Efficacy of Donepezil on Cognitive Functions in Mild Cognitive Impairment

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ABSTRACT: Efficacy of donepezil on cognitive functions in mild cognitive impairment

Objective: The condition characterized by clinically distinctive cognitive impairment and likely to affect occupational and social functioning is known as Mild Cognitive Impairment (MCI). Acetylcholinesterase inhibitors have been used for the treatment of MCI up to now. However, there have been few studies to show the efficacy of these drugs on cognitive functions. The aim of this study was to investigate the effects of donepezil on cognitive functions in patients with MCI.

Method: This study included 51 patients. 26 patients were randomized to the study group and 25 to the control group. The study group received donepezil HCl for 24 weeks. The control group did not receive any psychotropic drugs. Cognitive functions of all patients were evaluated by seven subscales of the Wechsler Memory Scale-Revised (WMS-R) at baseline, 4th week and 24th week of the study.

Results: There was a significant difference in figural memory, verbal paired associates and logical memory subscale scores between the groups (p<0.001). Although there was an improvement in verbal paired associates and logical memory subscale scores in the study group, there was a decrease on the figural memory test scores.

Conclusion: It was found that donepezil led to an improvement especially in memory and attention in MCI. The decrease in figural memory scores can be explained by the fact that donepezil does not exert the same effect on all areas of the brain.

Key words: MCI, Cognitive functions, Donepezil, WMS-R

INTRODUCTION

Mild Cognitive Impairment (MCI) is a popular subject in clinical research on aging-related cognitive disorders (1). By definition, the level of cognitive impairment and the impact on everyday functioning is mild. Individuals with this condition have a new onset of deficit in at least two areas of cognitive functioning (e.g., memory, attention or speed of information processing). Furthermore, MCI causes marked distress or interferes with the individual’s social, occupational or other important areas of functioning and represents a decline from a previous level of functioning (2,3). MCI can be amnestic, single nonmemory domain or involving multiple cognitive domains (4).

Investigations showed that MCI is useful both clinically and as a research entity and a concept encompassing much more than a pre-clinical state of Alzheimer Disease (AD) (1,4,5).
Studies conducted so far have focused on conversion of MCI into AD. One study with a follow-up period of 84 months demonstrated that patients with MCI (16 patients) showed progression to AD at a higher rate (69%) (5). Recent studies showed that the progression of the patients with MCI to Alzheimer disease is higher than the progression of the normal elders to Alzheimer disease. This rate is indicated as 10-15% in a year (1-3% a year in normal elder) (3,6-9).

Donepezil is a cholinesterase inhibitor which is safely used in mild and moderate Alzheimer disease. For the patients with mild and moderate AD, it was shown to be effective and useful in cognition and activities of daily living (10,11). Recently conducted controlled studies started to test the efficacy and reliability of Donepezil on MCI (1,4).

In many studies on the cognitive effects of Donepezil, tests that are likely to cause a high standard of error and which are unlikely to provide details about cognition have been used, therefore, those studies offer little information on the cognitive effects of the drug. Moreover the effect of the drug wasn’t known sufficiently on the cognitive functions as attention, verbal memory, logical memory and visual reproduction. In this study WMS-R which tested randomized controlled study was to test the effects of Donepezil on cognitive functions such as attention, verbal memory, logical memory and visual reproduction.

**MATERIAL AND METHODS**

**Patient Population**

The study population was selected among the patients presenting to the outpatient clinics of Izzet Baysal University Medical Faculty Neurology and Psychiatry with the primary complaint of forgetfulness. The study was conducted between May 2002 and February 2004. The patients were first interviewed by a psychiatrist or a neurologist. This was a free clinical interview and applied MMSE test. The exclusion criteria for all patients were mental retardation, psychiatric disorder, drug and alcohol addiction except for nicotine, other physical illnesses that affect cognitive function and the patients who had taken neurotropics drug for the last three weeks. The study group consisted of 51 patients aged between 61-72 years have diagnosis of MCI to the criteria of DSM-IV (from axes provided for further study: Appendix B) (Table 1) and MMSE test score was ≥24 and ≤26.

**Table 1: Criteria for mild cognitive impairment**

A. The presence of two (or more) of the following impairments in cognitive functioning, lasting most of the time for a period of at least 2 weeks (as reported by the individual or a reliable informant):
   1. Memory impairment as identified by a reduced ability to learn or recall information
   2. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
   3. Disturbance in attention or speed of information processing
   4. Impairment in perceptual-motor abilities
   5. Impairment in language (e.g., comprehension, word finding)

B. There is objective evidence from physical examination or laboratory findings (including neuroimaging techniques) of a neurological or general medical condition that is judged to be etiologically related to the cognitive disturbance.

