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EEG changes during long-term treatment with donepezil in Alzheimer's disease patients

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Summary. In this pilot study, we examined the long-term treatment effect of donepezil on the quantitative EEG (qEEG) in 12 Alzheimer's disease patients. The qEEGs of the mean absolute and relative amplitudes of betal, alpha, theta and delta activities were obtained at baseline and during donepezil treatment. Comparisons of awake qEEG prior to and during treatment were performed using a 2-way analysis of variance (ANOVA) with repeated measures.

In patients with mild dementia (n = 5), the qEEG analysis showed a significant reduction of the mean absolute theta activity ($p = 0.05$) by donepezil, particularly in frontal and temporo-parietal areas. In patients with moderate/severe dementia (n = 7), a significant decrease in the mean absolute beta 1 activity ($p = 0.02$), particularly in the frontal and occipital areas may be attributed to disease progression which was not counteracted by the long-term treatment.

The differences in qEEG in patients with different stages of dementia under donepezil treatment may be related to different compensatory capacities due to structural and functional brain disturbances.

Keywords: Alzheimer's disease, EEG, quantitative EEG (qEEG), donepezil, cholinesterase inhibitor.

Introduction

The development of therapies for Alzheimer's disease (AD) has focused on agents designed to correct or moderate the loss of cholinergic function within the central nervous system (CNS). Tetrahydroaminoacridine (THA) and physostigmine were the first widely used cholinesterase inhibitors (ChEI). However, due to their lack of selectivity for acetylcholinesterase (AChE) in the CNS and the resultant peripheral cholinesterase (ChE) inhibition, they are

associated with undesirable systemic side effects (Summers et al., 1986; Stern et al., 1988; Farlow et al., 1992). Furthermore, THA also causes hepatotoxicity in many patients (Farlow et al., 1992).

Donepezil is a new cholinergic drug unlike the other cholinesterase inhibitors. Pre-clinical studies have shown it to be highly selective for AChE in the CNS, to have a longer duration of inhibitory action than either THA or physostigmine, and not to be associated with any hepatotoxicity (Rogers and Friedhoff, 1996).

Electrophysiological studies revealed increases in the theta and delta bands and a decrease in the alpha and beta bands in the baseline EEGs of AD patients (Stigsby et al., 1981). Neuropsychological and neurophysiological studies that investigated the influences of drugs on AD patients found that the acute administration of some cholinergic drugs which improved memory and attention also exhibited a tendency to shift the EEG into more normal patterns (Agnoli et al., 1983) while anticholinergic drugs induced opposite effects (Agnoli et al., 1983; Neufeld et al., 1994). Other studies, however, have shown that the EEG changes depended on the duration of treatment. For example, Shigeta et al. (1993) showed that the early EEG improvement with THA reverted to the pre-treatment value within 30 weeks.

Investigation of the long-term efficacy of donepezil showed improvements in cognition during a period of 38 weeks which then decreased, as would be expected in a progressive disease, but this decrease was smaller compared to that in patients not receiving this drug (Rogers and Friedhoff, 1998). We were interested in exploring the long-term effects of donepezil on the quantitative EEG (qEEG) in AD patients with different stages of dementia.

Materials and methods

Patients and drug protocol

Twelve patients (6 males, age 58–86 years) with the clinical diagnosis of AD according to DSM-IV (APA, 1994) and NINCDS-ADRDA (McKhann et al., 1984) criteria participated in an open label study of donepezil for a period of 5.8 ± 3.0 months. The study was approved by the hospital ethics committee. Staging of dementia was performed by the Clinical Dementia Rating (CDR) examination (Hughes et al., 1982). The subjects were divided into two groups, one of mildly demented patients (CRD1, $n = 5$) and the other of moderately/severely demented patients (CDR2, $n = 5$; CDR3, $n = 2$, respectively) (Table 1).

Donepezil treatment was started with 5 mg/d and could be increased to 10 mg/d, depending upon the patient's tolerance to treatment (Table 1). Other drugs were kept unchanged throughout the study, (patients on benzodiazepine had been excluded from the study).

EEG studies were carried out before treatment with donepezil and were repeated after 3–6 months of treatment.

EEG procedure

EEGs were recorded on an 18-channel Grass machine which was connected to a Biologic Brain Atlas commercial computer system with data acquisition and field mapping capabilities for 21 electrodes as described in detail elsewhere (Neufeld et al., 1994).

