Beneficial Effect of Cholinesterase Inhibitor Medications on Recognition Memory Performance in Mild to Moderate Alzheimer’s Disease: Preliminary Findings

Timothy A. Crowell, PsyD, Juno Paramadevan, BA, Laila Abdullah, BS, and Michael Mullan, MD, PhD

ABSTRACT

Cholinesterase inhibitor (ChEI) medications (ie, donepezil, rivastigmine, and galantamine) have been useful in slowing the progression of the mild to moderate stages of Alzheimer’s disease (AD). Findings supporting this have largely relied on a global error score from the Alzheimer’s Disease Assessment Scale and have not described the nature of the memory problems. We examined this issue by comparing learning, recall, and recognition scores among 2 groups of mild to moderately demented AD patients. Participants were patients from a memory clinic who either were on ChEI treatment (AD+ChEI, n = 14) or had never taken a ChEI (AD–ChEI, n = 14). Participants underwent a comprehensive neuropsychological evaluation, including administration of the CERAD Word List Memory test. Results indicated no significant group difference for learning and delayed free recall, but the AD+ChEI group had significantly fewer errors than the AD–ChEI group on the CERAD Recognition test. Our findings provide preliminary evidence that the aspect of memory that is most affected by ChEIs appears to be facilitation of retention of new information in memory. The implications of this on clinical care and functional abilities as well as future directions are discussed. (J Geriatr Psychiatry Neurol 2006;19:13-15)

Keywords: cholinesterase inhibitor; dementia; memory; Alzheimer’s disease

Although the exact pathogenesis of Alzheimer’s disease (AD) remains unclear, the widespread loss of central cholinergic innervation is one of its key features. This theory is supported by past research demonstrating that drugs resulting in cholinergic blockage (eg, scopolamine) cause significant memory deficits. Such findings contributed to the hypothesis that pharmacological enhancement of acetylcholine neurotransmission could alleviate the symptoms of AD. Over the past decade, cholinergic therapy has become the most widely used approach in symptomatic treatment of AD. Cholinesterase inhibitors (ChEI) include donepezil, rivastigmine, and galantamine.

Several large, multicenter, longitudinal studies have demonstrated the utility of ChEIs in treating the symptoms associated with the mild to moderate stages of AD. Such studies have generally shown that, compared with equivalent groups of AD patients not taking ChEIs, those taking such medications demonstrate symptomatic benefits including relative maintenance of cognition and independent activities of daily living.

Although the apparent generalized cognitive and functional benefits associated with ChEIs are impressive, a better understanding of the specific impact of ChEIs on memory functioning might be more clinically useful. Unfortunately, the studies to date have largely relied on the total error score from the Alzheimer’s Disease Assessment Scale (ADAS–Cog). Although individual “subtest” scores for ADAS–Cog sections could be examined, such scores are not typically reported or analyzed separately in the literature. Without such analyses it remains unclear whether all aspects of memory function assessed are equally affected by ChEIs. That is, the ADAS–Cog total error score does not allow for differential interpretation of learning and immediate recall (acquisition), delayed free recall (retrieval), or ability to consolidate new material in memory (retention). Such information is potentially quite valuable because it has practical and clinical impli-
cations for the care of AD patients on ChEI medications (eg, does repetition of important information assist the patient, do retrieval cues facilitate recall?)

The aim of this study was to examine the nature of the effect of ChEIs on memory performance and provide specific information on the effects of ChEIs on acquisition, retrieval, and retention scores. We examined these issues by comparing two groups of mild to moderately demented AD patients: a group involved in ChEI treatment and a similar group of AD patients who had never taken ChEI medication.

MATERIALS AND METHOD

Participants were 28 individuals who had been referred to and evaluated at an outpatient memory clinic over a 2-year period. All were referred for memory complaints and subsequently underwent a comprehensive evaluation including a neurological and psychiatric examination. Diagnosis of probable AD was based on consensus committee meeting using NINCDS-ADRDA criteria.5 Of the patients seen in the clinic, a total of 14 patients had been taking a ChEI medication (AD+ChEI). Twelve had been taking donepezil and 2 were on rivastigmine. They had all been taking the medication for a minimum of 1 month before the neuropsychological testing, and no compliance problems were reported by their spouses or other collateral respondents. Among other AD patients evaluated in the clinic during the same 2-year period, we arbitrarily chose 14 patients who had not previously taken ChEI medication (AD–ChEI). These 14 patients served as our comparison group, and they were of similar age, education, and severity of dementia (as determined by Mini-Mental State Examination [MMSE] score). MMSE scores for the total sample ranged from 20 to 27 points. A summary of the sample demographic characteristics is presented in Table 1.

