Effects of Perampanel on Electroencephalography

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Abstract

Objective: Perampanel (PER), a noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, has been approved as adjunctive therapy for focal and generalized epilepsy. Limited information is available regarding the measurable impact of anti-seizure medications (ASM). In this study, we aimed to investigate the effects of PER on electroencephalography (EEG) background activity and interictal epileptic discharge.

Methods: This study included all patients with a clinical diagnosis of epilepsy who underwent routine EEG before and after PER treatment between 2018 and 2023. EEG findings were examined according to their background activity and clinical features such as risk factors of epilepsy, the occurrence of sleep-related seizures, sleep disorders, intellectual disability, abnormality of magnetic resonance imaging and EEG, multifocal features on EEG, the duration between EEG and initiation of PER treatment, frequency of seizures before and after PER treatment (seizure freedom or >50% reduction in seizures), previous epilepsy surgery, the number of current and previous ASM, and dosage of PER.

Results: In a total of 11 patients, epilepsy type was focal in 8 (73%), all of the patients were on polytherapy, and 4 of them had undergone epilepsy surgery. PER treatment resulted in seizure freedom in 36% of patients and a >50% decrease in seizures in 55% of patients. There was no statistically significant relationship between background activity, phase reversal, and equipotential in EEG before and after PER treatment. In addition, pre- and posttreatment responses to activation procedures and disruption in sleep structure did not differ significantly. The relationship between seizure freedom and phase reversal decrease after PER treatment was statistically significant. The relationship between a >50% decrease in the frequency of seizures and epileptic discharges also reached statistical significance.

Conclusion: To summarize, seizure freedom following PER treatment appears to be associated with reduced epileptic discharge, and EEG monitoring might help determine prognosis.

Keywords: Perampanel, epileptic discharges, epilepsy, treatment response

INTRODUCTION

The effects of anti-seizure medications (ASM) on electroencephalography (EEG) have attracted interest since the discovery of scalp EEG in 1924.[1] Changes in alpha rhythm and mental processes after the use of various medications have been defined.[2] In studies of healthy subjects, phenytoin, phenobarbital, valproate, carbamazepine, oxcarbazepine, and gabapentin slow down the background rhythms on EEG.[3-6]

Traditionally, the frequency of seizures reported by patients or relatives is used to measure response to ASM.[7] Nevertheless, patients are usually unaware of up to 60% of their seizures when they are awake and up to 80% of their seizures during sleep.[8,9] In addition, patients might not be aware of epileptiform activity when they appear.[10,11] Accordingly, the epileptiform discharge burden on EEG rather than the declared seizure frequency might be a more reliable measure of disease activity.[12-17] Given these factors, long-term EEG recordings that assess epileptiform discharge burden might provide a more objective indicator of prognosis and improvement after ASM initiation.[11-18]

Perampanel (PER), a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, receptor antagonist, received approval from the European Medicine Agency (EMA) for use as an adjunctive therapy for both focal and generalized epilepsy, and it has demonstrated efficacy in various off-label clinical scenarios, from myoclonic epilepsy to status epilepticus.[19-22] Among all available ASMs, PER is the sole medication that directly inhibits glutamatergic pathways.[23]

Little is described about the measurable effect of ASM on epileptiform discharge in focal and generalized epilepsy. Few studies have investigated the effects of newer ASMs. This study aimed to evaluate the effects of PER on EEG.[24] Our results might provide a different

perspective on the effects of PER on the central nervous system and the potential use of EEG to monitor the efficacy of PER.

METHODS

This study included all patients with a clinical diagnosis of epilepsy who underwent routine EEG before and after PER treatment between 2018 and 2023. Patients whose EEG data were unavailable before or after treatment were excluded from our study. A structured recording protocol was used. All outpatient EEG recordings consisted of 2h of awake and sleep periods, and all patients underwent hyperventilation and intermittent photic stimulation at the beginning and end of the recording twice per 5 min.

Gold EEG electrodes were placed at Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, Fz, Cz, Pz, P3, P4, O1, and O2 according to the international 10-20 system, and EEGs were recorded on a 21-channel digital machine. The Oz electrode was applied as a system reference during recording. Bandpass was 0.3-70 Hz. Gains (all channels) were adjusted for each subject to optimize the range of the analog-to-digital converter. All EEG data were reported by a well-experienced epileptologist and clinical neurophysiologist (C.G.). EEG endpoints were assessed by manual counting. Phase reversals and equipotential were counted by a clinical neurophysiologist (İ.E.).