C. There is evidence from neuropsychological testing or quantified cognitive assessment of an abnormality or decline in performance.

D. The cognitive deficits cause marked distress or impairment in social, occupational, or other important areas of functioning and represent a decline from a previous level of functioning.

E. The cognitive disturbance does not meet criteria for a delirium, a dementia, or an amnestic disorder and is not better accounted for by another mental disorder (e.g., a Substance-Related Disorder, Major Depressive Disorder).

The cognitive functions detailed had been used to measure cognitive functions. The aim of this...
Efficacy of donepezil on cognitive functions in mild cognitive impairment

males). They were listed sequentially to the application date. They received Donepezil 5mg/day for 30 days and then 10mg/day followed for 24 weeks. Twenty-five patients who have even numbers assigned into the control group (14 female and 11 male) received no psychotropic drug. All the participants have social security and drugs were billed to their health insurance. Being a prospective controlled study; both Donepezil and control groups were informed about the study and their written approval was taken. Besides being consistent with Helsinki Declaration; good clinical practice guidelines; and the law and procedures of the country the study was implemented; the approval of ethical committee of Izzet Baysal University’s Hospital was also taken.

Study design

The study group consisted of 51 patients. Donezepil were given to patients (Donepezil group, n=26) randomly after initial interview. The control group (n=25) was followed up without any medication. All patients were called for monthly interview during six months. The tests were applied at the beginning, in the 4th and 24th weeks. Fifty-one patients were subjected to the seven subscales of WMS-R (12,13), Mini-Mental State Examination (MMSE) (14) and the Hamilton Depression Rating Scale (HAM-D) (15). The second interview was carried out in the fourth week. During the interview; we evaluated the side effects as well. The last interview was carried out in the 24th weeks and side effects were evaluated. In all three interviews we used WMS-R test during the evaluations. During the first and the last interviews we used WMS-R, Hamilton Depression Rating Scale (HAM-D) and MMSE test to evaluate our patients.

Scales

WMS-R: Wechsler Memory Scale-Revised (WMS-R), developed by Wechsler (1987), is a comprehensive memory test and the modified version of WMS. Memory is a complex function involved in all steps of cognitive processes. Among the primary cognitive processes were verbal/figural (visual) memory, sensorial/short term/long term memory, which is related to sensorial channels, and recognition/recall memory. The scale has the power to measure verbal and figural memory, memory for concrete and abstract material, immediate memory and delayed memory thoroughly. WMS-R is a neuropsychological test which can be used to make diagnosis and evaluate effectiveness of treatment (12,13). In this study the seven subscale of WMS-R which was general information and orientation, mental control, figural memory, logical memory I, verbal paired associates I, visual reproduction I and number sequencing used.

MMSE: The MMSE is widely used test to evaluate briefly the cognitive state of patients and normal scores are considered when up to 26. Scores between 10 and 20 points are indicative for moderate or severe dementia, while scores between 21 and 26 for mild dementia or MCI (14).

HAM-D: This widely used test that measures depression rate is applied by the clinician. HAM-D has 17 items and 0-4 points can be taken for each one. Maximum score is 53 (15).

Statistical Analysis

A sample size of 25 patients per treatment group was estimated based on the detection of differences between the control and drug treatment on primary efficacy variables (0.5 on WMS-R) with 80% power at a 0.05 significance level (4). For each variable the differences between the control and Donepezil groups were analyzed with Student-t test and the differences between and within groups were analyzed by Repeated Measures ANOVA .P values less than 0.05 were considered statistically significant. Statistical analyzes were performed by SPSS 11.0.

RESULTS

The study included fifty-one patients diagnosed MCI. The mean age was 65.4±3.3 years for the donepezil group and 66.7±3.4 years for the control group. There was no significant difference in age, gender and education between the study and control groups (p>0.05). Eight patients (30.7%) in the study group and seven patients in the control group (29.4%) were on medications for hypertension and type II diabetes which were unlikely to disturb cognition. There was no significant difference in medical conditions between the groups. All demographic data
are shown in Table 2.

The baseline MMSE score average of the study group who received Donepezil was 25,0±0,6 while the control group’s was 24,4±0,8. The final MMSE score average of Donezepil group was 25,3±1,34 and the control group’s was 24,8±1,07. There was no significant difference between the groups regarding baseline and final MMSE scores. The baseline HAM-D score average of the study group was 8,9±1,7 and the control group’s was 8,4±1,1. There was no significant difference between the groups for HAM-D scores.

