Ictal Electroencephalographic Correlates of Posttreatment Neuropsychological Changes in Electroconvulsive Therapy: A Hypothesis-Generation Study

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Objectives: Electroconvulsive therapy (ECT) has been associated with memory and neuropsychological changes, but which features of ECT are associated with those changes have not been well investigated. The aim of this hypothesis-generation study was to examine correlations between ictal electroencephalographic (EEG) characteristics and cognitive side effects after ECT.

Methods: Eight patients with major depressive disorder were examined with the Wechsler Memory Scale–Revised (WMS-R), the Stroop test, the Trail Making Test, and verbal fluency before and after ECT treatment. Seven ictal EEG measurements (eg, slow-wave phase amplitude, postictal suppression) were manually rated by 3 independent psychiatrists. The correlations between ictal EEG measurements, changes in WMS-R subset scores, and non–memory-related neuropsychological assessments were examined with Spearman rank correlation.

Results: Verbal memory, general memory, attention/concentration, delayed memory of WMS-R subset scores, and the Stroop test scores improved significantly after ECT treatment. Postictal suppression and slow-wave amplitude correlated positively with delayed memory and visual/verbal discrepancy score. Slow-wave amplitude correlated negatively with letter fluency. The longer the polyspike wave duration, the higher the attention/concentration test results.

Conclusions: Certain ictal EEG measurements were associated with changes in several neuropsychological test results that had improved 2 weeks after the final ECT treatment. A hypothesis-testing study with a larger sample is needed to verify the relationships between EEG measurements and neuropsychological test performance.

Key Words: depressive disorder, electroconvulsive therapy, anterograde amnesia, Wechsler Memory Scale–Revised, attention/executive function

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Electroconvulsive therapy (ECT) is 1 option in the treatment of psychiatric illness, particularly depression, and is considered to be a rapidly acting, effective therapy.[1] On the other hand, ECT is known to bring about neuropsychological changes, the most prominent of which include anterograde amnesia and a temporally graded retrograde amnesia.[2,3] Our own studies revealed that in patients with depression, ECT not only improved depressive symptoms, but also caused changes in neuropsychological function. Patients exhibited memory impairments such as anterograde amnesia[4] and altered executive function after ECT treatment.[5]

Various indices of the adequacy of ECT administration have been studied to predict therapeutic effects and side effects. Ictal and interictal electroencephalogram (EEG) has received much attention,[6,7] and postictal suppression has repeatedly been shown to predict therapeutic efficacy.[8–10] Sackeim et al[11] reported that retrograde amnesia assessed by autobiographical memory correlated with increased theta activity of interictal EEG in left frontotemporal regions after ECT treatment. However, Perera et al[9] reported that ictal EEG did not correlate with retrograde amnesia. We are not aware of any other studies of ictal EEG measurements in relation to deficits in memory and executive function.

How does ictal EEG in ECT affect immediate and delayed memory and executive function? Although there is some ongoing debate,[12,13] the frontal lobes seem to be involved in episodic memory and executive function. On the other hand, there is increasing evidence that the prefrontal cortex, the amygdala, and related parts of the striatum and thalamus are involved in the pathophysiology of depression.[14,15] If ECT affects the metabolic function of the frontal lobes in state-dependent depression, it may also affect memory and executive function.

Based on our supposition that ECT-induced cognitive side effects are closely related to seizures in ECT, in the present hypothesis-generation study, we evaluated cognitive side effects approximately 2 weeks before and 2 weeks after bilateral pulse wave ECT. In addition, we examined the correlations between ictal EEG features (eg, polyspike phase, slow-wave phase, regularity, stereotypy, postictal suppression) and changes in Wechsler Memory Scale–Revised (WMS-R) subset scores and various non–memory-related neuropsychological test scores.

MATERIALS AND METHODS

Subjects

Subjects were 8 consecutive inpatients with depression who were referred to the Department of Psychiatry at Nagoya City University Hospital for ECT. The patients had failed to respond to previous treatment with at least 1 full-dose antidepressant medication for 4 weeks or longer or could not tolerate such medication. All subjects fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for unipolar major depression or bipolar disorder, with depression as the most recent episode.[16] Diagnosis was determined by at least 2 psychiatrists based on a clinical interview and a review of psychiatric records. Patients with the following conditions were excluded: history of schizophrenia; schizoaffective disorder; significant neurological illness; substance abuse; substance dependence; another significant illness; grave abnormality on chest radiography, brain computed tomography, or EEG; or ECT treatment within the previous 6 months.

The study protocol was approved by the Ethics Committee of Nagoya City University Medical School. All subjects were informed of the study purpose and procedures and provided written consent.

Electroconvulsive Therapy and Medication

Electroconvulsive therapy was administered through electrodes positioned at the standard bifrontotemporal location. In that position, each electrode was placed on a perpendicular line 3 cm above the midpoint of the line joining the external auditory meatus and the outer canthus of the eye. For pulse wave stimuli, a Thymatron System IV ECT apparatus (Somatics Inc, Lake Bluff, Ill) containing a built-in EEG system (Fp1-A1, Fp2-A2, international 10–20 system) was used. Stimulation dose was calculated using the half-age method.[17] A low 0.5 preset program using 0.5-ms pulse width was selected, adjusting frequency to maximize duration.[18] The criterion for an adequate seizure was an EEG seizure lasting longer than 20 seconds. If no EEG seizure occurred, restimulation at a 10% higher stimulus intensity was immediately performed, up to a maximum of 3 stimulations/session. Motor seizures were monitored by a cuffed leg. Anesthetic agents were 2.0 to 2.5 mg/kg intravenous propofol and 3 mg vecuronium bromide.

Antidepressants remained unchanged at a minimal dose, usually 40 to 50 mg/d of fluoxetine equivalent, throughout the course of ECT. Antidepressant equivalence was calculated according to the World Health Organization Defined Daily Dosage method (World Health Organization Collaborating Centre for Drug Statistics Methodology, ATC/DDD System, 2006). Lithium carbonate and sodium valproate were withdrawn before the first ECT. The use of benzodiazepines was permitted during the study to alleviate insomnia and anxiety (n = 4). Benzodiazepine dosage at the time of the first ECT session was 4 mg/d or less of lorazepam or equivalent. Three patients were administered antipsychotics (eg, chlorpromazine, levomepromazine, sulpiride). We compared baseline neuropsychological test scores of benzodiazepine- and antipsychotic-treated patients with those of the remaining patients. There were no statistically significant or substantively important differences.

Measurements

An independent research psychiatrist and a speech therapist evaluated the patients 3 to 14 days before and approximately 14 days after a course of ECT. Depression severity was measured with the 17-item Hamilton Rating Scale for Depression (HAMD).[19] None of the 8 patients had visual or auditory deficits, difficulties with language, or impaired orientation at baseline. Overall cognitive function was assessed with the Mini Mental State Examination (MMSE),[20] and memory was evaluated with the Wechsler Memory Scale–Revised (WMS-R).[21] The difference between verbal memory and visual memory (visual/verbal discrepancy score) indicates seizure focus in the left hemisphere in partial epileptic patients[22] but fails to show significant lateralized cerebral pathology.[23] We presumed that the visual/verbal discrepancy score would indicate the degree of lateralization even in patients with depression and associate with seizure in ECT. Verbal and letter fluency were used as indications of focused attention.[24] Parts A and B of the Trail Making Test were used to assess attention and executive function. The reliability and validity of these tests have been established in the Japanese population.[25]

Electroencephalographic Analysis

Electroencephalograms were available for 96.5% of the ECT administered. Ictal and peri-ictal EEG measurements, including polyspike phase maximal amplitude (mV), polyspike phase duration (s), slow-wave phase maximum amplitude (mV), slow-wave phase duration (s), regularity (global seizure strength, 7-point scale ranging from 0 to 6), stereotypy (global seizure patterns, 4-point scale ranging from 0 to 3), and postictal suppression (degree of postictal bioelectric suppression, 4-point scale ranging from 0 to 3) were manually rated by 3 experienced psychiatrists using standard methods.[8,10,26,27]

