Brain Dopamine Receptor Stimulation and the Relief of Parkinsonism: Relationship between Bromocriptine and Levodopa

U. K. Rinne, MD, and R. Marttila, MD

The relationship between brain dopamine receptor stimulation by bromocriptine or levodopa and the relief of parkinsonism was studied in 24 patients with Parkinson disease. Bromocriptine, 30 mg daily for 20 weeks, elicited an improvement in the parkinsonian clinical features, but this was less than the subsequent improvement with levodopa and benserazide, 800 mg and 200 mg daily, respectively. There was a negative correlation between the pretreatment severity of the disease or changes in cerebrospinal fluid homovanillic acid (HVA) and improvement in parkinsonian disability during bromocriptine treatment. Furthermore, it was found that clinical improvement and HVA responses in the cerebrospinal fluid after dopamine receptor stimulation by bromocriptine may predict the clinical response to levodopa.

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Recent evidence indicates that drugs stimulating brain dopamine receptors directly could be beneficial in the treatment of patients with Parkinson disease [4, 6, 13, 19]. Among these agents, bromocriptine has been proved to be superior to levodopa [13, 14], although contrary results have also been described [10, 16].

Our previous results with piribedil and bromocriptine indicate a definite relationship between dopamine receptor activation and relief of parkinsonism. Furthermore, it was found that homovanillic acid (HVA) responses in the cerebrospinal fluid to dopamine receptor agonists reflect activation of dopaminergic receptors in the parkinsonian brain [17, 19]. For further clarification, the present study was done to investigate whether therapeutic and HVA responses to dopamine receptor stimulation by bromocriptine may predict the clinical response to levodopa.

Patients and Methods

Twenty-four patients with idiopathic parkinsonism were investigated; their main clinical features are shown in Table 1. None had been treated with levodopa before participating in this study. Anticholinergic treatment had been started previously in 9 patients and was continued unaltered. All patients were admitted to the hospital for initiation of treatment. Thereafter they were examined at intervals of four weeks.

The initial daily oral dose of bromocriptine (2-bromo-α-ergokryptin, Sandoz AG, Basel, Switzerland) was 2.5 mg for the first three days and 2.5 mg twice a day for the rest of the first week of treatment. Thereafter the daily dose was increased by 2.5 mg every week, if tolerated, to a maximum of 30 mg daily. During treatment the daily dose of bromocriptine was 30 mg except in 1 patient, for whom it was 15 mg.

Bromocriptine treatment was continued for 20 weeks. Following withdrawal of bromocriptine, levodopa treatment was built up in 21 patients by using levodopa in combination with benserazide (Madopar, Hoffmann-LaRoche, Basel, Switzerland). The initial dose was one capsule containing 200 mg of levodopa and 50 mg of benserazide daily; the dose was increased by one capsule every fourth day until a maximum daily dose of four capsules was reached. Thereafter the patients were examined after one, three, and six months' treatment.

In order to detect any toxic effect of the treatment, the following laboratory examinations were carried out before the trial and at 8 to 12-week intervals: hemoglobin, hematocrit, leukocytes, serum alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum creatinine, and urinalysis.

Quantitative clinical assessments were carried out with the rating scale for parkinsonian symptoms and functional disability [9]. Adverse reactions were similarly assessed. The evaluations were made at the beginning of the trial and at various intervals during the described treatment. The degree of improvement was calculated as a percentage of the pretreatment value.

From the Department of Neurology, University of Turku, Turku, Finland.

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Address reprint requests to Prof Rinne, Department of Neurology, University of Turku, SF-20520 Turku 52, Finland.

Table 1. Some Characteristics of Parkinsonian Patients Treated with Bromocriptine

Sex	No. of Patients	Age (yr)	Duration of Disease (yr)	Degree of Disability[a] I	II	III	IV	V
Female	14	64 ± 3	3.4 ± 0.3	0	2	9	3	0
Male	10	64 ± 2	4.4 ± 0.8	0	1	8	1	0
Total	24	64 ± 2	3.8 ± 0.4	0	3	17	4	0

[a]According to Hoehn and Yahr [12].