Memory Testing Measures

All participants underwent a comprehensive neuropsychological evaluation. The primary memory component of the assessment was the Consortium to Establish a Registry for Alzheimer’s Disease battery (CERAD) Word-List test.7 This test allows for interpretation of acquisition, retrieval, and retention abilities. Acquisition was determined by the total number of words correctly recalled immediately after each of 3 consecutive visual presentations of the same 10-item word list. Retrieval was assessed by the number of items correctly freely recalled from the original word list after an approximate 5-minute delay (during which time all participants were administered a visual cognitive test). Finally, retention abilities were assessed by total errors (ie, false positives plus false negatives) on the recognition test. This test immediately follows the retrieval test and involves a forced yes–no choice for 20 words that were either present or absent on the original word list. Retention abilities are assessed in this manner because retrieval tests provide a measure of what is able to be freely recalled, not what is actually stored in memory.

RESULTS

One-way analysis of variance (ANOVA) was used to compare the groups (AD–ChEI and AD+ChEI) on demographic variables and level of performance for the MMSE and each CERAD memory measure. The groups did not differ in terms of age, education, or MMSE score (all Ps > .05).

As shown in Table 2, ANOVA revealed no statistical difference among groups for CERAD immediate recall (F1,26 = 3.49, P > .05) or delayed recall (F1,26 = 1.83, P > .05). However, a statistically significant group difference was found for Recognition memory performance (F1,26 = 4.50, P < .05), indicating that the AD–ChEI group made significantly more errors on the recognition trial than the AD+ChEI group.

CONCLUSIONS

Our findings provide preliminary evidence that, in mild to moderate AD patients, the primary benefit of ChEI treatment on memory appears to be facilitating retention of new material in memory. When compared with a similar group of patients not taking ChEI medication, those on such medication performed equally well on learning and recall tests but were significantly better at discriminating among recently presented and distractor material. These findings are consistent with previous research showing that AD patients on ChEI treatment make fewer errors

Table 1. Demographic Information by Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD–ChEI (n = 14)</th>
<th>AD+ChEI (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.6 ± 8.0</td>
<td>75.6 ± 7.0</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.7 ± 2.9</td>
<td>14.4 ± 3.7</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>MMSE</td>
<td>23.3 ± 2.3</td>
<td>23.1 ± 2.6</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

Note: AD–ChEI = probable Alzheimer’s disease without cholinesterase inhibitor medication; AD + ChEI = probable Alzheimer’s disease with cholinesterase inhibitor medication; MMSE = Mini-Mental State Examination.

Table 2. Groups Means on CERAD Word List Memory Tests

<table>
<thead>
<tr>
<th>Measure</th>
<th>AD–ChEI (n = 14)</th>
<th>AD+ChEI (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning trials total correct</td>
<td>10.7 ± 3.6</td>
<td>12.9 ± 2.6</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Delayed free recall correct</td>
<td>0.86 ± 1.1</td>
<td>1.5 ± 1.4</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Recognition total errors</td>
<td>6.5 ± 2.4</td>
<td>4.3 ± 3.1</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Note: CERAD = Consortium to Establish a Registry for Alzheimer’s Disease.
on cognitive testing and demonstrate symptomatic benefits compared with those not undergoing such therapy. Our findings add to these previous studies by more clearly identifying the aspect of memory that is most affected by ChEIs.

Family members, caretakers, and clinicians who work with those in the mild to moderate stages of AD can benefit from these findings. That is, it appears that those AD patients who are on ChEI therapy maintain a relatively stronger capacity to learn and retain new material. As such, interventions and practical tools (eg, repeated exposure to important information, calendars, memory notebooks, etc) designed to prompt or cue the individuals may help sustain their degree of independence and sense of self-worth. Given the increased prescribing of ChEI drugs by primary care physicians to those suspected of being in the very early stages of AD or even in cases of mild cognitive impairment (MCI), there are also potential implications of our findings on other clinicians who follow these patients. Specifically, geriatric psychiatrists, neurologists, and psychologists who perform cognitive testing on patients already taking ChEI medications should be aware of the potential impact of these medications on recognition memory scores and interpret such scores accordingly (ie, understand that recognition memory scores may appear relatively intact compared with delayed free recall scores).

Although intriguing and potentially quite useful, these preliminary findings are based on cross-sectional data from a small, clinic-based population. Additional studies on this topic, with larger, more generalizable samples and other memory measures, must be conducted before we can make more definitive conclusions. Other measures of retention such as discrimination index and total correct might also be examined. It may also be beneficial to include an analysis of results from other cognitive domains (eg, language, visual, and executive functioning) to determine if there are other important distinctions among the groups. Finally, future studies might also track amnestic MCI patients over time to determine if recognition memory scores improve with ChEI treatment and if such scores decline at a slower rate than for those not taking ChEIs.

References