Bromocriptine in the Management of End of Dose Deterioration in Parkinson's Disease

J.D. Grimes, D.B. King, O.S. Kofman, P. Molina-Negro, A.F. Wilson and S. Bouchard

ABSTRACT: Thirty-three patients with advanced Parkinson's disease complicated by end of dose deterioration were treated with bromocriptine. The drug was slowly increased so that by treatment week 24 the mean daily dose of bromocriptine was 22mg and levodopa had been decreased by an average of 15 percent. The majority of improvement in daily fluctuations and Parkinsonian disability score was documented by 8 weeks, at which time the mean daily bromocriptine dose was only 12mg.

End of dose deterioration was reduced in 78 percent of the patients (mean 43% improvement). Total Parkinsonian disability score was decreased by 33 percent. Adverse effects were minimal; the most common was mild transient early treatment nausea which occurred in 15 percent of the patients.

The slow introduction of small doses of bromocriptine, combined with minimal levodopa reduction, can give Parkinsonian patients significant improvement in end of dose deterioration.

RÉSUMÉ: Nous avons traité à la bromocriptine 33 patients atteints de la maladie de Parkinson sévère, compliquée par le phénomène de déterioration de fin de dose. La drogue a été augementée lentement jusqu'à la 24ième semaine de traitement ou la dose moyenne quotidienne était 22 mg et la lèvodopa était diminuée en moyenne de 15 pourcent. La plus grande amélioration a été remarquée dans les fluctuations quotidiennes et l'échelle d'incapacité parkinsonnienne a été observée dans 8 semaines, lorsque la dose moyenne quotidienne du bromocriptine n'était que 12 mg. La détérioration de fin de dose a été reduite dans 78 pourcent des patients (amélioration de 43 pourcent). L'échelle d'incapacité totale parkinsonnienne a été diminuée par 33 pourcent. Les complications étaient minimales, le plus fréquente était une nausée transitoire au début rapportée par 15 pourcent des patients. L'introduction graduelle de petites doses de bromocriptine, combinée avec une réduction minimale de lèvodopa, peut apporter aux patients parkinsonniens une amélioration considérable surtout contre la déterioration à la fin des doses.

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Fluctuations in disability over a day are seen in untreated Parkinson's disease and the classic example is episodic freezing of gait (Marsden et al., 1982). A marked change in the type, frequency and severity of daily fluctuations became obvious soon after the introduction of levodopa therapy (Barbeau, 1971). The most common of these mobility changes is a gradual loss of benefit after each dose of levodopa and the terms "end of dose deterioration" or "wearing-off effect" accurately describe this. This type of fluctuation occurs in up to 65 percent of patients receiving levodopa for five years (Shaw et al., 1980). The suggested pharmacological defects involved in this problem include; a short plasma half-life of levodopa (Shoulson et al., 1975) and a gradual loss of the ability of brain to synthesize and store dopamine (Marsden, 1980). The gradual, dose related increase in Parkinsonism typical of end of dose deterioration must be differentiated from the sudden, severe non-dose related mobility loss that characterizes the on-off phenonemon. This very disabling problem is fortunately much less common than the wearing-off effect, being documented in about 10 percent of longterm levodopa treated patients (Shaw et al., 1980).

The standard initial treatment for end of dose deterioration is to shorten the interval between levodopa doses. Another approach is to utilize direct-acting dopamine agonists that have a longer plasma half-life (Fahn, 1982). Bromocriptine causes more prolonged dopamine-receptor stimulation than dopamine and patients with dose-related mobility swings on levodopa may achieve a

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From the Ottawa Civic Hospital (Dr. Grimes); Victoria General Hospital, Halifax (Dr. King); Mount Sinai Hospital, Toronto (Dr. Kofman); Notre Dame Hospital, Montreal (Dr. Molina-Negro); Royal Alexandra Hospital, Edmonton (Dr. Wilson); Sandoz Canada, Montreal (Dr. Bouchard)

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Reprint requests to: Dr. J.D. Grimes, Suite 304, 1081 Carling Ave., Ottawa, Ontario, Canada K1Y 4G2

more stable response with the addition of bromocriptine (Parkes, 1979). Previous experience with bromocriptine has shown that end of dose failure (Grimes and Hassan, 1983) is improved more than the on-off phenomenon (Glantz et al., 1981). Initial experience with bromocriptine in daily fluctuations was with high doses (Parkes et al., 1976); more recently much lower doses have been shown to be effective (Teychenne et al., 1982).

