Should Dopamine Agonists be Given Early or Late in the Treatment of Parkinson's Disease?

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ABSTRACT: The long term consequences of the use of a dopamine agonist, bromocriptine, in the treatment of Parkinson's disease are reported. In a first study in 82 patients showing late side effects of levodopa, bromocriptine permitted a significant decrease of the gastro-intestinal adverse effects. In contrast, no significant improvement of end of dose deterioration from levodopa was noted. In cases where levodopa had ceased to be active, bromocriptine produced an improvement in the clinical state. The drug was ineffective in the very advanced stages of the disease or in the cases of dyskinesias without "on-off" effects. Bromocriptine did not significantly improve freezing or "on-off" effects, but reduced other side effects of levodopa, in particular dystonia. In a second group of 29 patients who had never received levodopa treatment, bromocriptine was shown to be very effective as a first treatment of the disease. The most important finding was the absence of long term side effects similar to those usually observed under levodopa: in this group and in comparison with 38 patients taking levodopa, dyskinesia, dystonia, oscillations in performance and especially "on-off" effects were not noted. However, a partial loss of efficacy of bromocriptine was observed in 27% of cases. In a third group of 10 patients, bromocriptine introduced according to a low and slow protocol was found to be active in a limited number of patients only.

RÉSUMÉ: Les auteurs rapportent leur expérience concernant l'utilisation à long terme d'un agoniste dopaminergique, la bromocriptine dans le traitement de la maladie de Parkinson. Dans une première série de 82 patients présentant des complications sous lévodopa, la bromocriptine a permis une réduction des effets gastrointestinaux tardifs de la lévodopa. Par contre elle n'a assuré qu'un contrôle imparfait des déteriorations de fin de dose sous Dopa. Elle permet une relance de l'efficacité de la lévodopa dans les cas où celle-ci a cessé d'être active mais elle reste inefficace aux stades très avancés de la maladie et en cas de dyskinésies sans effets "on-off". La bromocriptine n'améliore pas les effets "on-off" ou le freezing mais réduit les dystonies induites par la lévodopa. La bromocriptine est aussi efficace comme premier traitement de la maladie (29 patients n'ayant jamais reçu de lévodopa). La constation importante est l'absence de complications à long terme telles que celles observées habituellement sous lévodopa: dans cette série et par rappot à un groupe contrôle de 38 patients sous lévodopa, nous n'avons pas observé de dyskinésie, de dystonie, de fluctuation dans la performance (en particulier pas d'effet on-off). Un épuisement partiel de l'efficacité a été observé dans 27% des cas. Enfin, une 3e étude sur 10 patients montre que seul un petit nombre de malades semble amélioré par de faibles doses introduites selon une posologie lentement évolutive.

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Several dopamine agonists have been introduced into the treatment of Parkinson's disease (Goldstein et al., 1980; Calne et al., 1983). Most of them are ergot derivatives and bromocriptine is the main one. We have not studied pergolide or lisuride. We have started using CU 32085 but only recently (18 months follow-up only) and in too limited a number of cases (20 patients) to permit conclusions.

In this paper we propose to report our findings with early and late therapy with bromocriptine and to compare the results in order to answer the question: "Should dopaminergic agonists be given early or late in the treatment of Parkinson's disease?"

121 patients were studied between March 1976 and December 1982. In all cases the diagnosis of idiopathic Parkinson's disease was certain. When bromocriptine proved effective, a follow-up of at least six months was undertaken.

I — Late Treatment With Bromocriptine

In the first part of this study, we would like to report on the results of late therapy with bromocriptine in patients taking levodopa for over 18 months. At this stage bromocriptine was either given with levodopa, or when possible, substituted for it.

Patients and Methods

This population included 82 patients. All of them had late side-effects of levodopa. As these patients failed to respond to increasing doses of levodopa, bromocriptine was given. All these patients were admitted to hospital. Before introducing bromocriptine, we arranged a three day period in a specialized unit with staff trained in the observation and quantification of parkinsonian symptoms. As discrepancies between information provided by the patient and objective measurements are by no means uncommon, we found this observation period to be absolutely necessary.

