Bromocriptine in Parkinsonism

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Summary

Bromocriptine, a drug acting directly upon dopaminergic receptors, has been found to have a significant therapeutic action in a double-blind study of 20 patients with idiopathic Parkinsonism who were already receiving conventional therapy, including levodopa. Neurological deficits improved by almost 20% in severely disabled patients; amelioration of mildly affected patients was about 10%. Adverse reactions were similar to those encountered with levodopa—they were all dose-dependent and reversible. These observations are discussed in relation to certain theoretical advantages which might be expected from a drug which acts directly on dopaminergic receptors.

Introduction

As a result of the introduction of levodopa many patients with Parkinsonism have derived worthwhile and at times dramatic amelioration of their motor disabilities. Nevertheless, current antiparkinsonian treatment is poorly tolerated by some 25% of patients, and in at least a further 25% the improvement achieved by optimal therapeutic regimens is limited. The advent of extracerebral decarboxylase inhibitors (Yahr, 1973), such as carbidopa, has reduced the incidence of certain adverse reactions to levodopa, such as nausea, but many patients remain in whom severe deficits persist in spite of concerted efforts with all the antiparkinsonian drugs available at present.

One factor contributing to the failure of patients to respond well to treatment with levodopa may be the reduced striatal concentration in Parkinsonism of the enzyme responsible for converting levodopa to dopamine—L-aromatic aminoacid decarboxylase (Lloyd and Hornykiewicz, 1970). Another possible source of difficulties is the production of active metabolites of levodopa other than dopamine—for example, noradrenaline—which may be responsible for some of the unwanted reactions encountered in treating Parkinsonism. Both of the above drawbacks might in theory be overcome if a drug could be found which entered the brain and selectively activated dopaminergic receptors—a dopamine agonist. Such an agent could still operate when the enzymic machinery required to convert levodopa to dopamine had been destroyed by the underlying condition of Parkinsonism, and if the drug was relatively specific for dopaminergic receptors adverse effects would not be generated by activation of other synapses. The ideal antiparkinsonian drug would also have a predilection for those dopaminergic receptors which are impaired in Parkinsonism.

Clinical experience with dopaminergic agonists has not been very encouraging. Apomorphine is therapeutically active but it causes prominent emesis and has to be administered by injection (Cotzias *et al.*, 1970). Another dopamine agonist which has been investigated recently is piribedil, but this drug also precipitates vomiting and psychiatric adverse reactions are quite common (Vakil *et al.*, 1973). Bromocriptine is a new dopaminergic agonist developed to inhibit prolactin secretion (Pozo and Flückiger, 1973) which has also been found active in animal models of Parkinsonism (Corrodi *et al.*, 1973). It has been used in man to suppress lactation by dopaminergic production of prolactin inhibitory factor in the hypothalamus (Pozo and Flückiger, 1973). We report here our experience of treating Parkinsonian patients with this drug.

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Patients and Method

Twenty patients, aged 50-77 years (mean 65), with idiopathic Parkinsonism were investigated. There were 12 men and eight women. Eleven patients were receiving anticholinergic drugs and 19 were taking levodopa (mean dose 3·5 g/day), and their routine treatment was not altered.

The study was performed in three stages: (*a*) The dose of bromocriptine was built up to maximum tolerated intake, (*b*) treatment was then maintained at optimum levels for six to 12 weeks, and (*c*) placebo was administered for six weeks.

The initial dose of bromocriptine was 2·5 mg twice daily, and this was increased by 2·5 mg each week until unwanted effects were encountered or an arbitrary upper limit of 30 mg/day was reached. An optimum maintenance dose was established at 70%-80% of the intake which produced adverse reactions. The mean optimum dosage was found to be 18·8 mg/day (range 7·5-30), which was reached over an average period of 8·8 weeks (range 3-16).

On attaining the maximum tolerated dosage (or 30 mg/day) patients were allocated at random into one of four groups who were treated for 6, 8, 10, and 12 weeks. The variation in duration of treatment was undertaken in an effort to reduce the risk of the "blind" evaluator decoding the change to placebo.

CLINICAL EVALUATIONS

An arbitrarily defined clinical scoring protocol was employed using a scale from 0 (normality) to 4 (maximum deficit) for functional disabilities assessed from the history—washing, eating, dressing, and writing. The physical signs were evaluated after clinical examination using a similar five-point scale for walking, posture, facial expression, rising from a chair, balance, finger dexterity, rigidity, tremor, speech, and sialorrhoea.

Evaluations were performed at outpatient attendances at intervals of two weeks. The same physician performed all the clinical assessments on every patient; he was unaware of treatment regimens.

CARDIOVASCULAR OBSERVATIONS

Cardiovascular observations were made with an Arteriosonde (Roche) automatic blood pressure recorder at every outpatient attendance. The patient lay down on a couch and measurements of blood pressure and pulse rate were made after one and three minutes. The patient then stood up and after one minute the recordings were repeated. The initial findings (after lying for one minute) were discarded since the first observations were only

performed as a manoeuvre to acclimatize the patient to the recording situation.

