Bromocriptine in the Long-Term Management of Advanced Parkinson's Disease

J. David Grimes and Mohamed N. Hassan

SUMMARY: Thirty-seven patients with advanced Parkinson's disease who initially tolerated, and responded to bromocriptine therapy were followed for 12 to 50 (mean 28) months. Using a method of gradual increase of bromocriptine, with concomitant levodopa reduction, the peak effect of the drug was apparent by three months, at which time the mean daily dose of bromocriptine was 23.9 mg and Sinemet (levodopa + carbidopa) had been reduced by 34 percent.

Eight patients had sustained improvement without further drug changes for an average of 29 (range 14-50) months. After periods of improvement varying between 3 and 30 months, 29 patients had a fall-off from peak effect. Peak effect was regained in 21 of these 29 patients for an average of 16 additional months by initially increasing bromocriptine or Sinemet, or by eventually increasing both drugs. The main adverse effect was a confusional state which necessitated late withdrawal of bromocriptine in four patients. The best results were in younger patients with end-of-dose deterioration and levodopa induced dyskinesias.

With cautious introduction, and intermittent dosage adjustment, bromocriptine can be of long-term benefit to patients with advanced Parkinson's disease. The majority of patients have a gradual late fall-off in effect which can frequently be reversed with dosage adjustment.

RÉSUMÉ: Trente-sept patients avec une maladie de Parkinson avancée qui ont initialement toléré, et réagi à la thérapie bromocriptine ont été étudié pour une période d'environ douze à cinquante mois (moyenne 28). Utilisant une méthode d'augmentation graduelle de bromocriptine, avec une réduction de la dose existante de la drogue levodopa, l'éffet maximum de la drogue était apparent après une période de trois mois, après quoi la dose moyenne quotidienne de bromocriptine était 23.9 mg et de Sinemet (R) (levodopa + carbidopa) a été réduite par 34 pourcent.

Huit patients ont soutenu une amélioration sans aucun changement supplémentaire de drogues pour une moyenne de 29 mois (fourchette 14-50). Après des périodes d'amélioration variant entre trois et 30 mois, 29 patients on eu une baisse de l'éffet maximum. L'éffet maximum s'est poursuivi repris dans 21 de ces 29 patients pour une moyenne de 16 mois additionnels en augmentant initialement la bromocriptine ou le Sinemet ou par une augmentation éventuelle des deux drogues. L'éffet adverse principal était un état de confusion qui nécessita une retraite tardive de la bromocriptine chez quatre patients. Les meilleurs résultats se voyaient chez des jeunes patients avec une déterioration de fin-de-dose et une dyskinesie induite par la levodopa.

Avec une introduction prudente, et une dose règlée de façon intermittente, la bromocriptine peut être béneficiaire aux patients avec la maladie Parkinson avancée pour de longues périodes. La majorite des patients ont une diminution graduelle de l'éffet ce qui peut fréquemment être renversé par un adjustment de dose.

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Over the last decade, levodopa has been the basic treatment for Parkinson's disease. However, long-term levodopa therapy is associated with a progressively increasing incidence of drug failure as well as drug induced complications including dyskinesias and diurnal fluctuations. Shaw et al. (1980) in a survey of 178 patients treated with levodopa for six years recorded an 80 percent incidence of dyskinesias and a 70 percent occurrence of loss of initial benefit; 65 percent of their patients developed end of dose deterioration (wearing off effect). These treatment limitations were recognized very early in the levodopa era (Barbeau, 1971).

Bromocriptine was originally shown by Calne et al. (1974) to have antiparkinsonian effect, and this was subsequently confirmed in larger groups of patients by other investigators including Lieberman et al. (1980). The initial high incidence of adverse effects necessitating early drug withdrawal has been reduced by slow bromocriptine addition with concomitant reduction of levodopa (Grimes and Hassan, 1981). Good therapeutic effect has been reported with daily doses as low as 15 mg (Teychenne et al., 1982).

The indications for bromocriptine have slowly been defined. All authors agree that there is no consistent good response in patients who do not respond initially to levodopa. The best results are in patients with end-of-dose deterioration and levodopa induced dyskinesias (LeWitt and Calne, 1981).