The polyspike phase was defined as the period between offset of stimulation and the terminating point, at which visually discernible slow-wave activity fully replaced early, chaotic polyspike activity. The slow-wave phase was defined as the period from that time point to seizure termination. Maximal amplitudes during the polyspike and slow-wave phases were defined by the largest peak-to-peak deflections in the relevant phase, and mean maximal amplitude was determined for each patient. Seizures were rated as more stereotypic if a clear progression from low-amplitude, chaotic polyspike activity to high-amplitude, slow-wave activity was seen, without reappearance of chaotic, polyspike activity or marked variability in amplitude during each phase. Seizures were rated as having greater regularity if slow-wave activity of high-amplitude regularly predominated during the slow-wave phase. Higher numbers indicate increasing stereotypy and regularity of the ictal EEG recording. Postictal suppression was rated as follows: 0, cannot determine where the seizure ends; 1, seizure termination is clear but suppression is poor; 2, good seizure suppression, but transition to flat is gradual; and 3, good seizure suppression, and transition to flat

is abrupt. Interrater reliability among the 3 raters was examined by calculating the analysis of variance intraclass correlation coefficient (ICC). Ictal EEG measurements were rated by independent raters blind to the subjects. An analysis of variance ICC above 0.7 generally indicates good reliability.

Statistical Analysis

All statistical tests were 2-tailed, and the statistical significance level was set to $\alpha = 0.05$. Because our sample size was small, we used nonparametric tests. The effect of depression on neuropsychological test results was examined with Spearman rank correlation. Within-group changes in depression severity and neuropsychological test scores obtained before and after the course of ECT were examined with Wilcoxon signed rank test. The percentage change in HAMD scores, each WMS-R subset score, and pre-ECT neuropsychological test scores were the dependent variables. Ictal EEG measurements were averaged across all ECT sessions for each patient and were used to examine the association between ictal EEG measurements and cognitive changes. Spearman rank correlations were computed. The SPSS version 11.5 software (SPSS Inc., Chicago, Ill) was used for all statistical analyses.

RESULTS

Table 1 shows the clinical and demographic characteristics of the 8 patients. All of the patients experienced major depressive disorder. Before ECT, each subject had received a mean (SD) of 2.3 (0.7) antidepressant medication trials. Maximal antidepressant dose in fluoxetine equivalents before ECT was 55.3 (17.5) mg/d. During the course of ECT, patients received 55.5 (37.2) mg/d of fluoxetine equivalents and 26.0 (47.4) mg/d of chlorpromazine equivalents.

The charge of electricity delivered with the pulse wave apparatus was 190.6 (78.5) millicoulombs. Analysis of variance ICCs assessing interrater reliability of ictal EEG ratings were 0.68, 0.79, 0.93, 0.98, 0.90, 0.66, and 0.78 for polyspike phase amplitude, polyspike phase duration, slow-wave phase amplitude, slow-wave phase duration, regularity, stereotypy, and postictal suppression, respectively. The reliability of polyspike phase amplitude and stereotypy ratings was less than satisfactory. Therefore, we omitted those variables from subsequent analyses.

TABLE 1. Patient Background Characteristics and Ictal Electroencephalographic Measurements (n = 8)

	Mean (SD)
Age, yrs	44.2 (4.2)
Sex, men-women	4:4
Education, yrs	14.6 (9.6)
Age at onset, yrs	38.6 (4.9)
No. mood episodes	1.5 (0.6)
Duration of current episode, mo	23.0 (7.2)
Baseline HAMD	15.0 (2.2)
Posttreatment HAMD	7.6 (1.9)
No. ECT sessions received	10.8 (2.2)
Polyspike amplitude, mV	3.8 (2.1)
Polyspike duration, s	91.4 (28.9)
Slow-wave amplitude, mV	569.2 (117.5)
Slow-wave duration, s	73.5 (42.0)
Regularity, 0–6	5.1 (0.5)
Stereotypy, 0–3	2.1 (0.4)
Postictal suppression, 0–3	2.1 (0.4)

TABLE 2. General Cognitive Function, Memory Performance, and Attention/Executive Function

	Pulse Wave ECT (n = 8)	
Function	Pretreatment	Posttreatment
MMSE	27.5 ± 3.2	29.0 ± 1.7
WMS-R		
Verbal	90.3 ± 15.9*	100.4 ± 20.0*
Visual	99.5 ± 14.2	105.1 ± 13.1
General	90.3 ± 16.3*	112.5 ± 13.8*
Attention/concentration	101.4 ± 18.1*	110.8 ± 15.0*
Delayed	90.1 ± 24.6*	103.3 ± 19.1*
Attention/executive tests		
Word fluency (animal)	14.6 ± 2.8	16.8 ± 4.9
Letter fluency ("a")	11.0 ± 3.8	10.5 ± 4.0
Trail Making A (s)	39.2 ± 15.8	42.9 ± 20.8
Trail Making B (s)	102.7 ± 44.1	86.5 ± 42.4
Stroop test		
Incongruent (s)	35.2 ± 19.3*	26.9 ± 10.3*
Error	1.3 ± 1.4	1.1 ± 1.2

*Showed statistically significant within-group prechanges/postchanges ($P < 0.05$) according to Wilcoxon signed rank test.

The mean HAMD scores decreased from 15.0 (6.2) to 7.6 (5.5) ($P = 0.01$). The proportion of patients showing greater than 50% reduction in scores or scoring 8 or less on the HAMD was 62.5%.

On average, patients underwent the posttreatment neuropsychological assessments 15.6 (2.6) days (range, 11–19) after the last ECT session. One patient scored 20 on the MMSE before ECT and 29 after ECT. When that patient's score was excluded from analysis, the mean MMSE score was 28.6 (1.0) before and 29.0 (1.8) after ECT, respectively. This indicates that all the patients were free of gross cognitive impairment, such as dementia, and had high MMSE scores. Among prechange/postchange scores in cognitive functions, word fluency and letter fluency were significantly correlated with prechange/postchange in HAMD scores ($\rho = 0.76$, $P = 0.03$; $\rho = -0.74$, $P = 0.04$, respectively).

Table 2 shows the general cognitive function and memory scores, as well as attention/executive function before and after the course of ECT treatment. The WMS-R scores for verbal memory, general memory, attention/concentration, delayed memory, and the Stroop test scores improved significantly ($P < 0.05$).

We evaluated correlations of ictal EEG measurements, averaged for each patient across repeated ECT administrations, with the percent change in cognitive function from baseline with Spearman rank correlation. The polyspike wave duration correlated with the WMS-R attention/concentration subset scores ($\rho = 0.76$, $P = 0.03$).

Slow-wave amplitude correlated with the delayed memory and visual/verbal discrepancy scores ($\rho = 0.88$, $P = 0.04$; $\rho = 0.71$, $P = 0.047$, respectively) as did postictal suppression ($\rho = -0.73$, $P = 0.04$; $\rho = -0.89$, $P = 0.003$, respectively). Regarding non–memory-related neuropsychological tests, slow-wave amplitude correlated with letter fluency ($\rho = -0.78$; $P = 0.02$).

DISCUSSION

In the present hypothesis-generation study, we investigated the correlations between post-ECT memory change, attention/executive function, and ictal EEG measurements. We established that after ECT treatment, scores on the WMS-R verbal, general, and delayed memory subsets; the attention/concentration subset; and the Stroop test improved significantly. Furthermore, greater postictal suppression and slow-wave amplitude correlated with higher baseline visual/verbal discrepancy scores and delayed memory scores, respectively. Finally, longer polyspike duration correlated with higher attention/concentration scores; and in non–memory-related neuropsychological tests, higher slow-wave amplitude correlated with lower letter fluency.

