EFFECTS OF 6 MONTHS OF TREATMENT WITH DONEPEZIL AND RIVASTIGMINE ON RESULTS OF NEUROPSYCHOLOGICAL TESTS OF MMSE, NPI, CLOCK AND BENDER IN PATIENTS WITH ALZHEIMER'S DISEASE

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Abstract- Alzheimer's disease is the most common degenerative disease of brain. Nowadays, acetyl cholinesterase inhibitors, including donepezil, rivastigmine and galantamine, are standard treatments to slow down disease progression. Purpose of our study was to show effects of treatment with donepezil and rivastigmine and to compare these effects between two drugs. Samples selected from patients who had Alzheimer` disease with DSM IV criteria and were candidate of receiving donepezil or rivastigmine for the first time. We used four neuropsychological tests including MMSE, NPI, Clock and Bender to assess patient's cognitive and behavioral changes during treatment with two drugs. Patients divided to two groups (each group 35 cases), one group taking donepezil and the other rivastigmine. The four tests were completed once before starting treatment and then, 1 month, 3 months and 6 months after treatment with Donepezil and Rivastigmine. MMSE, 6 months after treatment with Donepezil, improved from 20.63 before treatment to 21.83, which was statistically significant. Also, MMSE, 6 months after treatment with Rivastigmine, improved from 20.03 before treatment to 22.71, which was statistically significant. About Clock test, there was a significant improvement from 5.74 before treatment to 6.4 after 6 months of treatment with Rivastigmine; while this significant improvement was not seen in patients receiving Donepezil. In two other tests, no significant differences were seen before and after treatment. Also, No significant difference was detected between two groups and so no different effects on these tests between Donepezil and Rivastigmine in 6 months period of treatment.

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INTRODUCTION

Alzheimer's disease is the most common and one of the most important degenerative diseases of brain.

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In United States, more than 80% of people above age of 85 are affected. In general, brain is progressively atrophied in frontal, temporal and parietal lobes and neuronal count decreases in AD. The most significant clinical symptom is progressive forgetfulness, which affects retentive memory most. Gradually disorientation to time, place and persons appears. As the disease progresses, patient's behavior, verbal and writing abilities will be affected (1, 2). In fact cognitive impairment in Alzheimer's

disease (AD) is the main feature contributing to the clinical picture of the illness (3, 4).

Nowadays, the most common treatment being used to slow down disease progression, include Donepezil, Rivastigmine and Galantamine, which all of them act as inhibitors of acetyl cholinesterase. Recently, Memantine, a NMDA antagonist, is approved and best used for treatment of late stage AD, which can be combined with an acetyl cholinesterase inhibitor for better result. Several studies have examined the efficacy and safety of these treatments in short-term and long-term mostly Donepezil and Rivastigmine and some of them studied differences between these two drugs (6-12).

Saine *et al*. studied on functional and cognitive effects of Donepezil. They used MMSE test to assess cognition and TFLS (Texas Functional Living Scale) to assess functional abilities of patients. They showed that after 12 months treatment with Donepezil improvement in results of both tests has happened (13). In a study done by Auriacombe *et al.* efficacy and safety of Rivastigmine has been evaluated. In this study, tests of MMSE, IADL (Instrumental Activities of Daily Living) and Global Function Test were used and improvement of results found in all of them (14). Lopez Pousa *et al.* designed a study to determine differential efficacies of treatment with acetyl cholinesterase inhibitors, including Donepezil, Rivastigmine and Galantamine, in patients with mild to moderate AD over 6 month period; they used MMSE as an indicator of cognitive functions in subjects. After 6 months, they found no statistically significant differences among three drugs; and of course, they found drugs to slow progression of the disease (16). Borkowska *et al.* have shown the effects of one-year treatment with Donepezil and Rivastigmine on results of neuropsychological tests. They used MMSE, ADAS, TMT (trail making test) and Stroop color word interference test in their study. At the end of study, they found improvement on ADAS (global cognitive functioning) and TMT-A (psychomotor speed) and no change or worsening on other tests. However, such treatment is unable to prevent the deterioration of working memory and executive functions (5).

