CORRELATIONS AMONG ELECTROENCEPHALOGRAPHY AND SERUM DRUG LEVEL IN MAJOR DEPRESSION: PREDICTION OF RESPONSIVENESS TO ANTIDEPRESSANT TREATMENT

Gökben HIZLI SAYAR,¹ Serdar NURMEDOV,² Nevzat TARHAN³

¹ Assist.Prof.Dr., ³ Prof.Dr. Department of Psychiatry, Uskudar University, Neuropsychiatry Istanbul Hospital, Istanbul, Turkey
² Dr. Department of Genetics and Bioengineering, Fatih University, Istanbul, Turkey
* Dr. Gökben HIZLI SAYAR, Department of Psychiatry, Neuropsychiatry Istanbul Hospital Alemdag Cad. Site Yolu No.29 Ümraniye/Istanbul, Turkey
E-mail: ghizli@npistanbul.com

ABSTRACT

Objective: To examine the correlations among electroencephalography and serum drug level parameters to predict the responsiveness to antidepressant treatment in patients with major depression.

Methods: Subjects received sertraline, 50 mg daily, for four weeks. On the first day before the initiation of treatment, 1 hour and 3 hour afterwards oral sertraline ingestion, on the 7th day and on the 4th week of treatment, all patients underwent assessments using electroencephalography. One hour and 3 hours after oral ingestion of 50 mg oral sertraline, serum drug level was measured. Serum drug level measurement was repeated on the 7th day and on the 4th week of the treatment. Depression was rated using Hamilton Depression Rating Scale (HAMD) while anxiety was rated using Beck Anxiety Scale (BAS) obtained before treatment (at baseline), on the 7th day and on the 4th week of the treatment.

Results: A significant decrease in theta activity at the 1st hour electroencephalography after single dose of sertraline ingestion was examined. A significant alpha decrease after 7 days of sertraline treatment and beta activity decrease after 4 weeks of sertraline treatment were observed on electroencephalography measures.

Conclusion: These findings support that the use of electroencephalography measures have the value of predicting treatment outcome in depression. If these results will be replicated in other studies, usage of electroencephalography and serum drug levels may become a useful biomarker for predicting treatment outcome in major depressive disorder.

Key words: electroencephalography, major depressive disorder, predictors of treatment response, serum drug level

MAJÖR DEPRESYONDA ELEKTROENSEFALOGRAFİ VE SERUM İLAÇ DÜZEYİ İLİŞKİŞİSİ: ANTİDEPRESAN TEDAVİYE YANITIN YORDANMASI

ÖZET

Amaç: Majör depresyonu olan hastalarda antidepressan tedaviye yanıtın yordanması için elektroensefalografi ve serum ilaç kan düzeyi ilişkisinin incelenmesi amaçlanmıştır.

Yöntem: Hastalar dört hafta boyunca sertralin 50 mg/gün antidepressan tedavide tutulmuşlardır. İlk ilaç dozunun verilmesinden önce elektroensefalografi incelemesi, ilk dozdan 1 saat ve 3 saat sonra, tedavinin 7. günü ve 4.
INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disease burden worldwide, and is the leading risk factor for completed suicide. It frequently leads to substance abuse and lowered work productivity and is a risk factor for physical illnesses such as cardiovascular disease. Although controlled efficacy trials suggest that most patients respond to treatment within eight weeks, the “Sequenced Treatment Alternatives to Relieve Depression” trial found that fewer than 50% of patients responded to the first trial of a serotonin selective re-uptake inhibitor and antidepressant, and less than one-third achieved response or remission with an initial medication remains a challenge for most patients with MDD.

There is growing evidence that in certain circumstances the electroencephalography (EEG) can be used to predict which patients are likely to respond to treatment. Elevated theta and alpha band EEG activity found to be related to depressive disorder. Relative excess alpha power has been related to depression severity and changes in baseline theta band were found to be related with response to antidepressant treatment. However, there are contradictory reports about predictive value of EEG parameters about the clinical outcome. We hypothesized that the reason for the contradictory findings is that the serum drug level (SDL) of antidepressants did not taken into account.

The aim of this study was to examine the correlations among EEG and SDL parameters to predict the responsiveness to antidepressant treatment in patients with major depression.

MATERIALS and METHODS

Study Design

Patients who met the Structured Clinical Interview for DSM-IV criteria for depression were eligible for the study. The study protocol conformed to the Helsinki Declaration; all patients were fully informed and signed consent forms before inclusion in the study, which was approved by the Board of Research Ethics. After obtaining informed consent, subjects had a complete neurological and physical examination with a thorough review of systems. Subjects were screened with a complete blood count, thyroid function tests, and electrolytes within three months of the treatments. Concomitant medication for depression was authorized, provided the dose administered had been stable for at least 1 month before enrollment and remained stable throughout the study.