Table 1. Clinical features of the study patients

Patient No.	Age/sex	MMSE	Disease severity (baseline)	Daily dose of donepezil	Other drugs
1	68/F	27	Mild	5 mg	Metaprolol
2	72/M	25	Mild	10 mg	Aspirin
3	61/F	25	Mild	10 mg	Isosorbide
4	74/F	26	Mild	5 mg	Glibenclamide Aspirin Isosorbide
5	76/F	25	Mild	5 mg	Metaprolol Nifedipine
6	85/M	20	Moderate	5 mg	Vitamine E
7	58/F	11	Severe	10 mg	Fluoxetine
8	86/M	15	Severe	5 mg	Vitamine E
9	70/M	22	Moderate	5 mg	Fluoxetine Simvastatin
10	73/M	22	Moderate	5 mg	Fluvoxamine
11	74/F	17	Moderate	5 mg	Fluoxetine
12	76/M	22	Moderate	10 mg	Fluoxetine Thyroxine

M male, *F* female, *MMSE* Minimental State Examination, *Mild* mild dementia (CDR1), *Moderate* moderate dementia (CDR2), *Severe* severe dementia (CDR3)

The EEG was recorded with eyes closed for four minutes on a computer system which allows visual inspection of the EEG trace in real time on a color monitor. Portions of the recording containing ocular, muscle and movement artifacts were discarded. Sixteen samples of 2-sec epochs of artifact-free EEG were digitized at 128 samples per second. The low-frequency filter was set at 1 Hz and the high-frequency filter at 35 Hz, and a 50 Hz notch filter was used.

A fast Fourier transformation was applied on the 16 samples of 2 sec epochs which were then averaged. Frequency spectra were calculated from 18 electrode values, whereas values under Fp1, Fp2, and Fpz were extrapolated. This transformation yielded a value representing the amplitude in the different frequencies.

The EEG variables included the delta (0–3.5 Hz), theta (4–7.5 Hz), alpha (8–11.5 Hz), and beta1 (12–15.5 Hz) bands. Logarithmic transformations of the mean absolute amplitude (log a) and the mean relative amplitude [$\log(x/(1 - x))$] were performed to approach gaussian distributions, where a represents the mean averaged amplitude and x represents the fraction of averaged amplitude in each frequency band. The EEG activity compared before and during treatment was derived from electrodes of 3 cortical areas: the frontal (F = Fp1, Fz1, Fp2, F7, F3, Fz, F4, F8), the temporo-parietal (TP = T3, T4, T5, T6, P3, Pz, P4), and the occipital (O = O1, Oz, O2).

Comparisons were performed by means of a 2-way ANOVA with repeated measures. The following factors were used to compare the baseline EEG between mild and moderately/severely AD patients: 1) "state" as "between" factor with 2 levels (mildly versus moderately/severely demented AD patients) and 2) "areas" as "within" factor with 3 levels (F, TP, and O). A comparison of qEEG before and during treatment for the mildly and for the moderately/severely affected AD patients was performed using two "within" factors: 1) "treatment" as "within" factor with 2 levels (before and during treatment) and 2) "area" as

"within" factor with 3 levels (F, TP, and O). We calculated the qEEG differences before and during treatment (main treatment effect), between different cortical areas (main regional effect), and the different effects of the treatment in different cortical regions (regional-treatment interactions), resulting in a significance level of $p \leq 0.05$.

When ANOVA analysis was performed, the Bonferroni correction was applied to determine the effect of treatment on each brain area of interest (n = 3) in detail, resulting in a significance level of $p \leq 0.016$.

The investigator carrying out the EEG analyses was blinded to the diagnostic category of the patients.

Results

A comparison of the baseline qEEG recordings of the 2 study groups showed no significant differences in the mean absolute and relative EEG spectral bands (there was found out decrease in the absolute theta activity in AD patients with mild dementia, however those was not statistically significant). In addition, no statistically significant changes were observed during the treatment with donepezil regarding the mean relative qEEG activity in the different frequencies. Regarding the whole group of patients donepezil caused a statistically significant treatment effect, consisting of a decrease in the absolute beta1 activity (ANOVA: $p = 0.03$), due to a significant decrease in the F and O areas (Bonferroni correction: $p = 0.005$ and $p = 0.009$, respectively), with only a tendency towards decrease in the TP area (Table 2).

Table 2. Differences in qEEG activity before and during treatment with donepezil in various cortical areas of Alzheimer's disease patients with dementia

	Freq.	Treatment-related difference • (±SD)		
		Frontal	Temporo-parietal	Occipital
A	Delta	−0.40 ± 1.39	−0.30 ± 1.06	−0.18 ± 0.75
	Theta	−0.19 ± 0.52	−0.17 ± 0.42	−0.07 ± 0.26
	Alpha	−0.04 ± 0.28	−0.12 ± 0.33	0.10 ± 0.44
	Beta 1	−0.08 ± 0.07*	−0.06 ± 0.09	−0.07 ± 0.08*
B	Delta	−0.54 ± 0.56	−0.38 ± 0.34	−0.17 ± 0.19
	Theta	−0.13 ± 0.11*	−0.10 ± 0.08*	−0.08 ± 0.13
	Alpha	−0.03 ± 0.26	−0.11 ± 0.22	0.32 ± 0.37
	Beta 1	−0.05 ± 0.08	−0.04 ± 0.09	0.05 ± 0.14
C	Delta	−0.29 ± 1.82	−0.24 ± 1.41	−0.18 ± 1.00
	Theta	−0.24 ± 0.69	−0.23 ± 0.57	−0.08 ± 0.32
	Alpha	−0.09 ± 0.30	−0.13 ± 0.41	−0.06 ± 0.44
	Beta 1	−0.11 ± 0.06*	−0.08 ± 0.10	−0.15 ± 0.20*

