Citicoline in the Treatment of Parkinson's Disease

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ABSTRACT

Eighty-five patients with an established diagnosis of primary Parkinson's disease were randomly assigned to receive their usual dose of levodopa (mean, 381 mg daily) plus 1,200 mg of citicoline daily or half their usual dose of levodopa (mean, 196 mg daily) plus the citicoline. Results of the Webster Rating Scale, a pegboard test, drawing, writing, and walking tests, a test of emotional state, and an overall assessment, administered before and after four weeks of treatment, revealed no significant between-group differences. Improvements on the tests were shown by more patients who received half their levodopa dose plus citicoline than by those who continued to receive their usual levodopa dose plus the citicoline. It is concluded that the levodopa-saving effect of citicoline could be used to decrease the incidence of side effects and retard the loss of efficacy of levodopa in long-term treatment.

INTRODUCTION

In the long-term treatment of Parkinson's disease, levodopa plus a decarboxylase inhibitor (DCI) is the principal and most successful therapeutic regimen.[1-4] Prolonged use of oral levodopa, however, is marked by a progressive loss of efficacy and the development of side effects, such as dyskinesia and the "on-off" phenomenon.[5-7] These complications usually occur after three years of levodopa treatment.

A reduction in the dose of levodopa without loss of therapeutic efficacy and with fewer side effects thus would be a positive development in the treatment of Parkinson's disease. Citicoline, an intermediate of phospholipid metabolism[8,9] that is absorbed when given orally,[10] has been shown to have a levodopa-saving effect after oral or intravenous administration.[11-16] Citicoline increases dopamine synthesis in the striate body through activation of tyrosine-hydroxylase[17,18] and

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inhibits dopamine uptake by synaptosomes, which is followed by an increase in dopamine levels. Citicoline may act by inducing hypersensitivity in dopamine receptors, which are down-regulated during prolonged levodopa treatment.[19] Gerstenbrand and associates[20] have demonstrated positive effects of citicoline in the treatment of Parkinson's disease and in the posttraumatic Parkinson's syndrome.

The purpose of the present study was to determine the effects of replacing half of the levodopa/DCI dose with citicoline in patients with Parkinson's disease.

PATIENTS AND METHODS

The subjects were 85 outpatients with Parkinson's disease; 45 were women, 40 men; their mean age was 63 years (range, 44 to 74 years); and their mean duration of Parkinson's disease was four years.

Patients included in the study had a minimum of 5 points on the Webster Rating Scale; those with a secondary diagnosis of Parkinson's disease were excluded. The patients' treatment had been adjusted to low doses of levodopa/DCI; they received no other antiparkinsonian treatment during the study. All of the patients gave their informed consent to participate in the study. Eleven dropped out; thus 74 patients were evaluated. The background characteristics of the study completers and noncompleters were similar.

Procedure

For an initial one-week period, the patients continued to receive their low doses of levodopa/DCI. They then were assigned randomly to group I, which, for one week, received their usual treatment (mean, 381 mg of levodopa daily; 39 patients), or to group II, which received half their usual treatment (mean, 196 mg daily; 46 patients); both groups also were given an additional placebo. After assignment, for four weeks, patients received the usual treatment plus 400 mg of citicoline three times daily (group I) or half the usual treatment plus 400 mg of citicoline three times daily (group II). Citicoline and placebo solutions were of identical appearance. The capsules of levodopa/DCI 100% were identical, while those of levodopa/DCI 50% were similar to the previously administered capsules.

Six clinical, psychometric, and motor-function tests were conducted at weeks 0, 1, 2, 4 (after two weeks of citicoline), and 6 (after four weeks of citicoline). Intrasubject comparisons were analyzed with the Wilcoxon test for paired samples. Intergroup comparisons were analyzed with the Mann-Whitney U test.

RESULTS

Figure 1 shows the responses of the two groups of patients on the Webster Rating Scale, which is a measure of neurologic and clinical symptoms; higher scores represent more severe disease. There were no significant changes in the mean scores of either group, and the scores of the two groups did not differ significantly. In most patients, a small improvement or no change was noted.

