Evaluation of the effect of donepezil on cerebral blood flow velocity in Alzheimer's disease

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ABSTRACT

الأهداف: تقييم أثر الدوبنيزل على انسياب الدم الدماغي باستخدام تخطيط دوبلر عبر القحف (TCD).

الطريقة: أجريت تجربة سريرية في قسم علوم الأعصاب – مستشفى الزهراء – جامعة أصفهان للعلوم العصبية خلال الفترة من مارس 2008م حتى يوليو 2009م في المرضى المصابين بمرض الزهايمر في مجموعتين الحالة، والتحكم تحتوي كل مجموعة على 11 مريض. تلقت مجموعة الحالة عقار الدوبنيزل، وفحصت بأشعة دوبلر عبر القحف (TCD)، وبعد 4 أسبوع من العلاج بجرعة مقدارها 5ملغ كل يوم من عقار الدوبنيزل، و4 أسابيع جرعة مقدارها 10ملغ، أما المجموعة الضابطة تكونت من المرضى المصابين بالزهايمر الذين لم يتلقوا أي علاج وشخصت حالتهم مرة واحدة فقط. تم قياس الذروة الانقباضية (PSV)، والانبساط النهائي (EDV)، وسرعة الانسياب المتوسطة (MFV) للشريان الدماغي الخلفي (PSV)، والشريان الدماغي المتوسط (MCA) بواسطة أشعة دوبلر عبر القحف (TCD). كما أجري اختبار مصغر للقدارت العقلية (MMSE) أيضاً.

النتائج: لا يوجد أي اختلافات إحصائية بين المجموعة الضابطة، والمعالجة في مؤشرات العمر، والجنس. في مجموعة الحالة، وصل معدل اختبار القدرة العقلية المصغر 20.2±2.8 من القيمة الأساسية 15.8±3.3، بعد 4 أسابيع إضافية بجرعة مقدارها 10ملغ من عقار الدوبنيزل ووصلت القيمة إلى 20.6±3.9. في الشريان الدماغي الأوسط، كان الاختلاف بين قيم الذروة الانقباضية (PSV) وقيم سرعة الانسياب المتوسطة (MFV) بعد 4 أسبوع من العلاج بجرعة مقدارها 10ملغ من عقار الدوبنيزل مهم بقيمة إحصائية مقارنة مع القيم الأساسية. في الشريان الأوسط الدماغي (PCA) كانت قيم سرعة الانسياب المتوسطة (MFV)، والانبساط النهائي (EDV) بعد 4 أسبوع من العلاج بجرعة مقدارها 10ملغ من عقار الدوبنيزل مهمة بقيمة إحصائية مقارنة مع القيم الأساسية.

خاتمة: أن العلاج باستخدام عقار الدوبنيزل بجرعة مقدارها 10ملغ لها أثر في رفع سرعة انسياب الدم الدماغي، وقيم الاختبار المصغر للقدرات العقلية (MMSE) في المرضى المصابين بالزهايمر (AD)، نوصي الباحثين بإجراء المزيد من التجارب العديدة.

Objectives: To evaluate the effect of Donepezil on cerebral blood flow velocity using non-invasive transcranial Doppler (TCD) sonography.

Methods: This clinical trial was carried out in the Department of Neurology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran from March 2008 to July 2009, on Alzheimer's disease (AD) patients in 2 groups of case and control, each consisting of 11 patients. The case group who received Donepezil medication was examined by TCD before (baseline), after 4 weeks of oral treatment with 5mg per day Donepezil, and a further 4 weeks of 10mg per day Donepezil, orally. The control group comprised AD patients who did not receive any medications, and were examined by TCD only once. Peak systolic (PSV), end-diastolic (EDV), and mean flow (MFV) velocities of the posterior cerebral artery (PCA) and the middle cerebral artery (MCA) was assessed by TCD. Also, mini-mental state examination (MMSE) was carried out.