BIOCHEMICAL STUDIES

Administration of a dopaminergic agonist leads to a fall in the concentration in the cerebrospinal fluid (C.S.F.) of the major metabolite of dopamine—homovanillic acid (HVA). Changes in HVA can, therefore, facilitate the interpretation of the mechanism of drug action. Pretreatment with probenecid increases the precision of C.S.F. studies by blocking the active transport mechanism that removes HVA from the C.S.F. Biochemical studies were completed on five patients who gave informed consent for two lumbar punctures, one on placebo and the other on bromocriptine.

Levodopa therapy was stopped 48 hours before lumbar puncture. The patients remained in bed over this time and were given 6·0 g of probenecid by mouth over the 19 hours leading up to extraction of C.S.F. Bromocriptine was given in three doses of 2·5 g, given 10, eight, and six hours before lumbar puncture.

Results

The results of the last three evaluations during treatment with bromocriptine were compared with those of the three on placebo. An analysis of variance indicated that the deterioration on placebo was significant at the 0·1% level. The scatter of differences between bromocriptine and placebo scores for physical signs and functional disability in individual patients is shown in the diagram. Positive values represent a deterioration when placebo was introduced—that is, a therapeutic action of bromocriptine. One patient who failed to attend for an assessment was omitted from this analysis. The deterioration of individual physical signs and disabilities during placebo treatment is shown in table I.

We were interested to relate the extent of therapeutic activity of bromocriptine to the severity of Parkinsonism. The total disability scores at final assessment were therefore placed in ascending order, and the patients were divided into two groups by drawing an arbitrary line halfway down the list. The mean improvement induced by bromocriptine in the less severely disabled patients was 8·9%, while that for the more disabled group was 18·9%.

The dose was increased until adverse reactions were seen in 17 patients. Three patients reached 30 mg/day without experiencing any unwanted effects. All dose limiting problems were similar to those produced by levodopa. Though 19 of the patients were taking levodopa none admitted to adverse reactions when entering the study. The commonest unwanted effect was dyskinesia, which occurred in ten patients. Three patients suffered from hallucinations, three from emesis, six from dizziness (without hypotension), one from symptomless hypotension, from flushes, and three from constipation. Some patients had more than one adverse reaction, but all were reversed when the dose of bromocriptine was reduced, and the drug was well tolerated once optimum maintenance levels of intake were established.

Neither the patients nor the evaluator decoded the blind protocol.

The blood pressure and pulse rate lying and standing were compared on the last three evaluations with bromocriptine and the three assessments on placebo. No statistically significant trend emerged. The mean values for blood pressure taken lying down when patients were on bromocriptine and on placebo were 141/88 mm Hg and 147/91 mm Hg respectively, and the mean standing pressures were, respectively, 137/91 mm Hg and 139/94 mm Hg.

The C.S.F. concentrations of HVA are shown in table II. When taking bromocriptine the HVA level was reduced in four out of the five patients who consented to this study. The differences were not significant.

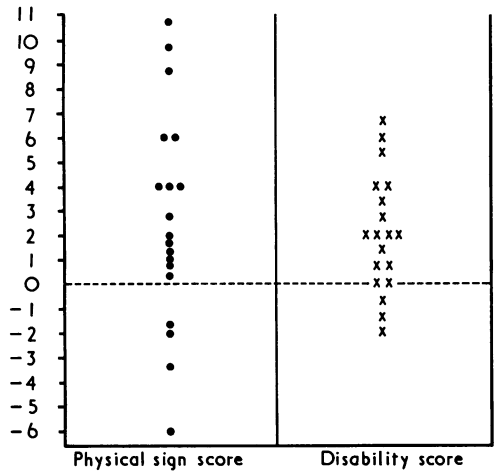
TABLE I—*Mean Increase in Score—that is, Deterioration—on Individual Clinical Features when Patients were Changed from Bromocriptine to Placebo. Values represent difference between Mean Score on Last three Assessments when taking Bromocriptine and Mean Score on three Assessments when taking Placebo*

Physical Signs		Functional Disabilities	
Tremor	0·46	Dressing	0·25*
Rigidity	0·11	Washing	0·28**
Speech	0·42*	Eating	0·02
Facial expression	0·26*	Writing	0·47**
Arising from chair	0·33*		
Balance	0·32**		
Finger dexterity	0·35*		
Sialorrhoea	0·16		
Sweating	0·05		
Gait	0·12		
Posture	0·04		

*Significant at 5% level.
**Significant at 1% level.

