

Long Term Effects of Piracetam on Spectral Analysis of EEG in Alzheimer's Disease and Minimal Cognitive Impairment

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ÖZET:

Alzheimer hastalığı ve hafif kognitif bozuklukta pirasetamin EEG spektral analizi üzerine uzun dönem etkileri

Amaç: Piracetamin inme sonrası afazi ve miyoklonik epilepside etkileri EEG'de spektral güç analizleri ile gösterilmiştir. Bu hastalarda pirasetamin kısmen alfa topografisinde düzenlenmesinde rolü olduğu bildirilmesine rağmen Alzheimer hastalarında veya hafif kognitif bozukluğu olan hastalarda piracetamin uzun süreli etkileri tam olarak tanımlanmamıştır.

Yöntem: Bu çalışmada 13 hafif kognitif bozukluğu olan hasta, 18 hafif veya orta derecede Alzheimer hastası ve bu hastalara yaş ve cinsiyet olarak benzer özelliklere sahip 16 sağlıklı bireyden oluşan kontrol grubunda başlangıç, 4 hafta süre ile 2400 mg piracetam kullanımı ve bunu takip eden 4 hafta süre ile 4800 mg piracetam kullanımı sonrası spektral EEG kayıtları incelenerek güç spektrumu analizleri yapılmıştır.

Sonuçlar: Alzheimer grubunda delta bant gücünün 2400 mg dozunda ortaya çıktığı ve bu durumun 4800 mg dozunda da devam ettiği görülmüştür. Teta bant gücünde anlamlı olarak azalmanın ortaya çıktığı, alfa ve beta bant güçlerinde ise değişikliğin ortaya çıkmadığı saptanmıştır. Hafif kognitif bozukluğu olan hastalarda da benzer sonuçlar elde edilmiştir.

Sonuç: Uzun süreli piracetam kullanımının Alzheimer hastaları ve hafif kognitif bozukluğu olan hastalarda EEG'de yavaş dalga bant güçlerini arttırmaktadır.

Anahtar sözcükler: Alzheimer hastalığı, hafif kognitif bozukluk, piracetam, spektral EEG

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ABSTRACT:

Long term effects of piracetam on spectral analysis of EEG in Alzheimer's disease and minimal cognitive impairment

Objective: Influence of piracetam in post-stroke aphasia and myoclonic epilepsy has been shown with EEG spectral power analysis. Particularly piracetam is involved in restoration of alpha topography in these patients. On the other hand long term effects of piracetam in Alzheimer's disease or minimal cognitive impairment (MCI) patients have not been determined so far.

Methods: We have evaluated spectral EEG analysis of 13 minimal cognitive impairment and 18 mild or less severe Alzheimer dementia patients after receiving piracetam 2400 mg and 4800 mg respectively for 4 weeks. Control group was consisted of 16 healthy subjects with similar age and sex characteristics. We analyzed EEG power spectrum before and after delivering 2400 or 4800 mg piracetam.

Results: In Alzheimer's disease group enhancement of delta band power began with 2400 mg piracetam and lasted on 4800 mg. Theta band power spectrum values significantly decreased. Alpha and beta band power spectrums were not changed. MCI patients have shown very similar results with AD patients

Conclusions: We have found that long term delivering of piracetam enhances slow-wave band powers of EEG both in Alzheimer's disease and MCI patients.

Key words: Alzheimer's disease, minimal cognitive impairment, piracetam, spectral EEG

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INTRODUCTION

Piracetam is a widely used drug in the daily clinical practice, because it has many therapeutical benefits and indications. Myoclonus, ischemic stroke, dementias of several origins and age-depending cognitive disturbances are several different indications of piracetam. The positive effect of piracetam on the cognitive functions has been reviewed in a meta-analysis study and until now

most of the studies had common outcome about clinically meaningful improvements of the measurement of changes of clinical global impression. Over almost a 30-year period all placebo controlled, parallel-group, double blind studies using global change of study of piracetam in patients with varying degrees of cognitive impairment have shown clinical efficacy of piracetam(1). The positive psychoactive and cognitive effect of the drug supports the

