Occasional Review

Bromocriptine in Parkinsonism*

IRIS PEARCE, JOHN M S PEARCE

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Summary and conclusions

A review of the effects of using bromocriptine in Parkinson's disease showed that it rarely helps patients not primarily improved by levodopa. Patients who show late failure with levodopa and whose response to treatment is declining are helped by combining the two drugs. High cost and severe psychosis are the main disadvantages of bromocriptine, and, although it is not recommended for patients who are doing well on levodopa, it is the best available drug for hospital use in patients who show late failure with levodopa.

Introduction

Bromocriptine is of value in treating several endocrine disorders; more recently it has been used in Parkinsonism. It has produced definite improvements in objective measurements of rigidity, tremor, bradykinesia, gait disorder, and total functional disability. This paper aims at summarising its mode of action and assessing its role in the treatment of Parkinsonism.

In animals bromocriptine appears to have a biphasic,¹ dose-dependent action. In low doses it inhibits dopaminergic transmission by enhancing reuptake of dopamine at the presynaptic level. In higher doses, however, it is a dopamine-receptor agonist. In the hypothalamus it stimulates specific neuronal dopamine receptors to release factors transported via the hypophyseal portal stalk to the pituitary gland. These factors have either an inhibitory or a releasing effect on hormone-producing cells in the pituitary. One of the factors released by dopamine agonist action is prolactin-inhibiting factor (PIF), which controls the anterior pituitary secretion of prolactin.

The action of bromocriptine in endocrine states^{2,3} depends on its ability to suppress hyperprolactinaemia. Thus it is of value in puerperal lactation, and in amenorrhoea and infertility associated with galactorrhoea in the presence of hyperprolactinaemia. Its role in treating male hypogonadism and impotence has not yet been adequately assessed. It is effective in controlling the endocrine manifestations of acromegaly.⁴ In normal people dopamine increases the release of growth hormone (HGH), and it is a useful paradox that in most acromegals treatment with bromocriptine reduces HGH concentrations by over half, with relief of somatic symptoms.²

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Department of Neurology, Hull Royal Infirmary, Hull HU3 2JZ
IRIS PEARCE, MB, BS, research fellow
JOHN M S PEARCE, MD, FRCP, consultant neurologist

Levodopa failure

The claims for the use of a dopamine agonist in treating Parkinsonism depend on the fact that levodopa has a substantial failure rate, as does levodopa in combination with a dopa-decarboxylase inhibitor (Sinemet, Madopar). Primary failure implies an inadequate clinical response despite an optimum regimen when levodopa is used for the first time; this includes those patients in whom the initial side effects are so severe as to rule out its use.⁵ Such primary failures are seen in 10-15% of our patients.

Late failures usually result from either a waning effect of the drug after its successful use for several years⁶ or from intolerable side effects (such as the on-off syndrome or drug-induced dyskinesia), which may develop two or more years after successful treatment has been established. These are attributed to hypersensitivity of the dopamine receptor or to false neurotransmitters derived from dopamine breakdown. The clinical course of events in these late failures tends to be stereotyped:

- The effect of each dose is not seen—for example, there is a smooth 24-hour response.
- Extra doses become necessary as the clinical response to the preceding dose declines.
- Early morning akinesia develops.
- The effect of each dose becomes shorter, lasting three to four hours, often interspersed with periods of intense dyskinetic choreic and athetoid movements simulating Huntington's chorea.
- Profound on-off swings become obvious, as periods of severe akinesia and freezing immobility accompanied by autonomic symptoms alternate with periods of increased mobility and hyperkinesia.

Possible rationale for a dopamine agonist

The above sequence of events commonly develops after two or more years of treatment, and is present in 50-60% of patients after five years of taking levodopa. We therefore have to consider an alternative attack on the dopaminergic system. Several theoretical advantages of a primary dopamine-receptor agonist as an attractive alternative to levodopa have been postulated,⁷ as follows:

- A dopamine agonist may have a more specific effect on those neurones affected by Parkinson's disease.
- There is no competition from dietary amino-acids as there may be with levodopa.
- A dopamine agonist may have a longer duration of action.
- The agonist will not require a dopa-decarboxylase inhibitor.
- Levodopa metabolites which may act as false transmitters would not result.