Despite more than eight years of clinical use, it is still not clear how long a good response to bromocriptine will be maintained, or if a fall-off from an initial good effect can be reversed. To date, only three long-term bromocriptine levodopa studies have been published. Calne et al. (1978) treated 35 patients for an average of 20 months; Rascol et al. (1979) followed 18 patients for 18 months; and Lieberman et al. (1980) reported on 28 patients with a mean treatment time of 34 months. Of these authors, only Lieberman discusses the drug adjustments necessary in long-term follow-up. He noted that deterioration which occurred in the first two months could be overcome by in-

From the Parkinson's Disease Clinic, Division of Neurology, Ottawa Civic Hospital and the University of Ottawa.

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

creasing bromocriptine, but that deterioration after two years, which was seen in 76 percent of his patients, could not be reversed by increasing bromocriptine or changing the dose of levodopa.

To try and answer some of these long-term management questions, we have reviewed our patients with Parkinson's disease who initially tolerated and responded to bromocriptine, and have been followed on the drug for more than one year.

MATERIALS AND METHODS

The Ottawa Civic Hospital Parkinson's Disease Clinic began an open trial with bromocriptine in early 1978 and 85 patients have now been treated. Thirty-seven of these patients were suitable for this present review. These patients initially tolerated and had beneficial effects from bromocriptine and have been followed on the drug for 12 to 50 (mean 28) months. Excluded from this review are 22 patients who were followed less than one year, 20 "de novo" patients treated with bromocriptine before levodopa, and six patients in whom bromocriptine was discontinued early because of side effects or lack of benefit.

These 37 patients (average age 67 years) had long-standing (mean 9 years), classical Parkinson's disease. All patients had advanced disease of grade 3 to grade 4 (Hoehn and Yahr, 1967). None of the patients were previously exposed to neuroleptic drugs.

The patients were all levodopa responders who had been treated with levodopa for periods of from two to 10 (mean 5) years. Prior to starting bromocriptine the patients were receiving Sinemet (levodopa + carbidopa) in daily dosages ranging from 187-1600 mg (mean 731 mg). Eight patients were on anticholinergics, 12 received amantadine, and four were on both drugs.

Patients were selected for bromocriptine treatment if they had (a) end of dose deterioration (28 patients) or (b) disabling bradykinesia (9 patients). Levodopa induced dyskinesias were present in 30 of the 37 patients. Previous attempts to increase the daily dosage or frequency of administration of levodopa had not been successful, or had induced an increase in involuntary movements.

Patients were excluded if they had severe dementia, severe drug induced confusion and hallucinations, or serious ischemic heart disease.

Bromocriptine was usually introduced at a dose of 2.5 mg on the first day. If nausea or postural hypotension did not occur, then the dose was increased to 2.5 mg twice daily with subsequent increases of 2.5 mg every five to seven days. Sinemet was frequently decreased by 50-100 mg per week as bromocriptine was increased. This was especially important in patients on high dose Sinemet (1000 + mg per day) with severe dyskinesias and fluctuations. Bromocriptine was usually given in three or four divided doses with Sinemet so that most patients initially achieved a q.i.d. schedule of bromocriptine with Sinemet. Bromocriptine increases were stopped when satisfactory improvement occurred or when adverse effects developed.

Stabilization of bromocriptine dosage was usually achieved by three months; during this period the patients were seen at two to four week intervals. Patients were then assessed every three to four months, and all clinical assessments were done at approximately the same time of day to avoid some of the changes associated with diurnal fluctuations.

On each clinic visit the following documentation was obtained. A ten point Parkinsonian disability form was completed. This included clinical staging (Hoehn and Yahr, 1967), and assessments for tremor, rigidity, bradykinesia, gait, postural stability, dyskinesias, fluctuations, disability in activities of daily living and dementia. Parkinsonian signs were scored 0 to 4 using a modified Columbia scale (Duvoisin, 1971); disability in activities of daily living was documented using a shortened Northwestern scale (Canter et al., 1961). Dyskinesias were rated on a 0-4 scale. Dementia was graded as absent, mild, moderate or marked. The severity of end of dose deterioration varied from mild slowing of gait with freezes and increased tremor (grade 1), to periods of immobility completely disabling the patient for more than 25 percent of the day (grade 4).

