Zonisamide Decreases Current-Source Density of High Beta Frequency of Electroencephalogram

Oh-Young Kwon[1], Sung-Pa Park[2]

[1]Department of Neurology and Institute of Health Science, Gyeongsang National University School of Medicine, Jinju; [2]Department of Neurology, Kyungpook National University School of Medicine, Daegu, Korea

Background and Purpose: The purpose of this study was to investigate changes in brain current-source density (CSD) of the high frequency band (22-30 Hz) induced by zonisamide (ZNS) in patients with newly diagnosed epilepsy and to correlate with the cognitive performances.

Methods: We conducted a 24-week, open-labeled, prospective study in 19 patients. Electroencephalography (EEG) and neuropsychological tests (NPs) were conducted at baseline and 24 weeks after starting the medication. Six patients were excluded due to artifacts in EEG. One patient did not attend follow-up studies. Twelve patients who completed follow-up EEG and NPs were included. We used low-resolution brain electromagnetic tomography to determine CSD, and we obtained statistical nonparametric maps for the high beta frequency band (22-30 Hz) between pretreatment EEGs and post-treatment EEGs.

Results: The CSD in the 22-30 Hz band decreased in the superior frontal, middle frontal, anterior cingulate, precentral, postcentral, and inferior parietal gyri of the left hemisphere, and the middle frontal, inferior frontal and anterior cingulate gyri of the right hemisphere. Among the NPs items, the performance of verbal fluency was significantly impaired after the 24-week ZNS trial.

Conclusions: The CSD changes suggest ZNS may diminish the activity of cerebral networks related to verbal fluency. **(2013;3:63-69)**

Key words: Electroencephalography, Current source density, Cognition, Zonisamide, Epilepsy

Introduction

Patients with epilepsy often experience cognitive dysfunction, and antiepileptic drugs (AEDs) can also adversely affect cognitive function. In general, these effects on cognition are less severe with modern AEDs than with classic AEDs, with the exception of topiramate and zonisamide (ZNS).[1-3] ZNS is an AED approved for adjunct treatment of partial seizures in adults.[4] It may also be effective for treating idiopathic and symptomatic generalized epilepsies.[5] ZNS is a tolerable antiepileptic drug for long-term use. Previous long-term studies have reported that 50-60% of patients will continue to take ZNS for more than 1 year.[6] Although the adverse effects of ZNS are generally mild to moderate, cognitive adverse events (CAEs) such as cognitive slowing, memory deficit, and language dysfunction are disturbing to patients.[1,7,8] The association between ZNS and CAEs has been confirmed by neuropsychological testing studies.[1,8] The incidence of CAEs is 2-11%.[8-10] Slow titration according to careful dosing schedules may be helpful to reduce CAEs because they are usually related to dose and titration.[8-10] The incidence of serious CAEs associated with early discontinuation of ZNS was 5.8% in a case-control study.[11] The most common CAEs were language impairment and cognitive slowing. Word-finding difficulty and dysfluent speech were the most common manifestations among language problems in the study.[11]

Electroencephalography (EEG) analyses may be helpful in investigating the cognitive function of patients with epilepsy and the effects of AEDs. However, visual inspection of multichannel EEG data is insufficient to determine the brain current source associated with cognitive processes, as many combinations of current sources with various locations and strengths in the brain may generate the same signal in scalp electrodes. Current-source analysis (CSA) using digital EEG data is used to directly measure the current source produced by neuronal activity. CSA uses mathematical methods to analyze the electrical potentials at scalp electrodes and to determine the location of current sources.[12] Low-resolution brain electromagnetic tomography (LORETA) is a CSA method that utilizes a distributed current-

source model. By assuming that the smoothest of all possible inverse solutions is the most plausible and that neighboring neurons are active simultaneously and synchronously, this technique localizes the cerebral activity current-source distribution (CSD) by current-density reconstruction and makes it possible to obtain three-dimensional functional images.[13]

