A Comparison of Bromocriptine (Parlodel®) and Levodopa-Carbidopa (Sinemet®) For Treatment of "De Novo" Parkinson's Disease Patients

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ABSTRACT: Fifty-one patients were enrolled in a double-blind, parallel group, multicentre study conducted to assess short-term efficacy and tolerance of bromocriptine (Parlodel®) or L-DOPA/carbidopa (Sinemet®) in patients never treated with amantadine, ergot alkaloids or L-DOPA-based drugs. An attempt to use the lowest effective dose was made. The responder rate for each group was approximately 78%; the mean daily dose for responders was 22.5 mg of bromocriptine or 250 mg of L-DOPA/carbidopa. The overall clinical improvement in each group was 62% (bromocriptine) and 55% (L-DOPA/carbidopa) for neurological assessment and 36% (bromocriptine) and 31% (L-DOPA/carbidopa) for functional disability. Comparison between groups did not show any significant difference for both neurological and disability assessments. The most frequent side effect was nausea (L-DOPA, N = 3; bromocriptine, N = 6).

RÉSUMÉ: Cinquante et un patients ont fait l'objet d'une étude multicentrique parallèle, à double insu, destinée à évaluer l'efficacité à long terme et la tolérance de la bromocriptine (Parlodel®) ou de l'association lévodopa/carbidopa (Sinemet®) chez des sujets n'ayant jamais été traités au préalable par l'amantadine, ni par les alcaloïdes de l'ergot, ni par les dérivés de la lévodopa. Dans la mesure du possible, la dose efficace la plus faible a été administrée. Le taux de répondeurs a été, dans chacun des groupes, de 78% environ. La dose moyenne quotidienne utilisée chez les répondeurs était de 22,5 mg de bromocriptine ou 250 mg de lévodopa/carbidopa. L'amélioration clinique globale dans chacun des groupes s'est chiffrée à 62% (bromocriptine) et à 55% (l-dopa/carbidopa) dans le cas des évaluations neurologiques, et à 36% (bromocriptine) et 31% (l-dopa/carbidopa) dans le cas de l'incapacité fonctionnelle. Une comparaison des résultats obtenus dans les deux groupes n'a pas révélé de différences en ce qui a trait aux évaluations neurologiques et aux évaluations de l'incapacité fonctionnelle. L'effet secondaire le plus fréquent a été les nausées (l-dopa, N = 3; bromocriptine, N = 6).

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Several studies investigating bromocriptine (Parlodel®), a semi-synthetic ergot alkaloid and a potent dopamine receptor agonist, in the treatment of Parkinson's disease have demonstrated a clear improvement in clinical symptoms when bromocriptine is given as adjunctive therapy in patients treated with conventional treatment including L-DOPA.[1,2,3,4,5] This was demonstrated by improvement in the signs and symptoms of the disease, a reduction of the L-DOPA dosage, and a resulting decrease in the incidence of dyskinesias.

Although there is controversy,[6] continuous long-term therapy (1-3 years) with L-DOPA is associated with complications and loss of the initial benefit in a large proportion of patients.[7] The duration of usefulness of L-DOPA is therefore limited[8] and this may be due to loss of presynaptic neurons.[9] The "wearing off" effect of L-DOPA is accompanied by the onset of other long-term complications related to L-DOPA therapy, including the on-off phenomenon, dyskinesias and early morning dystonia.[9,10] Reductions in fluctuations are usually achieved by increasing the frequency of administration of L-DOPA, which can potentially enhance the occurrence of dyskinesia.[11]

Studies using bromocriptine in hitherto untreated patients have shown the drug to be of benefit, but use of high doses

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leading to complications limited the evaluation of its long-term usefulness.[12,13,14] However, studies using lower doses showed that bromocriptine could be of long-term benefit.[15,16] Following long-term treatment (high or low dose), no end of dose deterioration was seen in these patients.[8,12,13,16,17] The incidence of dyskinetic side effects also were considerably lower than with long-term L-DOPA therapy.[12,15,16,17]

Bromocriptine acts directly on postsynaptic dopaminergic striatal receptors (activation of D_2 receptors).[18,19] Thus it does not require L-DOPA decarboxylase, which is usually depleted as the disease progresses.[20] Moreover, the progression of the disease leads to a greater loss of presynaptic dopamine neurons than postsynaptic dopamine receptor sites in the striatum.[8] These factors provide the rationale for the use of bromocriptine as a potentially beneficial first line therapy in Parkinson's disease.[17] Such an approach would not only avoid or delay the use of L-DOPA but could prolong its usefulness by allowing smaller L-DOPA doses to be administered, thus preventing the L-DOPA-related long-term problems.[21]

The objectives of the present study were to establish the optimal dose range and regimen of bromocriptine in the treatment of Parkinsonian patients previously untreated with ergot alkaloids, amantadine or L-DOPA-related drugs, and using equipotent doses (10 mg bromocriptine to 100 mg L-DOPA) as described by Calne[22] to compare the short-term efficacy and tolerance of bromocriptine (Parlodel®) to L-DOPA/carbidopa (Sinemet®).