Several dopamine agonists have been used: apomorphine is unacceptable because it requires administration by injection and vomiting is a frequent side effect; piribedil is too unpredictable in its clinical effects to be of value; lergotril is moderately effective but is hepatotoxic; and bromocriptine is potentially the best available drug of this group.⁸

In 1974 Calne *et al*⁷ reported a double-blind study comparing the effects of bromocriptine with placebo in patients who had been treated with levodopa. Appreciable deterioration occurred during the placebo phase and neurological deficits improved by almost 20% in severely disabled patients. We present here the results of bromocriptine treatment derived from subsequent reports and our own experience.

Clinical effects

There are 30 published reports on the use of bromocriptine in Parkinsonism; a total of 445 patients were treated but a completed assessment was made in only 386 (table). Methods of administration have varied widely. Some trials have been uncontrolled; some have compared bromocriptine with levodopa, while others have compared its effects with levodopa together with a dopa-decarboxylase inhibitor (Sinemet, Madopar). The dosage of bromocriptine has varied widely, from 2.5 to 300 mg per day. Most patients of whom there is an adequate description have shown primary or late failure of levodopa treatment.

The difference in results of bromocriptine used *de novo* compared with its use in those who have already completed and failed to sustain an adequate response to levodopa treatment is clinically important. The duration of treatment has varied from three to fifteen months. Objective scoring scales are necessary and have been adopted by most workers, the Webster scale or the North Western University Rating being the most common methods used.

Examples of patients and trial design, dosage, and toxicity extracted from recent publications

Author	No of patients	Disease duration (years)	Dose (mg/day)	Previous levodopa	Side effects		
					Hallucinations	Dyskinesia	On off syndrome
Godwin-Austen ¹²	23	5	7.5-40	22	3	2	1
Lees <i>et al</i> ¹⁷	86	3-10	30-120	56	16	29	11
Parkes <i>et al</i> ¹⁸	37		2.5-300	33	7	7	
Kartzincl ¹⁶	32	12	79-100	32	1	14	8
Gerlach ¹¹	20	8	20-50	20	3	4	3
Pearce (this series)	15	5-10	20-80	13	5	4	2

PERSONAL EXPERIENCE

We start with a 2.5-mg tablet twice daily, increasing by one tablet every two to three days until a therapeutic effect is apparent (usually at 20-40 mg per day). Further increases if necessary are made by using 10-mg tablets every six or eight hours. The dose of levodopa preparations is reduced, usually halving it at the onset of treatment. Adjustments of the doses of both drugs are often needed, and we stabilise patients in hospital.

Figure 1 shows the reduction in Webster scores (incorporating 10 clinical aspects of signs and disability) in a representative sample of six patients. They had not been treated with levodopa and were moderately (four patients) or severely (two patients) disabled before receiving bromocriptine. Their condition started to improve in the second week, usually after the starting dose of 2.5 mg twice daily had been increased to 20-30 mg per day. Further benefit was apparent at four weeks, and so far the clinical improvement has been sustained for one year and in some of our patients for three years.

By contrast figure 2 shows that the four patients who had primary levodopa failure (closed squares) secured no response with bromocriptine; their Webster scores actually increased (deterioration), this indicating progression of the underlying disease. In all four patients bromocriptine was withdrawn.

The late levodopa failures (closed circles) were regarded as partial failures. They showed varying degrees of response to levodopa but after two to eight years their condition gradually

FIG 1—Results on Webster scale and length of treatment, with primary bromocriptine treatment.

FIG 2—Results on Webster scale for levodopa failures.

deteriorated owing to progression of the disease and presumably receptor unresponsiveness. Reduction of levodopa dosage abolished their on-off swings and dyskinesia, but their Parkinsonian signs were then incapacitating. Adding bromocriptine then produced a useful improvement: scores dropped on average from 15 to 10 and this was maintained for at least six months, with a suggestion of slight deterioration at one year. Dyskinesias returned in some of these patients, but by no means all, and they were less embarrassing than those we have met with using higher doses of levodopa alone.

This modest improvement has occurred in 20-40% of this group of patients and we believe that it is clinically useful.

Pharmacological studies

There is no definite relation between the improvement in Parkinsonian signs and the plasma concentrations of dopa in patients treated with levodopa. With bromocriptine, however, Parkes^{9,10} has stated that after a single dose the degree of improvement is related to blood concentrations of the drug. Nevertheless, no relationship was observed between peak blood concentrations and the onset of clinical response.