EEG findings were examined according to background activity and clinical features such as risk factors of epilepsy (febrile seizures, head trauma, perinatal injury, central nervous system disorder, stroke, consanguinity, family history of epilepsy or febrile seizures), occurrence of sleep-related seizures, sleep disorders, intellectual disability, abnormality of magnetic resonance imaging (MRI) and EEG, multifocal features on EEG, duration between EEG and initiation of PER treatment, frequency of seizures before and after PER treatment (seizure freedom or >50% reduction in seizures), previous epilepsy surgery, number of current and previous ASM, and dosage of PER.

The primary endpoint of this study was the number of phase reversals and equipotential, as well as the change in the frequency of background EEG rhythms (alpha, theta, beta and delta) before and after PER treatment. The secondary endpoint was reduced seizures by more than 50% and seizure freedom after PER treatment.

Statistical Analysis

Categorical variables are presented as numbers (%), and continuous variables are presented as medians [minimum (min) and maximum (max)]. If non-parametric variables showed normal distribution, the independent samples t-test was used; if they did not, the Mann-Whitney U test was used. When parameters did not show normal distribution, the Wilcoxon test was used to assess statistical differences in continuous variables. The χ^2 test or Fisher's exact test was used to assess statistical differences in categorical variables. All statistical analyses were performed using the Statistical Package for the Social Sciences 22.0. A p value of <0.05 was considered statistically significant.

This study was approved by the Institutional Review Board of the Faculty of Medicine, Koç University (decision no: EMA/sk/258/2024, date: 20.02.2024). Oral informed consent was obtained from all patients. In a total of 11 patients, there were five female patients; the mean age was 30 [standard deviation (SD): 15.3, min: 8, max: 61], median age at epilepsy onset was 14 (min: 4, max: 20), and mean duration of epilepsy was 11 years (SD: 17.1, min: 0, max: 57). Epilepsy type was focal in 8 (73%) patients: all patients were on polytherapy and 4 of them had undergone epilepsy surgery. The patients' medical history consisted of febrile seizures in 2, head trauma in 3, cerebrovascular disease in 1, and central nervous system disorder in 1 of the patients. Family history of febrile seizures and epilepsy in 1 and epilepsy in 6. There was an intellectual disability in 4 of the patients. The demonstration features are detailed in Table 1.

PER treatment resulted in seizure freedom in 36% of patients and a >50% decrease in seizures in 55% of patients. EEG abnormalities were found in 91% of patients, multifocal EEG findings were described in 46%, and MRI was abnormal in 55% of patients. The mean duration from the initiation of PER treatment to the EEG recording was 221 days, and the mean duration from the PER treatment to the second EEG recording was 185 days. The median number of ASM was 4.2 (SD: 1.2), and the mean number of previous ASM use was 3.7 (SD: 2.3).

Table 1. Baseline characteristics of all patients (n=11)

Baseline characteristics	Findings
Mean age (SD) (years)	30 (±15.3)
Female gender; n	5
Median age at seizure onset (years)	14
Mean duration of epilepsy (years)	11 (±17.1)
Epilepsy type-focal (%)	8 (73%)
Number of current ASMs (median)	4.2
Seizure freedom after PER (%)	36%
>50% reduction in seizures	55%
Perampanel dosage (median) (mg)	4.5
Risk factors for seizures	
Febrile seizures (n)	2
Head trauma (n)	3
Central nervous system disorder (n)	1
Cerebrovascular disease (n)	1
Consanguinity (n)	0
Family history of epilepsy (n)	6
Febrile seizures in children	1

SD: Standard deviation, PER: Perampanel, ASM: Anti-seizure medications

MAIN POINTS

- Perampanel (PER), a non-competitive alpha-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid receptor antagonist, received approval from the European Medicine Agency for use as an adjunctive therapy for both focal and generalized epilepsy.
- The decreased rate of phase reversals was correlated with seizure freedom and a >50% reduction in seizures.
- Electroencephalography may be a valuable tool for evaluating patient response rates to PER.

RESULTS

The mean number of phase reversals on EEG were 722 and 411 before and after PER, respectively. The mean number of equipotential before and after PER was 74 and 323, respectively. There was no statistically significant relationship between background activity, phase reversal, and equipotential in EEG before and after PER treatment. In addition, pre- and posttreatment responses to activation procedures and disruption in sleep structure did not differ significantly. Beta activity was present in 4 patients on different ASM that were known to cause this activity on EEG. When we combined equipotentials and phase reversals as epileptic discharges, the pre-and post-treatment statistical results were not significant.

