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Effect of donepezil on EEG spectral analysis in Alzheimer's disease

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Abstract

EEG spectral analysis allows a quantitative analysis of changes in the frequency bands during disease progression in Alzheimer's disease (AD) and could be used to monitor treatment and disease progression.

Eightteen patients with probable AD were evaluated by Folstein Mini Mental State Examination (MMSE) and EEG spectral analysis before donepezil treatment, 2 months after 5 mg/day and 4 months after the dose was raised to 10 mg/day. EEG evaluations were done in 4 derivations (T3-T5, T4-T6, C3-P3, C4-P4).

Six months after treatment there was a significant reduction in the temporal delta amplitudes and an increase in the amplitudes of all the other frequency ranges including theta amplitudes both in the temporal and centroparietal derivations. MMSE scores increased during treatment but the change was not significant.

These findings show that donepezil exerts a positive effect on EEG in AD by decreasing delta activity and increasing alpha and beta activity. The increase in theta activity after treatment may reflect a therapeutic shift of delta activity to theta activity.

Key words : Alzheimer's disease ; Donepezil ; EEG spectral analysis.

Introduction

Alzheimer disease (AD) is a degenerative disorder with insidious onset and slow progression leading to a progressive decline of cognitive, functional and behavioural abilities. It has been shown that in AD there is an extensive dysfunction of the cholinergic system related to profound loss of the cholinergic neurons in the nucleus basalis of Meynert and decreased activity of both choline-acetyl transferase (ChAT) and acetyl choline esterase (AChE) (Davies and Maloney 1976, Perry *et al.* 1981, Bartus *et al.* 1982, Soininen *et al.* 1989, Zubenko *et al.* 1989, Petit *et al.* 1993, Claus *et al.* 1998a). This decreased activity is initially found in the entorhinal cortex and can be shown in the hippocampus and other neocortical regions, particularly the parietal and frontal regions afterwards (Bartus *et al.* 1982, Soininen *et al.* 1989, Petit *et al.* 1993, Claus *et al.* 1998a).

Pharmacological research also supports the theory of cholinergic involvement in AD and many attempts have been made to augment the cholinergic system in order to improve cognitive functions. One of these therapeutic approaches in AD is to reduce the catabolism of acetylcholine (Ach) by blocking AChE and the most significant improvement in cognitive symptoms has been obtained by using AChE inhibiting agents (Davis *et al.* 1992, Knapp *et al.* 1994, Rogers and Friedhoff 1994, Rogers and Friedhoff 1996). Among these donepezil (Aricept) is now being widely used for the treatment of mild to moderate AD and its efficacy in long term treatment has been shown to significantly improve cognitive functions (Rogers and Friedhoff 1994, Rogers and Friedhoff 1996).

The electroencephalogram (EEG) is of limited value in the assessment of AD and can be normal in the early stages of the disease in up to 50% of cases (Soininen *et al.* 1989). EEG studies in AD have shown that in concordance with the loss in cognitive abilities during disease progression there is slowing of the EEG characterised by reduction in alpha and beta waves and increase in theta and delta waves (Penttila *et al.* 1985, Soininen *et al.* 1991, Pritchep *et al.* 1994, Schreiter-Gasser *et al.* 1994). EEG spectral analysis allows a more detailed and quantitative analysis of these changes during disease progression when compared to conventional EEG (Claus *et al.* 1998b). Although there have been studies investigating the correlation of EEG spectral analysis and clinical findings in AD (Soininen *et al.* 1989, Petit *et al.* 1993, Claus *et al.* 1998a, Claus *et al.* 1998b), there are few studies investigating effect of treatment with anticholinesterase drugs on EEG findings (Shigeta *et al.* 1993, Kogan *et al.* 2001).

In this study we aimed to assess the effect of donepezil on EEG spectral analysis in patients with AD.