After a single oral dose Parkes observed peak concentrations at 30-120 minutes with sustained blood concentrations at four hours. Figure 3 shows serial plasma assays in four of our patients in a stable clinical state taking bromocriptine, during a 24-hour period. The results indicate a large variability in plasma levels among different patients. The highest concentrations (a) were seen in a young patient on a higher dose regimen than the others: the much lower concentrations (b,c,d) corresponded to lower but variable dose regimens in older patients.

FIG 3—Serial plasma assays of bromocriptine concentrations.

Throughout the hours tested there was a constant plasma concentration of bromocriptine which lacked the sharper peaks and troughs familiar in plasma dopa concentrations in patients treated with levodopa. The half life of bromocriptine is six to eight hours¹¹ and thus a smoother clinical effect may be predicted—which has been our experience in patients who respond to the drug.

Side effects and toxicity

Reports of toxicity are often incomplete, and sometimes brief references are made without sufficient amplification to show the severity of the reaction. Table II shows the side effects of bromocriptine, extracted from published results in 445 patients. The nature and incidence of toxicity are similar to those seen with levodopa or its analogues. There is, however, a qualitative difference: the psychological symptoms resulting from bromocriptine may occur with a low dosage (2.5–5 mg per day), and—instead of the mild nocturnal hallucinosis, the day-time depression, or (in more severe cases) a transient psychosis that characterised levodopa toxicity¹²—bromocriptine produces a severe psychosis in which the patient is violent and aggressive and suffers from intense delusions, which are often hostile and violent. When psychosis arises with levodopa it is almost invariably quickly reversed by reducing the dose or stopping the drug altogether. With bromocriptine, however, complete withdrawal of the drug may still leave a residue of severe psychotic illness that may persist for one to three weeks. In our experience the patient may be seriously ill with fever, delirium, and a psychotic delusional state. Since bromocriptine is an ergot derivative not surprisingly rare cases of acrocyanosis and digital vasospasm have been recorded with its use, but serious ischaemic complications have not.

Discussion

The effects of bromocriptine closely parallel those of levodopa and its analogues. In most patients the therapeutic response is initially seen with a dose between 20 and 40 mg per day. Nevertheless, some evidence suggests that in a few patients gradually increasing this dose up to 100 to 125 mg daily may achieve further improvement without untoward side effects. There is no evidence that in either low dose or high dose bromocriptine has a selective effect on any specific feature of the disease.

In patients who have failed to respond to the initial use of levodopa bromocriptine confers little additional benefit. On the

other hand, patients who develop the severe on-off syndrome¹³ or severe dyskinesia in response to levodopa may be better controlled when the drug is combined with bromocriptine. Used alone, bromocriptine produces similar on-off effects or drug-induced dyskinesias, as well as the more common early phase of nausea, vomiting, and mild hypotension. Nevertheless, when it is gradually introduced into the regimen of the patient who is responding to levodopa but has unsatisfactory swinging reactions it may confer useful benefit and gives a smoother action and allows the dosage of levodopa to be reduced.

The incidence of side effects of bromocriptine may be reduced by a gradual introduction (as was formerly the case with levodopa alone), in contrast to the rapid phase of stabilisation possible with Sinemet or Madopar. The total degree of improvement varies from 20% to 50% of pretreatment scores in various series, and compares favourably with levodopa in the responsive patient.

Hence the range of therapeutic activity and of drug toxicity with bromocriptine is remarkably similar to that of levodopa. Because of the more severe mental side effects in some patients, and because of the increased expense of prescribing bromocriptine, it might be concluded that it has no appreciable advantages over levodopa, and that its disadvantages argue against its widespread use in Parkinson's disease. In our experience, however, bromocriptine has a definite role, pending possible future improvements in drug treatment. It is most useful in patients in whom levodopa and a decarboxylase inhibitor produce a good therapeutic response but at the price of psychosis, severe dyskinesia, or the on-off syndrome which necessitate a reduction in dosage impairing its efficacy of the drug. If when reducing the dosage we simultaneously add bromocriptine a definite and clinically worthwhile¹⁴ therapeutic improvement is obtained in 20–40% of patients, allowing us to continue effective drug treatment and enabling the patient to remain more independent than would otherwise be possible.

Unlike levodopa treatment no deterioration in improvement has been seen with bromocriptine, though, since no patient has been treated for very long, this may become apparent in the future. There remains the interesting, if remote possibility that if bromocriptine is used and if, like levodopa, its effect were to diminish after two to six years, levodopa might then be effective as the second line of approach. This is purely speculative, but is worth further study.

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