However, the WMS-R baseline total scores were not significantly different between the two groups, the WMS-R total final scores were significantly different between the study and the control groups. When we looked at the all subscales of the WMS-R baseline scores, there was no significant difference between the groups for all these subtests. There was significant difference between groups for 24th. Week ‘logical memory’ and ‘verbal paired associates’ subscales. The Donepezil group had a higher rate of final logical memory and verbal paired associates. There was no significant difference between the two groups for 4th. week ‘general information and orientation’, ‘mental control’, ‘figural memory’ ‘visual reproduction’, ‘number sequencing’. There was no significant difference between the study and the control groups for 4th. week all subscales except 4th week figural memory score. Donepezil group had lower rate of 4th week figural memory score (Table 3).

A significant improvement was seen in the donepezil-treated group in ‘logical memory’ and ‘verbal paired association’ subscales at the 24th week. No significant differences were observed in ‘general information and orientation’, ‘mental control’, ‘figural memory’ ‘visual reproduction’, ‘number sequencing’ any of the study group scores. A significant worsening was seen in the control group’s ‘general information and orientation’, ‘mental control’ and ‘logical memory’ subscale at study duration.

Three patients of Donepezil group had adverse effects including nausea, vomiting and sedative effect. All adverse effects were transient and mild in severity.

### Table 2. Demographic Features of Donepezil and control groups

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>Donepezil n: 26</th>
<th>Control n:25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) *</td>
<td>65,4±3,3</td>
<td>66,7±3,4</td>
</tr>
<tr>
<td>Education (year)*</td>
<td>6,7±3,1</td>
<td>6,6±2,8</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>14/12</td>
<td>14/11</td>
</tr>
<tr>
<td>Comorbid illness</td>
<td>8/18</td>
<td>7/18</td>
</tr>
</tbody>
</table>

* Mean±SD; F: Female; M: Male

### Table 3. Distribution of WMS-R scale at baseline, 4. week and 24. week scores between Donepezil and control groups.

<table>
<thead>
<tr>
<th>WMS-R Sub-scale</th>
<th>Donepezil Mean±SD</th>
<th>Control Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6,03±0,95</td>
<td>6,23±0,97</td>
<td>p=0,7</td>
</tr>
<tr>
<td>4. Week</td>
<td>6,11±0,86</td>
<td>6,00±1,06</td>
<td>p&lt;0,05</td>
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<tr>
<td>24. Week</td>
<td>6,11±0,90</td>
<td>5,94±1,24</td>
<td>p=0,3</td>
</tr>
<tr>
<td>P value</td>
<td>p&gt;0,05</td>
<td>p&lt;0,05</td>
<td></td>
</tr>
<tr>
<td>Mental control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3,76±1,03</td>
<td>3,70±1,21</td>
<td>p=0,5</td>
</tr>
<tr>
<td>4. Week</td>
<td>3,76±1,03</td>
<td>3,41±1,93</td>
<td>p=0,2</td>
</tr>
<tr>
<td>24. Week</td>
<td>3,92±1,05</td>
<td>3,47±0,87</td>
<td>p=0,08</td>
</tr>
<tr>
<td>P value</td>
<td>p&gt;0,05</td>
<td>p&lt;0,05</td>
<td></td>
</tr>
<tr>
<td>Figural memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3,34±0,48</td>
<td>3,70±0,46</td>
<td>p=0,01</td>
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<tr>
<td>4. Week</td>
<td>3,00±0,74</td>
<td>3,76±0,43</td>
<td>p&lt;0,001</td>
</tr>
<tr>
<td>24. Week</td>
<td>3,58±0,49</td>
<td>3,88±0,33</td>
<td>p=0,02</td>
</tr>
<tr>
<td>P value</td>
<td>p&gt;0,05</td>
<td>p&gt;0,05</td>
<td></td>
</tr>
<tr>
<td>Logical memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4,53±1,44</td>
<td>4,58±1,66</td>
<td>p=0,7</td>
</tr>
<tr>
<td>4. Week</td>
<td>4,46±1,30</td>
<td>4,05±1,57</td>
<td>p&lt;0,001</td>
</tr>
<tr>
<td>24. Week</td>
<td>5,92±1,31</td>
<td>3,58±1,37</td>
<td>p=0,02</td>
</tr>
<tr>
<td>P value</td>
<td>p&gt;0,05</td>
<td>p&gt;0,05</td>
<td></td>
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<tr>
<td>Verbal paired association</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>2,61±0,63</td>
<td>2,76±0,83</td>
<td>p=0,6</td>
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<tr>
<td>4. Week</td>
<td>2,57±0,50</td>
<td>2,58±0,87</td>
<td>p=0,9</td>
</tr>
<tr>
<td>24. Week</td>
<td>3,50±0,51</td>
<td>2,00±0,61</td>
<td>p&lt;0,001</td>
</tr>
<tr>
<td>P value</td>
<td>p&lt;0,05</td>
<td>p&gt;0,05</td>
<td></td>
</tr>
<tr>
<td>Visual reproduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2,73±0,82</td>
<td>2,64±0,70</td>
<td>p=0,6</td>
</tr>
<tr>
<td>4. Week</td>
<td>2,73±0,91</td>
<td>2,58±0,61</td>
<td>p=0,5</td>
</tr>
<tr>
<td>24. Week</td>
<td>2,84±0,78</td>
<td>2,41±0,62</td>
<td>p=0,02</td>
</tr>
<tr>
<td>P value</td>
<td>p&gt;0,05</td>
<td>p&gt;0,05</td>
<td></td>
</tr>
<tr>
<td>Number sequencing</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3,23±1,14</td>
<td>2,72±1,13</td>
<td>p=0,1</td>
</tr>
<tr>
<td>4. Week</td>
<td>3,31±1,07</td>
<td>2,50±1,18</td>
<td>p=0,2</td>
</tr>
<tr>
<td>24. Week</td>
<td>3,46±1,20</td>
<td>2,52±1,12</td>
<td>p=0,006</td>
</tr>
<tr>
<td>P value</td>
<td>p&gt;0,05</td>
<td>p&gt;0,05</td>
<td></td>
</tr>
<tr>
<td>Total scores</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>26,19±2,72</td>
<td>26,04±3,32</td>
<td>p=0,001</td>
</tr>
<tr>
<td>Final</td>
<td>29,18±2,28</td>
<td>23,72±2,62</td>
<td>p&lt;0,001</td>
</tr>
<tr>
<td>P value</td>
<td>p&lt;0,05</td>
<td>p&lt;0,05</td>
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</table>