A: whole group of Alzheimer's disease patients with dementia (n = 12). B: group of Alzheimer's disease patients with mild dementia (n = 5). C: group of Alzheimer's disease patients with moderate/severe dementia (n = 7)

• mean absolute amplitude during treatment minus mean absolute amplitude before treatment (μv), ±SD. Negative numbers: decrease amplitude of EEG during treatment; positive numbers: increase amplitude of EEG during treatment. Note that statistical comparison was performed after logarithmic transformation of the mean absolute amplitude. * Significant difference (Bonferroni correction)

In AD patients with mild dementia, the qEEG analysis showed a significant main effect of treatment that is a decrease in the absolute theta activity (ANOVA: $p = 0.05$). The results of Bonferroni correction analysis showed a significant decrease in the F ($p = 0.008$) and TP ($p = 0.016$) areas, and only a tendency towards decrease in the O area (Table 2).

There was a significant decrease in the absolute beta1 activity (ANOVA: $p = 0.02$) during treatment in AD patients with moderate/severe dementia. These effects were significant decrease in the F and O areas (Bonferroni correction: $p = 0.008$ and $p = 0.001$, respectively) and only a tendency towards decrease in the TP area (Table 2).

Discussion

Reduction of the levels of choline acetyltransferase in the brains of patients with AD (Bartus et al., 1982) led to the development of a variety of cholinergic drugs (Agnoli et al., 1983) being used in the treatment of these patients, including donepezil (Rogers and Friedhoff, 1996).

Previous studies of occipital qEEG in different stages of AD showed that the percentage power of the theta band significantly increased in mild AD patients compared with elderly healthy controls (Penttila et al., 1985). A progressive decrease in the percentage power of the alpha band was observed in progressive stages of AD (Penttila et al., 1985). In the present study there was a trend of baseline EEG parameters (increase in the absolute theta activity in moderate/severe AD patients) that reflect disease severity, although this failed to read statistical significance, probably due to the small number of cases.

Acute administration of cholinergic drugs, such as physostigmine, to AD patients increased alpha activity and decreased theta activity (Agnoli et al., 1983), and a single dose of THA increased alpha/theta and alpha/delta ratios in AD patients (Alhainen and Riekkinen, 1993). It is interesting to note that not only cholinergic drugs improved the EEG in AD patients. For example, long-term treatment on AD patients with tebonin (Hofferberth, 1994; Kanowski et al., 1996) resembled that with some cholinergic drugs, in spite of different mechanisms of action. Common effects, included improved memory and attention performances, associated with increase in alpha frequency (Kanowski et al., 1996) and decrease in theta EEG activity (Hofferberth, 1994; Kanowski et al., 1996).

Our study of long-term donepezil treatment in the whole group of our AD patients revealed a significant decrease in beta1 activity in the F and O areas. For more detailed investigation the patients were divided into more homogeneous subgroups in terms of severity of dementia. We may expect that two dosages of donezepil (5 and 10 mg per day), that were applied in these subgroups, didn't influence in different way on the EEG changes during treatment in mildly and moderately/severely demented AD patients, because there was no predominance of one of these dosages in any of these subgroups. We found that donepezil treatment in mildly demented AD patients led to a significant decrease in the theta activity in the F and TP areas, counteracting

the EEG effect of the progressive nature of the disease. It is known that the main cortical regions affected in AD are the temporo-parietal association areas (Friedland et al., 1983; Risberg and Gustafson, 1988). Therefore, the qEEG improvement during treatment occurring mainly in the F and TP areas is of a considerable interest.

The EEGs of our patients with moderate/severe dementia showed decreased beta1 activity in the F and O areas during donepezil therapy. It is possible that the progression of the disease in these patients caused this deterioration, which was not counteracted by the long-term treatment.

The number of cases in this pilot study was too small to differentiate between those in whom donepezil was clinically effective from those with no therapeutic response. Further studies with larger number of patients are needed to confirm these results, especially in correlation with the clinical response. We would expect that the EEG will not change in some patients, either reflecting their clinically advanced stage or because of other biological factors. The demonstration of EEG improvement in some subgroups however, may help in the management of AD patients.

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