In contrast, there are some reports of no, or a minimal, effect on cognitive abilities after longitudinal treatment. Courtney *et al.* reported some positive effect on cognition after 2 years treatment with donepezil, compared with placebo, but found no differences on institutionalization and progression of disability after 3 years (17).

In view of these diverse findings, we started a study to show effects of treatment with Donepezil and Rivastigmine, as two drugs that commonly used for treatment of AD in Iran, on results of four neuropsychological tests including MMSE, NPI (Neuro-Psychiatry Inventory), Clock drawing test and Bender-Gestalt test; and to compare these effects between two drugs.

MATERIALS AND METHODS

Patients: Seventy patients with a mild to moderate stage of AD, never previously treated, have been studied. The diagnosis of probable Alzheimer's disease and the stage of the illness was done using DSM-IV and ICD-10 criteria. Patients in whom AD was diagnosed by neurologist and their plan for treatment was taking Donepezil or Rivastigmine divided to two groups; 35 patients entered into each group, while matched for sex, age and education level. Patients with plan of taking Donepezil entered into one of the groups and patients with plan of taking Rivastigmine entered into another. The allocation of patients to donepezil or rivastigmine was at the discretion of the physician (neurologist). In-fact, we chose patients whose plan of treatment was decided by the neurologist before and we did not interfere with their treatment choice. This selection of patients also was done with the purpose to match two groups for sex, age, and education level. Thirty-five patients were receiving donepezil, daily dosage 5-10 (mean 9.3) mg, and other thirty-five patients were treated with rivastigmine, with dosage 6–12 (mean 8.5) mg per day. As the groups were about to reach the completion number of 35 persons, we intentionally selected patients with needed sex, age and education level for each group, in order to match with the other group. After reaching 35 patients for each group, there were 10 persons (28%) below age of 65, 14 persons (40%) between ages of 66 and 75, 9 persons (25%) between ages 76 to 85, and 2 persons (5%)

above age of 85.also in each group 9 person (25%) uneducated, 12 persons (37%) with primary, secondary or high school diploma, 9 persons (25%) with B.Sc. and 4 persons (11%) with M.Sc. or Ph.D. degree participated. In each group, there were 18 women and 17 men. Exclusion criteria comprised vascular dementia, severe somatic, psychiatric and neurological diseases, and substance abuse.

We used four neuropsychological tests to assess the patients:

1. The Mini Mental State Examination (MMSE), measures different kinds of cognitive abilities such as temporal and spatial orientation, delayed recall, calculation, attention, obeying oral commands, reading and obeying commands, writing a sentence and copying a design.

2. The Neuro-Psychiatric Inventory (NPI) assesses 12 behavioral areas of patients including: Delusions, Hallucinations, Agitation, Depression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability, Aberrant motor behaviors, Night time behaviors, Appetite and eating disorders. For each area, there is four degree of Frequency and 3 degree of Severity and 5 degree of distress. Frequency is rated as: 1- Occasionally – less than once per week; 2- Often – about once per week; 3- Frequently – several times a week but less than every day; 4- Very frequently– daily or essentially, continuously present

Severity is rated as: 1- Mild– produce little distress in the patient; 2- Moderate– more disturbing to the patient but can be redirected by the caregiver; 3- Sever– very disturbing to patient and difficult to redirect. Distress is rated as: 1- No distress; 2- Minimal; 3- Mild; 4- Moderate; 5- Moderately sever; 6- Very sever or extreme. For each domain there are 4 scores; Frequency, Severity, Total (Frequency × Severity) and caregiver Distress. The total possible score is 144 (ie. A maximum of 4 in the frequency rating × 3 in the severity rating × 12 remaining domains). This relates to changes, usually over 4 weeks prior to completion.

3. The Clock drawing test: the patient is asked to draw a clock, put its numbers and putting clock hands to show a specified time (usually a quarter to three). The scoring is done using test scoring instruction with score of 10 for best clock drawing and score of 1 for worst clock drawing. This test is a simple way to show the severity of dementia in patient.

4. The Visual Motor Gestalt test (Bender): This test consists of 9 cards, on which of them a simple drawing. Cards are shown to the patient one by one and he is asked to copy that on the paper. The time spent for copying each card is considered too. After finishing the card 9, he is asked to draw again but this time without looking at the cards and to draw what he can remember (recall). The total score will be calculated using test instruction. This test is used to assess the visuo-spatial perception of the patient.

