Brief Reports

Improved Cognition in Alzheimer's Disease With Short-Term D-Cycloserine Treatment

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Objective: Glutamatergic neurotransmission is important for memory and cognition and is severely affected in Alzheimer's disease. D-Cycloserine exhibits partial agonist activity at the glycine site of N-methyl-D-aspartate subtype glutamate receptor, facilitating activation of the receptor and improving cognition and memory. **Method:** Seventeen patients with Alzheimer's disease received a three-phase, double-blind, placebo-controlled trial of 50 mg and 100 mg/day of D-cycloserine. **Results:** D-Cycloserine was associated with significant improvement in scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale (improvement of 3.0 points) when given at a dose of 100 mg/day. **Conclusions:** D-Cycloserine has cognitive benefits for patients with Alzheimer's disease.

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Although the degeneration of basal forebrain cholinergic neurons is thought to be an important cause of cognitive impairment in Alzheimer's disease (1), a number of other neurotransmitter systems are severely affected, including those using the excitatory amino acids aspartate and glutamate. Loss of both presynaptic excitatory amino acids and their postsynaptic receptors suggests that glutamatergic terminal degeneration and deficient excitatory amino acid neurotransmission may contribute to the symptoms of Alzheimer's disease. Evidence for these changes includes selective decreases in CSF concentrations of excitatory amino acids (2), reduced D-aspartate uptake (3), and decreased number of N-methyl-D-aspartic acid (NMDA) receptors in the frontal cortex and hippocampus in subjects with Alzheimer's disease (4).

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A potential therapeutic role for excitatory amino acid agonists in treating cognitive deficits of Alzheimer's disease is suggested by two findings: first, the NMDA receptor plays an important role in neuronal processes underlying cognition and memory; second, drugs that potentiate NMDA receptors facilitate learning. Thus, use of excitatory amino acid agonists to enhance NMDA-glutamatergic transmission may improve cognitive functions in Alzheimer's disease patients. However, excessive stimulation of NMDA receptors by excitatory amino acids and other agonists is neurotoxic and, therefore, would not be good therapeutic candidates. The NMDA receptor is a voltage-dependent ion channel with multiple modulatory sites. The manipulation of the glycine site of the NMDA receptor appears to be a safer way to enhance the neuronal NMDA-glutamatergic activity than excitatory amino acids themselves because it does not activate the receptor by itself but permits endogenous glutamate activation (5).

D-Cycloserine, an antibiotic used to treat tuberculosis at doses of 500–1000 mg/day, exhibits partial agonist activity on NMDA glycine sites. D-Cycloserine readily crosses the blood-brain barrier. At low doses, D-cycloserine facilitates activation of NMDA receptors isolated from the brains of Alzheimer's disease subjects (6), and learning is enhanced in animals through the same mechanism. In addition, a single 15-

mg dose of D-cycloserine significantly improves cognition in scopolamine-induced cognitive impairment in human subjects (7).

We previously conducted a double-blind, crossover study of D-cycloserine in Alzheimer's disease patients at the dose of 15 mg/day. However, this dose is too low to produce any clinical benefit (8). To evaluate further the cognitive benefit of D-cycloserine treatment for Alzheimer's disease patients, we increased the dose to 50 and 100 mg/day in this study.

METHOD

All subjects met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (9) for probable Alzheimer's disease and DSM-IV criteria for the diagnosis of dementia of Alzheimer's type. All subjects had Mini-Mental State scores in the range of 12–26 and Hachinski ischemia scores of less than 4 (10). Subjects with significant medical, psychiatric, or neurological illness other than Alzheimer's disease were excluded. Written informed consent was obtained after the procedure had been fully explained to both subjects and caregivers. Seventeen patients (six women and 11 men) were recruited. Their mean age was 72.2 years (SD=7.3, range=58–81). Their symptoms had been present for 4.4 years (SD=1.4, range=2–6). Their baseline average Mini-Mental State score was 18.8 (SD=5.3) and Alzheimer's Disease Assessment Scale cognitive score was 23.5 (SD=9.0).

All patients were randomly assigned, under double-blind conditions, to receive a 4-week trial of 50 mg/day of D-cycloserine, a 4-week trial of 100 mg/day of D-cycloserine, and a 4-week trial of placebo in random order. The total duration of the study was 14 weeks. There was a 1-week washout between each of the three phases to minimize carryover effect. Evaluation of scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale, Clinical Global Impression of Change, and Instrumental Activities of Daily Living was performed at the end of each 4-week treatment period. All scales were completed by a psychometrician who was blind to treatment assignment. Each subject had a caregiver who completed necessary evaluations and supervised medication compliance. At each visit, both the patient and caregiver were systematically asked if they had experienced or observed any side effect. In addition, physical and neurological examinations were performed at each visit. There were no dropouts from the study.