The times and dosages of medications were recorded. Mobility diaries were completed by the patients with end of dose deterioration. Initially these were filled out daily, but later in the study they were completed only during the week preceeding a clinic visit.

By review of these diaries and by questions regarding the previous day's level of function on a two-hourly basis, an accurate assessment of a patient's mobility status could be obtained. Changes in dosages and rescheduling of the times of drug intake were then made as necessary. Adverse reactions were noted and a subjective impression from the patient was recorded on each visit.

Routine hematological, biochemical, and urine studies were done before and during treatment. Follow-up chest x-rays were done in all patients.

RESULTS

The 37 patients had been treated with bromocriptine for periods ranging from 12 to 50 (mean 28) months: 15 for 12 to 24 months, 10 for 25 to 36 months, and 12 for 37 to 50 months. The peak effect of the drug was apparent by 3 months and peak effect was maintained for periods varying from 3 to 50 (mean 22) months.

At peak effect, the clinical response was quite variable, with 11 patients showing mild, 18 moderate and 8 marked improvement. A mild response indicates that the patient had a one level improvement in the severity of end-of-dose deterioration or bradykinesia, and some reduction in other specific Parkinsonian disabilities including gait, tremor, difficulty with activities of daily living, and dyskinesias. They felt subjectively improved but still had significant mobility impairment. Patients with moderate improvement showed a two-level reduction in the severity of fluctuations or bradykinesia and usually were able to function independently. Patients showing marked improvement had complete clearing of end-of-dose deterioration and were mobile independently all day. A marked response was not seen in any of the patients with severe bradykinesia. The details of bromocriptine and Sinemet dosages for the 37 patients are shown in Table 1.

After long-term follow-up the 37 patients can be divided into three groups. The first group includes 8 patients who have had sustained improvement and have maintained peak

Table 1: Sinemet and bromocriptine dosages for 37 patients treated for 12 to 50 months.

TREATMENT PERIOD	MEAN DOSAGE OF SINEMET (mg/day)	MEAN SINEMET REDUCTION (%)	MEAN DOSAGE OF BROMOCRIPTINE (mg/day)
Before bromocriptine	731 (range 187-1600)	—	—
At peak effect of bromocriptine	484 (range 125-850)	34	23.9 (range 3.75-50)
After long-term follow-up	566 (range 125-1000)	23	28.5 (range 3.75-60)

Table 2: Drug adjustments necessary to maintain peak effect in 21 patients treated with bromocriptine and Sinemet. Mean values shown in parentheses.

DRUG CHANGE	NO. OF PATIENTS	DOSAGE INCREASE (mg/day)
Increase bromocriptine	5	7.5 - 17.5 (13.0)
Increase Sinemet	7	62.5 - 250 (169.7)
Increase Both	9	Bromocriptine 2.5 - 17.5 (10.8) Sinemet 100 - 375 (201)

effect without drug changes for an average of 29 (range 14-50) months. Improvement in these patients was graded as follows; mild, 1 patient; moderate, 4 patients; marked, 3 patients.

The second group consists of eight patients who could not maintain their peak clinical response. After an average of 8.7 (range 6-18) months of improvement these patients deteriorated to a level which was at least one grade below that of the peak effect period. This deterioration could not be corrected with increases in bromocriptine or Sinemet.

The third, and largest group, consists of 21 patients who maintained peak effect for an average of 13.7 (range 3-30) months before a loss of response could be detected. The peak effect, however was regained for an average of 16 additional (range 4-33) months by initially increasing either bromocriptine or Sinemet or by eventually increasing the dose of both drugs. The drug adjustments necessary to maintain peak effect are shown in Table 2. In 6 of these 21 patients, a late increase in end-of-dose deterioration was arrested by increasing the frequency of drug intake from a t.i.d. or q.i.d. schedule, to five or six times per day, while maintaining the same total daily drug dosages.