These four tests were taken once before starting the treatment and then 1 month, 3 months and 6 months after reaching the treatment to the target dose of the drugs. As said before administration and clinical interview was carried out by a neurologist and cognitive evaluation and psychological interview was performed by a clinical psychologist, who was blind to detail of study. Patients visited in Iran Neurology Center first by neurologist and then if intended to take part in study, by a clinical psychologist.

Patients and their relatives and/or caregivers have been given full information about the study before entering, and signed consent. They were assured about keeping their information and test results confidential. This study was performed during the years 2003, 2004 and 2005.

Statistical analysis was done using SPSS program. To draw tables and charts, Microsoft Excel was used.

RESULTS

As we mentioned, 70 patients were divided in two equal groups; 3 patients were excluded from study, as they did not come back for follow-up. Of course, this dropout statistic is in addition to samples that did not tolerate the drug side effects and so did not reach to target dose for the drug and thus were not entered into the study. We added more patients as some excluded from study.

Table 1, presents the results on psychological tests before starting of treatment in each group of patients. Using independent samples *t* test, there was

Table 1. Results of MMSE, NPI, Clock drawing test and Bender in patients with AD before starting the treatment with donepezil or rivastigmine; Mean values and Standard Deviations

	MMSE		NPI		Clock		Bender	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Donepezil	20.63	6.1	52.83	32.39	5.09	3.2	66.69	22.05
Rivastigmin	20.03	6.2	51.6	31.97	5.74	2.66	70.23	26.58

no statistical difference between two groups in result of each test, before beginning of the treatment.

Tests also were done 1 month, 3 months and 6 months after treatment with donepezil and rivastigmine.

After statistical analysis, there was no significant difference between results of each test between two groups of donepezil and rivastigmine, 1 month after treatment. This comparison also was done between test results of one group with the other group, 3 months and 6 months after treatment with donepezil and rivastigmine; similarly, no significant difference in test results was found between two groups.

Tables 2 shows test results 1 month, 3months and 6 months after treatment with donepezil and rivastigmine in two groups of patients.

Figures 1, 2, 3 and 4 presents result changes of each test during 6 months period of treatment with donepezil and rivastigmine. In addition, in each group, using Paired samples t-test, test results before treatment were compared with test results 1 month, 3 months and 6 months after treatment with either rivastigmine or donepezil. This comparison was done in order to evaluate the drug effect on each test in 6-months period.

According to analysis results, in patients taking donepezil, a statistically significant improvement ($P = 0.04$) was found in MMSE result after 6 months of treatment; but there was no statistically significant changes in NPI, Clock and Bender tests after 6 months of taking treatment. Of course, there were some improvements, as seen in charts, but these are not significant. Similar analysis was performed for patients taking rivastigmine; according to results, there was a significant improvement ($P = 007$) in MMSE performance after 6 months of taking drug. In addition, another significant improvement ($P = 0.038$) was found about Clock drawing test after 6 months. There was no other statistically significant change in results of NPI and Bender. Of course there was some improvements, but not significant. Using One-way ANOVA test, baseline results of each test was compared with its results 1 month, 3 months and 6 months after treatment with donepezil in relation with sex, age and education level; In which no significant changes was detected.

The same comparison was performed for rivastigmine and no significant changes were found either. Resulting that sex, age and education have no significant effect on changing the test results during treatment with either donepezil or rivastigmine.

Table 2. Results of MMSE, NPI, Clock drawing test and Bender in patients with AD, 1month, 3 months and 6 months after starting the treatment with donepezil or rivastigmine; Mean values and Standard Deviations

		MMSE		NPI		Clock		Bender	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Donepezil	1 mo	20.4	6.42	51.6	31.9	5.1	3.1	66.5	24.7
	3 mo	20.8	6.2	51.5	33.8	5.3	3.1	65.3	25.2
	6 mo	21.83	6.6	53.5	35.9	5.4	3.3	67.2	29
Rivastigmine	1 mo	20.8	6.8	50.8	31.5	6	2.5	67.8	23.9
	3 mo	20.7	6.6	53.4	31.8	6.1	2.7	67.4	25.2
	6 mo	22.71	5.81	52.5	34.8	6.4	2.9	66.2	23.9