Methods

Patient Population

This report includes the results obtained in 51 patients (bromocriptine group: 25, L-DOPA/carbidopa: 26), of whom 49 completed the double-blind part of the study (Part 1). Patients were approximately 65 years of age with mainly mildly to moderately severe Parkinson's disease (mainly stages II and III). Patients' characteristics were not statistically different between the two treatment groups.

Ten patients in the bromocriptine group and six patients in the L-DOPA/carbidopa group were previously treated with anticholinergics (trihexyphenidyle, benztropine, orphenadrine, ethopropazine). The majority of patients (21 in the bromocriptine group; 17 in the L-DOPA/carbidopa group) were classified stage II or III (Hoehn and Yahr scale[23]) at the beginning of the study.

Dosage

Treatment was initiated with 5 mg per day (2.5 mg b.i.d.) of bromocriptine or 50/12.5 mg per day (25/6.25 mg b.i.d.) of L-DOPA/carbidopa. The daily doses were increased every 3 weeks over a titration period of 15 weeks by 5 mg of bromocriptine or 50/12.5 mg of L-DOPA/carbidopa until a stable therapeutic effect was observed, or up to a maximum of 30 mg/day of bromocriptine or 300/75 mg/day of L-DOPA/carbidopa.

In order to ensure double-blindness, identical capsules containing either bromocriptine or L-DOPA/carbidopa were prepared.

Experimental Design

This was a multicentre study conducted under a double-blind parallel group design (Part 1 of the Study).

Baseline observation consisted of two visits with a 2-week interval. Thereafter, dose titration started, lasting up to 15 weeks (one visit every 3 weeks) during which time medication dosage was progressively increased until stable improvement was seen or to a maximum of 30 mg/day of bromocriptine or 300/75 mg/day of L-DOPA/carbidopa. The maintenance period was 6 weeks, with 2 visits at 3-week intervals, after which the patients were classified as responders or non-responders to their randomly allocated treatment. For responders, the lowest effective dose was defined as the lowest resulting in a stable improvement (lack of further improvement when dose increased for two consecutive titration visits).

Parameters used to assess efficacy were: 1. Clinical status (Hoehn and Yahr classification);[23] 2. Rating of neurological signs and symptoms using the Columbia University Scale;[24] 3. Rating of functional disabilities using the Northwestern University Disability Scale (NUDS).[25]

Side effects were reported at every visit. Routine laboratory tests, chest X-rays and ECG were performed at baseline and at the end of the study.

Statistical Methodology

Comparison between groups was done by a 2-way analysis of covariance for repeated measurements.[26] Values at week 18 and week 21 (maintenance period) were simultaneously compared after an adjustment of the baseline measures (day 0 used as covariate).

Comparison within each treatment group was performed by a 1-way analysis of variance for repeated measures[26] to determine difference over time from day 0 through week 18 and week 21. If the 1-way model was declared significant, then contrasts using the Bonfferoni technique[27] were done to determine which individual time points were significantly different from baseline.

The power of tests for the efficacy parameters has been established retrospectively at $\pi = 69\%$ (assuming an intra-class correlation of $\psi = 50\%$) and the significance level was fixed at α - 0.0166.

Prior to the application of the parametric models, all tests for assumptions (homogeneity of slopes vector; test for interaction) were performed. A linear transformation or an Anova model was used in case of test violation. For all inferential tests the population represented by the K visits were assumed to be independently normally distributed.

Results

Two of the 51 patients were withdrawn from therapy: in the bromocriptine group, 1 patient dropped out because of side effects (confusion); in the L-DOPA/carbidopa group, 1 patient dropped out for personal reasons.

At the end of the maintenance phase, the mean daily dosage was 24.1 ± 1.7 mg of bromocriptine or 252 ± 14 mg of L-DOPA/carbidopa. When patients were subdivided into responders and non-responders for each treatment group, the daily doses were: 22.5 ± 2.0 mg of bromocriptine for the responders (19 out of 24) and 30 ± 0 mg (the maximum allowed dose) for the 5 non-responders; 250 ± 16 mg of L-DOPA/carbidopa for the responders (19 out of 25) and 258 ± 27 mg for the 6 non-responders. Patients in both groups were treated for a mean duration of 19.5 weeks.