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therapeutic indication of piracetam in such cases, where cognitive deficits are present (2). Piracetam may improve cognitive functions, but previous studies have failed to demonstrate a clear benefit for the treatment of Alzheimer's Disease (AD). In a 1-year, double-blind, placebo-controlled, parallel-group study with a high dose of piracetam (8 g/d po) authors concluded that improvement doesn't observed in two groups of healthy volunteers, but their results support the hypothesis that long-term administration of high doses of piracetam might slow the progression of cognitive deterioration in patients with AD. The most significant improvements which were observed are the recalling of picture series recent incidenting and remote memory (3). A single dose of piracetam influenced the functional state of the brain of healthy volunteers in a dose dependent manner as measured with global correlation dimension of multi-channel resting EEG. The reported effects of piracetam on EEG power spectral values converge to decreased power in the slow band and increased power in the alpha band (4). We have considered that if piracetam therapy has an influence on cognitive performance then long term effects of piracetam might be quite different from single dose application because of possible induction of neuroplastic changes in the networks of brain as shown in the EEG activity in the cerebral cortex. This study aims to emphasize dose dependent effects of piracetam on EEG frequencies in minimal cognitive impairment (MCI) and Alzheimer disease patients (AD) in eight-week time period.

MATERIAL and METHODS

This study is a randomized prospective study and the clinicians who were performing the tests and analyzing the spectral EEG were blind. We enrolled 13 MCI and 18 mild or less severe AD patients of comparable age who were fulfilling criteria of National Institute of Neurological and Communicative Disorders and Alzheimer's disease of probable and possible Alzheimer's disease (5). Control group consisted of 16 healthy subjects with similar age and sex characteristics. This study was compatible with Helsinki protocol and written informed consent was obtained for all subjects. Cognitive function was

assessed using the adapted Turkish Mini-Mental State Examination (MMSE) (6) and Alzheimer's disease Assessment Scale (ADAS-Cog) (7) in AD patients and MMSE was performed in MCI patients. We recruited AD patients who took (7-20) points from MMSE and (10-35) points from ADAS-Cog. For all AD patients Global Deterioration Scale (GDS) (8) had to be between 1 and 3 for patients to be included in the study. The patients who got 1, from the GDS score was excluded from the study. The cutoff MMSE for MCI was set to be greater than or equal to 24, but none of the controls had a MMSE score lower than 25. Control group consisted of 16 individuals without any memory problems. All the MCI subjects underwent detailed examination and those who have dementia and neurological, physical, and psychiatric disorders were excluded before being recruited for the study. During diagnosis of MCI, 20-item word recalling test was used to differentiate them from normal subjects. Physical examination and glucose, ALT, AST, BUN, creatinin, thyroid function tests, B12 and folic acid levels of all AD patients and MCI individuals have been confirmed to be in normal limits. The subjects who were included the study were not taking any other medication that can effect the EEG spectrum analyses. The diagnostic procedures were performed at the beginning of the study and as our aim was to investigate the long term effect of pirecatam on spectral EEG, the repeated cognitive tests were not performed after EEG recordings.

We obtained three EEG for every MCI, AD patient and control subjects; first at the beginning of study with out pirecatam medication, second after taking piracetam 2400 mg for 4 weeks and and third after taking pirecatam 4800 mg for following. The control group's EEG recordings were obtained at the beginning of the study, and after the following 4th and 8th weeks. This practice has lasted for 8 weeks. EEGs were recorded by digital 32 channel apparatus Profile (Medelec Ltd U.K.) using the international 10/20 system and Ag/AgCl electrodes. EEG data were collected with linked mastoid reference. Impedances were less than 3 k_Ω. Amplified signals were band pass filtered from 0.5–70 Hz. For each subject, 10 epochs of 2 sec of multichannel EEG signals free of signs of impaired wakefulness, ocular movements and other artifacts

were selected for analysis. The power spectrum of each multi-channel EEG segment was computed on the basis of a Fast Fourier transform of the data. For each channel the powers in delta, theta alpha and beta-band were calculated by summing components in bands from 0.5 to 3.5 Hz, 4 to 7.5 Hz, 8 to 13 Hz, and 13.5 to 20 Hz respectively. Mean values of each treatment groups (AD, MCI and control group) were compared with each other and changes with treatment in EEG parameters were evaluated repeated ANOVA test. Probability values of $p < 0.05$ are reported to be significant.