A probenecid test was carried out twice on 12 volunteer patients, once prior to treatment and again after 20 weeks of treatment with bromocriptine. The probenecid test was performed as described earlier [21] by giving 100 mg per kilogram of body weight of the drug orally in eight doses over 24 hours. A sample of CSF was collected by lumbar puncture before the first probenecid dose and again 6 hours after the last dose. The CSF samples were stored deep frozen until assayed. HVA was analyzed by the method of Andén et al [1] and 5-hydroxyindoleacetic acid (5-HIAA) by that of Ashcroft and Sharman [3].

Results

Therapeutic Effects

The improvement in total disability and in the main clinical symptoms of the parkinsonian patients during long-term treatment with bromocriptine are shown in Table 2. Bromocriptine elicited a significant ($p < 0.001$) improvement in total disability in patients with Parkinson disease. The effect seemed to increase within the first months of treatment while the dose was being gradually built up. All the main parkinsonian symptoms were improved, but the reduction in tremor seemed to be somewhat greater than the decrease in rigidity and hypokinesia.

The distribution of patients according to degree of improvement after 20 weeks of treatment (Table 3) shows that half (52%) had moderate improvement but only 17 patients had marked or very marked improvement during bromocriptine treatment. Moreover, 7 patients (31%) showed no response or only minimal improvement of no practical clinical importance.

Table 3. Number of Patients Showing Various Degrees of Improvement after Five Months' Treatment with Bromocriptine

Degree of Improvement	Patients (N = 23) No.	%
Very marked (80–100%)	1	4
Marked (50–79%)	3	13
Moderate (20–49%)	12	52
Minimal (0–19%)	7	31

Subsequent treatment with levodopa (800 mg/day) and benserazide (200 mg/day) for six months after the bromocriptine therapy resulted in marked further improvement in total disability and in various symptoms (see Table 2).

Adverse Reactions

The main clinical side-effects during bromocriptine treatment included nausea, anorexia, and dizziness (Table 4). Mental disturbances and abnormal involuntary movements were noted in a few patients. Due to severe nausea and dizziness, 1 patient who had been receiving 7.5 mg of bromocriptine daily had to be withdrawn from treatment after three months.

Laboratory examinations showed that serum aspartate aminotransferase increased slightly in 2 patients after 12 and 20 weeks of treatment, respectively. Myeloid metaplasia was detected in the peripheral blood of 1 patient after 20 weeks of treatment. Further examination of the bone marrow and spleen revealed a myeloproliferative disorder with polycythemia vera and myelofibrosis.

The side-effects of bromocriptine were qualitatively similar to those of levodopa. However, bromocriptine produced more nausea and mental changes and fewer involuntary movements than did levodopa and benserazide (see Table 4).

Table 2. Percentage Improvement of Parkinsonian Patients during Treatment with Bromocriptine or with Levodopa and Benserazide

Variable	Duration of Treatment (mo) Bromocriptine 1 (N = 24)	2 (N = 24)	3 (N = 24)	4 (N = 23)	5 (N = 23)	Levodopa and Benserazide 1 (N = 21)	3 (N = 21)	6 (N = 21)
Total disability	9 ± 2	17 ± 3	22 ± 4	26 ± 4	31 ± 4	31 ± 5	45 ± 4	49 ± 5
Tremor	21 ± 4	35 ± 5	37 ± 5	43 ± 5	46 ± 6	42 ± 7	58 ± 6	64 ± 7
Rigidity	11 ± 3	16 ± 3	24 ± 4	30 ± 5	34 ± 5	30 ± 5	45 ± 4	49 ± 4
Hypokinesia	5 ± 2	13 ± 3	18 ± 4	21 ± 4	23 ± 4	26 ± 5	35 ± 5	41 ± 5

Values are mean ± SEM.