Table 1 represents the distribution of changes in clinical stage at the end of the maintenance phase. Forty-two percent of patients in the bromocriptine group and 32% of patients in the L-DOPA/carbidopa group presented clinical status improvement by at least one stage. The remaining patients showed no change in their clinical status. No patients deteriorated.

Table 2 represents the mean neurological assessment scores and the percentage improvement observed from day 0 to the last maintenance visit (week 21). The total mean score improved by 62% in the bromocriptine group and 55% in the L-DOPA/carbidopa group. In general, all parameters improved in both groups to a similar extent with the exception of "arising from chair" which was significantly improved in the bromocriptine group as compared to the L-DOPA/carbidopa group. This last observation might be related to the large variation between the 2 groups at baseline.

Table 3 presents descriptive statistics for NUDS assessment scores. The total mean score was significantly ($p \leq 0.001$) improved with bromocriptine and less markedly improved (but not significantly) with L-DOPA/carbidopa. Statistically significant improvement was noted in all parameters in the bromocriptine group and in all parameters but hygiene in the L-DOPA/carbidopa group. There was no statistical difference between the two groups for all parameters.

The most frequent side effect observed was transient nausea (mild to moderate) occurring in 6 patients in the bromocriptine group and 3 patients in the L-DOPA/carbidopa group. Three patients in the bromocriptine group and 4 in the L-DOPA/carbidopa group had to have their medication dosage reduced because of side effects (increased tremor and nausea in the bromocriptine group; stiffness, bloating and anxiety in the L-DOPA/carbidopa group). No dyskinesias or "on-off" phenomena were noted in either group.

Table 1: Distribution‡ of Changes in Clinical Stage

	Bromocriptine		L-Dopa/Carbidopa	
Improvement				
IV to III	1	(4%)	0	(0%)
III to II	6	(25%)	4	(16%)
III to I	1	(4%)	1	(4%)
II to I	2	(8%)	3	(12%)
[TOTAL]	[10]	[(42%)]	[8]	[(32%)]
No change				
V to V	0	(0%)	1	(4%)
IV to IV	2	(8%)	1	(4%)
III to III	5	(21%)	5	(20%)
II to II	6	(25%)	3	(12%)
I to I	1	(4%)	7	(28%)
[TOTAL]	[14]	[(58%)]	[17]	[(68%)]

‡Data are expressed as the number of patients (n)
Values in parentheses represent the percentage

Overall Evaluation

On termination of the double-blind part of the study, an overall evaluation was performed by the investigators. The therapy was considered good to very good in 72% of patients in the bromocriptine group and in 61% of patients in the L-DOPA/carbidopa group. Tolerance was assessed good to very good in 87% of patients in both groups. The bromocriptine group and the L-DOPA/carbidopa group had respectively 77% and 79% of patients classified as responders.

Table 2: Neurological Assessment‡ (Columbia Scale)

	Bromocriptine Group (n = 24)			L-Dopa/Carbidopa Group (n = 25)		
	Day 0	Week 21	Improvement	Day 0	Week 21	Improvement
Clinical Status	2.71±0.15	2.25±0.17***	17%	2.32±0.21	1.96±0.22***	16%
Tremor	3.29±0.80	1.29±0.46***	61%	3.68±0.69	1.28±0.30***	65%
Rigidity	7.71±0.94	2.46±0.54***	68%	6.44±1.00	2.68±0.80***	60%
Bradykinesia	2.33±0.19	1.21±0.26***	48%	2.24±0.21	1.16±0.26***	48%
Sialorrhea	0.33±0.18	0.17±0.10NS	50%	0.24±0.15	0.08±0.06NS	67%
Seborrhea	0.33±0.13	0.17±0.10*	50%	0.24±0.11	0.08±0.06NS	67%
Swallowing	0.17±0.10	0.04±0.04NS	77%	0.08±0.26	0.04±0.04NS	86%
Arising from chair	1.21±0.22	0.42±0.15***+	65%	0.72±0.19	0.48±0.18 **	33%
Posture	1.50±0.16	0.71±0.14***	53%	1.08±0.21	0.68±0.18***	37%
Gait	1.13±0.15	0.54±0.13***	52%	0.92±0.18	0.56±0.16***	39%
Postural stability	0.92±0.20	0.29±0.13***	69%	0.72±0.17	0.40±0.17***	44%
Total	18.92±0.90	7.29±1.19***	62%	16.36±1.68	7.44±1.55***	55%

‡Data are expressed as mean score ± S.E.M.; a smaller score means improvement.
*$p \leq 0.017$ **$p \leq 0.010$ ***$p \leq 0.001$ NS not significant
+Statistical significance between the two groups in favor of the bromocriptine group.

