A Crossover Trial of Bromocriptine in the Treatment of Vascular Dementia

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Seven patients with vascular dementia completed an 8-month randomized double-blind crossover trial of bromocriptine in a dosage of up to 30 mg per day. Patients were assessed using a modified UCLA Parkinson Rating Scale of symptoms and signs, and neuropsychological testing including the Wechsler Adult Intelligence Scale–Revised, Wechsler Memory Scale, modified Thurstone Word Fluency Test, Wisconsin Card Sort, a test of visual vigilance, and a reaction time task. Subjects failed to perform significantly better on any measure while on bromocriptine, and on several measures their performance while on the drug was worse.

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Vascular dementia is characterized clinically by varying degrees of loss of initiative, apathy, bradykinesia, and impairment in other aspects of frontal lobe function [1]. These manifestations may relate in part to ischemic destruction of projections from midbrain dopaminergic neurons to the striatum, mesolimbic structures, and frontal cortex and may therefore be remediable by administration of dopaminergic agents. Ross and Stewart [2] reported successful treatment with bromocriptine (but not levodopa/carbidopa) of a patient with bilateral presumptive damage to the nigrostriatal bundle due to a hypothalamic lesion, and Jackson and colleagues [3] reported improvement in patients with progressive supranuclear palsy who were treated with bromocriptine.

Methods

Patients

Patients were recruited from the Neurology Inpatient Service at the Jackson Veterans Administration Medical Center. Informed consent was obtained from all patients and from their spouses or guardians if the patient's dementia was felt to preclude adequately informed consent. The study was continuously monitored by the Investigational Review Board of the University of Mississippi Medical Center. Twelve patients were recruited for the study. One patient dropped out after recurrence of syncope, 1 after recurrent lacunar infarction, and 1 patient developed palpitations, even when the dosage of drug (later determined to be placebo) was reduced. Data on 2 patients were incomplete. The 7 patients who completed the study are described below.

Two patients were white, 5 were black, and all were men. Ages ranged from 52 to 78 years, with a mean of 63. The subjects had between 3 and 17 years of education (mean 8 years). All had a history of hypertension, were on antihypertensive medications (a diuretic in 7, hydralazine in 4, clonidine in 2, propranolol in 2, metoprolol in 1), and 5 were actually hypertensive when first seen. Serum creatinine ranged between 1.3 and 2.3 mg/dl, mean 1.6 (115–203 mole/L, mean 141), and no patient had any disorder other than hypertension to account for reduced renal function. Five patients had a history of lacunar infarction, 1 of cortical infarction. All patients had become relatively inactive and lost interest in their surroundings. The families of 6 patients were aware of their deterioration in mental function. On examination, 5 patients were frankly bradykinetic, 5 had a reduction in language fluency, 6 had gait apraxia, and 5 were experiencing urinary incontinence. All patients had reasonably good language content with intact naming and semantic comprehension. Neurological signs such as pronation drift, impaired fine motor movement, paratonia, and extensor plantar responses were found in all patients. Only 1 patient was disabled by focal motor dysfunction at the beginning of the study, and another lost his ability to walk because of a recurrent lacunar infarction during the study. Computed tomographic (CT) scans revealed one or more lacunar infarctions in 6 cases, a single cortical infarction in 2, diminished periventricular attenuation in 5, and enlarged ventricles in all 7 patients.

Procedure

Subjects received 2.5-mg bromocriptine tablets for 4 months and identical-appearing placebo tablets for 4 months. The order of administration was randomized and known only to the pharmacist who dispensed the medication. Dosage was begun at 1 tablet three times a day and increased monthly up to 4 tablets three times a day, providing a maximum bromocriptine dose of 30 mg per day. Only 1 patient was unable to tolerate this dosage and received a maximum of 22.5 mg per day. Subjects were seen monthly by the principal investigator (S.E.N.), at which time compliance was assessed, side effects ascertained, and symptoms and signs documented using a modified version of the UCLA Parkinson Rating Scale [4]. In addition, word generation (animals, words starting with F) was tested, and subjects were timed as they rose from their chair, walked a standard course of about 75 feet, and sat down again. Throughout the study, other drugs including antihypertensives, antidepressants, pulmonary medications, and, in 2 patients, anticonvulsants were maintained and adjusted as clinically indicated.

