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A Controlled Trial of Piracetam in Intellectually Impaired Patients with Parkinson's Disease

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Summary: Twenty patients with Parkinson's disease and marked intellectual impairment or dementia participated in a double-blind placebo controlled trial of the nootropic, piracetam. A standardized neurological examination, a neuropsychological test battery, and a functional scale, The Sickness Impact Profile, were completed for all patients. They were then assigned by blind randomization to drug or placebo conditions receiving 3.2 g of piracetam or an identical amount of placebo for 12 weeks. The dose was increased to 4.8 g for an additional 12 weeks. Neurological, psychological, and functional measures were rated as improved, unchanged, or worsened in comparison to baseline performance. Twenty-five percent of the patients did not complete the trial for reasons unrelated to the medication. Although there was a significant improvement on one subtest of the functional scale, no significant effects were demonstrated in cognitive or neurological measures. **Key Words:** Parkinson's disease—Piracetam—Dementia.

Intellectual impairment occurs in some patients with Parkinson's disease (PD) (1), but little is known about treatment. Piracetam, a nootropic that is structurally similar to gamma-aminobutyric acid (GABA), has been reported to improve some aspects of cognitive function in elderly patients (2). Its effect in Alzheimer's disease is negligible (3). The cognitive enhancement appears to be unrelated to a specific disease process. We chose to examine this agent in Parkinson's disease, which is associated with a broad range of cognitive deficits, attributable to many etiological factors including cortical and subcortical pathology. The present study used a double-blind placebo controlled parallel design to examine the effects of piracetam in patients with PD. Three domains of function were assessed, each of which can be impaired in PD and can contribute to the overall impression of deficit.

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METHODS

Subjects

Twenty patients with PD participated in the study. The criteria for the diagnosis of idiopathic PD was the presence of two or more of the following features: tremor, rigidity, bradykinesia, stooped posture, and shuffling gait. Patients were excluded if the onset of these symptoms was associated with head injury, encephalitis, or concurrent use of medications such as phenothiazines. Patients were also excluded if dementia preceded the onset of the motor changes. One patient was not demented but had a moderate cognitive impairment, defined as scoring 2 standard deviations below normal on a majority of the neuropsychological tests described in the next section. All others met DSM-III criteria for dementia (4). Several patients were included who were severely impaired and unable to complete neuropsychological testing. In these individuals, only functional capacity and parkinsonian symptoms were assessed. None of the patients met

DSM-III criteria for major depression, as assessed by a standardized interview with the patient and a family member (4).

All patients were taking levodopa alone or with carbidopa throughout the study. The daily dose of levodopa ranged from 100 to 1,600 mg, with a mean dose of 536.6 mg/day. Several patients had a history of confusional or hallucinatory state; however, there was no evidence of such episodes throughout this clinical trial. None of the patients received anticholinergic or psychotropic medications at any point during the study.

Procedure

Subjects were assessed before the trial with a standard battery of neurological, neuropsychological, and functional measures and were randomly assigned to either the piracetam or placebo group. The initial dose was 3.2 g/day for 12 weeks. At the end of the 12-week period the dose was increased to 4.8 g/day for an additional 12 weeks. At the end of the 24-week period subjects received the same battery of tests, and all were permitted to enter on open trial. The drug placebo status of individual patients remained unknown until all patients completed the trial.

Neuropsychological Battery

Subjects received the following tests at baseline and after 24 weeks.

The *modified Mini-Mental Status Examination* (mMMS) is a brief test of intellectual function that is an extended version of the original MMS test (5). This modification has been described elsewhere (6) and has a maximum score of 57. In previous studies we found the mean mMMS for healthy elderly people to be 52.5 (±4.3) (7).

The *Selective Reminding Test* (SRT) is a memory test commonly used to evaluate the efficacy of drugs on memory. The subject is given up to 12 trials to learn a list of 12 unrelated words. After each trial the subject is "selectively" reminded of only those words that have not been recalled. Performance measures include total recall, retrieval from long-term storage, and intrusion errors (8,9).

The *Digit Symbol subtest of the Wechsler Adult Intelligence Scale—Revised* (DSYM), is a test of visual motor performance, which is often affected in PD and dementia (10).

Controlled Word Association test (CFL), and *Category Naming* (CATEG) are linguistic tests that are also sensitive to dementing illnesses. They measure verbal fluency and word retrieval ability (11).

Reaction Time (RT) is a visual motor test that is presented in two conditions. In a simple reaction time condition, the subject responds to a stimulus by lifting a finger. In choice reaction time, there is a differential response to two different stimuli, either tone or light (12).