Subjects and methods

A total of 18 patients (10 women, 8 men) who attended the neurological outpatient clinic of the Akdeniz University Medical Faculty and fulfilled

Table 1

Patient characteristics and MMSE scores at baseline and 2nd and 6th month follow-up

NO	Sex	Age	Disease duration (years)	MMSE Score		
				0	2	6
1	M	73	5	24	24	23
2	F	59	8/12	19	18	14
3	F	80	5	21	18	–
4	F	80	4	19	18	21
5	M	66	7	13	27	27
6	F	58	1	14	16	21
7	F	70	8	9	7	6
8	M	72	4	16	17	10
9	F	68	1	7	8	7
10	M	76	2.5	14	12	10
11	F	73	5	14	13	–
12	M	74	4	13	16	–
13	M	66	4	18	24	20
14	F	76	1	22	22	26
15	F	69	2	21	21	20
16	M	86	7	9	12	12
17	M	75	7/12	23	21	27
18	F	58	4	17	16	24
Mean		71.1 ± 7,7	3.7 ± 2,3	16.28 ± 5.03	17.22 ± 5.46	16.33 ± 5.05

Abbreviations : M : Male, F : Female, MMSE : Mini Mental State Examination.

the NINCDS-ADRDA criteria for probable AD and were enrolled in the study. The mean age of the patients was 71.1 ± 7,7. Mean disease duration was 3.7 ± 2,3 years. All patients had an extensive physical and neurological examination and blood biochemistry, haemograms, vitamin B12 levels, thyroid hormone profiles and cranial magnetic resonance imaging (MRI) or computed tomography (CT) investigations. All blood tests were normal and no patient had any psychiatric problem interfering with the diagnosis. Cortical atrophy was detected in 15 patients while 3 had normal CT/MRI examinations. Patients in whom other causes for dementia could be identified were excluded from the study. The demographic data and MMSE scores for the patients are given in Table 1.

All patients who entered the study received a Folstein Mini Mental State Examination (MMSE) and had an EEG recording prior to treatment. All patients were started on 5 mg/day donepezil and were followed up with MMSE and EEG at the end of the second month. After 2 months the dose of donepezil was raised to 10 mg/day and patients continued the drug at the same dose until the end of the 6. month when they had a final examination with MMSE and EEG.

EEG recordings and data analysis

EEG's were recorded with the use of a 16-channel EEG recorder, in accordance with the international 10-20 system using a time constant of 0.3 s and a 70 Hz low-pass filter. Recordings were done at the same time of day, with the subject lying awake and having the eyes closed. Patients were continuously watched to ensure awakeness. Digital amplitude measurements were taken every 1 ms for a 10 s epoch of each EEG. EEG spectral activity was computed at 0.1 Hz intervals ranging from 1-30 Hz. EEG spectral analysis evaluations were done in 4 derivations (T3-T5, T4-T6, C3-P3, C4-P4) and 6 frequency ranges (1-3.5 Hz, 4-7.5 Hz, 8-10 Hz, 10.5-13 Hz, 13.5-20 Hz and 20.5-30 Hz). Amplitude spectral analysis of the EEG was computed by the Transient Response Frequency Characteristics (TRFC) method and therefore the results of Fast Fourier Transformation (FFT) are given in dB for each frequency band. The details of this method have been explained elsewhere (Basar 1972 ; Basar 1981 ; Basar-Eroglu *et al.* 1992). Pretreatment values were compared with values obtained on the 2. and 6. month.

Statistical analysis

Statistical analysis was done by using the SPSS 9.0 for Windows software. The differences of means between the groups were tested by analysis of variance (one-way ANOVA of the repeated measures type with post-hoc corrections done with the Tukey test) using a SPSS 9.0 software. The level of significance was set at $p < 0.05$.