The present multicentre study was undertaken to study the therapeutic effect of low dose bromocriptine in treating end of dose deterioration.

Materials and Methods

Forty Parkinsonian patients with daily mobility fluctuations were enrolled in this multi-centre open trial. These patients had a mean age of 62 years (range 40-79) and had longstanding (mean 9.2 years) classical Parkinson's disease. All the patients had disease of grade 3 or 4 severity (Hoehn and Yahr, 1967) and all had previously responded to levodopa. The initial mean daily dose of levodopa-dopa-decarboxylase inhibitor (levodopa-DCI) was 687mg. Patients were selected for bromocriptine treatment if they had definable increases in Parkinsonism which had a clear relationship to individual doses of levodopa. Patients whose fluctuations were primarily non-dose related (classic on-off) were excluded. Patients were not accepted for the study if they had severe dementia, a history of significant drug induced confusion and hallucinations, or serious ischemic heart disease.

The patients had a minimum of seven clinical assessments over the 26 week study. Every attempt was made to perform the initial and followup exams at the same time of day and the same post levodopa time to avoid the changes associated with diurnal fluctuations. Neurological assessment included, clinical stage (Hoehn and Yahr, 1967), tremor, rigidity, bradykinesia, gait, postural stability, daily mobility fluctuations, disability in activities of daily living, dyskinesia and dementia. Parkinsonian signs were scored 0-4 using a modified Columbia scale (Duvoisin, 1971); dyskinesias were rated on a 0-4 scale; disability in activities of daily living was recorded using a shortened Northwestern scale (Canter et al., 1961). Dementia was graded as absent, mild, moderate or marked. The severity of end of dose deterioration varied from mild slowing of gait with some freezing and increased tremor (grade 1), to periods of immobility completely disabling the patient for more than 25 percent of the day (grade 4). The scores for these 10 assessments were added to give a total disability score (maximum possible score 40). Diaries, documenting mobility each hour of the day were also completed. These diaries were used to initially document, and later show improvement in, daily fluctuations. Informed consent was obtained.

Bromocriptine was introduced by giving a dose of 2.5mg with food at bedtime for three days. If nausea or postural hypotension did not occur, then 2.5mg twice daily was given. The dose was increased by 2.5mg every two weeks until stable improvement occurred or a maximum dose of 30mg daily was reached. An attempt was made to establish the lowest effective bromocriptine dose. Small reductions in levodopa were made as the dose of bromocriptine was increased (Grimes and Hassan, 1981). This change was usually made to reduce dyskinesias. If nausea occurred, bromocriptine was given after food. An attempt was made to try and achieve a 3 times a day bromocriptine-levodopa dosage schedule. Anticholinergic or amantadine dosage was not changed.

Statistical analysis included descriptive statistics, all values being expressed as means. One way analysis for repeated measurements was performed to determine variations over time. Contrasts were done to determine where the individual time points were significantly different when compared to baseline (day 0). In addition, the data were assessed to try and document a correlation between mean daily dose of bromocriptine and stage and duration of Parkinson's disease (previously reported in part; Grimes, 1984). The dose of bromocriptine after six months of treatment was compared with the stage at the start of therapy. Graphic representation and correlation coefficients were obtained; P values were calculated. The data relating to disease duration and bromocriptine dose were analyzed with scatter diagrams, correlation coefficients were calculated from a linear regression model and P values were assessed.

Routine, hematological, biochemical and urine studies were done before, during, and at the end of the six month study. All patients had initial and followup chest x-rays.