Table 4. Percentage of Patients with Clinical Side-Effects during Treatment with Bromocriptine or with Levodopa and Benserazide

Variable	Pre-treatment (N = 24)	Duration of Treatment (mo)							
		Bromocriptine					Levodopa and Benserazide		
		1 (N = 24	2 (N = 24)	3 (N = 24)	4 (N = 23)	5 (N = 23)	1 (N = 21)	3 (N = 21)	6 (N = 21)
Gastrointestinal									
Nausea	4	58	50	46	26	32	28	20	0
Vomiting	0	17	0	0	0	25	10	5	0
Autonomic									
Sweating	0	17	13	13	0	0	10	5	5
Dizziness	0	50	46	25	35	41	24	5	15
Cardiac disturbances	0	4	0	8	4	0	0	0	0
Involuntary movements	0	8	17	0	0	0	10	20	30
Mental disturbances									
Anorexia	0	33	33	29	22	9	5	0	15
Insomnia	13	21	17	17	9	9	10	0	0
Anxiety	4	17	21	21	4	9	10	10	15
Confusion	0	4	8	4	4	9	0	0	0
Hallucinations	0	8	4	0	0	5	0	0	0

Factors Governing Bromocriptine Response

When we analyzed the possible clinical variables governing a patient's response to bromocriptine, a significant ($p < 0.01$) negative correlation was found between the pretreatment severity of the disease and the degree of improvement in total disability after 4, 16, and 20 weeks of treatment with bromocriptine. There was a tendency toward negative correlation of improvement with the patient's age and duration of illness, which, however, did not reach the level of statistical significance. No differences were noted in clinical responses between male and female patients.

After 20 weeks of bromocriptine therapy, the pretreatment concentration of HVA in the CSF and its response to probenecid showed a significant ($p < 0.05$) positive correlation with the improvement in tremor but not with that of other symptoms.

During bromocriptine treatment the basal concentration of HVA in the CSF decreased ($p < 0.05$) (Table 5). Bromocriptine treatment also led to a decrease in probenecid-induced accumulation of HVA ($p < 0.01$). No changes occurred in either the basal concentration of 5-HIAA in CSF or its response to probenecid (see Table 5).

The decreased concentration of HVA in the CSF of parkinsonian patients after 20 weeks' treatment with bromocriptine showed a negative correlation with the improvement in hypokinesia ($p < 0.05$) and a tendency for a similar correlation with improvement in tremor and rigidity. Furthermore, there was a negative relationship ($p < 0.05$) between probenecid-induced accumulation of HVA in the CSF and improvement in total disability during bromocriptine treatment. No relationships were noted between concentrations of HVA in the CSF and the occurrence of clinical side-effects during bromocriptine therapy.

The concentrations of 5-HIAA in the CSF either

Table 5. Effect of Bromocriptine Treatment on Basal Concentrations and Probenecid-Induced Accumulations of HVA and 5-HIAA in the CSF of Parkinsonian Patients

Time	No. of Patients	HVA (ng/ml)		5-HIAA (ng/ml)	
		Basal	Probenecid	Basal	Probenecid
Before therapy	12	20.8 ± 2.2	145.0 ± 17.2	20.0 ± 3.3	46.5 ± 7.4
During therapy	10	10.3 ± 2.3	92.6 ± 15.3	18.4 ± 2.3	62.2 ± 8.6
Significance		$p < 0.05$	$p < 0.01$	$p > 0.05$	$p > 0.05$

Values are mean ± SEM.
HVA = homovanillic acid; 5-HIAA = 5-hydroxyindoleacetic acid.

prior to or during treatment with bromocriptine did not correlate with improvement of the patients or with clinical side-effects.

Relationship between Bromocriptine and Levodopa Responses

As with bromocriptine, there was a negative correlation ($p < 0.01$) between the pretreatment severity of disease and the degree of improvement in total disability after one, three, and six months of treatment with levodopa and benserazide.

Statistical analyses showed a positive correlation between the improvement in total disability ($p < 0.01$), tremor ($p < 0.01$), rigidity ($p < 0.01$), hypokinesia ($p < 0.05$), and functional performance ($p < 0.01$) during bromocriptine therapy and during treatment with levodopa and benserazide for one to six months.