Results

Baseline mean MMSE scores were 16.28 ± 5.03 (range 7-24). Five patients had mild AD (mean

MMSE score : 22.22 ± 1.30, range 21-24), 10 had moderate AD (mean MMSE score : 15.70 ± 2.41, range 13-19) and 3 had severe AD (mean MMSE score : 8.33 ± 1.15, range 7-9) (Table 1).

All patients could be followed up with MMSE and EEG examinations at the end of the second month but 3 patients failed to come to the final follow-up examination and could not be evaluated by MMSE and EEG at the end of the 6. month and in one other patient only the MMSE could be made at the end of the 6. month.

After two months of treatment the mean MMSE score increased to 17.22 ± 5.46 and the amplitudes of the 1-3.5 Hz delta frequency band in the temporal derivations (T3-T5 and T4-T6) were significantly reduced ($p < 0.05$ and $p < 0.005$ respectively). In the centroparietal derivations this reduction in delta amplitudes was not observed and only the amplitudes in the 20.5-30 Hz frequency band increased significantly ($p < 0,005$) (Fig. 1f). There also was a significant increase in the amplitudes of the 8-10 Hz and 10.5-13 Hz alpha and 13.5-20 Hz beta frequency bands in the T3-T5 derivations ($p < 0.005$) but in the T4-T6 derivations this increase was seen in the 4-7.5 Hz theta ($p < 0.05$) and 13.5-20 and 20.5-30 Hz beta frequency bands ($p < 0.005$) (Figs. 1b-f).

At the end of the 6. month EEG spectral analysis could be evaluated in 12 patients and MMSE in 15 patients. In these 15 patients the MMSE scores were increased from 16.33 ± 5.05 to 17.87 ± 7.36 but this difference was not significant. The improvement in MMSE scores still didn't reach significance after the patients with mild and moderate AD were separately analyzed. When the EEG's obtained at the end of the 6. month were compared with the baseline recordings there was a significant reduction in the amplitudes of the 1-3.5 Hz delta frequency band ($p < 0.005$) and a significant increase in the amplitudes of all the other frequency ranges ($p < 0.005$) in the temporal derivations (Figs. 1a-f). In the centroparietal derivations theta, alpha and beta amplitudes were significantly increased ($p < 0.005$ and $p < 0.05$) when compared to baseline but delta amplitudes remained unchanged. The amplitudes of the theta frequency band were increased significantly both in the temporal and centroparietal derivations at the end of the 6. month ($p < 0.005$).

These findings show that in AD donepezil treatment reduces the amplitudes of the delta frequency band and increases the amplitudes of the alpha and beta frequency bands in the temporal derivations and that this positive effect is also seen in the alpha, betha and theta frequency bands in the centroparietal regions after prolonged treatment with higher doses. The positive effect of donepezil could not be shown in the theta frequency band and on the contrary amplitudes were increased after 6 months of treatment.

Discussion

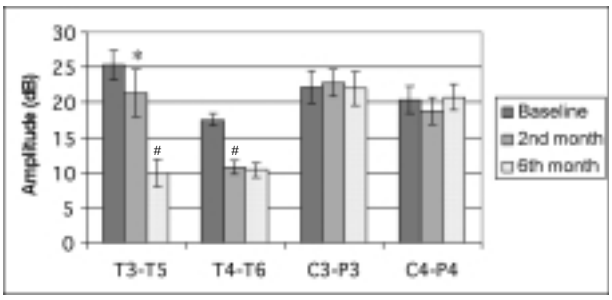
The results of this study show that in patients with AD 6 months of treatment with donepezil significantly decreases the amplitudes of delta waves in the temporal region and increases the amplitudes of theta, alpha and beta waves in the temporal and centroparietal regions of both hemispheres. We also could show that this effect is even seen in the temporal regions after the first 2 months of treatment with 5 mg/day donepezil and after the last 4 months of treatment with 10 mg/day of donepezil. No significant effect of donepezil on MMSE scores after 6 months of treatment could be demonstrated.