Table 3: Northwestern University Disability Scales‡ (N.U.D.S.)

	Bromocriptine Group (n = 24)			L-Dopa/Carbidopa Group (n = 25)		
	Day 0	Week 21	Improvement	Day 0	Week 21	Improvement
Walking	1.88±0.34	1.04±0.24***	45%	1.64±0.44	1.20±0.40**	27%
Dressing	1.75±0.30	1.17±0.24**	33%	1.56±0.40	1.12±0.36**	28%
Hygiene	1.92±0.39	1.33±0.34**	31%	1.40±0.40	1.00±0.35NS	29%
Eating/feeding	1.71±0.37	1.08±0.25***	37%	1.32±0.34	0.92±0.31***	30%
Speech	1.92±0.32	1.25±0.30***	35%	1.36±0.24	1.12±0.22**	18%
Total	9.17±1.46	5.88±1.21***	36%	7.28±1.72	5.36±1.58NS	31%

‡Data are expressed as mean score ± S.E.M.; a smaller score means improvement.
**$p \leq 0.010$ ***$p \leq 0.001$ NS not significant
No statistical significance was noted between the two groups.

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Discussion

The treatment of "de novo" patients with bromocriptine as single therapy requires higher dosages than when it is used as adjunct to L-DOPA therapy. We found a mean effective daily dosage of 22.5 mg (responders) in agreement with the average dosage range of 20 to 40 mg found in other studies.[12,17,28,29] Moreover, the literature mentions a mean daily dosage of bromocriptine slightly lower when given as add-on: 12-20 mg[21,28,30] in patients mildly to moderately disabled. One must, however, consider the constraints of some of the published studies in terms of the maximum doses allowed which were, in some instances, rather low.

Our data on the dosage (22.5 mg bromocriptine; 250 mg Sinemet) also confirm the relative potency of 1:10 between bromocriptine and L-DOPA/carbidopa dosages.[22,31] This ratio is also respected when considering the wide range of variability in optimal dose generally observed among patients treated with these two medications. In this study, the range was of 50 to 300 mg/day in the L-DOPA/carbidopa group and 5 to 30 mg/day in the bromocriptine group.

The benefits of both treatments used in this study ranged between 48 to 68% in the Parkinsonian cardinal signs and approximately 35% in the total score of daily living activities. The clinical stage was improved by 17 and 16% in 71% and 47% of patients on bromocriptine and L-DOPA/carbidopa, respectively. These levels of improvement compare favorably with the presently accepted standards for efficacy of L-DOPA/carbidopa therapy.

Both treatment regimes (L-DOPA/carbidopa and bromocriptine) produced similar improvement, as concluded by Rascol et al.[17] Tremor and rigidity were more improved than bradykinesia. Stall-Schreinemachers et al[29] found a better improvement in rigidity than in tremor and no significant improvement in bradykinesia whereas Teychenne et al[28] observed a significant improvement in tremor (50%) and bradykinesia (32%) and no improvement in rigidity. As observed by Lees and Stern,[12] our study shows that 50% of patients (48% L-DOPA/carbidopa, 50% bromocriptine) had a total disability score improved by 25% or more.

It is not possible to comment on the effectiveness of the study treatment in more advanced cases of Parkinson's disease since numbers for severe (Stages IV and V) disease are not sufficient (see Table 2) for statistical analysis.

The present results did not show any statistical difference in the efficacy of the two treatments. One can assume that at least in the short-term period, bromocriptine therapy seems to be as effective as L-DOPA/carbidopa therapy in treating "de novo" Parkinsonians as already reported.[32]

However, transient nausea was present in more patients in the bromocriptine group than in the L-DOPA/carbidopa group. A high incidence of gastrointestinal side effects has already been reported in "de novo" patients treated with bromocriptine.[33] Domperidone, a peripheral dopaminergic blocking agent, has been reported to counteract such problems.[34]

Long-term follow-up of patients suggests that oscillations of performance, drug-induced dyskinesias, on-off phenomenon, and other long-term problems usually observed with L-DOPA therapy have not been observed with bromocriptine therapy.[12,17,28,31] It will be of interest to determine if similar results are found and if benefit can be maintained following a longitudinal follow-up of the patients in this study, since some papers report in the literature a significant decrease in the number of patients who can be maintained on the single therapy.[21,33] The possibility of prevention of complication related to long-term levodopa therapy should lead one to consider the use of bromocriptine early in the treatment course for mild to moderately disabled Parkinsonians.

Later on, it may be appropriate to add L-DOPA/carbidopa as the patient begins to deteriorate. If the initial studies by Rinne[21] are confirmed, this approach to therapy may prevent the crippling side effects encountered later and extend the useful treatment period of L-DOPA/carbidopa.

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