Complex cognitive tasks such as language processing are associated with neuronal beta and lower gamma frequency oscillations.[14] The increase in high-frequency synchronization may indicate a general mechanism enabling transient associations between neuronal assemblies. EEG beta activity is the dominant frequency during active wakefulness and reflects functional excitation and intense mental activity. Among beta frequency activity subtypes, the high beta bands (beta-2 and beta-3), in particular, are positively correlated with mental activity.[15] Functional coupling of EEG activity and brain metabolic activity increases with increasing EEG frequency.[16] Analysis of the high beta frequency band (beta 3, 22-30 Hz) may be useful to investigate neurocognitive functions under various situations. The combination of EEG neuroimaging and neuropsychological tests (NPs) is useful to elucidate the mechanism of ZNS-induced cognitive dysfunction. The objectives of this study were to investigate changes in the brain high beta frequency band (22-30 Hz) CSD induced by ZNS monotherapy in patients with epilepsy and to compare the CSD changes with the NP results.

Subjects and Methods

Subjects

Patients with newly diagnosed partial or generalized epilepsy, aged 16-40 years, were recruited from the epilepsy clinic at Kyungpook National University Hospital. All enrolled patients had had at least two epileptic seizures during the preceding 2 years or one seizure in addition to unequivocal supporting evidence of epilepsy, such as epileptiform discharges on EEG and positive findings on brain imaging. We included only right-handed patients to exclude the effects of handedness on cerebral CSD. Patients with progressive neurological disorders, head injury, mental retardation (Korean Wechsler Adult Intelligence Scale IQ<70),[17] alcohol or drug abuse, ongoing use of any centrally acting medications, severe psychiatric problems, or other severe medical disorders that required frequent changes in medication or dosage were excluded.

Study design

This was a 24-week, open-label, prospective study and was approved by the institutional review board of Kyungpook National University Hospital. All subjects gave written informed consent at enrollment. We acquired demographic and epilepsy-related characteristics through an epilepsy questionnaire and patient diaries. ZNS was titrated over a 4-week interval: 50 mg twice daily during the first 2 weeks and 100 mg twice daily during weeks 3 and 4. Thereafter, the dose regimens were adjusted individually based on the investigator's clinical judgment according to the patient's clinical response and tolerability. The ZNS dosage was titrated up to 200 mg twice daily if attacks did not subside. Patients who took >400 mg/day or experienced intolerable adverse events were withdrawn from the study.

Each patient was interviewed by a trained epileptologist (S.P.), who also reviewed the medical charts to collect demographic and clinical information for entry into a computerized database. Information collected included seizure type and frequency, age at onset, epilepsy duration, history of febrile convulsions, and magnetic resonance imaging (MRI) abnormalities. The scalp EEG and NPs were conducted on the same subjects at baseline and at 24 weeks after starting ZNS. EEG recordings and NPs were conducted on the same day. We observed ZNS-induced CSD changes in the high beta frequency band and correlated them with the NP results.

EEG recording

EEGs were recorded for at least 30 min in each patient using a 32-channel digital EEG machine (Telefactor Aurora® EEG machine, Grass-Telefactor, Melbourne, Australia). The patients were lying during the recording, with eye closing, relaxed resting state with usual provocation methods (eye opening-closure, hyperventilation and photic stimulation). During the procedure the patients were well cooperated. All EEGs were recorded at 200 Hz using 19 channels based on the international 10-20 system (Fp_1, Fp_2, F_3, F_4, C_3, C_4, P_3, P_4, O_1, O_2, F_7, F_8, T_3, T_4, T_5, T_6, F_Z, C_Z, and P_Z) with reference to the Pz.

Current-source analysis by cross-spectral analysis using LORETA

After recomputing the EEGs to the average referential montage, five artifact-free segments of 6 sec were selected from the waking state parts without epileptiform discharges during the recording of each EEG (filtered from 1.6-70 Hz). We used the data review and processing module in Brain Electrical Source Analysis software

(v. 5.1, MEGIS, Gräfelfing, Germany) to obtain the segments. Frequency-domain analysis in the 22-30-Hz frequency band was applied to the selected 6-sec segments (1,200 sample points). LORETA-KEY (KEY Institute for Brain-Mind Research, Switzerland) was used to calculate the intracerebral CSD in the frequency-domain analysis.

Our version of LORETA used a three-shell spherical head model registered to the Talairach human brain atlas, and the data were available as digitized magnetic resonance images from the Brain Imaging Center of the Montreal Neurologic Institute.[18] Registration between the spherical and Talairach head geometries used the realistic EEG electrode coordinates reported by Towle et al.[19] The LORETA solution space was restricted to the cortical gray matter and hippocampus in the Talairach atlas, as defined by the corresponding digitized probability atlas. In total, 2,394 voxels were produced at 7-mm spatial resolution under this neuroanatomical constraint.[13,20]

Neuropsychological testing

Neuropsychological tests were conducted in a sound-attenuated, temperature-controlled room by a single examiner. According to the literature and our own clinical experience, several cognitive measures were selected as being particularly sensitive in patients with epilepsy. The following parameters were assessed. Memory function was measured using list learning, immediate and delayed word recall, word recognition, and visual reproduction based on the Memory Assessment Scale obtained from Psychological Assessment Resources.[21] Attention deficit was tested using digit spans (forward and backward) from the Wechsler Memory Scale-Revised.[22] Attention, visuomotor tracking abilities, and mental flexibility were assessed with the Trail Making Test, parts A and B (TMTA and TMTB, respectively) from the Halstead-Reitan Battery.[23] Verbal fluency was investigated using semantic fluency tests from the Boston Diagnostic Aphasia Examination, Third Edition.[24] Testing sessions lasted 30-40 min. If a seizure occurred during the NPs, that test was suspended, and the data were not evaluated.

Statistical analysis

Five segments of 6-sec epochs were selected from a test EEG and a retest EEG from each patient. Thus, 60 EEG data pairs (12 patients × 5 epochs, 2 conditions of test and retest) were obtained. Paired-sample t-tests for all 12 patients were computed for the log-transformed LORETA power at each voxel in the 22-30 Hz frequency band to evaluate differences between the two conditions. These voxel-by-voxel t-values were displayed as statistical nonparametric maps (SnPMs).

Higher scores on the NPs indicated better performance for all cognitive test items except the TMTA and TMTB, for which the required time was defined as the dependent measure, and higher scores indicated worse performance. Data for continuous variables are expressed as mean ± SD, and those for categorical variables are expressed as frequencies (percentages). The Wilcoxon signed-rank test was used to evaluate the test-retest changes in NPs scores induced by ZNS monotherapy. Statistical analyses were conducted with SPSS 15.0 (SPSS, Chicago, IL, USA), and results were considered statistically significant at $p < 0.01$.

Results

Patients

A cohort of 19 patients with newly diagnosed epilepsy was enrolled. Six patients were excluded due to difficulty selecting artifact-free EEG segments. One patient did not follow up with the EEG and NPs. Twelve patients with newly diagnosed epilepsy who

Table 1. Demographic and clinical characteristics of subjects (n=12)

Characteristic	
Age, yr, mean (SD)	24.6 (7.8)
Gender, % male	41.7
Education, yr, mean (SD)	12.8 (1.9)
Seizure type, no. (%)	
Simple partial seizure plus GTCS	1 (8.3)
Complex partial seizure plus GTCS	2 (16.7)
GTCS only	7 (58.3)
Myoclonic seizure plus GTCS	2 (16.7)
Age at onset, yr, mean (SD)	22.6 (8.7)
Duration of epilepsy, yr, mean (SD)	2.0 (2.0)
Previous history of febrile convulsion, no. (%)	1 (8.3)
MRI abnormality, no. (%)	0 (0.0)
ZNS dosage at last visit, mg/d, mean (SD)	237.5 (64.4)
Seizure frequency, /3 months, mean (SD)	
Baseline	2.5 (2.5)
At 24 weeks	0.9 (1.7)[*]
Epileptiform discharges on EEG, no. (%)	
Baseline	6 (50.0)
At 24 weeks	1 (8.3)
Seizure freedom at 24 weeks, no. (%)	9 (75.0)

SD, standard deviation; GTCS, generalized tonic-clonic seizure; MRI, magnetic resonance imaging; ZNS, zonisamide; EEG, electroencephalography.
[*]Wilcoxon Signed Ranks Test, $p < 0.01$.

completed follow-up EEG and NPs were finally included. The demographic and clinical characteristics of the 12 enrolled patients are summarized in Table 1. The patients included seven females and five males, and the mean age was 24.6 years. One of the 12 had simple partial plus generalized tonic-clonic seizures (GTCSs), two had complex partial seizures plus GTCSs, seven had GTCSs only, and two had myoclonic seizures plus GTCSs. The mean daily ZNS dosage was 237.5 mg (range, 200-400 mg). After 24 weeks of treatment, the seizure frequency decreased significantly ($p < 0.01$). Seizures were re-duced in 11 patients (91.7%), and seizure freedom occurred in nine patients (75%). Brain MRIs were normal in all patients.

Current-source analysis

The CSD in the 22-30 Hz band of EEG background activity decreased in the various areas of the both cerebral hemispheres ($p < 0.01$, Fig. 1). The decrement of CSD was observed in the superior frontal, middle frontal, anterior cingulate, precentral, postcentral, and inferior parietal gyri of the left hemisphere. In the right hemi-

Figure 1. Statistical nonparametric maps (SnPMs) of 22-30 Hz frequency band of electroencephalogram background activities in a zonisamide (ZNS) monotherapy trial of patients (n=12). The current-source density (CSD) of the frequency band after 24 weeks of ZNS compared with that at baseline decreased in the various areas of the both cerebral hemispheres ($p < 0.01$). The decrement of CSD was observed in the superior frontal, middle frontal, anterior cingulate, precentral, postcentral, and inferior parietal gyri of the left hemisphere. In the right hemisphere, that was observed in the middle frontal, inferior frontal and anterior cingulate gyri.
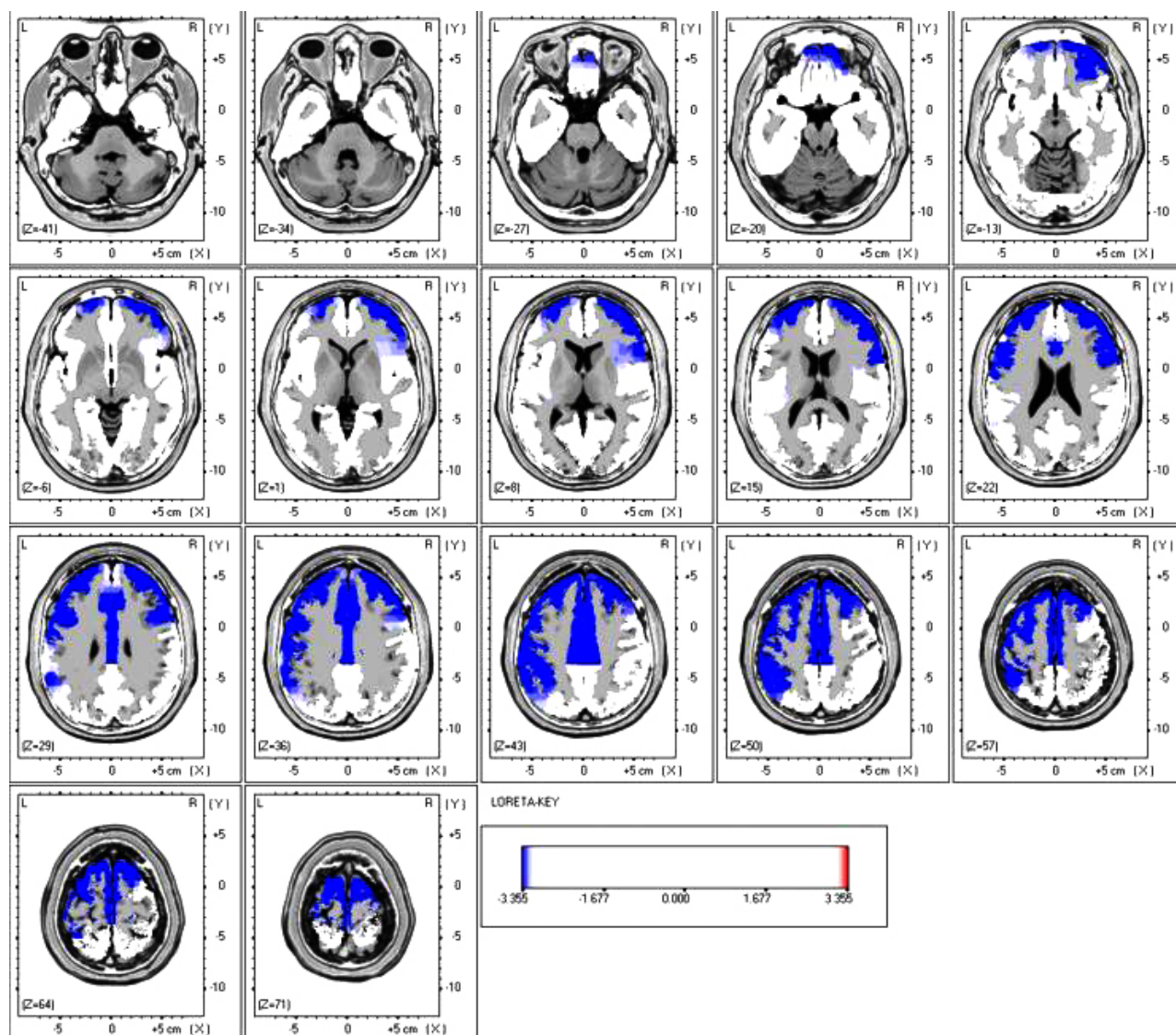
Table 2. Neuropsychological outcomes (n =12)

Battery	Baseline	At 24 weeks	p-value*
	mean (SD)	mean (SD)	
List learning	59.3 (7.5)	58.3 (12.7)	0.608
Immediate word recall	10.8 (1.3)	10.4 (1.7)	0.336
Delayed word recall	10.7 (1.6)	10.4 (2.0)	0.546
Word recognition	12.0 (0.0)	12.0 (0.0)	1.000
Visual reproduction	8.4 (2.2)	7.4 (2.7)	0.215
Digit Span, forward	9.3 (2.1)	8.2 (3.1)	0.166
Digit Span, backward	7.7 (2.2)	6.3 (2.0)	0.080
Trail Making Test, part A, time (sec)	34.6 (16.7)	35.3 (23.3)	0.538
Trail Making Test, part B, time (sec)	67.7 (26.9)	88.6 (55.0)	0.054
Verbal fluency	17.4 (3.0)	13.7 (4.7)	0.012

Higher scores indicate better performance on all cognitive tests, except for the Trail Making Tests.
* Wilcoxon Signed Ranks Test for comparison between baseline and at 24 weeks of ZNS trial.

sphere, that was observed in the middle frontal, inferior frontal and anterior cingulate gyri.

Neuropsychological tests

The results of NPs before and after the ZNS intake are summarized in Table 2. Verbal fluency performance decreased significantly after the 24-week ZNS trial ($p<0.05$). Although not statistically significant, a tendency for decreased scores on the backward digit span ($p=0.08$) and for increased TMTB scores ($p=0.054$) was observed.

Discussion

Zonisamide is a well-tolerated AED, as 50-60% of patients taking ZNS have continued to take the drug for more than 1 year in previous long-term studies.[6] However CAEs have been associated with the use of ZNS.[1,3,4,7-9,25] The incidence of CAEs is 2-11%,[8-10] and they include cognitive slowing, memory deficits, and language dysfunction.[1,4,8] In a previous study, 5.8% of patients discontinued taking ZNS due to CAEs.[11] Language impairments such as word-finding difficulty, nonfluent speech, and cognitive slowing were most common among the CAEs in the study.[11] In two Korean studies, ZNS monotherapy for a minimum of 6 months induced memory loss (35%) and attention deficit (25%) as CAEs,[3] and poor performance on NPs may be related to the high dosage, particularly dosages >300 mg/day.[1] We also demonstrated that verbal fluency decreased significantly, and backward digit span and TMTB tended to impair after taking ZNS, although we could not measure the impact of ZNS dosage on cognitive performances due to the small number of subjects.

Functional neuroimaging, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), do not directly evaluate neuronal activity but measure regional cerebral blood flow and blood oxygenation changes in the brain. This shortcoming of PET and fMRI may be overcome by CSA of EEG, which measures neuronal activity. A distributed CSA model such as LORETA localizes cerebral activity using CSD reconstruction and makes it possible to obtain functional neuroimages.[13] However, little attention has been paid to applying this technique in studies testing cognitive function or cognitive effects of AEDs in patients with epilepsy. In our previous study, the CSD of the high beta frequency band increased in the bilateral anterior cingulate gyri, left parahippocampal gyrus, and a small area of the right anterior parahippocampal gyrus after a 24-week levetiracetam (LEV) trial in patients with refractory partial epilepsy. In the previous study, verbal memory and executive function improved.[26] In contrast, the CSD of the high beta frequency band decreased in the superior frontal, middle frontal, anterior cingulate, precentral, postcentral, and inferior parietal gyri of the left hemisphere, and the middle frontal, inferior frontal and anterior cingulate gyri of the right hemisphere after the 24-week ZNS trial in the present study. Verbal fluency decreased significantly after the trial. The changes in CSD caused by LEV and ZNS agreed well with the direction of their effects on cognitive function. Gamma-aminobutyric acid (GABA)ergic dysfunction in the prefrontal cortex or an adverse effect of the sulfa moiety has been proposed as mechanisms for ZNS-induced language impairment.[1,27] The CSD changes in the present study may reflect GABA dysfunction in specific brain areas.

A study using fMRI and EEG simultaneously showed that cognitive

operations during conscious rest may be associated with the beta-3 frequency band.[28] In another study, which tested verbal fluency using a blocked-design fMRI paradigm, the middle frontal, inferior frontal, anterior cingulate gyri, and medial prefrontal cortex of the left cerebral hemisphere were significantly activated during the experimental condition.[29] In our results, the CSD in the high beta frequency band decreased in the anatomical structures relevant to cognitive decline. Based on the fMRI results, the decrease in the high beta frequency band CSD in the anterior cingulate and middle frontal gyri of the left cerebral hemisphere may be an explanation for the decreased verbal fluency observed in this study.

The present study had some limitations. We used fewer than the 32 available channels, which could have resulted in some localization errors, particularly in the basal aspects of the brain.[30] The localization accuracy of LORETA increases when using 25-89 electrodes and plateaus thereafter.[31] However, fewer electrodes may be sufficient to localize activity changes using the LORETA SnPM method.[32,33] It has also been observed that current-source estimations using LORETA in a three-shell head model are similar when using 19-46 scalp electrodes when the electrodes are evenly distributed.[31]

It was also difficult to observe CSD changes according to ZNS dosage because the number of patients was small. There were also limitations with regard to the NPs. First, as the number of patients was small, we cannot exclude individual susceptibility to AEDs. Any AED can elicit cognitive dysfunction in patients with susceptibility, and ZNS may not be a harmful drug in the majority of patients. Second, the impact of ZNS on mood should be considered when evaluating cognitive performance. The deleterious effects of depression on cognition have been demonstrated in patients with temporal lobe epilepsy.[34] However, as we did not measure mood changes, we do not know whether the impaired cognition was the direct effect of ZNS or an indirect effect of ZNS mediated by mood changes. Therefore, larger-sized studies measuring cognition and mood simultaneously are necessary to elucidate the effects of ZNS on cognition.

In conclusion, the CSD in the high beta frequency band decreased in the superior frontal, middle frontal, anterior cingulate, precentral, postcentral, and inferior parietal gyri of the left hemisphere, and the middle frontal, inferior frontal and anterior cingulate gyri of the right hemisphere after the 24-week ZNS trial. We also demonstrated that verbal fluency impaired after taking ZNS. We suggest that ZNS may decrease the activities of the neuronal networks in various areas including the frontal lobes and the anterior cingulate gyri of both hemi-

spheres, adversely affecting cognitive function. Decreased activity in the anterior cingulate gyrus and middle frontal lobe of the left cerebral hemisphere may be associated with impairment of verbal fluency.[29]

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