Using our rating scale with four increasing levels (Rascol et al., 1979), the results were judged as follows: *Good*, if regardless of the initial severity of clinical symptoms, the score returned to 0 or 1 and the side effects of levodopa disappeared; *Average*, for both a one point improvement and a decrease of the side effect of levodopa; *Poor*, for absence of objective change but

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with a subjective improvement; *Failure*, corresponding to either intolerance or to ineffectiveness of the drug.

Results

Seven patients developed *gastrointestinal disorders* after several years of well tolerated treatment with levodopa. The two failures were due to inadequate efficacy of bromocriptine on the parkinsonian symptoms. In the other five patients, levodopa was discontinued and bromocriptine alone suppressed the disorder and achieved satisfactory control of the disease. In three cases, the addition of small doses of levodopa resulted in better control without any recurrence of gastrointestinal problems.

Eleven patients showed "*end of dose deterioration*" which was objectively assessed during the observation period by variation in the scores according to the time of drug administration. In this group, we noted only four good results with bromocriptine alone or in association with low doses of levodopa. There were two equivocal results and five treatment failures.

These data stand midway between the widely accepted view that bromocriptine is highly effective and absolutely indicated in such cases due to its longer half-life, and the conclusion of Lees and Stern (1981) that bromocriptine has nothing to offer in such patients.

Eighteen patients complained of progressive *decrease in the efficacy of levodopa*. No change in scores could be found through the day, but they were lower than at the initial phase of levodopa treatment. Results were good in 10 cases, although loss of efficacy occurred after 18 to 24 months in four of these cases. Moderate results were obtained in four other patients and there were four treatment failures. In all these cases, the previous dose of levodopa was maintained. The benefit of this additive effect extended over several years, but it did not prevent the problems occurring in the final stages of the disease with total loss of efficacy of bromocriptine and levodopa and very often dementia. We observed such a failure in four patients who had benefitted from the combination of levodopa and bromocriptine for 18 months to three years. This corroborates our finding of 1979 concerning the inefficacy of bromocriptine at very advanced stages of the disease (Rascol et al., 1979).

Late treatment with bromocriptine was also initiated in a number of patients with dyskinesias, "on-off" phenomena, dystonias, and freezing. Any of these disorders can occur in isolation, but as the disease progresses their association is common. In eight patients suffering from painful paroxysmal *dystonia* (legs — six cases, oromandibular — two cases), good results were obtained in six cases (two treated with bromocriptine alone, four with a 75% decrease of levodopa), a moderate result in one case, and there was one treatment failure.

Nine of the patients who were started on bromocriptine were experiencing severe *on-off phenomena*. By "on-off" effects, we mean the random fluctuations in performance which are totally unrelated to time of drug dose. We noted only two good results in this group, one in a patient treated with bromocriptine monotherapy at very high doses (150 mg. a day) followed for a period of two years. In seven cases, the results were poor. However, these patients reported that they felt better and preferred to continue the combination of bromocriptine and levodopa, even though we were not able to confirm any objective improvement, probably because of daily random fluctuations.

Twenty-one patients presented with *dyskinesias without "on-off" phenomena*. The dyskinesias were of varying intensity, at times very severe, and disturbing for family or social life in all cases. These patients had not been adequately controlled by various changes in levodopa dosage. We obtained several good results; in three of these levodopa therapy could be discontinued, in the other four cases levodopa was decreased by at least 75%. The improvement was still remarkable after follow-up period ranging from 18 months to seven years. In an additional four patients, the results were graded as moderate, and there were 11 treatment failures in this group.

No improvement with bromocriptine was noted in any of the patients exhibiting *freezing*.

Discussion

To sum up, good results were obtained in 34 of 82 patients treated (41.5%) and reasonable or average results in 14 cases (17%). Thus, the hypothesis that a post-synaptic agonist could correct the side effects of long term levodopa therapy has not been supported by the late use of bromocriptine.

Three questions arise from these observations: 1) Does bromocriptine act in the treatment of Parkinson's disease as a pure post-synaptic dopamine agonist? Pharmacological studies in animals show that bromocriptine has a significant pre-synaptic site of action (Goldstein et al., 1980). Could better results be expected from more selective agents? 2) To what extent are dopaminergic receptors modified by previous long term levodopa therapy? Can the observations of levodopa induced super sensitivity observed in animals be applied to patients with Parkinson's disease? The action of bromocriptine on such dopa-modified receptors is unknown. 3) Since bromocriptine is considered as a selective D2 agonist (Kebabian and Calne, 1979), our results suggest that the dopa side effects that are not modified by bromocriptine (dyskinesia, "on-off" phenomena or freezing) are not due to actions at D2 receptors. They may be the consequence of the action of dopa on D1 receptors and/or non-dopaminergic (perhaps toxic) mechanisms. It would be interesting to investigate the long term efficacy of non-selective D1 and D2 dopamine agonists (other than levodopa) on these clinical side effects of levodopa.

