantly higher than that of Madopar alone. There was no significant difference between CB 154 and Madopar treatment although the former therapy seems to be more efficient than the latter (Table 2 and Fig. 1).

A placebo effect must be considered, but we do not attribute the improvement obtained to this in view of the long duration of effectiveness of

the treatment, the nature of the disease, its organic basis, and the objective evaluation of clinical signs.

The necessity for rather high doses of CB 154 (mean 60 mg/day) has been demonstrated. The mean dose is a little lower than that of Kartzinel *et al.* (1976a) who, in some arbitrary way, proposed the maximum level of 100 mg/day. These data are at variance with those of Gerlach (1976) who, using smaller dosages, did not find the same improvement in his patients; otherwise our data agree with those of Kartzinel *et al.* (1976a) who compared the results obtained by CB 154 treatment with those obtained by treatment with L-dopa plus carbidopa (Sinemet).

Taking into consideration the dosage, the effectiveness of CB 154 is maximal at the lower doses (30 mg a day), while continuing improvement seen at the higher doses (60–80 mg/day) is less marked (Fig. 2), confirming the previous observations of Kartzinel *et al.* (1976a).

The addition of CB 154 to Madopar treatment permitted us to reduce the previous treatment by about 50% in quantity and the number of daily doses.

The side effects of CB 154 are similar to those appearing with L-dopa treatment whether or not associated with a decarboxylase inhibitor. We underline the unusual appearance of a depressive reaction in five patients. Two of the latter had an identical reaction with Madopar treatment, suggesting unpredictable hypersensitivity to dopaminergic stimuli in these cases.

On-off phenomenon or important swings in symptomatology during CB 154 therapy were never observed, and were seen in only one case during CB 154 plus Madopar treatment. This observation, even if restricted to a limited number of patients, seems to confirm the usefulness of bromocriptine in reducing the on-off phenomenon as suggested by Kartzinel and Calne (1976).

In conclusion, on the basis of the results of these trials, we suggest that CB 154 alone and combined therapy with CB 154 and Madopar, even if further investigations are required, is an important advance in the management of Parkinson's disease.

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