Sinemet-induced dyskinesias were reduced by at least one grade in 26 of 30 patients with the addition of bromocriptine and concomitant reduction of Sinemet. In two patients, these involuntary movements were unchanged while in the remaining 2 patients they became slightly worse.

Twenty-nine patients have continued on bromocriptine. The drug was withdrawn late in four patients because of the development of confusion and hallucinations. Two patients, in whom there was loss of efficacy of bromocriptine, were changed to another dopamine agonist and two patients died from causes unrelated to bromocriptine therapy.

In twelve patients bromocriptine therapy was temporarily stopped, either as a test of continuing efficacy or because of adverse effects, and in all cases, there was a worsening of parkinsonism. The deterioration after stopping bromocriptine was usually obvious within 48 hours but in one patient it did not become apparent until 10 days after stopping the drug.

Anticholinergics were discontinued in 5 of 8 patients with no worsening of parkinsonism and this resulted in a lessening of confusion in three cases. Withdrawal of amantadine was attempted in 10 of 12 patients. This however, led to an increase in parkinsonism and the drug was therefore continued in all patients.

Multiple haematological, serum biochemical, and urine studies, showed no significant changes from baseline results. Follow-up chest X-rays in all cases have not shown any new abnormalities.

Adverse Effects

A toxic confusional state was the most common side effect of bromocriptine therapy. This was a transient problem in six patients as the drug was being introduced and cleared with bromocriptine reduction or anticholinergic withdrawal. Four other patients however, developed a late onset (mean 23 months treatment) severe confusional state with hallucinations and bromocriptine had to be stopped. Any attempt to reintroduce the drug at lower dosage resulted in an increase in confusion and hallucinations. These patients were older (mean age 70 years) and all had moderate dementia when bromocriptine was started.

Other side effects were less serious and much less frequent. Two patients, despite significant Sinemet reduction, had an increase in dyskinesias with dosages of bromocriptine over 15 and 30 mg daily respectively. Both patients however, eventually gained mild improvement on low-dose bromocriptine. Cold-sensitive digital vasospasm occurred in three patients. This developed after one or two years of treatment; it was mild and not dose limiting. Gastrointestinal problems were minimal with mild indiges-

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tion occurring in three patients and one patient reported an increase in constipation. Nasal stuffiness and mild alopecia were each noted in two patients. One patient complained of an increase in libido. Postural hypotension occurred transiently in the early treatment period in one patient.

DISCUSSION

Our experience has demonstrated that bromocriptine can be of long-term benefit to patients with advanced Parkinson's disease. A minority of patients (8 out of 37) have had sustained benefit for up to four years without any drug adjustment. The majority of patients, however, had a gradual loss of effect which was frequently reversed by increasing the dosages of bromocriptine or Sinemet or both, or by increasing the frequency of drug intake. The 78 percent incidence of eventual loss of peak benefit in this series is in agreement with the 76 percent reported by Lieberman et al. (1980).

The basic pathology of Parkinson's disease is slowly progressive. In assessing long-term medication response it is often difficult to differentiate drug failure from disease progression. Long-term follow-up of levodopa treated patients shows that the majority will have a gradual loss of initial benefit. It seems reasonable to assume, that at least part of the late loss of response in bromocriptine treated patients is related to disease progression.

In this series, patients with end-of-dose deterioration had the best long-term results. All eight of the patients with sustained peak effect had had end-of-dose deterioration. Seven of these patients have had moderate to marked levels of improvement for an average of 29 months. In contrast, none of the patients with severe bradykinesia ever achieved a marked response. Of the eight patients who failed to maintain their peak clinical response, five had bradykinesia as their major disability, and they obtained only mild to moderate levels of improvement for an average of 16 months. Bradykinetic patients were on the average seven years older than those with end-of-dose deterioration and their disease duration three years less.