II — Early Treatment With Bromocriptine

In the second part of this paper, we would like to report the results obtained with early use of bromocriptine in 39 previously untreated patients.

Patients and Methods

Out patients were divided into two groups. The first comprised 29 patients treated between March 1976 and December 1981. In these cases, bromocriptine was introduced at low doses and gradually increased accordingly to its effectiveness and the patients' tolerance. In this group, the mean dose was 56.5 ± 5.5 mg. with a range of 17.5 to 120 mg. The second group of ten patients entered the study between December 1981 and December 1982, and were treated according to the low dose protocol proposed by Teychenne et al. (1981).

Table 1 summarizes the clinical features for the first group of patients. Most of these patients were mildly disabled, Stage I or II according to the Hoehn and Yahr (1967) scale. In all cases, evolution of the disease was slow or moderate. No cases of "malignant" Parkinson's disease were included.

Table 1: Clinical data for 29 patients receiving early treatment with bromocriptine

Sex	Male	15
	Female	14
Age range (years)	40-50 :	3 patients
	50-60 :	7
	60-70 :	6
	70-80 :	9
	80-90 :	4
Mean age (years)	65.9 ±	2.3
Duration of illness	Less than 5 years :	17 patients
	5-10 years :	7
	More than 10 years :	5
Clinical stage (Hoehn and Yahr, 1967)	I :	11 patients
	II :	11
	III :	6
	IV :	1
	V :	0

Table 2: Results of early treatment with bromocriptine in 29 patients

Result	Number	Dose
Good	14	mean = 61.6 − 8.1 mg. (range 29 to 120 mg.)
Average	5	mean = 46.0 ± 12.8 mg. (range 25 to 90 mg.)
Poor (leading to addition of dopa)	6	mean = 55.4 ± 13.8 mg. (range 25 to 120 mg.) Dopa: mean = 470.89 ± 15.4 mg.
Failures	4	mean = 51.9 ± 15.4 mg. (range 17.5 to 90 mg.)

Results

Table 2 shows the results assessed after a mean period of one year according to our own scale of four grades in ascending order of severity (Rascol et al., 1983). Good results correspond to an improvement of at least 40% and average results to improvement ranging from 20 to 40%. In half the cases, bromocriptine alone gave satisfactory results and was continued as monotherapy. Among the failures, one patient had his daily dose increased to a maximum of 25 mg. only, because at the time (1976) maximum dose was set out at 30 mg. daily. Two other patients had their treatment stopped after they developed side effects (postural hypotension and confusion). Poor results comprised patients with insufficient response to bromocriptine, which led us to add levodopa after several months of monotherapy. In all these cases, a beneficial effect from levodopa was observed. This point is worth emphasizing. Patients initially treated with bromocriptine can respond well to levodopa later.

Adverse effects are listed in Table 3. These were not uncommon, but in this group of patients their severity was sufficient to require withdrawal of the drug in only four cases. Hallucinations appeared in four patients, limiting the amount by which the dose of bromocriptine could be increased. All other side effects were of short duration. They either regressed spontaneously (e.g. edema) or were controlled by additive therapy (e.g. gastric disorders treated by metoclopramide or domperidone).

Table 4 shows the duration of follow-up on 23 patients who were treated for more than one year. The remarkable point is that no patient has ever presented with abnormal movement, dyskinesias, dystonias, on-off phenomena, or any marked end-of-dose deterioration. On the other hand, in six cases we noted a decrease of efficacy after two years, which was significantly improved by a further increase (by 20 to 300%) of bromocriptine. So far no patients have suffered any loss of efficacy, but as we have already pointed out, our population is made up of patients with slow or average progression of their disease.