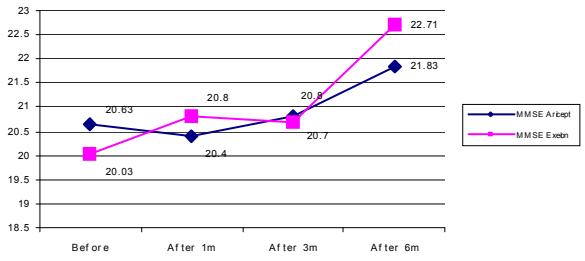

Fig. 1. Changes of MMSE results during 6 months treatment with donepezil and rivastigmine in patients with AD.

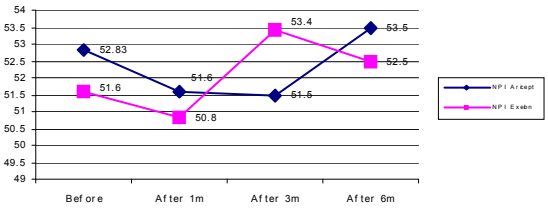

Fig. 2. Change of NPI results during 6 months treatment with donepezil and rivastigmine in patients with AD.

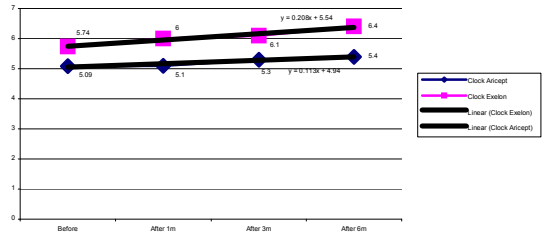

Fig. 3. Changes of clock test results during 6 months treatment with donepezil and rivastigmine in patients with AD.

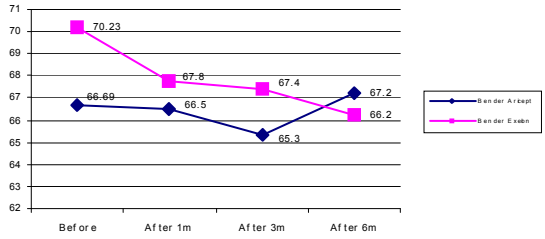

Fig. 4. Changes of bender test results during 6 months treatment with donepezil and rivastigmine in patients with AD

DISCUSSION

In this study, we tried to show the relation between taking acetyl cholinesterase inhibitor drugs, donepezil (Aricept) and rivastigmine (Exelon), and changes of neuropsychological tests of MMSE, NPI, Clock and Bender, as different indicators for assessing the patient during treatment.

As mentioned before, there was significant improvement in MMSE after 6 months in patients receiving donepezil; this finding was expected theoretically and has been shown in previous similar studies too.

In addition, there was significant increase in MMSE result in patients taking rivastigmine and, as seen in chart 1, in comparison with patients receiving donepezil, in patients taking rivastigmine, MMSE with lower baseline has reached higher score after 6 months; of course this difference between two drugs, in improving MMSE, is not statistically significant but can be considerable.

In the group whom treated with rivastigmine, there was a significant improvement in results of Clock drawing test after 6 months treatment; this significant change was not seen in patients taking donepezil. This may suggest that rivastigmine is more effective than donepezil in improving clock test results after 6 months; but after statistically comparison between two groups, there was no significant difference between two drugs in improving clock test results. This means that may be rivastigmine is better than donepezil in improving visuo-spatial perception of the patient but not that much to create significance.

As mentioned above, there were no other significant changes in results of other tests during six months period of our study. This may suggest that acetyl-cholinesterase inhibitor drugs have no major effects on behavioral areas of Alzheimer's disease and thus no considerable effects on caregiver's burden.

As seen in chart 4, we detected some improvement in Bender test results that may suggest improvement of visuo-spatial perception of patients under acetyl-cholinesterase inhibitors but these findings are not statistically valuable.

We suggest similar studies to be done with bigger samples and longer periods in order to obtain precise conclusions about the effects of these drugs, as today's most common treatment for AD, on patient's daily living performance.

Conflict of interests

The authors declare that they have no competing interests.

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