The response of HVA in the CSF during bromocriptine treatment seemed to predict the therapeutic response to levodopa, because the concentration of HVA in the CSF during treatment with bromocriptine was negatively correlated with improvement in total disability ($p < 0.01$), rigidity ($p < 0.05$), hypokinesia ($p < 0.01$), and functional performance ($p < 0.01$) during treatment with levodopa and benserazide.

Discussion

The results of the present study give further support to a beneficial effect of bromocriptine in the treatment of patients with Parkinson disease [4, 10, 14, 16, 19]. Furthermore, there was no loss of efficacy during long-term treatment, indicating that tolerance to the antiparkinsonian action of bromocriptine does not develop. However, the therapeutic efficacy of bromocriptine in a maximum dose of 30 mg daily was less than that of levodopa (800 mg/day) in combination with benserazide (200 mg/day). A similar finding has been reported by Gerlach [10], but Kartzinel et al [13] and Lieberman et al [14] have found bromocriptine to be superior to levodopa alone or combined with carbidopa. One reason for this discrepancy in results may be the difference in dosage of bromocriptine, because in Gerlach's study and in ours, a lower daily dose of bromocriptine was used than in Kartzinel's and Lieberman's series. On the other hand, the present results showed a correlation between the therapeutic effects of bromocriptine and levodopa, indicating that bromocriptine mimics the action of levodopa. This is in agreement with the finding of Parkes et al [16] that bromocriptine does not improve the condition of parkinsonian patients who had previously failed to respond to levodopa or who had lost their response to the drug.

The possible relationship between the therapeutic activity of bromocriptine and the severity of parkinsonism has been a matter of great interest. Dopamine agonists may be effective even in cases of advanced Parkinson disease in which a great loss of presynaptic dopaminergic neurons has occurred but enough functional postsynaptic receptors are retained in the striatum to support the dopamine agonist activity. Indeed, severely disabled parkinsonian patients have been reported to have an even better response to bromocriptine than patients who have only mild disease [4, 14]. In other studies no correlation was found [13, 16]. Our findings and those of Godwin-Austen and Smith [11] suggest that the more severely disabled patients respond less well than those with milder disease. Moreover, in agreement with previous findings [18, 20], a similar relationship was found with regard to response to levodopa. The findings imply that in advanced cases of Parkinson disease, there is not only presynaptic loss of dopaminergic neurons but also a loss or dysfunction of postsynaptic receptors.

The pharmacological stimulation of dopamine receptors is associated with decreased turnover of endogenous dopamine [2, 15], and the blocking of these receptors increases dopamine turnover [8, 15] as a result of feedback mechanisms. Similarly, the treatment of patients with dopaminergic agonists [5, 6, 19] or antagonists [5] is associated with corresponding changes in the concentration of HVA in lumbar CSF. Thus a decreased concentration of HVA in the CSF and its diminished response to probenecid in the present study support the opinion that bromocriptine stimulates dopamine receptors in the parkinsonian brain. However, there is evidence that bromocriptine may have presynaptic action at the dopaminergic synapses [22] and also an effect on the noradrenalin [7] and serotonin [7, 22] neurotransmitter systems. Our statistical analyses showed a significant correlation between dopamine receptor activation by bromocriptine and improvement in parkinsonian disability. This suggests that the therapeutic efficacy of bromocriptine and other dopamine receptor agonists [17, 19] may depend on the functional capacity of the extrapyramidal dopaminergic neurons. A similar relationship has not been found between HVA changes in the CSF and the relief of parkinsonian symptoms with levodopa [21]. This suggests either that the effect of dopamine receptor agonists on the brain dopaminergic mechanisms is more specific than that of levodopa or else that nondopaminergic neurons of the striatum determine the response to agonists.

The results of the present study showed that HVA response in the CSF to bromocriptine correlated with the therapeutic effects of both bromocriptine and combined levodopa and benserazide. Thus, HVA re-

sponse in the CSF to dopamine receptor stimulation by bromocriptine may be useful as a provocative test of brain dopaminergic mechanisms and in predicting the therapeutic response to levodopa.

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