The *Continuous Performance Task* (CPT) is a test of sustained attention. Ten different letters are presented in random order on a screen and the subject responds with a button press to the letter "X." The test lasts for 15 min (12).

Neurological Examination

All subjects received a standard, quantifiable, neurological examination rating extrapyramidal signs and symptoms on the Unified Parkinson's Disease Rating Scale (UPDRS) (13).

Functional Capacity

The *Sickness Impact Profile* (SIP) is a standardized questionnaire that measures functional abilities. It is completed by a family member (14). The areas assessed by the SIP are sleep and rest, home management, recreation and pastimes, physical activities (including ambulation, mobility, body care, and movement) and psychosocial activities (including social interaction, alertness behavior, emotional behavior, and communication). The items have been found to be independent of each other and to be reliably assessed by an informant.

Data Analysis

Comparisons were made between the baseline measures and measures at the end of the 24-week, double-blind interval. The changes in raw scores were analyzed using parametric methods. In addition, we determined a minimum "meaningful" change for each test and subtest, and rated performance as improved, unchanged, or worse. The number of tests demonstrating a change in each direction was calculated. In addition, a *Global Rating* of neuropsychological performance (i.e., improved, unchanged, worse) was made by two neuropsychologists after reviewing all of the scores. In cases with missing data, Global Ratings were assigned based on remaining available data. This maximized the number of patients who could be assessed. The patient who was unable to complete any of the neuropsychological tests was eliminated from the analysis of this variable. Agreement between the two rat-

ers was nearly perfect. When differences occurred scores were reviewed and a single rating was chosen. A meaningful change in UPDRS and SIP scores was defined as 5 points in any direction, and based on a change of this size, ratings of improved, unchanged, and worse were made. All change ratings were subjected to nonparametric analysis.

RESULTS

Five of the 20 subjects who began the study could not complete the study for reasons unrelated to medication. Three entered extended care facilities and could no longer be in a controlled clinical trial. Two others developed unrelated medical conditions that warranted treatment regimens not permitted within this study protocol. There were more dropouts in the piracetam group, resulting in a smaller "n" than in the placebo group, although the difference was not significant.

Table 1 provides demographic and disease severity information on the final piracetam and placebo groups as well as on the five discontinued patients. All groups were similar in age, duration, and initial mMMS scores. The piracetam group had significantly more severe PD symptoms, resulting in higher UPDRS scores than the other groups.

There were no significant differences between the drug and placebo groups in raw score changes from baseline to post-treatment performance on any measure.

For each measure, the classification of improved, unchanged, and worsened was subjected to nonparametric analysis (Tables 2 and 3). There were significantly more subjects categorized as improved on the SIP score in the piracetam group compared with the placebo group ($p < 0.05$). There were no other significant group effects in neuropsychological or neurological measures.

TABLE 1. *Description of groups in the study*

Group n	Piracetam 6	Placebo 9	Discontinued 5
Age	77.5 (69–84)	70.1 (49–81)	71.0 (61–83)
Education	19.2 (12–19)	12.8 (5–20)	16.8 (14–19)
Duration of illness	5.6 (3–7)	8.2 (2–10)	9.4 (5–13)
Modified Mini-Mental	31.8 (26–41)	32.2 (21–52)	30.2 (19–56)
Unified PD Rating[a]	68.5 (52–86)[b]	41.4 (20–66)[b]	53.8 (41–86)

Numbers represent means, with ranges in parentheses.
[a] $p < 0.05$ for ANOVAs comparing all group means for each variable.
[b] Significantly different group means in post-hoc analysis.

The subscales of the SIP were examined. There was significantly more improvement in the drug group than in the placebo group on the rating of recreation and pastime. This subscale assesses interest and amount of time spent in hobbies, leisure activities, and community involvement. There were no significant changes on any of the other subscales.

DISCUSSION

There was a small but significant improvement in functional capacity, measured by the SIP, in the piracetam as compared with the placebo group. Three of the six subjects showed an improvement in these scores and none of the subjects in the placebo group demonstrated an improvement. Improvement was seen in the subscale that measures recreation and pastime. There was no difference in any other measure. Four of five patients in the piracetam group had worse parkinsonian symptoms based on increased UPDRS scores. However, this result does not significantly differ in the drug and placebo groups.