Dyskinesias were reduced in the majority of patients. This experience is in agreement with that of other authors including Calne et al. (1978) and Rascol et al. (1979). This reduction in dyskinesias is related to the decrease in levodopa and its partial replacement by bromocriptine. It is not year clear if low dose bromocriptine (mean 15 mg daily) as advocated by Teychenne et al. (1982) will be therapeutically satisfactory for patients on high doses of levodopa with severe dyskinesias and daily fluctuations. Our experience has been the same as that of LeWitt and Calne (1981), that these patients require at least 30 mg of bromocriptine daily, usually combined with a 30-50 percent levodopa reduction. Marsden and Parkes (1976) suggested that severe dyskinesias and the most difficult to manage fluctuations (classic on-off) develop on a background of chronic levodopa over-dosage. With this information and the experience that bromocriptine addition and levodopa reduction can improve fluctuations and dyskinesias, it is attractive to consider making this drug change much earlier, for example; with patients who are just beginning to develop dyskinesias and subtle end-of-dose failure.

The presence or development of a mild confusional state with some hallucinations does not seem to be a contraindication to initiate or continue bromocriptine therapy. This condition often responds to a reduction in dosage of bromocriptine or Sinemet, or withdrawal of an anticholinergic.

Mild to moderate dementia was present in many of our patients at the start of bromocriptine therapy. We have found it best not to use the drug in severely demented patients because of the frequent early development of a toxic confusional state. Dementia may eventually affect more than 30 percent of patients with Parkinson's disease (Lieberman et al., 1979). Some of our patients have had a marked motor improvement with bromocriptine, but eventually the drug had to be discontinued because of the late development of confusion and hallucinations. This problem occurred in four patients in this series and when bromocriptine was stopped they all had a marked deterioration in mobility. This predisposition of the demented patient to develop severe drug induced confusion, now appears to be the major treatment limiting factor in the management of patients with advanced Parkinson's disease.

Frequent adjustments in drug dosage and timing are necessary in the long-term management of these patients. In trying to reverse a fall-off from peak effect it is usually best to increase bromocriptine first. The high cost of bromocriptine, and the experience of others (Teychenne et al., 1982) suggesting good results with low doses have led us more recently to try and keep daily bromocriptine doses below 30 mg daily. If increasing bromocriptine does not restore peak effect, then an increase in the daily dose of Sinemet, or an increase in the frequency of administration of Sinemet without changing the total daily dosage may be required. The use of the smaller dose Sinemet tablets (levodopa 100 mg + carbidopa 10 mg) adds a certain amount of flexibility by allowing 50-100 mg changes in individual levodopa doses as required. The importance of careful follow-up care is demonstrated by our group of 21 patients with unsustained effect who, with drug adjustments, were returned to their peak level of improvement for an average of 16 additional months.

Despite the longer duration of action of bromocriptine, frequent drug administration is usually necessary. In this series of patients, bromocriptine dose frequency varied from three to six (mean 3.5) times daily, while Sinemet was given three to seven (mean 4.5) times daily.

Pleuropulmonary changes, possibly related to long-term bromocriptine therapy were reported by Rinne (1981) and LeWitt and Calne (1981). A total of eight patients, some of whom were receiving up to 100 mg of bromocriptine per day, developed pleurisy with effusion, pleural thickening and pulmonary infiltrates. Bromocriptine was stopped in some patients, while in others the drug was continued with the addition of antituberculous or steroid therapy and with the subsequent resolution of the chest lesions. All of our patients are questioned for chest symptoms on each visit and have had annual chest X-rays and so far no pulmonary abnormalities have been detected. Until this question is completely resolved we recommend initial and annual chest X-rays for patients treated with bromocriptine.

The addition of bromocriptine, usually combined with levodopa reduction, is an effective therapeutic maneuver in some patients with advanced Parkinson's disease. The best long-term results are in younger patients, without dementia, who have end-of-dose deterioration and levodopa induced dyskinesias. Older bradykinetic, demented patients will not have as good an initial result, and peak effect will be maintained for a shorter time. Most patients will gradually lose their initial improvement, however, a further period of benefit can usually be gained with careful adjustments in dosage and timing of bromocriptine and levodopa.

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