TABLE II—*Concentrations of Homovanillic Acid (ng/ml) in C.S.F. of Five Patients after Placebo and after 7·5 mg of Bromocriptine. Levodopa was stopped 48 Hours before Lumbar Puncture and Probenecid was given by Mouth (1·5 g × 4) over 19 Hours before Lumbar Puncture*

Case No.	Probenecid + Placebo	Probenecid + Bromocriptine
1	171	120
2	130	66
3	114	129
4	111	29
5	111	66



Increase in scores for functional disabilities and physical signs when patients were changed from bromocriptine to placebo. Values represent mean of the last three evaluations on bromocriptine subtracted from mean of three assessments on placebo.

Discussion

Previous studies with the dopaminergic agonists apomorphine and piribedil have shown that these agents are capable of alleviating Parkinsonism (Cotzias *et al.*, 1970; Vakil *et al.*, 1973), but no previous drug of this type has been tolerated well. Our findings with bromocriptine offer some encouragement since adverse reactions were easily controlled by adjustment of dosage.

Dopaminergic agonists may prove to have advantages over conventional treatment for Parkinsonism. It might be possible to develop an agonist with relatively selective actions, confined to the striatal dopaminergic synapses in which transmission is diminished in Parkinsonism. In our study the low incidence of hypotension, emesis, and psychiatric symptoms may represent an increased affinity of bromocriptine for striatal receptors—certainly by comparison with apomorphine and piribedil.

One of the most interesting observations to emerge is the relatively greater therapeutic action of bromocriptine in the more

severely disabled patients. This could be interpreted in terms of advanced striatal disease leading to increased denervation supersensitivity. Alternatively, this finding may simply derive from greater room for improvement by a dopaminergic agonist because in patients with gross disease there is substantial depletion of striatal L-aromatic aminoacid decarboxylase and so a more limited response to levodopa.

Dopaminergic agonists, however, also carry certain theoretical disadvantages. Accumulating evidence indicates that these drugs tend to decrease the release of dopamine by a control system involving presynaptic receptors (Farnebo and Hamberger, 1973) and a negative feed-back loop (Walters *et al.*, 1974). Most of our patients were taking levodopa, and presumably maintaining a certain level of therapeutic response by dopamine release. The fact that further improvement was obtained with a dopamine agonist suggests that if this drug reduces dopamine output the consequences are of minor importance. Nevertheless, it would clearly be of interest to establish the relative therapeutic potency of bromocriptine with and without concomittant administration of levodopa. Another important area for further investigation is the possible potentiation of bromocriptine by simultaneous administration of a phosphodiesterase inhibitor such as caffeine or theophylline since these agents would be expected to delay the destruction of cyclic adenosine monophosphate formed in striatal neurons as the result of dopaminergic activation (Kebabian *et al.*, 1972).

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New Approach to Assessment of Cardioselectivity of Beta-blocking Drugs

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Summary

Propranolol, practolol, and placebo were each given intravenously at weekly intervals to six normal subjects, and their effects on respiratory function tests and heart rates assessed. The reduction in the exercise heart rate after each of the two drugs was most comparable at six hours, indicating a similar degree of cardiac beta-blockade, when the plasma concentration ratio of practolol to propranolol was 28:1. The peak flow rate (PFR) was higher at all times during exercise than at rest. There were significant differences between the changes in resting and exercise PFR after placebo and the reductions after propranolol (except at 24 hours), but not after practolol—and the latter's influence on PFR seemed to be intermediate to that of propranolol and placebo. At six hours, when the cardiac beta-blocking activity of the two drugs was almost the same, there was a significant difference (P 0·025) between the reductions in exercise PFR associated with each drug.

Small though significant differences ($P < 0.05$) were found only between the changes in FEV_1 after placebo and the reductions after each drug at one, two, and three hours, and there was no significant difference beween the effects of the two drugs. This study supported the suggestion that beta-sympathetic stimulation contributes to the bronchodilatation evident during exercise. Moreover, it emphasizes the importance of assessing airway resistance both at rest and during exercise and of comparing the pulmonary effects of different drugs when their cardiac beta-blocking activity is equivalent.

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Introduction

The extent to which commonly used beta-blocking drugs affect airway resistance in normal adults is controversial (McNeill, 1971). The relative cardiac and bronchopulmonary activity of such drugs is usally assessed by giving arbitrary doses of each drug and determining their effects at arbitrary fixed times after administration. Clinically, however, it may be more important to compare unwanted side effects such as bronchoconstriction at times when desirable cardiac effects are similar.

Beta-adrenoceptor blocking drugs produce little or no slowing of resting heart rate but greatly reduce that during strenuous exercise (Robinson *et al.*, 1966). This has been taken as evidence that beta-sympathetic stimulation of the heart increases with exercise, and hence a useful index of cardiac beta-blocking activity is how much the heart rate associated with vigorous exercise is reduced. By analogy, if the bronchodilatation accompanying exercise (Jones *et al.*, 1962) is also due to sympathetic stimulation, the effect of