Patients with depression exhibit memory and non–memory-related cognitive impairments.[28–30] Before ECT treatment, the impairments may be caused by the depressive state. After a course of ECT, the impairments may be caused not only by the depressive state, but also time-dependent, ECT-induced side effects. Because patients may be confused in the 2 to 7 days after the final ECT administration, the timing of post-ECT cognitive test administration is an important consideration.[31] Furthermore, the degree of cognitive side effects may depend on the interval between the final ECT treatment and testing. For example, Perera et al[9] administered cognitive tests 2 to 7 days after the ECT course and reported that ictal EEG measurements were not associated with acute disorientation, retrograde amnesia, and verbal and nonverbal anterograde amnesia in unilateral ECT and bilateral, high-dose ECT treatment. However, they found that verbal, nonverbal, and delayed memory declined significantly after bilateral ECT treatment.[31] Hihn et al[4] administered the WMS-R 3 to 5 days after mainly unilateral ECT and found that general memory and visual memory subset scores improved significantly from baseline, but delayed memory scores did not. The group did not evaluate the association between cognitive side effects and ictal EEG features. Patients in the present study received bilateral ECT, and we administered the cognitive tests approximately 14 days after the ECT course. Therefore, our results are not comparable to the Perera et al[9] and Hihn et al[4] studies. We assume that after 2 weeks, ECT-induced acute cognitive confusion had decreased, and depressive, state-dependent memory deficits began to improve in parallel with amelioration of depression. Post-ECT MMSE scores changed from a baseline mean of 27 to 29, demonstrating a lack of ECT-induced acute-phase cognitive deterioration. It was demonstrated that when patients were tested within 2 to 7 days of bilateral high-dose ECT, their modified MMSE scores decreased significantly compared with baseline.[31]

The cognitive process of memory has been divided into the 3 stages of encoding, consolidation, and retrieval. Based on positron emission tomographic studies of episodic memory, Tulving et al[12] reported that the left and right prefrontal lobes are part of extensive neural network subserving the encoding and retrieval of episodic events. Furthermore, Kopelman[32] reported that the degree of retrograde amnesia covaried with frontal lobe function in amnesic patients. In patients with depression, neuroimaging studies have revealed neurophysiological abnormalities in areas of orbital and medial prefrontal cortex, the amygdala, and related parts of the striatum and thalamus.[14] In addition, in a single-photon emission computed tomography imaging study, ictal cerebral blood flow patterns showed that bifrontal ECT increased cerebral blood flow in the prefrontal and anterior cingulate regions, and bitemporal ECT increased cerebral blood flow in the lateral frontal cortex and anterior temporal lobes.[33] In a proton spectroscopy study, patients with depression were reported to have functional abnormalities in the left dorsolateral prefrontal cortex.[15] These studies provide converging evidence for frontal lobe involvement in episodic memory and depression. Thus, we speculate that the improvement in patients with depression showed on the verbal memory, general memory, attention/concentration and delayed memory of WMS-R subsets, and the HAMD resulted from the amelioration of prefrontal cortex dysfunction through ECT-induced seizure, but did not result from decreased ECT-induced cognitive side effects. Moore and Baker[22] reported that visual/verbal discrepancy score predicted only left-side focus in patients with epilepsy. Patients with depression also had functional abnormalities in the left dorsolateral prefrontal cortex, despite ongoing controversy.[15,34,35] In our study, postictal suppression and slow-wave amplitude, which have been reported to be associated with the efficacy of ECT in depression, correlated with visual/verbal discrepancy scores. However, it remains to be determined what the visual/verbal discrepancy score reflects in patients undergoing ECT treatment.

The most persistent adverse cognitive effect in ECT is retrograde amnesia,[36] which we did not assess in this study. Squire and Alvarez[37] noted that the medial temporal lobe memory system was involved in the consolidation process. Furthermore, the magnitude of retrograde amnesia for autobiographical events correlated with increased Θ activity in left frontotemporal regions, based on pretreatment and posttreatment EEG.[11] However, ictal EEG measurements did not correlate with retrograde amnesia assessed by autobiographical memory.[8]

Concerning non–memory-related neuropsychological tests, Fujita et al[5] reported that Stroop test, word fluency, and Trail Making Test scores tended to improve after ECT treatment. In the present study, Stroop test scores improved significantly after ECT treatment, but they did not correlate with ictal EEG measurements. Letter fluency, which correlated with ictal EEG measurements, tended to deteriorate after ECT treatment. Patients with depression had impaired performance in the left prefrontal cortex during verbal fluency tasks in a functional magnetic resonance imaging study,[25] and both word and letter fluency in a verbal

fluency task ameliorated with successful treatment of depression.[38] Thus, decreased letter fluency might be a result of ECT treatment, and approximately 14 days after treatment, ECT-induced cognitive side effects may still remain. The association of verbal fluency and other tests of executive function with the efficacy of ECT treatment and its cognitive side effects needs to be explored further.

In patients with depression, deficits in executive function were classified into 3 groups: set shifting, updating, and inhibition.[39] Verbal fluency involves set shifting, and the Stroop test is associated with inhibition. Slow-wave amplitude, which was a significant ictal EEG measurement in the present study, seems to be linked to set shifting.

Our study has several weaknesses. First, the patient sample size was small. Thus, it was a hypothesis-generation study. A hypothesis-testing study with a larger sample size is warranted to confirm the findings of the present study. Second, antipsychotics and benzodiazepines may have affected the memory and executive performance of our patients. Stewart[40] reported that impairments in visuospatial ability, speed of processing, and verbal learning occurred in patients treated with benzodiazepines, although such deficits may be insignificant in the daily functioning of most patients. In the present study, ECT ameliorated anterograde amnesia, especially verbal memory, general memory, attention/concentration, and delayed memory, although most of our patients were taking benzodiazepines for insomnia. We assume that their cognitive impairments were partially the result of depression and partially the result of benzodiazepine treatment. However, their anterograde memory improved along with their depression. Thus, the degree of cognitive impairment that was due to benzodiazepines is unclear. Cropley et al[41] reported that dopamine activity modulated a range of frontal executive-type cognitive processes, such as working memory, attention, and sequential organization, and that alterations of dopamine activity in fronto-striato-thalamic circuits might contribute to cognitive impairments. Therefore, dopamine-blocking drugs may have affected cognitive function in our patients. In a clinical research setting of ECT treatment, patients with unipolar depressive episodes have high rates of psychotropic drug use.[42] Our patients also took psychotropics, including antipsychotics, benzodiazepines, and antidepressants. Nevertheless, we made only small changes to medications during ECT treatment, and we believe that the before- and after-ECT comparisons are valid. Third, we used 2.0 to 2.5 mg/kg of propofol for anesthesia to prevent patients from waking during the ECT procedure. Therefore, our findings may not generalize to other ECT procedures in which 1.0 mg/kg of propofol is typically used. Fourth, the severity of our patients' depression before treatment was not great. Most of our patients were treatment-refractory, partially remitted patients with major depression. They had a mean of 2.3 (0.7) antidepressant medication trials, and their maximal antidepressant dose in fluoxetine equivalents before ECT was 55.3 (17.5) mg/d. However, their depression was only partially remitted, and they were willing to receive ECT treatment.

In conclusion, certain ictal EEG measurements were associated with changes in some neuropsychological test results that showed improvement 2 weeks after the final ECT treatment. A hypothesis-testing study of a larger sample size is necessary to verify the relationship between EEG measurements and neuropsychological performances.

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Regular Article

Postictal cardiovascular response predicts therapeutic efficacy of electroconvulsive therapy for depression

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Abstract Physiological parameters such as blood pressure (BP) and heart rate (HR) reflect autonomic response after seizure and may correlate with therapeutic efficacy in electroconvulsive therapy (ECT). However, the literature has been inconclusive with regard to the relationship between the effectiveness of ECT and physiological markers without atropine. In a consecutive sample of 24 patients with a drug-resistant major depressive episode who underwent modified sine or pulse wave ECT without atropine, the correlation was examined between BP and HR before, and 2 min after electrical stimulation and therapeutic efficacy on depressive symptoms. When mode of stimulation (sine wave or pulse wave) and baseline Hamilton Rating Scale for Depression (HRSD) were controlled for, postictal diastolic BP, systolic BP, HR and rate pressure product (RPP) were all found to be significant predictors of post-treatment HRSD. When these predictors were entered into stepwise regression, both postictal systolic BP and HR remained as significant predictors. The higher these postical physiological parameters, the more effective the course of ECT. It may be useful to examine such sensitive physiological parameters as BP, HR or RPP to determine effective or non-effective electrical seizure.