Results

Thirty-three patients completed the study and improvement could be documented in most of the neurological and functional disability parameters being assessed (Table 1). Significant improvement ($P < 0.001$) occurred in the four cardinal parkinsonian disabilities (tremor, rigidity, bradykinesia and gait disorder) as well as in postural stability and activities of daily living. End of dose deterioration was reduced in 78 percent of patients (1 grade, 48%; 2 grades, 30%). On the end of dose deterioration scoring scale (1-4) there was an overall 43 percent improvement. Dyskinesias were only slightly reduced. Parkinsonian disability score was reduced by 33 percent (18 → 12). An initial mean Hoehn and Yahr stage of 3.2 fell to 2.5 at 24 weeks (24% improvement).

The mean improvement in relation to the mean daily dose and duration of bromocriptine treatment is shown in Figure 1. Following eight weeks of treatment, statistically significant improvement ($P < 0.001$) was noted in total score, clinical stage

Table 1: Mean percent improvement in individual Parkinsonian disability scores for 33 patients treated with bromocriptine for 6 months (* = P<0.001; ** = P<0.05).

	Day 0	Week 24	Percent Improvement
Tremor	1.41	0.73	48*
Rigidity	2.49	1.64	34*
Bradykinesia	2.49	1.88	24*
Gait	1.33	0.76	43*
Postural Stability	1.03	0.61	41*
Disability in Activities of Daily Living	2.03	1.49	27*
End of Dose Deterioration	2.39	1.36	43*
Dyskinesia	1.51	1.06	30**

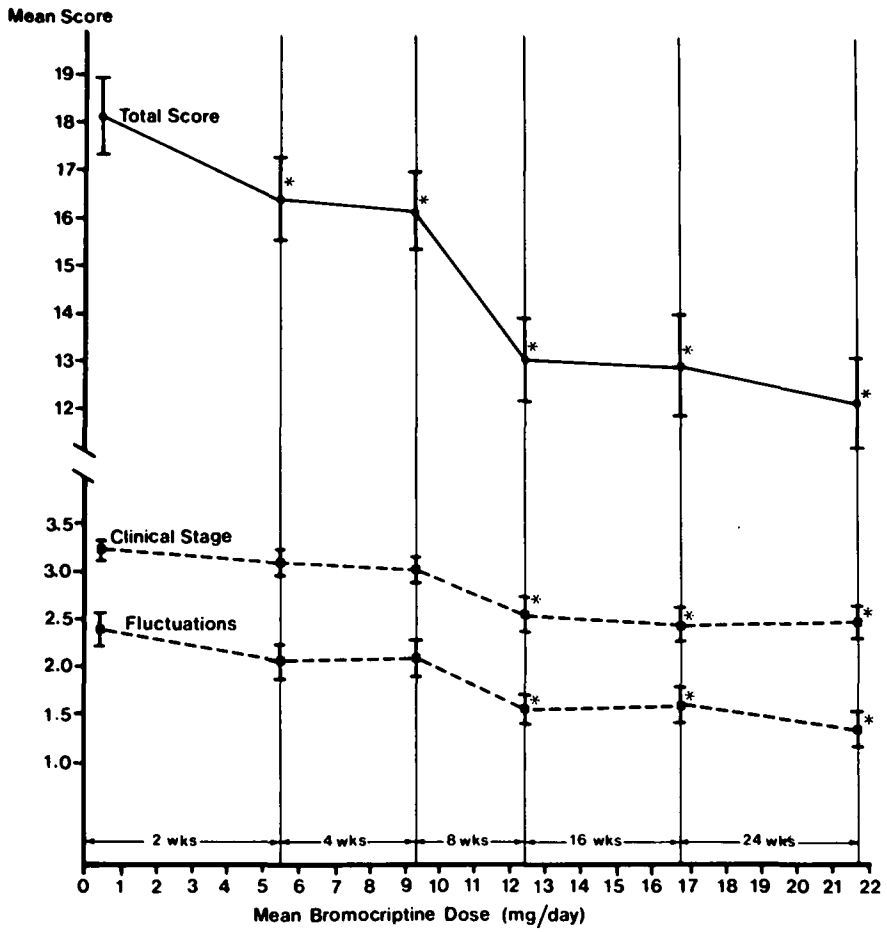

Figure 1 — Mean improvement in total score, clinical stage and end of dose deterioration (fluctuations) compared to the mean daily bromocriptine dose and duration of treatment. Each point represents the mean ± the standard error of the mean.