Results: There were no significant differences between the case and control groups, in terms of age and gender. In the case group, the mean MMSE score reached 20.2±2.8 from a baseline value of 15.8±3.3 after 4 weeks of oral treatment with 5mg/d Donepezil, and reached 20.6±3.9 after 4 more weeks at 10mg/d Donepezil. In the MCA, the difference in PSV and MFV values after 4 weeks of treatment with 10mg/d Donepezil was statistically significant compared with the baseline values. In PCA, the values of MFV and EDV after 4 weeks of treatment with 10mg/d Donepezil were statistically significant in comparison with the baseline value.

Conclusion: Donepezil (10mg/d) increased cerebral blood flow velocity and MMSE score in our AD patients, but more extensive trials are recommended.

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Alzheimer's disease (AD) is a disorder with progressive neurodegeneration of the brain, determined clinically by deterioration in cognition, activities of daily living, and behavior.[1] The neuropathological processes that cause AD includes the loss of cholinergic neurons in brain areas associated with learning and memory, executive function, behavior, and emotional responses, and extracellular deposition of B-amyloid protein in senile plaques, and the formation of intracellular neurofibrillary tangles.[2] Loss of cholinergic function is the main cause of AD.[2,3] Thus, the preferred strategy of treatment is to increase acetylcholine (Ach) in the brain of patients with AD using cholinesterase inhibitors (AchEIs), such as Donepezil. These drugs reduce synaptic Ach breakdown, prolong its ability to stimulate post-synaptic receptors and strengthen the release of Ach in the brain.[4] Recent hypotheses maintain that the cholinergic denervation affects the functional characteristics of the brain vessels.[5-8] Levels of endothelial nitric oxide production depend on the sufficient cholinergic innervation of small arteries.[6,9-12] Regional cerebral blood flow is coordinated according to the metabolic needs of neurons,[9-12] and research in this field can provide information on integration of the cerebrovascular system.[8,13] The vascular effects of AchEI has been shown in patients with vascular dementia.[14] Regional cerebral blood flow velocity can be investigated through the noninvasive transcranial Doppler (TCD) sonography method.[15,16] In one study,[17] Donepezil had no effect on neurocognition and social cognition in young individuals. In another study,[18] Donepezil preserved cognition and global function in patients with severe AD. Donepezil is the drug of choice and is approved by the Food and Drug Administration for the treatment of AD.[19] This study evaluates the efficacy of Donepezil on cerebral blood flow velocity using non-invasive TCD sonography, and may provide valuable information on the treatment of AD, and form the foundation for future studies and research in this field.

Methods. This clinical trial was carried out in the Department of Neurology, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran from March 2008 to July 2009. Patients from Alzahra Hospital and an outpatient neurology clinic in whom the diagnosis of AD was made according to the criteria of the ICD-10/DSM-III-R and assessed by TCD (Multi Dop X4, DWL, Sipplingen, Germany) were included in the study. The TCD provides an evaluation of the cerebrovascular hemodynamics, structure, and anatomy. Its clinical applications include assessment of blood flow velocity in the cerebral vasculature in children and adults.[20] The method of sampling was consecutive non-random sampling. The inclusion criteria were age between 50-80 years, and the exclusion criteria are history of stroke, non treated hypertension, diabetes mellitus, smoking during the past 10 years, hypercholesterolemia, and taking AchEI drugs one month prior to the study. All participants were aware of the study design and informed consent was obtained. The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol. Data were recorded according to the usual clinical practice and patient privacy was maintained at all times.