Figure 2 shows the patients' mean scores on the pegboard test (the numbers of pegs plugged in 30 seconds), which measures the degree of akinesia, rigor, and tremor. Group I scored 7.4 at week 2 and 7.7 at week 6 (not significant);

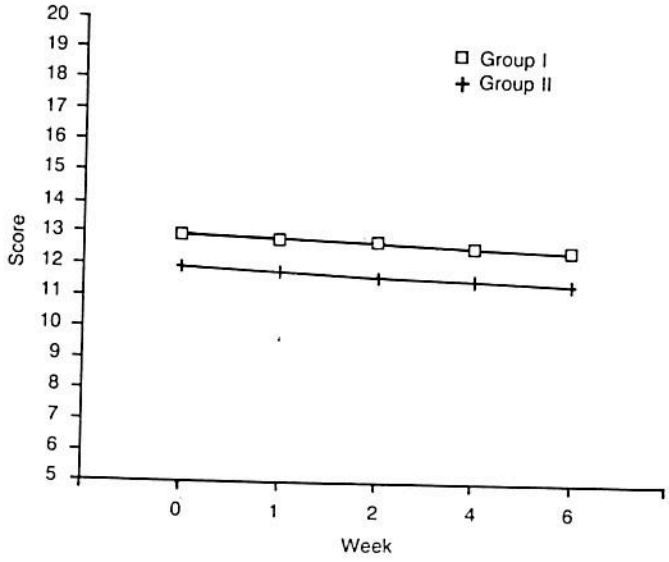

Figure 1. Mean scores on the Webster Rating Scale of patients with Parkinson's disease treated with their usual levodopa dose plus citicoline (group I) or with half their usual levodopa dose plus citicoline (group II).

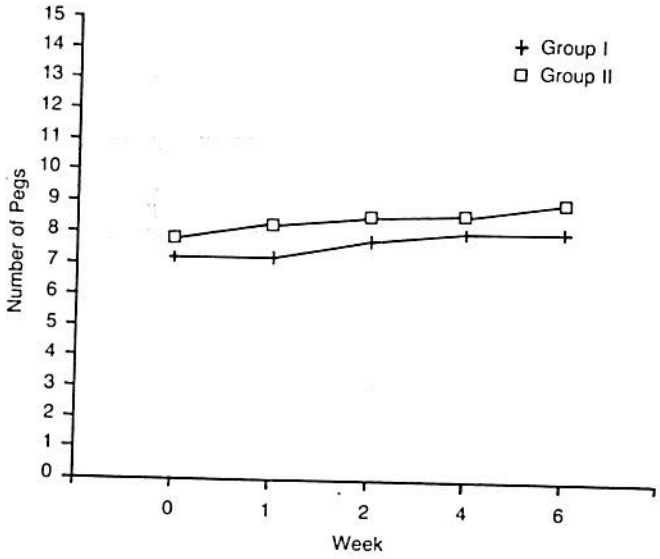

Figure 2. Mean scores on the pegboard test of patients with Parkinson's disease treated with their usual levodopa dose plus citicoline (group I) or with half their usual levodopa dose plus citicoline (group II).

group II scored 8.1 at week 2 and 8.6 at week 6 ($P \leq 0.01$). The differences between groups were not significant. Akinesia also was assessed on a standardized walking test (time required to walk 10 m). No significant changes or group differences were found.

Figure 3 shows the patients' mean scores on the drawing test, which measures the degree of tremor. The drawings were evaluated by the physician on a visual analog scale from 0 (very good) to 100 (bad). The group I scores did not change significantly (from 54.0 at week 2 to 56.1 at week 6). The group II scores improved significantly, from 51.7 at week 2 to 46.0 at week 6 ($P<0.05$). Improved scores were seen in 26% of group I and 36% of group II patients; there was no change in scores in 39% of group I and 34% of group II. These differences were not significant. Tremor also was assessed on a writing test; slight improvement was noted in group II, but no changes or group differences were significant.

Figure 4 shows the patients' scores on an assessment of their emotional state; on a 100-mm visual analog scale, 0 indicates deep depression and 100, no depression. A slight improvement was noted in group II (from 56.8 to 60.8), but no changes or group differences were significant.

On an overall assessment of the course of disease during the trial made by both patients and physicians, no group differences were found; about half of all pa-