Key words cardiovascular response, depressive disorder, electroconvulsive therapy.

INTRODUCTION

Electroconvulsive therapy (ECT) is widely used to treat depression and is considered to be a rapidly acting and effective therapy.[1] There is a theory that generalization of the cerebral seizure to the diencephalon is essential for therapeutic effect,[2] and physiological indices of central generalization have received some research attention.[3] ECT produces an acute surge in plasma catecholamines, cortisol, growth hormone, lutenizing hormone, neurophysin, oxytocin, prolactin, vasopressin, and other hormones and peptides,[4–9] and an acute decrease in plasma γ-aminobutyric acid (GABA).[10] However, none of these acute biochemical changes has shown consistent associations with efficacy.[11] Electroencephalographic (EEG) activity during and following seizure has also received much research attention.[12–14] It was recently reported that the EEG features associated with efficacy might reflect individual differences in the strength of the inhibitory process that terminates the seizure and could help isolate the biological variability that predisposes to positive or negative clinical response to ECT.[14]

Hemodynamic parameters such as blood pressure (BP), heart rate (HR) or rate pressure product (RPP, which is defined as heart rate multiplied by systolic blood pressure) represent another class of possible physiological markers and have been examined with regard to their relationship to therapeutic efficacy of

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ECT. If the cerebral seizure to the diencephalon is essential to the efficacy of ECT, then BP, HR or RPP may be considered to be more suitable indices than EEG seizure activity, which primarily reflects cortical activities.[15] One study supported the relationship between BP or RPP and therapeutic efficacy,[16] while some others failed to do so.[17,18] The use of atropine prior to anesthesia may possibly affect physiological parameters, and one significant study demonstrated that postictal RPP of the second and third sessions under no-atropine condition correlated with therapeutic efficacy.[16]

In the present study we examined BP and HR before electrical stimulus and 2 min after application of the stimulus under no-atropine conditions, in order to study the relationship between these physiologic parameters and therapeutic efficacy on depressive symptoms through the course of ECT.

METHOD

Subjects

The subjects were a consecutive series of depressed inpatients who had not responded to at least 4 weeks of standard pharmacotherapy and were referred for ECT at the Department of Psychiatry, Nagoya City University Hospital. All subjects fulfilled DSM-IV criteria for unipolar major depression, or bipolar disorder/most recent episode depressed.[19] The diagnosis was determined by at least two psychiatrists through a clinical interview and a review of the psychiatric records. Patients with the following conditions were excluded: past or present history of schizophrenia, schizoaffective disorder, significant neurological illness, substance abuse or substance dependence, or any other significant medical illness; grave abnormality on X-ray, computed tomography, or EEG; and/or the administration of ECT within the previous 6 months. Ten days before and after a course of ECT, the severity of depression was assessed using the Structured Interview Guide for the Hamilton Rating Scale for Depression (HRSD).[20] An independent psychiatrist who was not directly involved in the clinical management of the patients completed the ratings. The study protocol was approved by the Ethics Committee of Nagoya City University Medical School. All subjects were informed as to the purpose and procedures of the study, and provided written consent to participate in the study.

Electroconvulsive therapy and medication

Electroconvulsive therapy was administered through electrodes positioned bilaterally on the fronto-temporal region. In Japan we used the sine wave ECT apparatus until 2003, when use of the pulse wave ECT device was approved by the regulatory agency. For sine wave stimuli, CS-1 sine-wave device (Sakai Medical, Tokyo, Japan) was used. Stimulation was delivered at 100–120 V for 5–6 s to produce a tonic–clonic seizure. For pulse wave stimuli, Thymatron System IV (Somatics, Lake Bluff, IL, USA) was used. The stimulation dose was calculated using the half-age method.[21] We selected the Low 0.5 preset program, which used a 0.5-ms pulse width and adjusted the frequency to maximize the duration.[22] The attending anesthesiologist recorded the cardiovascular parameters (HR, and systolic and diastolic BP) during each ECT session after administration of the anesthetic agent and muscle relaxant (before electrical stimulus), and 2 min after application of the electrical stimulus for sine wave ECT or pulse wave ECT. We recorded the EEG seizure during the ECT administration. To ensure the validity of seizure induction, we set the minimum seizure duration to 20 s. If an EEG seizure did not occur or lasted <20 s, re-stimulation at higher stimulus intensity was subsequently carried out by increasing the voltage by 5 V to a maximum of 120 V for sine wave stimuli, or increasing the pulse wave stimuli by 10% up to 100%, for a maximum of three stimulations per session. Seizures were further monitored clinically in a cuffed leg. For patients undergoing sine wave ECT, a mixture of 1.0% sevoflurane and oxygen was inhaled, and 3 mg vecronium bromide was used i.v. for muscle relaxation. Intravenous injection of 2 mg/kg propofol and 3 mg vecronium bromide was performed for patients given pulse wave stimuli. When we began to use the pulse wave device in January 2004, it became harder to produce EEG seizures and we changed the anesthetic agent from sevoflurane to propofol after consulting with an anesthesiologist.

Antidepressants remained unchanged at a minimal dose, usually 20–30 mg/day of fluoxetine equivalent, through the course of ECT. The antidepressant equivalence was calculated according to the World Health Organization (WHO) defined daily dosage method.[23] Lithium carbonate and sodium valproate were withdrawn before the first ECT. Due to clinical considerations, the use of benzodiazepine was permitted during the study to alleviate insomnia and anxiety. Benzodiazepine dosage at the time of the first ECT session never exceeded 4 mg/day of lorazepam or its equivalent. Eight patients were given antipsychotics and two received antiparkinson drugs. One patient used atropine for bradycardia following anesthesia. No patients received antihypertensive medications.

Statistical analysis

We analyzed physiological parameters of all valid ECT sessions. Predictors of HRSD improvement were investigated for each physiological parameter (baseline or postictal systolic and diastolic BP, HR, and RPP, respectively) separately through multiple regressions, always controlling for baseline HRSD and mode of stimulation, because these variables have been found to be significant predictors of post-treatment HRSD. When significant variables emerged, we entered them into stepwise multiple regression (P to enter, <0.05; P to remove, >0.10) in order to look for the strongest predictor(s) of post-treatment HRSD while always forcibly controlling for baseline HRSD and mode of stimulation. The significance level was set at $P < 0.05$, two-tailed. We used SPSS 11.5 (SPSS, Chicago, IL, USA, 2002) for all statistical analyses.

RESULTS

Of 26 consecutive patients (11 in the sine wave group, 15 in the pulse wave group), one patient developed angina and another refused ECT due to delirium in the pulse wave group during the study period. We therefore included 24 patients (11 in the sine wave group and 13 in the pulse wave group) in the following analyses.

Table 1 shows the clinical and demographic characteristics of the 24 evaluable patients. Prior to ECT, each subject in the sine wave group had received 2.1 ± 0.7 (mean ± SD) antidepressant medication trials. Maximal antidepressant dose in fluoxetine equivalents prior to ECT was 50.5 ± 22.1 mg/day. The actual average amount of electricity delivered with the pulse wave apparatus was 224.2 ± 91.7 mC, while the electrical dose in sine wave machine could not be measured due to the limitation of the apparatus used. During the course of ECT, patients received 41.3 ± 25.5 mg/day fluoxetine equivalents. The mean HRSD scores decreased from 18.1 ± 7.2 to 9.1 ± 6.4 ($P < 0.001$, paired t-test, two-tailed). The proportion of patients with >50% reduction or scoring ≤8 on the HRSD was 54%. No significant differences in antidepressant medication trials, maximal antidepressant dose, antidepressant dosage during ECT or major tranquilizer during ECT were noted between the sine and pulse wave groups. Neither pretreatment HRSD nor post-treatment HRSD differed significantly between the two groups.