In this study, 19 patients with AD were initially allocated to the case group. Out of the 19 patients, 5 did not continue participating in the study after 4 weeks of treatment with Donepezil, one patient in the second round of follow up did not cooperate with performing TCD, and 2 were excluded due to discontinuation of the drug because of agitation side effects, and finally 11 patients remained in the case group. Also, 11 patients with AD were allocated to the control group. The case group comprised patients who were treated with Donepezil, and TCD was performed every 4 weeks. The control group consisted of AD patients who did not use any medication, and the inclusion and exclusion criteria were similar to those for the case group, and TCD was performed only once. The case group patients were evaluated with TCD first before the treatment with Donepezil (baseline), a second time after 4 weeks of oral treatment with 5mg/d Donepezil, and a third time after a further 4 weeks (end of the eighth week) of treatment with 10mg/d Donepezil (5mg every 12 hours). Totally, the group was evaluated with TCD 3 times with intervals of 4 weeks, and cerebral vessel blood flow velocities were recorded. Each time before TCD, the dose of Donepezil and the regular consumption of the drug was ensured, and then the patient underwent TCD. In all cases, with a 2MHZ-probe of TCD, the P2-segment of the posterior cerebral artery (PCA) and M1-segment of the middle cerebral artery (MCA) were evaluated. Peak systolic blood flow velocity (PSV), end-diastolic flow velocity (EDV), and mean flow velocity (MFV) were recorded with TCD. The PSV is less prone to TCD artifacts and is more sensitive than the MFV.[15,21] The PSV, MFV, and EDV were measured in centimeters per second (cm/s). To measure the grade of dementia, the Mini-Mental State Examination (MMSE) was performed. The test evaluates some factors including orientation to time and place, attention, information recording, recall, naming objects, sentence repetition, obeying 3-stage commands, carrying out the written commands, writing sentences, and ability to draw geometric forms. The MMSE scores range between zero and 30, which are lower in AD patients than in healthy individuals without dementia.[20] Also, for all patients, the necessary data, including patient age, gender, history of

co-morbidities, medication intake, MMSE scores, and TCD data (cerebral artery blood flow velocity) were recorded on a checklist.

After normal distribution of the data obtained from TCD was ensured, the datum was analyzed using the Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL, USA) version 16, and statistical tests such as repeated measures ANOVA. The 2 groups were compared using paired t-test, and *p*-values less than 0.05 were considered significant. Considering the fact that there were no statistically significant differences between the baseline of the case group and the control group in terms of age, gender, MMSE scores, and TCD findings, the comparison was performed between baseline values (before Donepezil intake) and the values obtained after taking 5mg/d and 10mg/d doses of Donepezil in the case group.

Results. Demographic data of the patients in the case group and control group are presented in **Table 1**, and shows no statistically significant differences among the characteristics of the 2 groups. The MMSE score at baseline level in the case group was 15.8±3.3, and this significantly increased to 20.2±2.8 after 4 weeks of treatment with 5mg/d Donepezil (p=0.0001), and to 20.6±3.9 after the next 4 weeks (end of the eighth week) of treatment with 10mg/d Donepezil (p=0.001 compared with baseline). Values of PSV, MFV, and EDV in the MCA are shown in **Table 2**. The difference between the values of PSV and MFV in the case group after 4 weeks of treatment with 10mg/d Donepezil and the corresponding baseline values were statistically significant (p=0.002 for PSV, and p=0.025 for MFV). However, the difference between the EDV value of the 10mg/d Donepezil regimen and the corresponding baseline value was not statistically significant (p=0.126). None of the PSV, MFV, or EDV value changes from the baseline values after 4 weeks of oral treatment with 5mg/d of Donepezil was statistically significant. The PSV, MFV, and EDV values in the PCA are presented in **Table 3**. The changes in the values of MFV and EDV from the baseline values in the case group after 4 weeks of treatment with 10mg/d Donepezil were statistically significant (p=0.015 for MFV, and p=0.014 for EDV). The effect of 10mg/d Donepezil on PSV was not statistically significant (p=0.637). The PSV, MFV, and EDV values with the 5mg/d Donepezil regimen did not exhibit a statistically significant change from the baseline value.

Discussion. In this study, emphasis was placed on the dynamic properties of cerebral vasoregulation in AD, and cerebral blood flow was studied by TCD.[15,16,22] The MMSE scores increased in the control group as the Donepezil dose increased, and comparison between 5mg/d and 10mg/d Donepezil regimens and the baseline showed that MMSE scores increased significantly. In other words, both the 2 doses, 5mg/d and 10mg/d, of Donepezil were effective in increasing the MMSE scores. Similar results were obtained in the study of Rosengarten and colleagues[22] that was carried out on 10 AD patients in 2006.

Regarding the cerebral blood flow velocity, the values of PSV and MFV in MCA and the values of MFV and EDV in PCA with the 10mg/d Donepezil dose significantly increased compared to the baseline values. This finding shows a dose-dependent increase in cerebral arterial blood flow velocity following Donepezil administration. These effects indicate the functional abnormalities in the cerebral vascular system in AD. Cholinergic innervation of small vessels is required for adequate levels of endothelial nitric oxide (NO) synthesis, a molecule causing vasodilatation.[5,6,11,12] This

Table 1 - Demographic data of the case and control groups.