Exclusion criteria included evidence of dementia on neuropsychological testing, or meeting the Structured Clinical Interview for DSM-IV criteria for organic brain syndrome, organic mood disorder, substance dependence within the last six months, a diagnosis of a significant central neurological disorders including brain mass, epileptic seizures, stroke, transient ischemic attack within two years, cerebral aneurysm, dementia, Parkinson’s disease, Huntington’s chorea, multiple sclerosis, or other major central nervous system dysfunction. Subjects with acute, unstable medical conditions that required stabilization (e.g. uncontrolled hyper-
tension) prior to treatment were also excluded.

Patients were given sertraline, 50 mg daily, for four weeks. The study group received continuous treatment with a single agent throughout the trial. Treatment continued at this dosage through four weeks and if reduction in dose was clinically indicated, the subject was removed from the study.

Outcome Measures

EEG data were collected using SCAN LT (Neuroscan Medical Systems, Neurosoft Inc. Sterling, VA, USA) system. This consisted of a 21-channel EEG device with sampling rate of 250 Hz, notch filtering at 50 Hz, high pass filter of 0,159 Hz and low pass filter of 30 Hz. EEG data were recorded while the subject rested in a reclining chair during 3-min eyes-closed segments. Manual artifact rejection of data was performed by an experienced neurologist. On the first day before the initiation of treatment, one hour and three hours afterwards oral sertraline ingestion, on the 7th day and on the 4th week of treatment, all patients underwent assessments using EEG.

Serum level of sertraline was measured using liquid chromatography mass spectrometry. Serum samples of 1 ml were extracted with organic solvents after alkalization with sodium bicarbonate. In serum, the limit of detection for sertraline was below 5 nmol/l. At baseline, one hour and three hours afterwards oral sertraline ingestion, SDL was measured. SDL measurement was repeated on the 7th day and on the 4th week of the treatment in the morning immediately before administration of the next dose.

Depressive symptom changes were measured by validated Hamilton Depression Rating Scale. The 17-item HAMD (HAMD-17) score, constitutes a valid and reliable measure of the severity of depressive symptoms. Secondary outcome parameters included response and remission rates. Response was defined as a decrease in the HAMD-17 total score of at least 50%. Patients with HAMD-17 scores of less than eight and who did not meet criteria for major or minor depression was considered to be in remission. Efficacy parameters were assessed by an independent rater who was blind to the patient treatment status. Beck Anxiety Scale (BAS) was used to evaluate the frequency of anxiety symptoms. BAS is a self assessing, Likert type scale which is rated between 0-3 and includes 21 items. Total point increases with the severity of anxiety. It was developed by Beck and colleagues and validity and reliability studies in our country were performed by Ulusoy and colleagues. The HAMD-17 and BAS scores were obtained before treatment (at baseline), on the 7th day and on the 4th week of the treatment.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences 16.0 for Windows (SPSS Inc., Chicago, IL). The following statistical tests were performed: Spearman correlation, repeated-measures analysis of variance (ANOVA), post-hoc tests, and multiple linear regression. The results for all items were expressed as mean±SD, assessed within a 95% reliance and at a level of p<0.05 significance.

RESULTS

The study population consisted of 12 females and one male, with an average of 34.2±12.3 years. Duration of current major depressive episode was 3.3±1.1 years for the study group.

There was a significant decrease in theta activity at the 1st hour EEG after single dose of sertraline ingestion. A significant alpha decrease after seven days of sertraline treatment and beta activity decrease after four weeks of sertraline treatment were observed on EEG measures. Serum drug levels found to be significantly increase with repeated ANOVA measures (F=33.7, p<0.001). At post hoc measures the increase in serum drug levels found to be related to difference of 1st hour - 3rd hour and 3rd hour - 1st week levels of sertralin.

The mean baseline HAMD score for the study group decreased from 16.54 to 11.42 at the 7th day and decreased to 5.73 at the 4th week (p<0.001). At the end of the 4-weeks treatment period, all of our patients demonstrated significant mood improvements, as indexed by a reduction of more than 50% on the HAMD score. The mean baseline BAS score for the study group decreased from 23.15 to 19.5 at the 7th day and decreased to 15.27 at the 4th
week (p<0.001). Decrease in depression and anxiety scores were found to be statistically significant at the 1st week and 4th week when compared to baseline measures (Friedman test results for HAMD p<0.001; for BAS p=0.035). Baseline, 1st hour, 3rd hour, 1st week and 4th week measures of HAMD, BAS, SDL and EEG measures were done. Treatment was generally well tolerated, and no serious adverse effects were reported.