Table 2 shows hemodynamic parameters before and after ECT stimulation. When we controlled for mode of stimulation (sine wave or pulse wave) and baseline HRSD, postictal diastolic BP, systolic BP, HR and RPP were all found to be significant predictors of post-treatment HRSD (Table 3). When we entered all these predictors into stepwise regression, both postictal systolic pressure and HR remained as significant predictors (model R = 0.53).

Table 1. Baseline characteristics of sine wave and pulse wave groups

	Mean	SD
Age (years)	49.9	11.9
Sex (male : female)	12:12	
Diagnosis (MDD:BD)	20:4	
Current episode in month	18.4	19.9
Previous episode	2.4	2.9
Age of onset (years)	39.8	14.1
Baseline HRSD	18.1	7.2
Post-treatment HRSD	9.1	6.4
Stimulus mode (sine: pulse)	11:13	
No. ECT administrations	10.3	2.1
Motor seizure duration (s)	50.3	20.8

BD, bipolar disorder; ECT, electroconvulsive therapy; HRSD, Hamilton rating scale for depression; MDD, major depressive disorder.

Table 2. Blood pressure, pulse rate and RPP before and after ECT

	Baseline		Postictal	
	Mean	SD	Mean	SD
Systolic BP	120.1	23.8	138.5	27.0
Diastolic BP	76.7	17.0	85.4	19.2
HR	80.6	18.8	84.3	20.6
RPP	9875	3790	11773	4093

BP, blood pressure; HR, heart rate; RPP, rate pressure product.

Table 3. Multiple regressions predicting post-treatment HRSD, controlling for baseline HRSD and mode of stimulation

Hemodynamic variable	β	P
Postictal diastolic BP	−0.16	0.013
Postictal systolic BP	−0.22	0.001
Postictal HR	−0.18	0.006
Postictal RPP	−0.23	<0.001

BP, blood pressure; HR, heart rate; RPP, rate pressure product.

DISCUSSION

The present study demonstrated that postictal diastolic BP, systolic BP, HR, and RPP predicted therapeutic efficacy after the course of ECT. The higher these postical physiological parameters, the more effective the course of ECT.

The extant literature had been inconclusive with regard to the relationship between the effectiveness of ECT and physiological markers. A significant relationship failed to be demonstrated between post-treatment HRSD scores and rise in systolic BP, that is, the difference between the post-anesthetic level of systolic BP and the maximum level attained after the administration of ECT, under atropine condition.[17] Similarly, correlations between the magnitude of peak postictal BP and HR increases and post-treatment HRSD were non-significant.[18] In contrast, in the present study postictal systolic BP and HR remained as the predictors of post-treatment HRSD under no atropine through stepwise regression among four predictors. Thus these parameters need to be examined as to whether they are useful markers of the effective seizure.

However, the use of atropine before electrical stimuli to prevent parasympathetic accident may have affected these results. Hemodynamics during and after seizure with or without atropine showed that, without atropine, BP and HR were elevated to maximum levels during the seizure, declined to near-baseline level, and then had a small transient re-elevation soon afterwards; but under atropine conditions maximum BP and HR during seizure gradually decreased to the baseline level without re-elevation.[24] Thus it was considered that atropine affected the correlation between postictal cardiovascular response and effectiveness of treatment.[25] In a randomized controlled trial postictal RPP was significantly higher in early remitters than in late remitters, and when no atropine was given the postictal RPP in the second or third ECT treatment appeared to reflect physiological effects relevant to therapeutics.[16] In the present sample no patients had significant cardiovascular side-effects without atropine before anesthesia. The present study appears to be the first to examine hemodynamic parameters through the course of the ECT session under no-atropine conditions.

Several caveats are in order before we conclude. First, although we could keep several potential confounders constant and carried out blinded assessments, the present study is not a randomized controlled trial, and may therefore be subject to unknown biases. Second, we used sevoflurane and propofol as anesthetics in the sine wave and pulse wave ECT, respectively. Loughnan *et al.* reported in a randomized cross-over trial that under the use of atropine, the HR in a sevoflurane group increased by 9.4 b.p.m. in comparison with a propofol group at 5 min after the stimuli, and the mean BP increased by approximately 9 mmHg in comparison with a propofol group.[26] However there were substantial concentration differences of sevoflurane (8% or 1%) and propofol (1.0–1.5 mg/kg or 2 mg/kg) between the Loughnan *et al.* study and the present study, so that we concluded that the results between the two studies could not be directly compared. Even so, hemodynamic parameters at 2 min after the stimuli predicted post-treatment HRSD when the different anesthetic groups were combined. We controlled for these possible confounders by always controlling for the stimulation mode in multiple regressions. Third, the antidepressant equivalence was calculated by fluoxetine equivalent. Glassman reported that all tricyclic antidepressants (TCA) delayed cardiac conduction and increased HR, but in healthy adult patients these are seldom of any clinical significance. Selective serotonin re-uptake inhibitors (SSRI) slow pulse rates modestly but do not influence PR, QRS, or QTc measures, and even this modest slowing seems to diminish or disappear within a few weeks. SSRI have no effect on conduction even in patients with pre-existing conduction disorders.[27] We therefore analyzed TCA and SSRI groups together and converted them into fluoxetine equivalents.

In conclusion, postictal systolic BP, diastolic BP, HR, and RPP predicted the therapeutic efficacy of ECT when measured without coadministration of i.v. atropine. It may be useful to examine such sensitive physiological parameters to determine effective or non-effective electrical seizure.

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Regular Article

Postictal suppression correlates with therapeutic efficacy for depression in bilateral sine and pulse wave electroconvulsive therapy

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Abstract Ictal electroencephalography (EEG) parameters in electroconvulsive therapy (ECT) for depression reportedly correlate with therapeutic response and stimulus dosage, particularly in right unilateral (RUL) ECT. The authors examined ictal EEG parameters as predictors of therapeutic effectiveness in bilateral (BL) sine and pulse wave ECT. A total of 30 consecutive depressed inpatients who had not responded to standard pharmacotherapy were treated using BL ECT given in either sine or pulse wave mode. Ictal EEG parameters (e.g. regularity, postictal suppression) were manually rated by three trained psychiatrists. Polyspike phase duration was significantly longer in sine wave ECT than in pulse wave ECT. Postictal suppression emerged as the only significant predictor of therapeutic outcome when baseline Hamilton Rating Scale for Depression and mode of stimulation were controlled for. Postictal suppression appears to offer a useful predictor of clinical outcome of depression in BL ECT. No EEG parameters were found to be differentially predictive between sine and pulse wave ECT.

Key words depressive disorder, electroconvulsive therapy, electroencephalography, postictal suppression.

INTRODUCTION

Electroconvulsive therapy (ECT) is widely used to treat depression and is considered to be a rapidly acting and effective therapy.[1] This approach is especially indicated for patients who are unresponsive to conventional antidepressant pharmacotherapies.

For decades, generalized seizure was thought to provide necessary and sufficient conditions for the antidepressant effects of ECT.[2] Various aspects of ictal and immediately postictal electroencephalography (EEG) parameters have been studied as possible predictors of antidepressant effectiveness. In the first place, seizure duration has been shown to have limited relevance to efficacy. Conversely, several studies have found that patients with superior clinical outcome had greater ictal amplitude in the delta frequency band and greater postictal suppression in right unilateral (RUL) or bilateral (BL) pulse wave ECT.[3–6]

In Japan, the authors used the sine wave ECT apparatus until 2003, when use of the pulse wave ECT device was approved by the regulatory agency. Sine wave ECT required approximately threefold greater stimulus energy compared to pulse wave ECT producing equivalent supra-threshold seizures.[7] However, no difference exists between the effectiveness of sine and pulse wave stimuli on depressive symptoms, and degree of stimulus dosage correlated with degree of cognitive impairment.[1] Pulse wave ECT, therefore, appears superior to sine wave ECT because of fewer cognitive problems.