The improvement in functional capacity without concomitant improvement in cognitive or physical symptoms is unusual. We previously reported in Alzheimer's disease that while functional status and mental status are related, there is a large proportion of the variance that is independent (15). The functional capacity is the only measure assessed by family members, who may see different aspects of the patient than the clinicians. The improvement in SIP scores in the absence of other measurable differences also supports a separation in functional capacity and cognition in these patients.

The choice of an appropriate neuropsychological battery is an important issue. There was a range of cognitive and physical impairments in these patients, and no cognitive measure could be used in all individuals. The Global Rating was a technique that permitted us to include the largest number of subjects. However, this is done at the expense of identifying specific domains affected by the drug.

There is a correlation between cognitive change and the severity of motor manifestations (16), and there were more severe motor disturbances at baseline in the piracetam group. If, in fact, this group was more impaired, it might have interfered with the assessment of a drug effect in the present study.

Five patients in this study did not complete the double-blind trial. The reasons for discontinuation were unrelated to the drug. All patients who with-

TABLE 2. *Neuropsychology results following double-blind administration of piracetam or placebo for each patient*

Group	Pt	mMMS	SRT	CFL	CATEG	RT	DS	CPT	Percent tests improved	Percent tests same	Percent tests worse	Neuropsych global rating
Piracetam	5	0	−1	−1	0	—	0	1	17	50	33	0
	8	1	0	1	1	1	—	1	83	17	0	1
	9	—	—	—	—	—	—	—	—	—	—	0
	10	0	−1	0	0	—	0	—	0	80	20	−1
	14	−1	−1	—	—	—	—	—	0	0	100	−1
	18	1	—	—	—	—	—	—	100	0	0	1
Placebo	2	1	1	0	0	1	0	—	50	50	0	1
	3	0	—	—	—	—	—	—	0	100	0	0
	4	1	1	0	0	—	—	—	50	50	0	1
	7	1	−1	0	0	−1	1	—	33	33	33	0
	11	−1	—	—	—	—	−1	—	0	0	100	−1
	12	−1	−1	−1	−1	0	0	−1	0	29	71	−1
	13	0	1	0	0	—	0	−1	17	66	17	0
	15	0	1	−1	−1	—	−1	—	20	20	60	0
	16	0	1	0	0	—	0	1	33	67	0	0

For each test, the results are expressed as change from baseline: 1 = improved; 0 = unchanged; −1 = worse; dashes indicate that test was not done.

CATEG, Category Naming; CFL, Controlled Word Association Test; CPT, Continuous Performance Task; DS, Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised; mMMS, modified Mini-Mental Status Examination; Pt, patient; RT, Reaction Time; SRT, Selective Reminding Test.

drew from the study entered a nursing home or other extended care facility or could no longer comply with study demands. This may be a common occurrence with PD patients who are both physically and cognitively impaired and may be due to social and family factors rather than the illness.

Clinical trials of drugs for the treatment of cognitive deficits including dementia are most informative if we can equally accept both negative and positive results. This study was a pilot project designed to examine the feasibility of testing a severely impaired population of patients with PD, and the planned group size of 20 could not have yielded adequate power to accept a negative finding. It would be sufficient to determine the value of a large trial, however. The relatively high attrition rate further reduced the power. Estimates of power in the present study range from 0.46 to 0.38, based on a moderate effect size.

TABLE 3. *Neurological (UPDRS scores) and functional (SIP scores) results following a double-blind trial of piracetam or placebo for each patient*

Group	Pt	UPDRS score	SIP change
Piracetam	5	−1	−1
	8	−1	1
	9	−1	1
	10	1	−1
	14	—	−1
	18	−1	1
Placebo	2	0	—
	3	−1	—
	4	1	—
	7	−1	0
	11	0	0
	12	−1	−1
	13	0	−1
	15	1	0
	16	−1	−1

Meaningful change on both measures was defined as a 5 point change from baseline in either direction as follows: 1 = improved; 0 = unchanged; −1 = worse; dashes indicate that test was not done.

In the present study, there is very little improvement in the placebo group, indicating that the negative findings are not a result of masking by a placebo effect. Additionally, although many tests were used, a positive effect was only present in a single domain. This suggests that at best, a minimal improvement in a very limited area can be expected with this drug. Given the large "n" necessary to yield adequate power and such minor improvements it is difficult to recommend a large trial with this agent in demented patients with PD.

In summary, there is no evidence that piracetam changes any motor or cognitive aspect of PD. It may have some benefit in improving functional status as assessed by a caregiver or family member. This functional improvement was characterized by a single subscale of one of our instruments, which was not sufficient to have clinical meaning.

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