Studies in experimental animals and in humans have shown an important role of the cholinergic system on the modulation of the EEG (Riekkinen *et al.* 1990). In rats destruction of the nucleus basalis of Meynert and treatment with anticholinergic drugs has been shown to cause slowing of the EEG which can be reversed by cholinergic drugs (Riekkinen *et al.* 1996). Our finding that treatment with donepezil has positive effects on EEG spectral analysis in AD does support the view that the cholinergic system modulates the electroencephalographic activity of the brain.

In AD increase in the amplitudes of theta waves in the frontal, parietooccipital and temporal regions can be seen even in the early stages of the disease (Soininen *et al.* 1989) but in up to 50% of patients the initial EEG can be normal (Soininen *et al.* 1989, Petit *et al.* 1993). This early increase in theta activity is followed by increased delta activity and decreased alpha and beta activity in the later stages of the disease (D'Onofrio *et al.* 1996, Comi and Leocani 2000).

Claus *et al.* demonstrated that these changes in the EEG, especially the reduction in parietooccipital alpha activity, are parallel to the reduction in the cognitive scores and reduction of cerebral blood flow on SPECT (Claus *et al.* 2000). In another study Lopez *et al.* showed that the increase in delta and theta activity in quantitative EEG is more prominent in patients with delusions and hallucinations (Lopez *et al.* 1991). Based on the results of these and other studies other investigators have tried to assess the utility of EEG spectral analysis in the staging of AD and have proposed that the wave analyses of the theta (4-5.5 Hz) and alpha (10-11.5 Hz) frequency bands are most valuable in the staging of the disease (Rodriguez *et al.* 1999).

Claus *et al.* investigated the efficiency of quantitative EEG in the prediction of survival in AD and concluded that low parietooccipital alpha and beta power in EEG spectral analysis are an important and independent predictor of cognitive and functional deterioration and mortality (Claus *et al.* 1998a, Claus *et al.* 1998b). In another study D'Onofrio *et al.* suggested that quantitative EEG is



***** = p < 0,05, # = p < 0,005

FIG. 1a. — Effect of treatment on amplitudes in the 1-3.5 Hz frequency range.

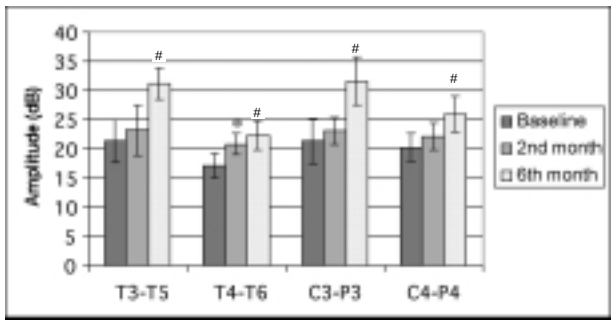


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FIG. 1b. — Effect of treatment on amplitudes in the 4-7,5 Hz frequency range.

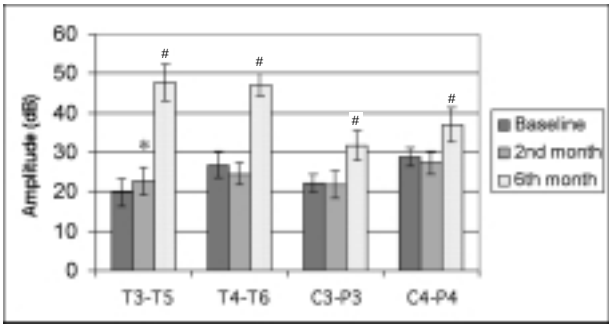

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FIG. 1c. — Effect of treatment on amplitudes in the 8-10 Hz frequency range.