Variable	Case (n=11)	Control (n=11)	*P*-value
Age (years)			
Mean ± SD	69.7±8.7	70.7±6.2	0.76
Min	56	62	
Max	80	78	
Gender			
Female	5	4	0.5
Male	6	7	

SD - standard deviation, Min - minimum, Max - maximum

Table 2 - Mean ± standard deviation of PSV, MFV, and EDV in the MCA of the case group.

Variable	Before treatment (baseline)	After 4 weeks with 5mg/d Donepezil	After a further 4 weeks with 10mg/d Donepezil	*P*-value
PSV	50.2±11.7	62.1±18.4	65.3±11.5	0.002
MFV	30.4±10.9	38.5±9.8	42.3±6.7	0.025
EDV	18.9±8.8	22.5±8.1	27.2±5.1	0.126

Values are in centimeter per second (cm/s)
PSV - peak systolic velocity, MFV - mean flow velocity,
EDV - end-diastolic velocity, MCA - middle cerebral artery

Table 3 - Mean ± standard deviation of PSV, MFV, and EDV in the PCA of the case group.

Variable	Before treatment (baseline)	After 4 weeks with 5mg/d Donepezil	After a further 4 weeks with 10mg/d Donepezil	*P*-value
PSV	37.5±9.9	38.2±15.4	41.6±9.9	0.637
MFV	23.3±4.9	24.7±7.6	29.8±4.9	0.015
EDV	13.20±4.3	14.5±4.7	19.3±4.6	0.014

Values are in centimeter per second (cm/s)
PSV - peak systolic velocity, MFV - mean flow velocity,
EDV - end-diastolic velocity, PCA - posterior cerebral artery

is compatible with the increased levels of blood flow velocity in cerebral vessels with Donepezil treatment. Also in Rosengarten's study,[22] cerebral arterial blood flow was increased with the administration of Donepezil. Similar results were obtained in the study of Claassen and colleagues[23] in 2006, and the findings of the study carried out by Lojkowska and colleagues in 2003.[24] Nakano and colleagues[25] reported an increase in cerebral arterial blood flow after one year of Donepezil administration. However, Nobili and colleagues[26] conducted a study on AD in 2002, in which AchEIs such as Donepezil had no role in increasing cerebral blood flow and even reduced the flow in a number of the participants.

Although our study only focused on patients without vascular risk factors, a possible vascular effect should be considered. In AD, amyloid angiopathy occurs and cerebral blood flow velocity will decrease.[5,8,12] Probable causes of this reduction are related to the morphological lesions due to the beta-amyloid deposition in cerebral vessel walls that leads to decreased vasodilatation.[8] Other causes may be brain atrophy leading to cerebral cortex stimulation, which in turn decreases the need for blood flow, and therefore, causes a smaller amount of increase in cerebral blood flow compared to the normal population.[5]

The effect of cerebral white matter changes in the elderly is still undetermined and is even more complex in AD. These changes are associated with age, cardiovascular risk factors, inadequate cerebral blood flow, and oxygen metabolism changes.[8,11] The severity of white matter change is associated with a reduction in cognitive performance and its possible role has been proposed in AD.[8,11,27,28]

Since improvement in cerebral arterial blood flow is achieved over a short time, more comprehensive research is necessary to elucidate the probable effect of these drugs on cognitive performance and slowing down of the disease progression. Limitations of this study were mainly related to patient participation. As AD is a low-prevalence disease, finding patients was difficult, and some of the patients were reluctant to perform TCD and did not continue participation. Therefore, the study was very time-consuming and prolonged. Another limitations was that we did not have measures of a constant cerebral metabolic rate.

In conclusion, our results indicate that Donepezil, especially in doses of 10 mg/d, is effective in increasing MMSE scores and cerebral arterial blood flow in AD patients. We recommend further more extensive clinical trials be carried out, comparing the effects of different AchEI drugs, and different doses of Donepezil on AD.

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