Table 1: Clinical data of Alzheimer patients (AD) and minimal cognitive impairment (MCI) subjects and control group

	AD	MCI	Control
Age	61.2±3.1	56.5±4.1	59.2±3.6
Sex (M/F)	10/8	7/6	8/8
Duration of Symptoms (Months)	36.2±2.8	44.1±3.2	--
MMSE	17.6±1.4	28.2±0.5	28.6±0.8
ADAS-Cog	28.5±4.9	--	--

RESULTS

Control group consisted of 16 individuals (age: 59.2±3.6 years) who entered the study with normal cognition (MMSE score 28.6±0.8). Eighteen AD patients' (age, 61.2±3.1years) and 13 MCI subjects' (age, 56.5±4.1 years) cognitive test results were summarized in table 1. There was no statistically significant age or sex difference between groups. The three groups did not differ in age and sex. EEG spectral band power analyses were evaluated with their own baseline values for all groups. After receiving 2400 mg piracetam, have shown a significant enhancement in delta band power spectrum ($p: 0.019$) according to their baseline power values. After increasing piracetam dose up to 4800 mg, delta power increase persisted but this enhancement was not statistically as significant as the difference between baseline and 2400 mg MCI group has also shown an enhancement of delta band power especially after receiving 4800 mg

Table 2: Changes of band powers before and after piracetam therapy (2400mg and 4800mg for 4 weeks consecutively).

	DELTA(µV2)			THETA(µV2)			ALPHA(µV2)			BETA(µV2)		
	AD	MCI	Control	AD	MCI	Control	AD	MCI	Control	AD	MCI	Control
0.day	11,104	6,938	6,76	7,741	3,66	3,23	7,664	7,759	7,12	3,398	2	2,65
2400mg	15,421*	8	6,50	8,801	2,11*	3,41	6,019	8,606	7,45	3,476	2,489	2,85
4800mg	15,893*	10,327*	6,86	6,22*	2,896	3,59	8,012	6,545	6,8	3,652	2,452	2,99

*: statistically different from baseline value

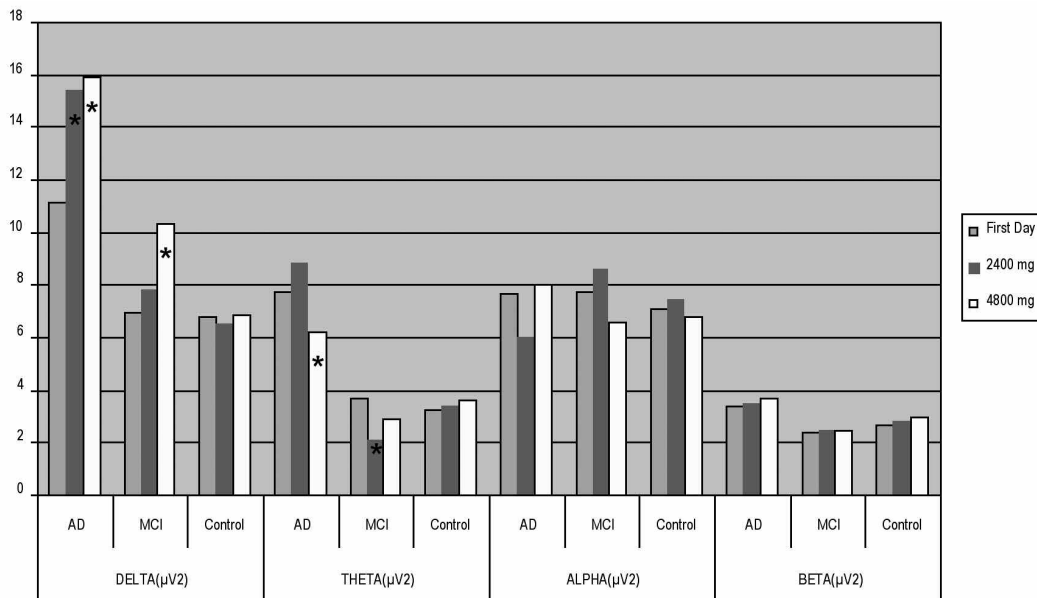


Figure 1. Changes of band powers before and after piracetam therapy (2400mg and 4800mg for 4 weeks consecutively). *: statistically different from baseline value

piracetam ($p:0.006$). The increase of delta band power after augmenting the piracetam dose to 2400 mg was not statistically significant.