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Ictal EEG parameters have been shown to differentiate low dosage RUL pulse wave ECT from moderately supra-threshold RUL pulse wave ECT,[6] but differences in ictal EEG expression due to wave mode or associated relationships to therapeutic effects have not yet been fully elucidated. The present study, therefore, compared ictal and peri-ictal EEG parameters between BL sine and pulse wave ECT, and investigated ictal EEG parameters predicting antidepressant therapeutic outcomes in BL sine and pulse wave ECT.

METHODS

Subjects

The subjects comprised 33 consecutive depressed inpatients who were referred for ECT in the Department of Psychiatry at Nagoya City University Hospital, Nagoya, Japan, following lack of response to previous treatment with at least one full-dose antidepressant medication for ≥4 weeks or intolerance to such medication. All subjects fulfilled Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for unipolar major depression or bipolar disorder, with depression as the most recent episode.[8] Diagnosis was determined by psychiatrists through a clinical interview and review of psychiatric records. Patients with the following conditions were excluded: past or present history of schizophrenia, schizoaffective disorder, significant neurological illness, substance abuse or substance dependence; any other significant medical illness; grave abnormality on chest radiography, brain computed tomography or EEG; or administration of ECT within the previous 6 months. Within 10 days before and after a course of ECT, depression severity was assessed using the Structured Interview Guide for the Hamilton Rating Scale for Depression (HRSD).[9] Ratings were completed by an independent psychiatrist not directly involved in the clinical management. This study protocol was approved by the Ethics Committee of Nagoya City University Medical School. All subjects were informed about purposes and procedures of ECT and provided written consent to participate in the study.

Electroconvulsive therapy and medication

ECT was given through electrodes positioned at the standard bifrontotemporal location. In that position, each electrode was placed on a perpendicular line 3 cm above the midpoint of the line joining the external auditory meatus and outer canthus of the eye. For sine wave stimuli, a CS-1 sine wave device (Sakai Medical, Tokyo, Japan) was used. Stimulation was delivered at 100–120 V for 5–6 s to produce a tonic clonic seizure. Two channels of EEG (C3-A1, C4-A2, international 10–20 system) were monitored and recorded onto paper from the end of stimuli using a Lifescope 12 monitor (Nihon Kohden, Tokyo, Japan). For pulse wave stimuli, a Thymatron System IV ECT apparatus (THYMATRON System IV, Somatics, Inc., Lake Bluff, IL, USA) containing an inbuilt EEG system (Fp1-A1, Fp2-A2, international 10–20 system) was used. Stimulation dose was calculated using the 'half age' method.[10] A LOW 0.5 preset program using 0.5 ms pulse width was selected, adjusting frequency to maximize duration.[11] The criterion for an adequate seizure was an electroencephalographic seizure lasting ≥20 s. If no electroencephalographic seizure had occurred after 20 s, re-stimulation at a higher stimulus intensity was immediately performed by increasing voltage by 5 V up to 120 V for sine wave stimuli, or by 10% for pulse wave stimuli, to a maximum of three stimulations/session. Motor seizures were further monitored in a cuffed leg. For patients undergoing sine wave ECT, a mixture of 1.0% sevoflurane and oxygen was inhaled, and 3 mg vecronium bromide was used intravenously for muscle relaxation. Intravenous injection of 2.5 mg/kg propofol and 3 mg vecronium bromide was performed for patients given pulse wave stimuli. When the authors started using the pulse wave device in January 2004, electroencephalographic seizures were harder to produce. The authors, therefore, consulted with an anesthesiologist and changed anesthetic agent from sevoflurane to propofol.

Antidepressants remained unchanged at a minimal dose throughout the course of ECT. Lithium carbonate and sodium valproate were withdrawn before first ECT. Due to clinical considerations, use of benzodiazepine was permitted during the study to alleviate insomnia and anxiety (sine wave group, $n = 13$; pulse wave group, $n = 6$). Benzodiazepine dosage at the time of the first ECT session was ≤4 mg/day of lorazepam or equivalent. In the sine wave group, four patients were given major tranquilizers, for example, chlorpromazine, levomepromazine or sulpiride, and one patient received the antiparkinson drug promethazine at 75 mg/day. In the pulse wave group, six patients were given major tranquilizers, for example, chlorpromazine, levomepromazine, risperidone or perphenazine, and one patient received biperiden 2 mg/day.

Electroencephalography analysis

A total of 73.8% of EEG in the sine wave group and 97.3% of EEG in the pulse wave group were examined. In the sine wave group, some ictal EEG were missing or were unsuitable for analysis due to artifacts during

recordings. Ictal and peri-ictal EEG parameters, including polyspike phase maximal amplitude (mV), polyspike phase duration (s), slow wave phase maximum amplitude (mV), slow wave phase duration (s), regularity (global seizure strength, 7-point scale ranging from 0 to 6), stereotypy (global seizure patterning, 4-point scale ranging from 0 to 3), and postictal suppression (degree of postictal bioelectric suppression, 4-point scale ranging from 0 to 3) were manually rated by three experienced psychiatrists using standard methods from the literature.[12–14]

The polyspike phase was defined as starting with the offset of stimulation and terminating point at which visually discernible slow wave activity fully replaced early chaotic polyspike activity. The slow wave phase was defined as the period from this time point until seizure termination. Maximal amplitudes during the polyspike and slow wave phases were defined by the largest peak to peak deflections in the relevant phase, then mean maximal amplitude was determined for each patient. Seizures were rated as more stereotypic if a clear progression from low amplitude chaotic polyspike activity to high amplitude slow wave activity was seen without reappearance of chaotic polyspike activity or marked variability in amplitude during phases. Seizures were rated as having greater regularity if slow wave activity of high amplitude predominated regularly during the slow wave phase. Higher numbers indicate increasing stereotypy and regularity of the ictal EEG recording. Postictal suppression was rated as follows: 0, cannot tell where the seizure ends; 1, seizure termination is clear, but suppression is poor (not flat); 2, good seizure suppression (very flat), but transition to flat is gradual; and 3, good seizure suppression (very flat), and transition is abrupt. Interrater reliability among the three raters was examined by calculating ANOVA intraclass correlation coefficient (ANOVA ICC).

Statistical analysis

All results are expressed as mean ± standard deviation (SD). The level of statistical significance was set at $\alpha = 0.05$. To investigate possible differences in ictal EEG parameters between sine and pulse wave stimuli, *t*-tests and χ^2 tests were used (two-tailed). Predictors of HRSD improvement among ictal EEG parameters were investigated for each parameter separately through multiple regression, always controlling for mode of stimulation and baseline HRSD. SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Among consecutive 33 patients (sine wave group, $n = 18$; pulse wave group, $n = 15$), two patients developed angina (sine wave group, $n = 1$; pulse wave group, $n = 1$) and one patient in the sine wave group refused ECT due to delirium during the study period. As a result, 30 patients participated in the study (sine wave group, $n = 16$; pulse wave group, $n = 14$). The pulse wave group contained a significantly greater proportion of women than the sine wave group (Table 1). All patients displayed normal results on routine hematological, biochemical and thyroid function testing, chest radiography and EEG.

Prior to ECT, each subject in the sine wave group had received 1.8 ± 0.7 antidepressant medication trials and each subject in the pulse wave group had received 2.2 ± 0.7 antidepressant medication trials. Maximal

Table 1. Clinicodemographic characteristics of the patient sample

	Sine wave ECT ($n = 16$)		Pulse wave ECT ($n = 14$)		
	Mean	SD	Mean	SD	*P*
Age (years)	53.9	11.0	49.4	13.3	0.32
Gender (% female)	25.0		60.0		0.03
Age of onset (years)	44.0	15.4	38.5	14.5	0.33
Number of previous episodes	1.8	1.6	2.7	2.9	0.27
Duration of current episode (months)	18.4	21.6	17.1	16.9	0.85
Polarity (% bipolar)	12.5		13.3		0.89
Number of ECT administrations	10.0	1.8	10.7	2.3	0.34
Baseline HRSD	18.8	6.6	17.7	7.4	0.67
Post-treatment HRSD	7.5	5.1	10.0	6.8	0.26

$P < 0.05$; t-test (two-tailed), χ^2 test.
ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression; SD, standard deviation.