Assessment

At the beginning of the study and at the end of each treatment arm, the patients underwent a battery of neuro-

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psychological tests. This included the Wechsler Adult Intelligence Scale–Revised (WAIS-R) subtests (vocabulary, arithmetic, picture arrangement, and block design), the Wechsler Memory Scale Logical Memory subtest, the Wisconsin Card Sort, a modified Thurstone Word Fluency Test (letters A, F, and S), animal name generation in 1 minute, reproduction of sequences of alternating symbols, a visual vigilance task, a reaction time task, the tapping test, and a grooved pegboard test. On the alternating symbols test, the subject was instructed to continue each of two sequences of symbols (+ + 0; + △ 0), first from direct observation, subsequently from memory. They were given 1 point for ability to produce a sequence once, and an additional point for producing it correctly two or more times; productions from immediate memory were scored similarly. On the visual vigilance task, the subject sat before a projection screen upon which 80 letters appeared one at a time for 5 seconds. The subject was instructed to press a buzzer when any one of the four letters, A, E, M, or U, appeared on the screen. Errors of omission and commission were tallied. On the reaction time task, the subject faced a small panel upon which there was a white readiness light and red and blue trial lights. The examiner announced "ready" as the white light was illuminated, and 3 seconds later, the red or blue light came on (order randomized according to method of Fellows [5]). The subject was first instructed to hit as soon as possible the telegraph key that was a color similar to that of the trial light. In the reversed condition, the subject was to hit the telegraph key of the opposite color. Twenty trials were administered for each condition, and the results were averaged.

Statistical Analysis

Symptom and sign scores on the modified UCLA Parkinson Rating Scale, word generation scores, and time to complete the standard walk were averaged for the last two monthly visits of each treatment arm. These averages and the scores on the neuropsychological tests were analyzed using the Mann-Whitney-Wilcoxon test [6, 7].

Results

On no measure did subjects perform significantly better while on bromocriptine than on placebo (Table). For many measures there was a trend favoring placebo, and on five this approached or achieved statistical significance: modified UCLA symptom score, WAIS-R IQ, Wisconsin Card Sort categories, visual vigilance errors of commission ($p < 0.1$), and visual vigilance errors of omission ($p < 0.05$).

Only 1 patient ever had a problem with drug compliance. The drugs were uniformly well tolerated: the only major complaint was dizziness (3 patients) and in only 1 patient was this clearly correlated with bromocriptine and of sufficient severity to warrant dosage reduction.

Other drugs were not changed in 3 patients. In 1 patient, clonidine was introduced halfway through the placebo phase, and the dose subsequently increased in the second month of the bromocriptine phase; in this same patient, amitriptyline was added in month 2 of receiving placebo and changed to doxepin in month 3 of receiving bromocriptine. In another patient, phenytoin and quinidine were introduced in the second month of the placebo phase of the study. In 1 patient, propranolol was introduced in the first month of the study, and the dosage later was increased halfway through the placebo phase. Finally, in 1 patient, cloni-