RESULTS

The mean scores on the Alzheimer's Disease Assessment Scale cognitive subscale were 24.05 (SD=10.99) in the placebo phase, 23.86 (SD=10.19) in the phase with 50 mg of D-cycloserine, and 21.12 (SD=8.82) in the phase with 100 mg of D-cycloserine. The mean improvement in scores on the Alzheimer's Disease Assessment Scale cognitive subscale with 100 mg of D-cycloserine was 3.0 points (SD=4.8). In order to assess treatment response to D-cycloserine relative to placebo, repeated measures analyses of variance (ANOVAs) were performed across all subjects with the within-subject factor of treatment phase (placebo and 50 mg and 100 mg of D-cycloserine). Highly significant differences among treatments were observed for scores on the Alzheimer's Disease Assessment Scale cognitive subscale ($F=6.39$, $df=2, 32$, $p<0.005$). Comparisons of the three phase treatments revealed significant differences between placebo and 100 mg/day of D-cycloserine treatment ($t=2.54$, $df=1, 16$, $p=0.02$, paired t test) and between 50 mg and 100 mg/day of D-cycloserine treatment ($t=3.06$, $df=1, 16$, $p=0.007$). Covariation of treatment order did not affect the overall results, indicating that the improvement in scores on the Alzheimer's Disease Assessment Scale cognitive subscale with 100 mg/day of D-cycloserine was not affected by treatment order.

The scores on the Instrumental Activities of Daily Living (placebo phase: mean=15.29, SD=7.08; 50 mg/day of D-cycloserine phase: mean=14.70, SD=7.00; 100 mg/day of D-cycloserine phase: mean=14.82, SD=6.64) ($F=0.42$, $df=2, 32$, $p=0.66$) and the Clinical Global Impression of Change (placebo phase: mean=4.29, SD=0.75; 50 mg/day of D-cycloserine phase: mean=4.12, SD=0.60; 100 mg/day of D-cycloserine phase: mean=4.00, SD=0.00) ($F=1.81$, $df=2, 32$, $p=0.18$) did not differ among the three treatment phases by repeated measures ANOVA. Only the paired t test between placebo and 100 mg/day of D-cycloserine revealed significant improvements on the Clinical Global Impression of Change ($t=1.81$, $df=1, 16$, $p=0.02$). No side effects from D-cycloserine treatment were observed by patients, caregivers, or the research psychiatrists.

DISCUSSION

Our findings suggest that short-term D-cycloserine treatment exerts a cognitive enhancing effect for Alzheimer's disease patients when given at a dose of 100 mg/day. The magnitude of this effect of D-cycloserine is comparable to that of the acetylcholinesterase inhibitor donepezil (11). The results are consistent with the critical role that NMDA receptors play in cognition. Our findings also provide Alzheimer's disease patients with an alternative to the cholinergic, antioxidant, estrogen, and anti-inflammatory therapies.

Our previous study did not demonstrate clinical benefits of D-cycloserine at the 15-mg dose (8). The trial of low-dose D-cycloserine was based on studies of normal humans in which scopolamine-induced cognitive deficits were improved by 15 mg of D-cycloserine (7). The scopolamine model in healthy subjects may not be an adequate therapeutic model for Alzheimer's disease. Three other studies also did not demonstrate clinical benefits of D-cycloserine when it was given for only 2 weeks or at doses lower than 100 mg/day (12, 13). Two studies of D-cycloserine treatment at a dose of 100 mg/day reported negative findings (14, 15). This may be because of a lack of sensitivity of the cognitive instruments to detect a modest improvement with D-cycloserine. The negative results with 50 mg/day of D-cycloserine in our study are consistent with previous negative findings when the patients received less than 100 mg/day. Taken together, these findings indicate that a dose of 100 mg/day of D-cycloserine is required

for the improvement of cognition in Alzheimer's disease patients.

Recently, vitamin E and selegiline were reported to sustain performance on activities of daily living of noninstitutionalized Alzheimer's disease patients for approximately 5 to 6 months (16). However, no effect on cognition was found with either treatment. In contrast, in our study, short-term D-cycloserine treatment enhanced the cognitive performance of Alzheimer's disease patients but did not unequivocally improve the activities of daily living or the global clinical impression scores. This indicates that 4 weeks of treatment may not be long enough to improve global function. Alternatively, the size of the effect may not have been large enough to be recognized in the majority of the patients. Our study used a crossover design and did not address the long-term effect of D-cycloserine treatment on the functional level of Alzheimer's disease patients. The definitive functional implication of D-cycloserine treatment needs to be addressed in long-term, parallel-design studies of large numbers of subjects to determine whether cognitive improvements persist and whether the overall functional capacity of patients with Alzheimer's disease is also maintained or improved by time.

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