Table 2. Comparison of ictal electroencephalography characteristics between sine wave and pulse wave electroconvulsive therapy

	Sine wave ECT ($n = 16$)		Pulse wave ECT ($n = 14$)		
	Mean	SD	Mean	SD	P
Polyspike phase duration (s)	8.4	5.4	4.7	2.3	0.02
Polyspike phase amplitude (μV)	132.5	61.7	99.5	32.3	0.08
Slow wave phase duration (s)	46.5	9.4	60.8	29.4	0.10
Slow wave phase amplitude (μV)	528.1	131.1	466.1	138.6	0.22
Regularity (0–6)	4.5	0.86	4.4	0.83	0.66
Stereotypy (0–3)	1.67	0.42	1.86	0.44	0.25
Postictal suppression (0–3)	1.95	0.56	1.7	0.52	0.26

$P < 0.05$; t-test (two-tailed).
ECT, electroconvulsive therapy; SD, standard deviation.

antidepressant dose in imipramine equivalents prior to ECT was 223.7 ± 116.9 mg/day in the sine wave group and 273.9 ± 92.1 mg/day in the pulse wave group. During the course of ECT, patients in the sine and pulse wave groups received 165.9 ± 83.4 mg/day and 246.1 ± 147.4 mg/day of imipramine equivalents and 40.9 ± 86.7 mg/day and 58.4 ± 133.4 mg/day of chlorpromazine equivalents, respectively. No significant differences in antidepressant medication trials, maximal antidepressant dose, antidepressant dosage during ECT or major tranquilizer during ECT were noted between sine and pulse wave groups.

The actual amount of electricity delivered with the pulse wave apparatus was 224.2 ± 91.7 mC, while electrical dose in the sine wave machine could not be measured. Mean HRSD scores decreased from 18.8 ± 6.6 to 7.5 ± 5.1 with sine wave ECT ($P < 0.001$, paired t-test, two-tailed) and from 17.7 ± 7.4 to 10.0 ± 6.8 with pulse wave ECT ($P = 0.002$, paired t-test, two tailed). The proportions of patients showing >50% reduction or scoring ≤8 on the HRSD were 63% and 43%, respectively ($P = 0.28$, χ^2 test, two-tailed). Neither pretreatment HRSD nor post-treatment HRSD differed significantly between the two groups.

Mean number of analyzable ictal EEG was significantly fewer in the sine wave group than in the pulse wave group (sine wave group, 7.4 ± 3.0; range, 3–12; pulse wave group, 10.4 ± 2.3; range, 6–14; $P = 0.004$, t-test, two-tailed). ANOVA ICC were 0.61, 0.71, 0.92, 0.89, 0.84, 0.67 and 0.82 for polyspike phase amplitude, polyspike duration, slow wave phase amplitude, slow wave phase duration, regularity, stereotypy and postictal suppression, respectively. Less-than-satisfactory reliability was observed for polyspike phase amplitude and stereotypy.

Table 2 shows a comparison of ictal EEG parameters between sine and pulse wave groups. Only polyspike phase duration differed between the two groups, being significantly longer in the sine wave group.

Table 3. Multiple regression predicting post-treatment Hamilton Rating Scale for Depression, controlling for mode of stimulation (sine or pulse wave) and baseline Hamilton Rating Scale for Depression

	β	SE	P
Baseline HRSD	0.30	0.05	<0.01
Sine wave or pulse wave	0.18	0.67	0.03
Postictal suppression	−0.15	0.34	0.01

$P < 0.05$; Adjusted $R^2 = 0.13$, $F = 13.9$, $P < 0.01$.
None of the other six electroencephalography parameters similarly entered in multiple regression was significant.
HRSD, Hamilton Rating Scale for Depression; SE, standard error of the mean.

Each ictal EEG characteristic was individually examined through multiple regression predicting post-treatment HRSD, always controlling for mode of stimulation (sine or pulse wave) and baseline HRSD. Only postictal suppression emerged as a significant predictor (Table 3).

DISCUSSION

When ictal EEG parameters were compared between BL sine and pulse wave ECT, only polyspike phase duration was significantly longer in the former mode. This finding is inconsistent with previous results, which have shown that higher stimulus dosage results in better therapeutic efficacy and shorter polyspike duration.[1,7,12] The significantly longer polyspike phase duration for BL sine wave ECT compared to pulse wave ECT may be associated with cognitive impairments and needs be examined in a future study.

The authors also found that postictal suppression was significantly associated with post-treatment HRSD when baseline HRSD and mode of stimulation were controlled for. This finding is in accordance with those of previous studies, which have shown a relationship between postictal suppression and therapeutic outcomes.[4–6] Evidence also indicates that a higher amplitude of slow wave activity is associated with therapeutic effects,[15–16] but the authors could not show this in the current study. Regarding the effectiveness of ECT and EEG features, for example, postictal suppression, Sackeim *et al.* hypothesized that postictal inhibitory response to the seizure, rather than seizure itself, is therapeutic.[17] In effective ECT, postictal suppression, prefrontal slowing following the ECT course, diminished cerebral blood flow (CBF) and metabolism suggest that relative enhancement in prefrontal inhibition is involved in the mechanism of action for ECT.[18] The authors have also reported decreased regional CBF in the left medial frontal area and left limbic region after successful ECT.[19] As effective ictal EEG could be differentiated from noneffective ictal EEG in RUL ECT, the suggestion has been made that ictal EEG parameters might be utilized to guide adequate stimulus dosage and, therefore, optimize therapeutic effectiveness.[3,20,21] However, even in RUL ECT, EEG features reportedly began to saturate when ECT voltage dose was only modestly above stimulus threshold. The window for electrical dosage effect on EEG seizure expression was, therefore, considerably narrower than that for efficacy.[6] Conversely, ictal EEG seizure in BL pulse wave ECT could be differentiated between low and high stimulus doses using computed fractal geometry methods.[22] Although in this study the authors could not examine the electrical dosage effect in ictal EEG parameters between BL sine and pulse wave ECT, the correlation between ictal EEG parameters and electrical dose in BL pulse wave ECT is thought to be a matter of clinical importance.

Several caveats should be noted, including: (i) a greater proportion of inadequate EEG in the sine wave group; (ii) lower agreement of ANOVA ICC for polyspike phase duration, polyspike phase amplitude and stereotypy, indicating that these parameters were ambiguous and difficult to define; (iii) change of anesthetic agents for sine and pulse wave ECT by the anesthesiologists worked with (however, in a randomized controlled trial, both sevoflurane and propofol groups exhibited equally good seizures and the sevoflurane group displayed slightly better morphology, which the authors failed to differentiate from)[23]; (iv) some patients in both groups were given antidepressants, minor tranquilizers such as benzodiazepines, antiparkinson drugs and major tranquilizers, and the psychotropics they received might have influenced seizure threshold, although the degree of effects on ictal seizure expression is unclear; and (v) the current study was not a randomized controlled trial and may, therefore, be subject to unknown biases.

This study adopted manual ratings for ictal EEG expression, as manual ratings correlate with computerized analysis of ictal EEG parameters.[6] If ictal EEG parameters in BL ECT had some potential as a useful marker for guiding stimulus dosage, psychiatrists would have to manually rate ictal EEG parameters in the clinical scene and then adjust stimuli dosage accordingly. Explicit criteria for rating ictal EEG parameters, including stereotypy, regularity and postictal suppression, will, therefore, be required to improve interrater reliability of ictal EEG,[24,25] and further ictal EEG parameters or other physiological markers need to be explored as clinically useful tools to adjust electrical dose.

In conclusion, when BL sine and pulse wave ECT were compared in terms of ictal EEG parameters, polyspike phase duration was significantly longer in sine wave mode. When baseline HRSD score and mode of ECT were controlled for, postictal suppression predicted around 13% of the variance in treatment response of cases. Further accumulation of clinical experience with BL pulse wave ECT is required to detect ictal EEG parameters or other physiological markers that could usefully predict and guide effective administration of ECT for depression.