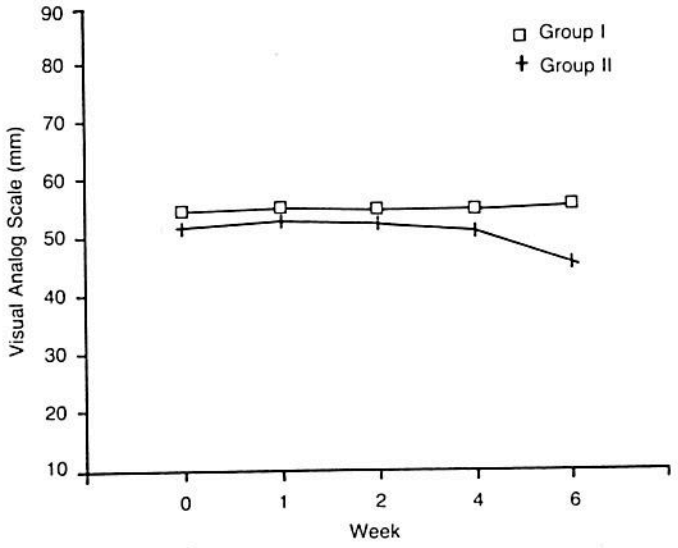

Figure 3. Mean scores on the drawing test of patients with Parkinson's disease treated with their usual levodopa dose plus citicoline (group I) or with half their usual levodopa dose plus citicoline (group II).

tients reported that treatment was effective, and none reported deterioration.

Side Effects and Treatment Withdrawals

Six patients in each treatment group reported nonspecific symptoms such as nausea, vomiting, dizziness, stomach trouble, and fatigue; the duration of symptoms was for a few days only.

Tremor occurred in one patient from group I and three patients from group II during citicoline treatment. Three patients in group I and six patients in group II withdrew from the study; one patient in each group withdrew because of tremor and three patients in group II withdrew because the treatment was inadequate. The other reasons for treatment withdrawal included poor compliance.

Results of laboratory tests conducted before and after the trial revealed no relevant changes on any of the measures.

DISCUSSION

Parkinson's disease requires long-term treament with levodopa/DCI. Severe side effects occur with this treatment, and thus development of an agent that would allow a decrease in the dosage of levodopa would be of great clinical benefit.[21,22] The positive effects of citicoline on membrane lipid resynthesis,[23] axonal flow of levodopa, tyrosine-hydroxylase activity, and levodopa reuptake at the

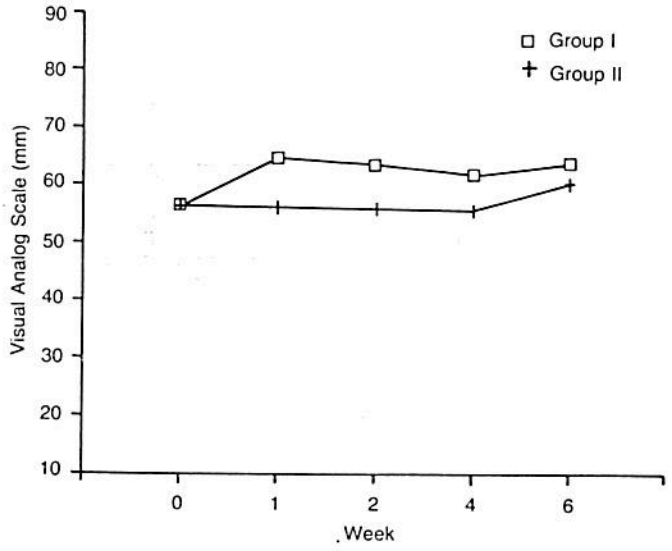

Figure 4. Mean scores on a test of emotional state of patients with Parkinson's disease treated with their usual levodopa dose plus citicoline (group I) or with half their usual levodopa dose plus citicoline (group II).

synapse[17] suggest that it may be effective in the treatment of Parkinson's disease. Several studies[11,12,14–16,20] have demonstrated that citicoline can compensate for a reduction in the dose of levodopa/DCI.

In the present single-blind study of 85 patients with Parkinson's disease, oral administration of 1,200 mg of citicoline daily was able to compensate for a 50% reduction in the dose of levodopa/DCI. This finding agrees with the results of Poewe and Gerstenbrand[13] and Gerstenbrand and coworkers,[20] who administered the citicoline intravenously, and of our own study[11] of oral citicoline.

Improvement on the six tests used in the present study was seen in more of the patients who received citicoline instead of half their levodopa dose than in the patients who received citicoline in addition to their usual dose of levodopa. The reduction of the mean dose of levodopa from 390 mg to 196 mg daily would be expected to result in a deterioration of symptoms, but substitution of half the levodopa dose with citicoline appeared to compensate for the dose reduction. The occurrence of tremor in the group II patients suggests that citicoline has a smaller effect on this symptom than on others.

The levodopa-saving effect of citicoline could be of significance in reducing side effects and in retarding the loss of effectiveness of levodopa in long-term treatment. Citicoline has been on the market for several years and seems to be well tolerated.

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