No change was observed in theta band analysis in AD patients after receiving 2400 mg piracetam, but in the MCI group theta band power decreased significantly ($p:0.001$). After receiving 4800 mg piracetam in both MCI and AD groups theta band power decreased, but this time it was statistically significant ($p:0.044$) only for AD patients. In alpha and beta band spectral power spectrum value changes were not statistically significant for either AD or MCI groups. Results were summarized in table 2 and figure 1.

DISCUSSION

Piracetam is indicated in long-term therapy of different types of ischemic strokes, in aphasias, and several forms of dementias and age-related cognitive impairments. Results provide compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment (2). Pierlovisi-Lavaivre et al. emphasized that the main effect of piracetam was to induce increased alertness (9), but results in human clinical trials on the cognitive enhancing effects of piracetam have not been consistent and in Down syndrome mouse model, it has been demonstrated to have only limited effects on cognitive performance (10).

In physiological aging process, alpha activity gradually decreases. The EEG changes induced by nootropics are reversing this process, suggesting that they have antagonistic efficacy in the geriatric changes (4). Piracetam specifically restores age-related alterations of membrane fluidity in animal and human brain, which may finally lead to improved brain function by enhancing signal transduction and energy metabolism, but the neurochemical basis of age-related and AD specific alterations of human membranes are not similar. Hippocampal membranes of AD patients showed significant lower hydrocarbon core fluidity compared with membranes from elderly non-demented controls. In the presence of piracetam, the difference of the membrane fluidity between AD and control membranes was no longer apparent (11).

Mindus' study points to a beneficial effect of

piracetam on mental performance in aging, non-deteriorated subjects (12) and his findings would be a commentary of piracetam's various effects for normal healthy subjects, AD patients and MCI patients. On the contrary to our results, reported effects of piracetam on EEG power spectral values converge to decreased power in the slow band and increased power in the alpha band, suggesting improvement in cognitive functions (13). Single dose of piracetam, showing effects at the lowest treatment level dose-dependently affects the spontaneous EEG in normal volunteers. The decreased EEG complexity is interpreted as increased coordination of brain functional processes (14). It has been also shown that the subtle change of brain global functional state after a single dose of piracetam is reflected by the non-linear measure of global dimensional complexity of the multi-channel EEG (15, 16) and single medium doses of piracetam selectively activate differently located or oriented neurons during cognitive steps of information processing (17).

In clinical trials piracetam was found effective in reducing psychomotor agitation (18). Earliest EEG changes in AD are an increase in theta activity, accompanied by a decrease in beta activity, which are followed by a decrease in alpha activity. Delta frequency increases later during the course of the disease (19). In our study we conclude that enhancement in delta band power spectrum, which is not dose-dependent in AD patients and dose-dependent in MCI patients (especially in 4800mg/day), would be as a result of sedative effect of piracetam. As our results were similar in AD and MCI patients, enhancing of delta band power activity does not seem to be related with cognitive levels of the patients.

In this study the cognitive assessment was performed at only the beginning of the trial, and our aim as to investigate the effect of piracetam in spectral EEG parameters, repeated cognitive assessment could not have been performed. This can be a limitation of our study because the patients' cognitive state would help us to disclose the medication effects that were found in spectral EEG. The clinicians who assessed the patients and analyzing the spectral EEG were blind to each other, so sedation effect was not interrogated.

Animal studies suggest that piracetam may improve neuronal efficiency, facilitate activity in neurotransmitter systems, and combat the age-related decrease in receptors on the neuronal membrane. However, for patients with probable Alzheimer's disease, as well as for adults with age-associated memory impairment, there is no clear-cut support for a mnemonic benefit of piracetam (20). The cognitive enhancer effect of piracetam appears in a few weeks and possibility of this treatment's effect in Alzheimer's disease was reported by Tariska et al.(21) but further investigations are still needed.

We emphasize that long term piracetam

medication effect might be quite different from single dose practices by enhancing slow wave activity independently from patient's cognitive level, that means both AD and MCI patients respond similarly to piracetam treatment. On the other hand we need more detailed electrophysiological correlations of clinical findings in different patient groups to understand underlying pathological processes.

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