**Statistically significant improvement compared to Day 0.*

and end of dose deterioration. At eight weeks the mean daily dose of bromocriptine was 12mg and levodopa-DCI had been reduced to 632mg from an initial mean daily dose of 687mg. At this time 65 percent of the patients were receiving less than 10mg of bromocriptine daily. By week 24, some further, but not statistically significant, improvements in total score and end of dose deterioration had taken place when the final mean daily dose of bromocriptine 22mg was reached. Levodopa-DCI dosage was then at a mean of 584mg daily. The overall reduction in levodopa dosage was 103mg (15 percent).

No significant positive relationship between mean dosage of bromocriptine and disease stage was found (correlation coefficient = 0.18; P = 0.31). After six months of treatment, stage II patients required a mean daily dose of 20.0 mg; stage III patients received 19.8mg daily and stage IV patients took a daily dose of 23.9mg.

The mean daily dose of bromocriptine is compared with the duration of Parkinson's disease in a scatter diagram and no positive correlation was identified (Figure 2). In addition a linear regression model showed a correlation coefficient of Y = 0.17 which was not significant (P = 0.33). Similar assessments were performed to compare levodopa-DCI dosage and Parkinson's disease stage and duration and again no positive correlation could be documented.

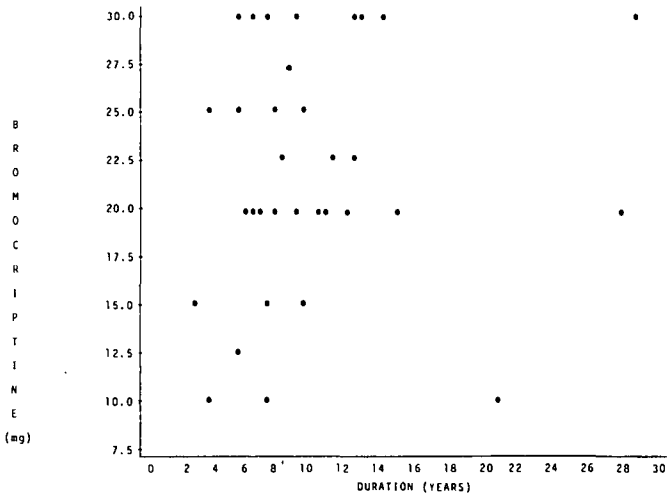

Figure 2 — The mean daily dose of bromocriptine compared with the duration of Parkinson's disease (33 patients).

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Adverse effects were minimal. The most common was transient nausea which affected 15 percent of the patients at the beginning of therapy. One patient developed severe hallucinations which cleared with a reduction in bromocriptine dosage. Leg cramps (1 patient) and diarrhea (1 patient) necessitated bromocriptine withdrawal. Other mild transient side effects reported included, visual blurring (1 patient), nasal stuffiness (2 patients), postural hypotension (2 patients) and lightheadedness (3 patients).

Hematological, serum biochemical and urine studies were unchanged during the study. Followup chest x-rays showed no new abnormalities.