Selected Test Results

	Patients on Placebo							Patients on Bromocriptine						
Test	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Modified UCLA symptom score[a,b]	2.3	1.7	2	0	7.7	0.6	1.2	3.5	1.2	3.5	0	8.4	8.2	1.2
Modified UCLA sign score[b,c]	11	6	5	3	10	7.5	2	10	6	8	2	9.5	7.5	2
Timed walk (seconds)[b]		36.5	35	26	116	157.5	28		28	44.5	30.5	175.5		28
WAIS-R IQ	56	64	63	72	65	61	87	53	62	62	63	61	59	90
Wechsler Memory Scale														
Verbal immediate	6	12	6	5	11	10	17	2	12	4	4	14	9	17
Verbal delayed	3	11	0	0	0	3	18	0	7	0	2	0	7	17
Nonverbal immediate	0	0	0	2	0	0	8	0	1	0	2	0	0	8
Nonverbal delayed	0	0	0	0	0	0	5	0	0	0	2	0	0	8
Wisconsin Card Sort														
Categories		3	0	1	0	0	0	1	0		1	0	2	0
Errors: perseverative		7	14	26	31	23	46	16	45		24	24	18	47
Errors: nonperseverative		13	11	9	14	23	2	9	1		12	18	9	2
Modified Thurstone	5	2	7	12	7	14	16	7	6	14	10	4	16	13
Animal name generation	4	9	10	10	1	5	16	3	8	6	9	3	4	13
Alternating sequences	4	7	0	7	2	1	8	0	8	0	4	1	2	8
Visual vigilance														
Omission errors	6	0	2	0	8	6	0	12	2	6	0	15	6	0
Commission errors	0	2	7	0	0	0	0	1	1	9	0	0	2	0
Reaction time: similar	1.41	1.13	1.28	0.96	1.56	0.92	0.58	1.47	1.01	2.23	0.92	2.18	1.18	0.59
Reaction time: reversed	1.70	1.45	2.06	1.66	2.85	1.45	1.13	1.73	1.84	5.27	1.66	6.51	1.45	1.03

[a]Sum of unweighted ratings (0 = absent, 1 = present, 2 = marked) for dressing, eating, getting out of bed, turning in bed, climbing stairs, use of toilet, and bathing.
[b]Mean of monthly ratings for last 2 months of treatment period.
[c]Sum of unweighted ratings (0 = absent, 1 = present, 2 = marked) for rigidity, akinesia, postural abnormality, depression, masked facies, speech, gait, getting out of chair, and handwriting.

WAIS-R IQ = Wechsler Adult Intelligence Scale–Revised intelligence quotient.

dine was initiated in month 3 of receiving bromocriptine, and the dosage later was increased in month 4 of receiving placebo.

Discussion

This study failed to demonstrate any beneficial effect of bromocriptine on the symptoms of vascular dementia. In fact, on several of our measures, there was a trend toward worse performance while on bromocriptine. In 4 patients, changes were made in other drugs which might affect higher cortical function, but in our judgment, these changes probably did not exert a substantial influence on the study outcome.

The considerable statistical power of the crossover design makes it unlikely that the lack of significant results favoring bromocriptine was due to small sample size [8]. On the other hand, it is quite possible that our sample was not representative of vascular dementia in general or that we failed to include a subclass of vascular dementia patients that might benefit from the drug. However, our experience with over 50 vascular dementia patients enrolled in a prospective diagnostic study of dementia (unpublished observations) suggests that the patients selected for the present study were quite typical.

The finding that bromocriptine may actually be harmful to patients with vascular dementia should lead to a search for other agents of potential benefit; it also increases the importance of making the sometimes difficult clinical distinction between Parkinson's disease and vascular dementia. Theoretically, our negative results suggest that the neurobehavioral features of vascular dementia cannot be attributed to reduced dopamine levels in the target organs of the midbrain dopaminergic projections. Our results are also congruent with animal studies, which suggest that a fairly narrowly defined range of tissue dopamine concentration is a necessary condition for normal function of the basal ganglia [9, 10] (and, by inference, mesolimbic and mesocortical systems). Increasing dopamine levels may only add to, rather than compensate for, dysfunction stemming from damage to other aspects of frontal lobe systems, such as may occur in vascular dementia.

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Loss of Evoked Potentials During Spinal Surgery Due to Spinal Cord Hemorrhage

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The cortical somatosensory evoked potential (SEP) disappeared during corrective spinal surgery in a patient with muscular dystrophy. The patient died 18 hours after surgery. Autopsy revealed an intramedullary hemorrhage 4 mm in diameter in the posterior horn of the cervical spinal cord. Microscopically, hypoxic neurons were seen adjacent to the hemorrhagic area, implying that the lesion was at least 6 hours old. The hemorrhage corresponded to the loss of SEPs and confirms that spinal cord monitoring can detect such lesions.

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Spinal cord monitoring during corrective spinal surgery is now routinely done. Most workers in this field

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