Discussion

These results agree with those of Lees and Stern (1981). These authors reported only one case of peak-dose dyskinesia out of 50 patients. They did not find evidence of end-of-dose deterioration, "on-off" phenomena or end-of-dose dystonia. However, in their population late bromocriptine failure was more frequently observed than in ours.

The absence of late adverse effects of bromocriptine, even after four to eight years follow-up, is the main advantage of the management of Parkinson's disease with bromocriptine "de novo". From a pathophysiological point of view, no satisfactory explanation is available. The importance of D2 specificity of bromocriptine as well as the lack of possible toxic metabolic

Table 3: Side effects in patients receiving early treatment with bromocriptine

Side Effect	Number of Patients
A. Leading to interruption of treatment	
• Severe postural hypotension	1
• Confusion	2
• Acute psychosis	1
B. Dose limiting	
• visual hallucinations	3
C. Transitory	
• gastrointestinal	10
• moderate postural hypotension	5
• edema (only at 50 mg.)	8
• palpitations	2

Table 4: Duration of follow up in 23 patients receiving early treatment with bromocriptine

Follow up period	Number of patients
1-2 years	9 (2 died)
2-3 years	5 (1 died)
3-4 years	1
4-6 years	5 (1 died)
6-8 years	3

Table 5: Occurrence of late side effects in patients treated with bromocriptine or levodopa

	Bromocriptine n = 23	Dopa n = 38
Mean Daily Dose	56.6 ± 5.5 mg.	732.9 ± 58.3 mg.
Peak-Dose Dyskinesia	0	14 (36.8%)
Dystonia	0	3 (7.8%)
"On-Off"	0	5 (13.2%)
Freezing	0	1 (2.9%)
Decrease of Efficacy	6 (27%)	10 (26.5%)

products (like 6-hydroxydopamine for levodopa) was previously suggested (Rascol et al., 1982).

This finding contrasts with the common late side effects of levodopa. We matched 38 patients treated over at least 2.5 years with bromocriptine or levodopa (combined with benzerazide or carbidopa) according to age, sex, stage, and progression of the disease. Table 5 shows the respective frequency of late side effects (dyskinesia, dystonia, "on-off" phenomenon, freezing, or decreasing efficacy) in the bromocriptine and levodopa treated groups.

The Problem of Dosage

Finally, we would like to raise the question of the dosage of bromocriptine in "de novo" patients. We present the results obtained recently in a second group of 10 "de novo" patients treated with bromocriptine according to the following protocol:

(1) — low dose of bromocriptine slowly increased according to the method proposed by Teychenne et al. (1981), up to 20 mg. over 20 weeks. These patients were included in a French multicentre study, the results of which will be published later;

(2) — placebo phase (single blind study) during four weeks;

(3) — third phase of bromocriptine according to the same protocol used for the 29 patients described above in the section "Early treatment with bromocriptine".

All these patients were assessed regularly according to the rating scale of Columbia University. Table 6 shows that at the end of the first phase (according to the low and slow protocol of Teychenne), an improvement of 9.5% was noted, which is not statistically significant. However, two patients showed a marked improvement. They felt better and a decrease of 75 and 50% in the rating scale was noted. The placebo phase was accompanied by recurrence of pretreatment symptoms.

In the cases that did not respond well to low doses, an increase of dosage to a mean of 58.9 mg. brought about a marked (36.9%) and significant improvement.

Table 6: Results of Treatment with Low Dose Bromocriptine

		Low Dose: 10 Patients		Unlimited Dose: 9 Patients
	Before Treatment	**20 mg. 20 Weeks**	**Placebo 4 Weeks**	**Mean Dose: 58.9 ± 13.9 (20-130 mg.)**
Columbia Rating Scale	40.5 ± 2.4	36.8 ± 2.0	41.3 ± 3.0	33.2 ± 1.6
		NS	$P < 0.05$	$P < 0.05$
Percentage Change	100%	90.5 ± 15.2%	119.3 ± 23.9%	63.1 ± 1.6
		NS	NS	$P < 0.05$

Conclusion

Until the results of the multicentre study are known, we conclude that low doses are effective in a limited number of patients only. In most cases, doses ranging from 30 to 70 mg. are necessary. Some patients respond only to very high doses (100 mg.). As far as we know, there are no criteria available to predict the effective dosage. So the therapeutic build up should be slow and rapid increases avoided. This requires considerable patience from both the practitioner and the patient.

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