Spearman correlation between the changes in depression, anxiety scores, serum drug levels and the changes in EEG measures are calculated. There found to be a highly significant negative correlation between serum sertraline levels and theta and alpha activity on EEG records after 3 hours of single dose of 50 mg oral sertraline ingestion. Also there found to be a significant correlation between BAS scores and theta decrease at 1st week - 4th week measures. Correlation between HAMD scores and gamma activity decrease at baseline - 4th week also found to be significant.

DISCUSSION

The main outcome of the study is that both the change in EEG and the SDL during treatment with a representative SSRI has a predictive value of treatment outcome in patients with major depression. No significant adverse effects were monitored in patients receiving treatment.

Presently, there is no reliable method for predicting whether a medication will lead to response or remission. Methods to predict which medication would most likely benefit an individual patient and could reduce patients’ suffering. Such instruments might include clinical features, biomarkers such as brain-imaging findings, EEG or genetic polymorphisms. Clinical characteristics have the advantage of being relatively easy to determine, but generally have not been useful for predicting response to medications. Symptoms such as anxiety or melancholia are associated with the recovery but have not been shown to be reliable predictors of response. Brain imaging also has been shown to have some promise for predicting response to treatment. Data suggest that pretreatment cerebral metabolism, white-matter lesions, or atrophy may be associated with outcome. Brain functional measurements show promise as a physiologic indicator of treatment effectiveness in depression. Several studies using positron emission tomography (PET) or single-photon emission computed tomography have documented reductions in prefrontal cortical perfusion or metabolism resulting from antidepressant medication treatment. However the burden and cost of these procedures have limited their use. Some genetic biomarkers, mostly genetic polymorphisms, have been shown to influence the outcome of SSRI treatment. Two promising polymorphisms are those in the promoter region of the serotonin transporter (5-HTTLPR) and in the 5-HT2A postsynaptic receptor, which in some studies have been associated with treatment response.

The use of the EEG offers two potential major means of addressing this problem. First it is able to provide direct data relating to neural activity that may be abnormal in certain disorders. As such there are opportunities for utilizing the EEG in a variety of ways as an objective outcome measure. Second, there is growing evidence that in certain circumstances the EEG can be used to predict which patients are likely to respond to treatment, thus potentially increasing the power of studies by decreasing non-response rates and increasing mean changes in outcome measure. Knott et al. found that depressed patients who responded to imipramine showed a trend for more alpha, but had significantly less theta compared to nonresponders. Cook et al. did not find pretreatment differences between fluoxetine responders and nonresponders in theta, but did find group differences in “cordance”, a measure based on a form of surface Laplacian. Pizza-galli et al. localized pretreatment theta increases to rostral anterior cingulate cortex in responders to nortriptyline. Similarly, Mulert et al. reported that depressed patients responding to either citalopram or reboxetine had increased pretreatment activity localizable to rostral anterior cingulate cortex. These findings suggest that pretreatment alpha or theta measures may be of value as predictors of clinical response to SSRI or other antidepressants. Our results are consistent with previous work demonstrating early changes in alpha and theta activity in EEG were predictive of response to treatment in
major depressive disorder. The relationship of these immediate EEG changes in control subjects to eventual clinical response in a depressed population is unclear.

Other EEG work with depressed subjects has found that changes from baseline in theta power early in the course of treatment may characterize groups of depressed patients who are more likely to respond to antidepressant treatment.

This study has several implications for clinical treatment. First, treatment with sertraline in patients with major depression is effective. Second, the response to treatment with sertraline was characterized by an early decrease in alpha and theta activity. Our findings should be interpreted in the context of the following limitations. The main limitation of this study is the non-controlled design, which likely restricted the statistical power. Second limitation is the rather small number of patients, which may have been too low to detect significance. Third, subjects were treated with a fixed dose of sertraline, and those receiving other psychotropic medications, with active substance abuse, or severe physical illness or major psychiatric comorbidity were excluded. The findings therefore may not be generalizable to less controlled treatment conditions or entirely naturalistic samples. Fourth, our primary endpoint was symptom improvement at day 48 of treatment. We cannot draw definite conclusions about the relationship between EEG, SDL and longer-term treatment outcome.

CONCLUSION

These findings support that the use of EEG measures have the value of predicting treatment outcome in depression when correlated with the serum drug levels. If these results will be replicated in other studies, usage of EEG and serum drug levels may become a useful biomarker for predicting treatment outcome in major depressive disorder. However, because of the small number of study patients and the conventional statistics, the results should be taken with caution.

REFERENCES