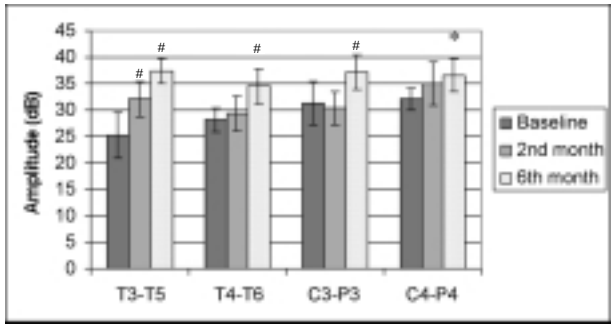

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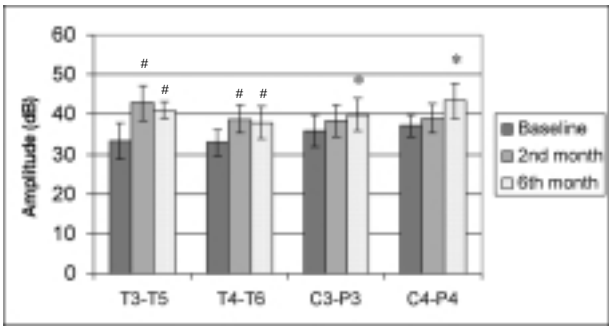
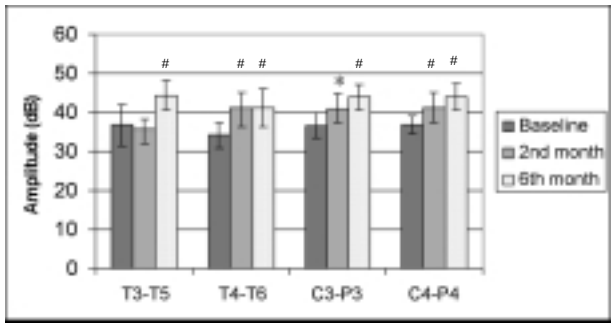
FIG. 1d. — Effect of treatment on amplitudes in the 10,5-13 Hz frequency range.



***** = p < 0,05, # = p < 0,005

FIG. 1e. — Effect of treatment on amplitudes in the 13,5-20 Hz frequency range.



***** = p < 0,05, # = p < 0,005

FIG. 1f. — Effect of treatment on amplitudes in the 20,5-30 Hz frequency range.

an useful test in differentiating AD from multiinfarct dementia (D'Onofrio *et al.* 1996).

Donepezil has been shown to be effective on cognition and global function in patients with mild or moderate AD (Rogers and Friedhoff 1996, Weiner *et al.* 2000). Kogan *et al.* investigated the effect of donepezil on quantitative EEG in AD (Kogan *et al.* 2001). They reported that donepezil caused a reduction in the theta activity in the frontal and temporoparietal areas in patients with mild disease while a reduction in beta activity was seen in the frontal and occipital areas in patients with moderate to severe disease. We demonstrated a significant improvement by significantly decreasing delta wave amplitudes and increasing alpha and beta wave amplitudes but we only investigated the temporoparietal regions as they are the site of main involvement in AD (Kwa *et al.* 1993). On the contrary we also found that the amplitudes in the theta frequency band increased despite treatment. Kogan *et al.* showed significant improvement in theta wave amplitudes only in mild patients but not in patients with moderate/severe disease (Kogan *et al.* 2001). Our patient group had more severe involvement than the patients in Kogan's study. These waves are usually encountered in the early phases of AD and continue to increase as the pathological process progresses (Rodriguez *et al.* 1999). An

explanation for the increase in theta amplitudes could be that there is a shift from lower to higher frequencies with treatment, so that delta activity diminishes and is replaced by theta activity. It is also possible that these waves become resistant to treatment in the advanced stages of the disease .

In conclusion our results suggest that slowing on EEG, which is a marker for the subsequent rate of cognitive and functional decline in AD, can be partly reversed by treatment with anticholineesterase drugs and support the studies showing a modulatory role of the cholinergic system on the EEG.

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