WMS-R: Wechsler Memory Scale-Revised

DISCUSSION

Using a sensitive neuropsychological test, we compared cognitive function between the patients who received and who did not receive Donepezil, in this prospective a randomized controlled study was carried out.

The patients who are diagnosed MCI are separated into two groups. The first group that goes on dementia after follow up and the second group will be stable or recover. In general, the first group that goes on dementia benefits from the medications that enhance the cognitive performance. The second group that takes non-pharmacotherapy and the follow up may be convenient. The most important part of MCI therapy is the follow up and highly specific and sensitive tests which show progression were considered important (16). The effectiveness of pharmacological treatment on MCI is still debatable. However, MCI shows a tendency to regress to dementia in some proportion of patients, which indicates the importance of the treatment. Studies have revealed conflicting results so far since it is difficult to evaluate the test results and different scales have been used in each study (17-20). There was little experience in randomized studies on pharmacotherapy in MCI (4,11).

We observed a significant improvement in logical memory and verbal paired associates test scores in Donepezil group especially in the 24th week of the therapy. In a functional brain imaging study, on the effectiveness of Donepezil on MCI demonstrated an increase in hippocampal volume and improvement in cognition (21). A brain perfusion (SPECT) study on Donepezil in AD patients showed an increased perfusion in some parts of the posterior-parietal region which influenced especially attention and recall (22).

In this study there was a significant deterioration in figural memory of the patients on Donepezil in the 4th week of the therapy compared to the control group. It may be because the patients on Donepezil have lower figural memory scores at baseline, though not significant and, that Donepezil does not exert the same effect in all areas of the brain, which is consistent with the results from several brain imaging and function studies (9,23,24).

Although there was no difference in other parameters between the groups, general information and orientation and mental control worsened in the control group. In fact, baseline scores of general information and orientation and mental control was different from those in the first and sixth months. However, these parameters were stable in the study group. Several other studies also emphasized the stabilizing effect of Donepezil (25-27). As to number sequencing and visual reproduction, both the study and control groups did not differ from each other and their baseline scores were not different from their scores in the fourth and twenty-fourth weeks of the study. Further, there was no significant difference between baseline MMSE scores and MMSE scores in the 24th week of the study in both groups and the difference in MMSE scores between the groups was not significant, either. Early diagnosis of MCI, developing the diagnostic tests, determining the methods of therapy that would slow the progression of MCI was crucial. Present therapy strategies about AD intend to enhance the cognitive capacity and slow the degeneration.

The limitation of this study is a small sample size. However, this study is one of the few randomized studies on the treatment of MCI with cholinesterase inhibitors and has revealed that a more sensitive and detailed scale will offer more accurate results which will help monitor the prognosis and treatment outcome in MCI. Studies with larger sample sizes, longer follow-up and neuropsychological tools are required to illuminate the pharmacotherapy in MCI.

Kaynaklar:


