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Effects of perampanel on cognition and quantitative electroencephalography in patients with epilepsy

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의학과 중개의학전공

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이 논문을 의학석사 학위논문으로 제출함
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Abstract

Objectives: Antiepileptic drugs (AEDs) are well known for their effects on cognition and electrophysiologic changes. However, perampanel is yet to be evaluated for its effects on cognitive function and electroencephalography (EEG). The purpose of the present study was to identify the effect of perampanel on neuropsychological (NP) tests, quantitative EEG (QEEG), and its relationship with the blood level of the drug.

Methods: Seventeen patients with epilepsy were enrolled in the study. EEG recordings were obtained and NP tests were conducted before perampanel intake and 6 months after treatment. The relative frequency band power, peak alpha frequency, and NP test scores were compared before and after drug administration. The serum concentration of perampanel was correlated with the QEEG changes.

Results: Delayed recall of the Rey Complex Figure showed significant improvement (20.03 vs. 22.94; P=0.004) following perampanel administration. Other cognitive function tests showed no significant differences before and after drug administration. Theta frequency band power increased in all brain regions (P=0.001−0.029) and alpha frequency power decreased in the frontal and parietal regions (P=0.011 and P=0.018, respectively). The theta/alpha ratio, which represents background EEG slowing, increased in all brain areas (P=0.002−0.024). This increment of theta/alpha ratio in the central region positively correlated with the blood level of perampanel (r=0.5, P=0.048). The peak frequency of the alpha rhythm decreased after perampanel intake (t=2.45, P=0.026).

Significance: Perampanel induced electrophysiological slowing, but

cognitive decline was not observed. Background EEG slowing correlated with the serum concentration of perampanel. Our results show the effect of perampanel on cognitive function and background EEG in adult patients with epilepsy for the first time.

Keywords : Perampanel, Epilepsy, Cognition, Quantitative EEG
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1. Introduction

Perampanel is a selective antagonist of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, and is used for partial-onset seizures with or without secondary generalization. This antiepileptic drug (AED) is usually prescribed as adjunctive treatment and is also used primarily in generalized tonic-clonic seizures.[1-4] Perampanel is extensively metabolized in the liver by cytochrome P450 and has a high affinity for protein. This drug has a relatively long half-life of 48 hours. Therefore, the patient can take the drug once daily.[5]

Cognitive dysfunction is a major comorbidity in many patients with epilepsy and could be the result of chronic use of AEDs. Since cognitive decline has a tremendous impact on the quality of life, the effect of a large number of AEDs on cognition has been actively studied.[6,7] It has been reported that gabapentin, carbamazepine, and topiramate were the AEDs that induce cognitive decline, while lamotrigine, levetiracetam, and oxcarbazepine showed much less negative effect on cognitive function compared to the older AEDs.[6] A new AED drug, perampanel, has also been studied for its effects on cognition in adolescent epilepsy patients aged 12-18 years.[8] However, the effects of perampanel on cognitive function have not yet been

studied in adults.

Electroencephalogram (EEG) spectral analysis is a method of quantifying the different frequencies in EEG signals. Spectral power analysis of EEG frequency can reflect the functional state of the brain. Thus, it has been a useful tool for assessing the pharmacological effects of central nervous system (CNS) drugs. Electrophysiologic changes due to AEDs can manifest as either a generalized slowing of or an increased beta frequency on EEG in general.[9] Changes in background EEG may be correlated with clinical cognitive function.[10-14] Since EEG changes in the spectral analysis are only intended to assess brain activity and do not directly reflect clinical changes in patients, neuropsychological (NP) tests are necessary for evaluating clinical cognitive function.[15]

Our objective was to determine how perampanel affects cognition and the EEG signal. Correlation of these effects was also analyzed with the serum concentration of perampanel.

2. Methods

2.1. Patients

This was a prospective study conducted at a single institution (Seoul National University Hospital) and included epilepsy patients who had started taking perampanel. The study aimed to enroll 30 patients in 2 years, from March 2017 to March 2019. The number of patients was decided based on previous studies that investigated the effects of AEDs on EEG.[14, 16, 17] The inclusion criteria were as follows: 1) epilepsy lasting over 2 years, 2) age between 19 and 65 years, 3) newly initiated perampanel, and 4) partial seizures with or without secondary generalized seizures. The exclusion criteria included severe medical conditions or ongoing disease, a history of psychogenic nonepileptic seizure, pregnancy or lactation, aspartate transaminase (AST)/ alanine aminotransferase (ALT) blood levels more than two times the normal, abnormal levels of total and direct bilirubin, central nervous system infections, demyelinating diseases, neurodegenerative diseases, chronic alcoholism or

drug addiction, suicidal thoughts or major depressive episodes within the past 6 months, and allergies to two or more AEDs. The criteria for dropping out of the study were voluntary discontinuation of perampanel intake, a change in the dose of another AED being taken concurrently, a serious adverse event, or a desire to discontinue participation.

All enrolled patients participated in an EEG test, an NP test, and answered a questionnaire before perampanel was prescribed. In the 5th and 13th weeks of the study, the patients visited a medical institution for the evaluation of the frequency of seizures and adverse drug reactions. At the end of the 25 weeks, the EEG test, NP test, and questionnaire were repeated. Blood samples were taken during the same period. Perampanel was administered orally once a day, and the dose of the drug was increased by at least 2 mg every two weeks, starting from 2 mg/day. For patients taking phenytoin, carbamazepine, and oxcarbazepine, which reduce the half-life of perampanel, doses were adjusted by 2 mg at weekly intervals. The maintenance dose of perampanel ranged from 4 mg/day to 12 mg/day. The maintenance dose was not changed for a month before the last EEG test.

2.2. EEG recording and processing/Spectral analysis

EEGs were recorded with the International 10-20 system. Cap electrodes were attached to Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4,

T6, O1, and O2. The signals were recorded at a sampling rate of 400 samples/s. A bandpass filter with zero phase shift was applied to all EEG data in the range of 0.3 Hz-70 Hz to reduce background noise. All electrode impedances were kept below 5 kΩ. The resting EEG was obtained for 10 minutes while the patient was seated in a comfortable chair. Patients were asked to close their eyes for 10 s and then open them for another 10 s while the state of vigilance was determined by an online visual inspection of EEG traces. This procedure was repeated 10 times.

A neurologist (ASJ), who was blinded to the clinical information, selected 3-s long EEG epochs from an artifact-free EEG period with physiological alpha activity of maximum amplitude in the occipital regions. An average of 33.1 epochs were extracted from one EEG.

All EEG analyses were performed using MATLAB 2014b (The MathWorks Inc., Massachusetts). EEG data were re-referenced to the common average reference, and band pass filtered (0.5-50 Hz) for analysis. Deterministic trends and direct current (DC) fluctuations were eliminated by removing the DC offset and detrending. Independent component analysis was applied to correct for stereotyped ocular and muscular artifacts with the EEGLAB toolbox (version 14.1b).

To observe spectral characteristics during the resting state in the eyes-closed state, the power spectra of each 3-s epoch were calculated using

Welch's method with NFFT=1024, 50% window overlap, and 1-s window length. The power spectra were averaged over all epochs. The relative power spectral density for each frequency bin was computed as the ratio between the absolute power and the mean power spectrum from 2 to 50 Hz. The frequency bands were defined as follows: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz). Peak frequencies of the alpha band were calculated in O1 and O2 leads.

2.3. Neuropsychological assessments

A full battery of NP tests was performed for all patients. The Mini-Mental Status Examination (MMSE) was used to measure general cognitive impairment.[18] For the language function, the Korean-Boston Naming Test (K-BNT) was administered,[19] and the Korean-California Verbal Learning Test (K-CVLT) was administered to determine the verbal memory and working memory function.[20] For attention and executive function, the Controlled Oral Word Association Test (COWAT), Trail Making Test (TMT) and digit span test were administered.[19, 21, 22] The Rey Complex Figure Test (RCFT) was included to evaluate the various executive functions of visuospatial capability, memory, attention, planning, and working memory.[23]

To evaluate depression, the Beck Depression Inventory-II (BDI-II) was administered.[24] The Buss-Durkee Hostility Inventory (BDHI) was used to

evaluate aggression[25] and the Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness.[26]

2.4. Analysis of serum perampanel concentration

The total serum concentration of perampanel was measured using high-performance liquid chromatography (HPLC) (1200 series, Agilent Technologies, Santa Clara, CA, USA) coupled with tandem mass spectrometry (MS/MS) (API3200, Applied Biosystems, Waltham, MA, USA). To determine the total concentration of perampanel, 50 μL of plasma was mixed with 50 μL of an internal standard (100 ng/mL trazodone in 50% methanol), and 300 μL of acetonitrile was then added. The mixture was centrifuged at 10,000 rpm for 5 minutes at 4 °C, and 2 μL of the supernatant was injected into the LC-MS/MS system.

2.5. Statistical analyses

The results of the EEG spectral analysis and NP tests were compared between the "baseline" and "follow-up" periods. The Shapiro-Wilk test was used to check the normality of data distribution. To determine the statistical significance between the "baseline" and "follow-up" responses, a paired T-test was used for the NP test items that satisfied a normal distribution. The

Wilcoxon signed-rank test was used for the NP test items that did not satisfy a normal distribution. A paired T-test was used to compare the results of the EEG spectral analysis before and after drug administration. The correlation analysis of serum concentration and EEG change was performed using the Pearson correlation coefficients.

A P-value of <0.05 was considered significant. Statistical procedures were performed with MATLAB (Version 2014b) and R (Version 3.5.3.)

3. Results

3.1. Clinical characteristics of the subjects

Detailed clinical characteristics of the participants are described in Table 1. Of the 25 enrolled patients, 8 patients dropped out because of personal decisions and uncontrolled seizures. None of the patients dropped out due to drug side effects. Seventeen patients completed, both, the EEG test and the NP tests before and after perampanel administration. Of the 17 patients who completed this study, 9 were female. The mean age of the 17 patients was 32.6 ± 12.2 years [21-65]. The average length of education was 14.9 ± 1.6 years and the majority of patients had received a college education (77%). The mean maintenance dose of perampanel was 5.65 ± 1.77 mg/day (range 4-8 mg/day). Fifteen patients were taking perampanel as adjunctive therapy, while 15 patients had partial epilepsy (88%). The efficacy of the drug was evaluated with the observed change in seizure frequency. More than 50% reduction in seizure frequency was considered effective. Eight patients (47%) showed good seizure outcomes after perampanel intake.

Eleven patients showed normal magnetic resonance imaging (MRI) findings (65%). Hippocampal lesions were observed in four patients (23.5%). 47% of the patients had no subjective side effects. Dizziness, reported by eight patients (47%), was the most common subjective side effect.

Table 1: Clinical characteristics of the patients, N=17

Pt.no	Sex	Age (years)	Handedness	Education (years)	Maintenance dose of PER (mg/dL)	Epilepsy type	Previous AEDs	MRI findings	Subjective side effects	Seizure frequency outcome
1	F	35	R	14	8	PE	CLB, OXC	Normal	–	≥50%–Responder
2	M	29	R	16	8	PE	LTG, OXC	Normal	–	Aggravation
3	M	21	R	15	6	PE	LEV, OXC	Normal	Dizziness	<50%–Responder
4	M	33	R	16	8	PE	CLB, LEV, LTG	HA	Dizziness, Personality change, Somnolence	<50%–Responder
5	F	30	R	16	4	PE	CLB, LEV, OXC	Normal	–	≥50%–Responder
6	M	59	R	12	4	PE	LEV, PGB	HS	Dizziness, Personality change	≥50%–Responder
7	F	65	R	12	6	PE	–	Normal	Dizziness, Behavior change	≥50%–Responder
8	M	31	R	14	8	PE	LEV, TPM	Normal	Somnolence	Unchanged
9	F	22	R	16	4	PE	LEV, TPM	HA	Dizziness	Unchanged
10	M	37	R	16	8	PE	CBZ, VPA	Normal	Dizziness	Aggravation
11	F	21	A	14	4	PE	CLB, LEV, OXC, ZNS	Normal	–	Unchanged
12	F	29	A	16	4	PE	–	Normal	Dizziness, Somnolence	≥50%–Responder
13	M	26	R	16	4	PE	LEV, OXC	Encephalomalacia	–	≥50%–Responder
14	M	25	R	16	6	PE	OXC	Normal	–	≥50%–Responder
15	F	24	R	16	6	IGE	LEV, OXC	Normal	–	≥50%–Responder
16	F	38	R	12	4	PE	CLB, LEV, TPM	Pachygyria	Dizziness, Somnolence	<50%–Responder
17	F	30	R	16	4	Unknown	LTG, TPM	HA	–	Unchanged

R, right; A, ambidextrous; PE, Partial epilepsy; IGE, Idiopathic generalized epilepsy; PER, Perampanel; CLB, Clobazam; OXC, Oxcarbazepine; LTG, Lamotrigine; LEV, Levetiracetam; PGB, Pregabalin; TPM, Topiramate; CBZ, Carbamazepine; ZNS, Zonisamide; VPA, Valproic acid; HA, Hippocampal atrophy; HS, Hippocampal scleros

3.2. Neuropsychological tests

Detailed statistical results of the NP test are listed in Table 2. After taking perampanel, the average questionnaire scores of the BDI-II/ESS/BDHI increased slightly, but without significance.

Most of the cognitive test scores showed no significant change after taking the medication. The mean score of the RCFT delayed recall test significantly increased from 20.03 to 22.94 (t=-3.39, P=0.004). The mean score of the long delayed cued recall test in the K-CLVT showed a tendency to increase following the administration of perampanel (12.82 vs. 13.65, V=23, P=0.057).

3.3. Quantitative EEG analysis

The statistical results of the quantitative EEG are presented in Table 3. The administration of perampanel induced a change in the background frequency power in the eyes-closed EEG signal. The power of the low frequency bands (delta, theta) tended to increase after taking perampanel, while the power in a higher frequency band (alpha) decreased (Figure 1). The theta frequency-band power significantly increased in all three brain regions (frontal, central, and parietal; P=0.02, P=0.029, and P=0.001, respectively). The alpha frequency-band power significantly decreased in the frontal and parietal areas

(P=0.011 and P=0.018, respectively). The power in the beta frequency band did

NP battery item	Baseline			Follow-up			*P*-value
	Mean	Median	SD	Mean	Median	SD	
Depression/Sleepiness/Aggression							
BDI-II	19.35	18	11.12	20.53	19	9.93	0.494
ESS	8.41	8	5.51	8.47	8	3.14	0.503*
BDHI	39.94	39	5.61	41.65	40	5.37	0.225
General cognitive function							
MMSE, Total	28.7	29	1.26	28.71	29	1.1	1.0*
Language function							
K-BNT	51.59	53	5.87	53.06	54	4.46	0.080
Visuo-spatial function							
RCFT copy score	31.76	33	2.73	32.29	32	1.72	0.27
RCFT copy time[a]	220.94	218	102.99	188.47	156	82.71	0.139
Memory function							
RCFT immediate recall	21.94	22.5	7.46	23.06	26.5	7.19	0.376
RCFT delayed recall	20.03	21.5	7.08	22.94	26.5	7.43	0.004
RCFT recognition	20.94	21	1.82	21.06	21	2.22	0.817
K-CVLT, Total	50.29	50	9.62	51.76	53	10.58	0.4
K-CVLT short delay free recall	11.24	12	2.56	11.12	10	3.08	0.871
K-CVLT short delay cued recall	12.59	14	2.27	13.24	14	2.05	0.085*
K-CVLT long delay free recall	12.18	13	2.94	12.29	13	3.12	0.808
K-CVLT long delay cued recall	12.82	14	2.63	13.65	14	2.03	0.057*
K-CVLT recognition	15	15	1.32	15.47	16	1.01	0.124*
Attention and executive function							
Digit span forward	7.64	8	1.11	7.53	8	1.01	0.821*
Digit span backward	4.94	5	1.6	5.35	5	1.66	0.262
COWAT animal	15.06	16	5.7	15.71	17	5.3	0.405
COWAT supermarket	16.29	15	5.1	17.24	14	7.12	0.387
COWAT ㄱ	12.18	11	4.8	11.71	11	6.01	0.632
COWAT ㅅ	10.06	10	3.94	10.65	9	4.9	0.428
COWAT ㅇ	11.24	11	4.15	10.24	8	4.75	0.782
COWAT fluency, Total	33.47	37	11.97	32.59	29	14.49	0.574
TMT A[a]	44	31	32.79	34.53	30	20.47	0.227*
TMT B[a]	119.94	111	77.54	108.29	100	61.42	0.36

not change after drug administration. The theta/alpha ratio, which represents slowing of the background EEG, also increased significantly in all brain areas after taking perampanel

Table 2: Results of the neuropsychological examinations

BDI-II, Beck depression inventory-II; ESS, Epworth sleepiness scale; BDHI, Buss-Durkee hostility inventory; MMSE, Mini-mental status examination; K-BNT, Korean-Boston naming test; RCFT, Rey complex figure test; K-CVLT, Korean-California verbal learning test; COWAT, Controlled oral association test; TMT, Trail making test.

[a] lower score means better performance

* Wilcoxon signed-rank test performed due to non-normal distribution

Relative frequency-band power	Frontal			Central			Parietal		
	Baseline	Follow-up	*P*-value*	Baseline	Follow-up	*P*-value*	Baseline	Follow-up	*P*-value*
Delta (2-4 Hz)	27.67 ±2.50	28.12 ±2.37	NS	28.13 ±2.39	28.63 ±1.81	NS	27.6 ±2.68	28.21 ±2.30	NS
Theta (4-8 Hz)	27.44 ±1.67	28.34 ±1.90	0.020	27.51 ±1.82	28.29 ±1.78	0.029	26.82 ±1.55	27.99 ±1.83	0.001
Alpha (8-12 Hz)	29.76 ±1.55	29.00 ±1.39	0.011	29.34 ±1.38	28.88 ±1.30	NS	30.25 ±1.22	29.69 ±1.21	0.018
Beta (12-30 Hz)	21.04 ±2.48	21.24 ±2.67	NS	21.76 ±2.15	21.70 ±2.49	NS	21.20 ±2.28	21.16 ±2.27	NS
Theta/alpha ratio	0.92 ±0.08	0.98 ±0.08	0.008	0.94 ±0.08	0.98 ±0.08	0.024	0.89 ±0.07	0.94 ±0.08	0.002

Table 3: Relative power from spectral analysis of eye-closed EEG

NS, Not significant;

A *P*-value <0.05 was considered significant.

* Paired T-test

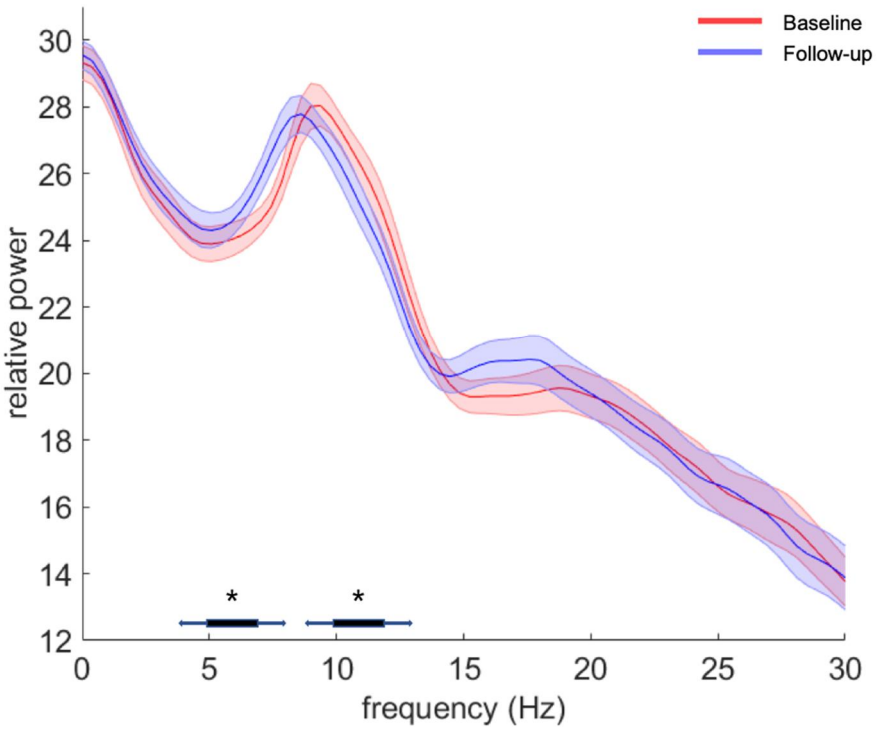

Figure 1: Average relative frequency band power in eyes-closed EEG

The power of the theta frequency band increased from baseline in the follow-up EEG (p=0.001-0.029), while that of the alpha frequency band decreased (p=0.002~0.024). The frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) channels were averaged. Statically significant frequency band sections are marked with *.

(frontal, central, and parietal; P=0.008, P=0.024, and P=0.002, respectively). Topographic analysis indicated an increase in theta power in the frontocentral area. A decrease in the power of the alpha band was evident in the occipital region (Figure 2).

Peak frequency of the posterior dominant alpha rhythm also significantly decreased in the follow-up EEG. Mean peak alpha frequency at the occipital area (O1 and O2 electrode) decreased from 9.97 Hz to 9.42 Hz after taking perampanel (t=2.45, P=0.026).

3.4. Correlation of EEG spectral power with the perampanel blood level

Serum levels of perampanel were measured in all 17 patients. The blood level of Pt. 1 could not be obtained due to a measurement error. Results of perampanel blood levels and theta/alpha ratio in the central area are listed in Table 4. The mean perampanel blood level was 242.88 ± 146.48 ng/mL [47.9 – 504]. The serum perampanel level has no correlation with the maintenance dose. However, the serum total concentration of perampanel correlated positively with the difference in the theta/alpha ratio in the central area (r=0.5, P=0.048) before and after drug administration. (Table 5, Figure 3).

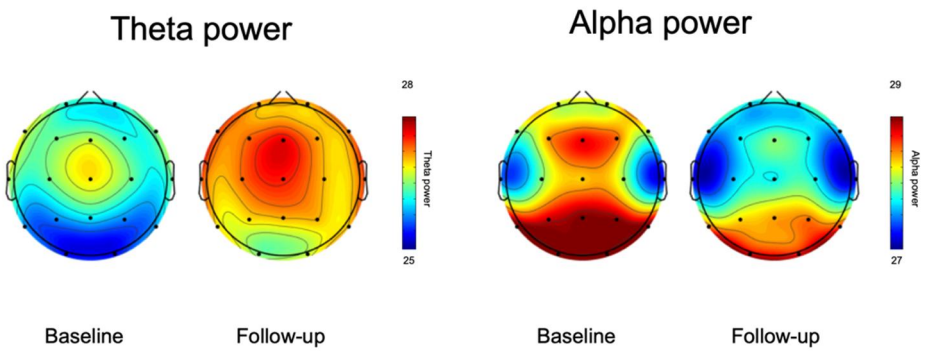

Figure 2: Topography of theta and alpha band power in eyes-closed EEG

The theta power increased mostly in the central and frontal areas. The alpha power decreased mostly in the occipital and central areas.

Table 4. Perampanel blood level and theta/alpha ratio in the central area

Pt. no	Perampanel Blood Level (ng/mL)	Theta/alpha ratio in the central area		
		Baseline	Follow-up	Difference
1	-	0.846	0.920	0.074
2	47.9	1.146	1.104	-0.041
3	196	0.871	0.937	0.066
4	73.6	0.965	0.899	-0.066
5	210	0.898	1.065	0.167
6	262	1.008	0.988	-0.020
7	465	0.831	1.007	0.176
8	504	0.933	1.061	0.128
9	308	0.940	0.959	0.019
10	112	1.082	1.166	0.084
11	97.6	0.920	0.976	0.056
12	307	0.996	1.015	0.020
13	108	0.956	0.974	0.018
14	251	0.895	0.867	-0.028
15	501	0.904	0.961	0.057
16	250	0.886	0.894	0.007
17	193	0.901	0.899	-0.002
Mean	242.88 ± 146.48	0.94 ± 0.08	0.98 ± 0.08	0.042 ± 0.07

Table 5. Correlation analysis between perampanel blood level and theta/alpha ratio difference

	Theta/alpha ratio difference		
	Frontal	Central	Parietal
Covariance	3.74	5.22	2.24
R(Correlation coefficient)	0.34	0.5	0.24
T-score	1.35	2.17	0.93
P-value	0.2	0.048	0.366

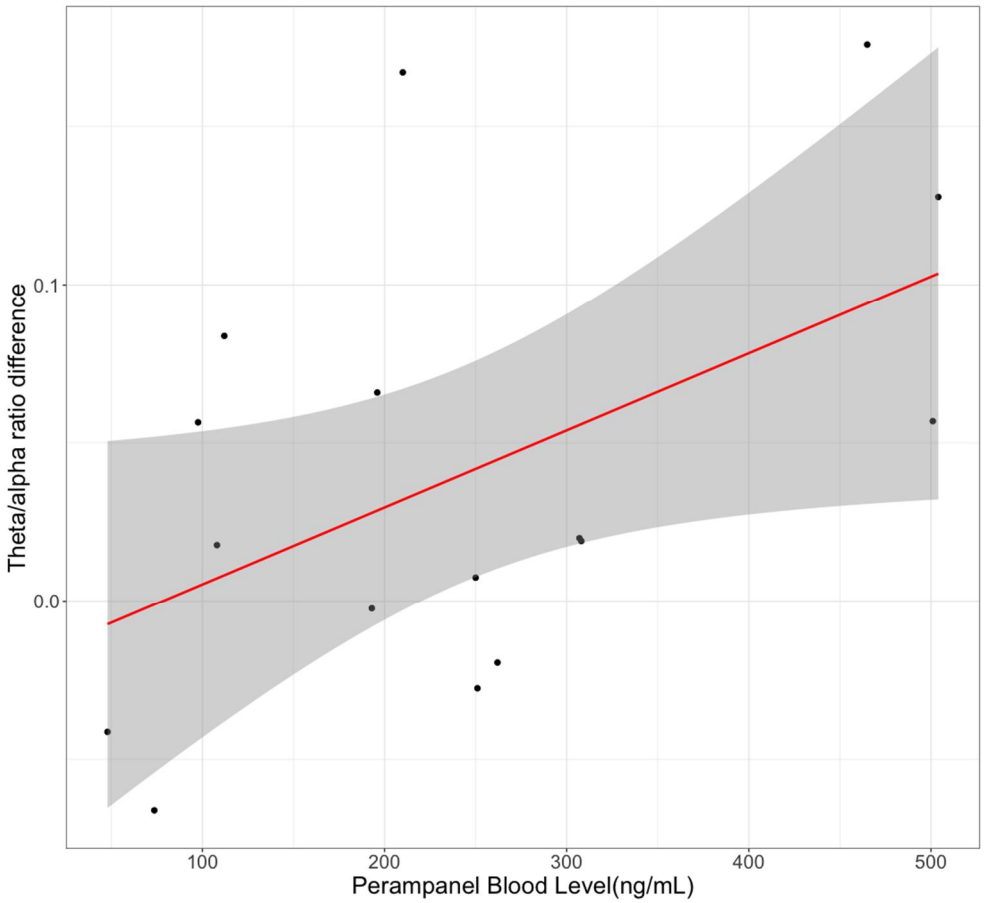

Figure 3: Scatter plot of perampanel blood level and theta/alpha ratio difference of the central area

The perampanel blood level correlated positively with the theta/alpha ratio difference in the central area (r=0.5, *p*=0.048). The grey area represents 95% confidence interval.

4. Discussion

In this study, we investigated the effect of perampanel on cognitive function through NP tests and quantitative EEG analysis. This was the first study to examine the effects of perampanel on cognitive function in adult epilepsy patients. Previously, the effect of perampanel on cognition had been studied in adolescent epilepsy patients. In that study, cognitive function was compared between groups taking adjunctive perampanel and those taking placebo; there was no significant difference in global cognitive function between the two groups. However, the perampanel group showed improved outcomes in the quality of episodic memory and worsened outcomes in the continuity of attention and speed of memory.[8] In the present study with adult population, no cognitive decline was observed with comprehensive cognitive tests following the six months administration of perampanel.

Delayed recall in RCFT was the only NP test item that showed significant improvement over the baseline score. RCFT delayed recall reflects, both, visuospatial memory and delayed recall functions. It has been reported that these cognitive functions are related to the presence of AMPA receptors.[27, 28] In a mouse experiment, spatial memory was selectively suppressed by binding only the GluA1 subunit.[29, 30] Perampanel is known to bind to the GluA2

subunit[31, 32] and induce GluA1 phosphorylation, which enhances synaptic currents.[33, 34] This particularity of binding with a specific AMPA subunit may preserve, or even improve, spatial memory after taking perampanel. In other studies, perampanel improved spatial working memory in a mouse model of ischemic stroke.[35, 36] These studies insist that perampanel has a neuroprotective effect with anti-inflammatory, anti-oxidative, and anti-apoptotic properties and upregulates the the PI3K/Akt pathway. Regardless, there seems to be a certain relation between perampanel and spatial cognitive function, as seen in our results. Our results indicate that perampanel does not worsen cognitive function, but the effect of perampanel on spatial memory function should be explored further with additional human and animal experiments.

The electrophysiologic effect of perampanel has not been studied much. One study investigated frequency power changes using magnetoencephalography (MEG) recordings.[37] The MEG data showed significant increases in the power of low frequency bands (1–4 Hz, 4–8 Hz, 8–13 Hz, 13–30 Hz) and a significant decrease in the high gamma range (50–90 Hz) after perampanel administration. In our EEG spectral analysis, the power of the theta frequency band significantly increased, while that of the alpha frequency band significantly decreased after taking perampanel. Naturally, the theta/alpha ratio, which indicates the slowing of background EEG activity,

increased in all regions of the brain. Furthermore, the perampanel serum level showed a positive correlation with the theta/alpha ratio difference of baseline/follow-up. This result suggests that an increase in the serum level of perampanel linearly increases background EEG slowing in patients with partial epilepsy. Peak alpha frequency, another indicator of cognitive function, also significantly decreased after taking perampanel. Cumulatively, our results imply a potentially negative effect of perampanel on cognition.

Many previous studies showed concordance between background EEG changes and cognitive function. AEDs such as carbamazepine[10], phenytoin[12], topiramate[38], and gabapentin[13] are increasing low frequency power and decreasing high frequency power in the resting EEG. These electrophysiologic changes are frequently associated with worsening of cognitive function. On the other hand, AEDs such as lamotrigine, levetiracetam, and valproate are known to reduce low frequency power,[11, 15, 39-42] which often positively correlates with cognitive functions. Our results show that perampanel is one of the AEDs that induces slowing of brain activity during the resting state. Therefore, based on the EEG findings, impaired cognitive performance following long-term use of perampanel is expected. However, neuropsychological tests revealed no impairment of cognition in our results. The reason for this mismatch between neurophysiologic and neuropsychological tests cannot be clearly explained, but a few factors should

be considered. Firstly, compensatory effects might obscure the direct relationship between EEG alterations and the behavioral effects of perampanel, particularly at a low dose. Secondly, there may be a practice effect in repeated NP tests. Patients may remember some of the previous questions and could, therefore, perform better in the post-drug test, regardless of the effect of the drug. Finally, changes in electrophysiology could be more sensitive than the actual changes in clinical cognitive function.

Several factors such as emotion, somnolence, and seizure frequency could affect cognitive performance in patients taking AEDs. In our study, there were no statistically significant changes in depression, sleepiness, or hostility after taking perampanel. Seizure outcome showed no statistical correlation with NP tests, quantitative EEG, and perampanel blood levels.

There are two limitations to our research. Firstly, the number of patients was relatively small. Secondly, most of the patients had received perampanel as adjunctive therapy. The AEDs that the patients had been taking previously may have affected the action of perampanel in the study.

5. Conclusion

In conclusion, our study suggests that perampanel may induce electrophysiological slowing without causing cognitive decline. Further studies using monotherapy with a larger sample size are needed to corroborate our results.

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초록

항경련제는 인지기능에 영향을 미치고 전기생리학적 뇌파의 변화를 일으키는 것으로 알려져 있다. 그러나 새로운 항경련제인 페람파넬은 인지 기능과 뇌파의 변화에 미치는 영향에 대해서 아직 평가되지 않았다. 본 연구는 신경심리검사, 정량적 뇌파 및 약물의 혈중 농도를 측정하여 페람파넬의 영향을 확인하고자 한다. 뇌파 검사와 신경심리 검사는 페람파넬 투약 전, 투약 6개월 후에 시행되었다. 뇌파를 정량적으로 분석하여 약물 투여 전후로 상대적 주파수 파워, 피크 알파 주파수를 비교했다. 최종적으로 17명의 뇌전증 환자의 검사 결과를 비교 분석하였다. 신경심리 검사 결과에서 레이 복합 도형 검사의 지연 회상 부분은 페람파넬 투여 후 상당한 개선(20.03 vs 22.94; P=0.004)을 보였다. 다른 인지기능 검사에서는 약물 투여 전후에 유의미한 차이가 나타나지 않았다. 세타 주파수 파워는 모든 뇌 부위(P=0.001−0.029)에서 증가했고, 알파 주파수 파워는 전두엽과 두정엽 부위(각각 P=0.011, P=0.018)에서 감소했다. 배경 뇌파의 서파화를 나타내는 세타/알파 비율은 모든 뇌 영역에서 증가했다(P=0.002−0.024). 투약 이후 대뇌 중심 부위의 세타/알파 비율의 증가치는 페람파넬의 혈중 농도(r=0.5, P=0.048)과 선형적인 상관관계를 보였다. 알파 리듬의 피크 주파수는 페람파넬 투약 후 감소하였다(t=2.45, P=0.026). 페람파넬 복용은 전기생리학적으로 뇌파의 서파화를 유발했지만 인지기능의 감퇴는 관찰되지 않았다. 배경 뇌파의 서파화는 페람파넬 혈중 농도와 상관관계가 있었다. 우리의 결과는 뇌전증을 가진 성인 환자에게서 페람파넬이 인지기능과 뇌파에 미치는 영향을 처음으로 보여준다.

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