Discussion

This study demonstrates that levodopa treated Parkinson patients who are experiencing end of dose deterioration can be significantly improved with the slow addition of small doses of bromocriptine. There are no published studies that focus just on the treatment of end of dose failure with bromocriptine. Hoehn (1981) in a review of the literature on bromocriptine states that the general impression was that patients with end of dose deterioration were more likely to improve with bromocriptine than patients with the on-off phenomenon and Lieberman et al. (1984) have confirmed this from their large experience with bromocriptine. Many authors use the term "on-off" to describe all Parkinsonian fluctuations and patients with end of dose failure and others with non-dose related fluctuations are usually grouped together in study results. However, Glantz et al. (1981) did report on bromocriptine treatment (mean 56mg daily) for 23 patients with classic on-off phenomena. In their study 39 percent of patients showed improvement. Our 78 percent rate of improvement for patients with end of dose deterioration is clearly better than this, and is in agreement with a previous report (Parkes et al., 1976). Our present study was only of six months duration but past experience (Grimes and Hassan, 1983) has shown that patients with end of dose deterioration very often have a good longterm response to bromocriptine. If more frequent smaller doses of levodopa do not clearly improve the wearing off effect, then the early addition of bromocriptine should be considered. Newer treatment concepts such as dietary manipulation (Nutt et al., 1984) and continous levodopa infusion (Quinn et al., 1982) require much more study and refinement before their introduction into general clinical use.

The dose of bromocriptine used in this study is much lower than that reported in the literature. Parkes et al. (1976) used doses of up to 300mg daily; the experience of Lieberman et al. (1984) is with daily doses varying from 25 to 100mg. Bromocriptine dosage has been slowly decreasing over the past few years and the present interest in lower dose therapy has been stimulated by the work of Teychenne et al. (1982). In the treatment of patients with levodopa-related complications, the dose of bromocriptine required appears to be in part related to the amount that levodopa is reduced. A larger decrease in levodopa leads to a higher final bromocriptine requirement (Grimes, 1984). The minimal (15%) reduction in levodopa in this series most likely is a factor in the low effective mean daily bromocriptine dose (22mg). Marsden and Parkes (1976) note that a simple reduction in levodopa dosage does not improve end of dose deterioration. The method of introduction of bromocriptine may also influence the final dose. Teychenne et al. (1982) comment that the optimum drug response is often delayed for several weeks and may be missed by rapid dosage increase. Bromocriptine was increased very slowly in this study (2.5mg every 2 weeks) and this may also have been a factor in the success of low dose therapy. It is of interest also to note the degree of improvement in relation to the dose of bromocriptine. The majority of improvement occurring in these patients is documented early in the study (by week 8) at a mean daily bromocriptine dose of 12mg, which is 10mg lower than the final dose. This suggests that in this group of patients with end of dose deterioration the dose of bromocriptine actually required may have been less than 22mg daily.

Analysis of our data shows no significant positive correlation between bromocriptine dose and severity or duration of Parkinson's disease. Larsen et al. (1983) however found that patients with more severe, longer duration disease required a very much higher bromocriptine dose (40-90mg daily) than those with mild, shorter duration disease (20-40mg daily). The differing result in these two studies is likely related to bromocriptine dosage limits, patient selection and the amount of levodopa reduction.

Dyskinesias were not significantly reduced and this is contrary to previous reported experience (Calne et al., 1978 and Rascol et al., 1979). These authors however combined bromocriptine introduction with a major levodopa reduction (30-90%). Further analysis of our series shows that the patients who had a greater reduction in levodopa (mean 42%) had more reduction in dyskinesias. This suggests that if dyskinesias are a major problem then a larger decrease in levodopa dose should be attempted with the realization that a higher bromocriptine requirement may result.

A major aim in the management of the individual Parkinson's disease patient should be to prevent the now well recognized, late levodopa complications. In the initial management of patients with Parkinson's disease the dose of levodopa should be kept as low as possible and quite good results have now been reported with very low initial levodopa dosage (Lees and Stern, 1983). Bromocriptine has been shown to induce less late treatment complications than levodopa (Stern and Lees, 1983) and there is now interest in the early addition of bromocriptine to levodopa before any of these complications have developed. Long-term experience is now being collected on the early addition of dopamine agonist therapy after a dose of levodopa-DCI of only 300-400mg daily is reached. Marsden and Parkes (1976) and Granerus (1978) have both commented that chronic levodopa over-dosage and dyskinesias precede the development of the on-off phenomenon. Therefore it seems reasonable that a reduction in levodopa and the introduction of dopamine agonist therapy should be seriously considered when any levodopa treated Parkinson patient develops dyskinesias and even subtle daily mobility fluctuations.

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