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ILAE GRAY MATTERS

OBITUARY

In Memory of Masakazu Seino

Professor Masakazu Seino passed away on March 7, 2007. He was born in Hokkaido, in the northern part of Japan, on July 25, 1930. He graduated from Hokkaido University School of Medicine in 1954. After graduation he moved to Tokyo First National Hospital. For 7 years (1954 to 1961) he trained himself as a neuropsychiatrist. He then went to Canada as a postdoctoral research fellow at the Institute of Neurological Research, University of British Columbia (Prof. Juhn A. Wada, Director). In 1963 he came back to Japan and moved to the National Musashi Institute for Mental & Nervous Disease in order to establish a ward for patients with epilepsy. During the next 12 years he completed three important works. First was the foundation of an association for people with epilepsy, which became the Japan Epilepsy Association in 1976; second was the introduction of serum level monitoring of antiepileptic drugs; and third was the introduction of the video-EEG monitoring method to analyze epileptic seizures. The latter two methods are now used for the classification and treatment of seizures throughout Japan. In 1975, Dr. Seino moved to Shizuoka with Prof. Toyoji Wada in order to build a national epilepsy center for comprehensive care, and then served as the medical director of the center at the request of the Japanese Ministry of Welfare. He worked diligently as the medical director and director-general until 1996, and then as honorary president at the Epilepsy Center in Shizuoka, Japan.

Dr. Seino wrote 71 articles and chapters as first author, and coauthored 141 articles and chapters. He was a board member of the Japanese Epilepsy Research Group from 1967 to 1981, and secretary general from 1973 to 1981. Since 1981 he served as a board member of the Japan Epilepsy Society. In 1989 he was elected president of the Japan Epilepsy Society (1989–1997). At the International Epilepsy Congress in Kyoto, 1981, Dr. Seino played a major role as secretary general. He was elected vice president of the International League Against Epilepsy (ILAE) (1981–1989), and served as treasurer from 1989 until 1993. He was a member of the ILAE Commission on Classification and Terminology (1981–2006), was chairman of the Rules Commission (1983–1985), the Commission on Nomination (1985–1989), and a member of the Commission on Constitutional Affairs (1993–2006). After retirement from the Japan National Epilepsy Center, Dr. Seino devoted himself to the Asia–Oceania Epilepsy

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Organization and to teaching courses on epileptology. His goal was to encourage treatment for people with epilepsy in Asian–Oceanian countries that was equivalent to the treatment received by epilepsy patients in European countries. Toward that goal, Dr. Seino organized the Commission on Asia-Oceania Affairs, and included the Asian Epilepsy Academy under the umbrella of the ILAE. His ideas are now being realized in the Asian-Oceanian countries, and his dreams will come true in the future.

A thousand winds blow the mountain cherry blossom loved by Dr. Seino. A cherry blossom petal flies to our heart. Masakazu Seino didn't pass away; he lives in our hearts forever.

Kazuichi Yagi

LETTERS/COMMENTARY

Neuroleptic Malignant Syndrome-like State in an Epileptic Patient with Organic Brain Comorbidity Treated with Zonisamide and Carbamazepine

To the Editors:

Neuroleptic malignant syndrome (NMS) involves the dopaminergic system. Dopamine agonists can lead to an NMS-like state when they are withdrawn. We found that cotreatment with zonisamide (ZNS) and carbamazepine (CBZ) led to a side effect that was similar to NMS. Our case is the first report of an NMS-like side effect associated with ZNS or ZNS in conjunction with CBZ. Our case should forewarn clinicians that abrupt interruption of ZNS,

and/or an increase in coadministered CBZ, could cause an imbalance in dopamine activity resulting in an NMS-like state in epileptic patients with organic brain comorbidity.

The patient was a 24-year-old man with severe mental retardation and symptomatic partial epilepsy. His electroencephalography showed a basic rhythm of high voltage 9–11 Hz predominantly in the occipital region, and occasional sharp waves in the right frontal, central, and parietal regions. Head computed tomography revealed no abnormality. Since his last secondarily generalized tonic–clonic seizure was observed at the age of 22, however, he has behaved violently toward his father. After that, he was referred to our psychiatric outpatient clinic. We determined that his violence could be associated with his epilepsy, and therefore gradually increased his ZNS dosage from 160 mg to 300 mg, resulting in a ZNS blood concentration of 35.6 ug/ml. This treatment resolved his complex partial seizure and initially decreased his violent impulses. However, his violent behavior returned, so we treated him with 3 mg/day of risperidon. This treatment had no effect and was quickly terminated. We then hypothesized that his violent outbursts could be a side effect of ZNS. Approximately two months after attempting risperidon, we stopped ZNS altogether and increased the CBZ dosage from 400 mg to 600 mg. He was also on a constant dosage of 1.6 mg clonazepam. On the fourth day of this new regimen, he became incontinent and drowsy and we advised him to begin taking ZNS again at a dosage of 300 mg/day. He gradually became agitated. After seven days, he was still agitated and suffered from sialorrhea, dysphagia, and choreiform movements such as retrocollis. His serum concentrations of ZNS and CBZ were 16.2 μg/ml and 8.7 μg/ml, respectively. On the 11th day he had a high fever (38.5°C), was perspiring heavily, and was excited. He was congenitally spastic, but we noted slightly increased muscle rigidity and the patient was no longer able to walk alone. He was immediately admitted to our psychiatric ward. We found no sign of infection or thyroid disease. Creatine phosphokinase (CK) was elevated to 1950 U/l (normal range: 62–287 U/l). His maximum CK level of 2826 U/l occurred the day after admission. Blood tests revealed that his white blood cell count (WBC) was 8200/mm^3 (his baseline WBC was approximately 4000/mm^3). C reactive protein was 0.04 mg/dl. Aspartate aminotransferase and alanine aminotransferase were 48 U/l (normal range: 10–33 U/l) and 27 U/l (normal range: 6–37 U/l), respectively. His blood pressure and heart rate were unstable, ranging from 130–170 to 65–100 mmHg and between 85 and 110/min, respectively. We diagnosed him with NMS-like state, and the medicines were all discontinued. Phenytoin (PHT) was administered intravenously. He was given 2000–3000 mL/day of fluids, but the high fever continued (38.5–39.2°C). On the day after admission, 40 mg/day of dantrolene was given intravenously. Subsequently the high fever gradually decreased. Within four days he was back at a normal body temperature, CK was 575 U/l, and all other laboratory tests were within normal limits. He became calm and his unstable blood pressure, heart rate, and diaphoresis all ceased. We concluded that he had recovered from his NMS-like state and dantrolene was discontinued.

DISCUSSION

In epileptic patients, ZNS exerts its anticonvulsant activities by blocking the spread or propagation of seizure discharges, just like PHT and CBZ (Leppik, 2004). Recently, a randomized controlled trial demonstrated that ZNS improves Parkinson's disease due to increased dopamine synthesis (Murata et al., 2007). ZNS could therefore cause an NMS-like state if the drug administration regimen leads to an imbalance in dopamine levels (Pope et al., 1986; Caroff and Mann, 1993).

In this patient, ZNS was abruptly discontinued while CBZ was simultaneously increased because we suspected that the violent behavior was probably caused by ZNS (Ettinger, 2006). We suspect that it was the sudden interruption of ZNS treatment that was mainly responsible for the initiation of the patient's NMS-like state. In addition, CBZ is a CYP3A4 inducer and accelerates the metabolism of ZNS, thereby promoting the development of the NMS-like state through a further decrease in ZNS blood concentration. In this case CBZ lowered the plasma level of ZNS nearly 50% in only three days, from 35.6 μg/ml to 16.2 μg/ml, despite the long half-life of ZNS (T1/2 = 63–69 h) (Leppik, 2004). The cerebral palsy may have also affected the developing NMS-like state, because organic brain disease and mental retardation are frequently seen in cases of NMS (Gurrera, 1999).

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