On the other hand, the relationship between seizure freedom and the decrease in phase reversals after PER treatment was statistically significant (p=0.03). The relationship between a >50% decrease in the frequency of seizures and epileptic discharges also reached statistical significance (p=0.0058).

The decrease in phase reversal and equipotential was not related to the dosage of PER, epilepsy type, age, sex, age at seizure onset, occurrence of intellectual disability, duration of epilepsy, abnormalities in MRI and EEG, number of current ASMs, number of previous ASMs, risk factors of epilepsy, and occurrence of sleep-related seizures.

DISCUSSION

Interictal spikes on EEG are strongly associated with the existence of epilepsy, and spikes reflect inhibitory mechanisms.[25] This study investigated the effects of PER on EEG in patients with epilepsy and showed that seizure freedom after PER treatment is related to a decrease in epileptiform discharge (phase reversals) on EEG. The findings of this study suggest that phase reversals may be a valuable marker of ASM response.

Interictal spikes are particularly indicative of epilepsy because they result from the paroxysmal discharges of large groups of neurons.[26,27] However, the connection between spikes and seizure generation remains contentious because of conflicting evidence.[28-30] Although earlier research examining short-term EEGs showed a limited link between seizure management and epileptiform discharges, recent studies investigating extended EEGs have demonstrated that a decrease in epileptogenic discharge burden is associated with enhanced seizure control.[13-15,17] The variations in the outcomes of these studies might be attributed to the disparity in the duration of EEG recordings utilised.[31] Extended EEG recordings might offer a more precise evaluation of epileptic discharge burden because they can account for fluctuations occurring within ultradian and circadian cycles.[32,33] In our study, even if the EEGs were not long-term monitoring, they were longer than the routine 20-min EEGs. Because we monitored only one sleep cycle, we believe we could measure ultradian fluctuations correctly. We observed synchronous and symmetrical sleep-related EEG activities in 90% of the patients. The efficacy of sleep did not change after treatment.

Similar to our findings, a recent study demonstrated that PER is more effective against epilepsy presenting with second bilateral synchrony on EEG and other epileptic discharges. Another study investigating the effect of PER on EEG spectral power and connectivity showed an increase in theta power, and researchers linked this interaction to increased sleepiness among PER users.[34] However, our study did not confirm this finding because we observed no remarkable change in background activity. In addition, one study reported increased beta activity among PER users, whereas another study did not replicate this finding, which is similar to our study.[34,35]

The current literature suggests that valproic acid, ethosuximide, and levetiracetam might decrease the epileptic discharge burden in both treatment-naive and treatment-resistant genetic generalized epilepsies.[31] Similarly, levetiracetam has been reported to create a consistent long-term reduction in interictal spikes over 4-18 months.[16,36] A study conducted with patients with focal epilepsy demonstrated that interictal epileptiform discharges decreased during treatment with carbamazepine. Moreover, the decreased interictal discharges were found to be related to seizure freedom.[37] In our study, a decrease in phase reversal among patients with seizure freedom was statistically significant, and the rate of decrease in seizures by >50% was nearly statistically significant. These findings might be interpretable in follow-up EEGs in patients with epilepsy, which provide valuable data regarding seizure outcomes.

Earlier research proposed the use of quantitative EEG (qEEG) to identify ASM-induced neurotoxicity.[4,38] However, qEEG has not been extensively used in neurological practice, and it is usually confined to research laboratories.[39] Therefore, the practical application of qEEG is limited. As in our study, even if visual inspection might be time-consuming in clinical practice, it provides valuable information about treatment response in patients with epilepsy.

Study Limitations

There are limitations to our study. First, only a small number of patients are eligible to be included in the study. Since PER is not within the scope of reimbursement by the social security institution and not all patients have undergone pre- and post-treatment EEG, this study included a small sample to analyze. Finally, this study could not isolate the exclusive impact of PER alone because it has not been approved for use as a monotherapy, which poses a potential constraint in our study. Additionally, variability in the PER dosage was observed because of personalized treatment approaches.

CONCLUSION

In conclusion, seizure freedom after PER treatment seems to be related to decreased epileptic discharge, and EEG monitoring might help determine prognosis. Conclusive findings could not be obtained regarding this matter because of the limited number of patients included in this study. Additional research is required to address this issue in a more extensive cohort.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Review Board of the Faculty of Medicine, Koç University (decision no: EMA/sk/258/2024, date: 20.02.2024).

Informed Consent: Oral informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.E., C.G., Concept: C.G., Design: C.G., Data Collection or Processing: İ.E., Analysis or Interpretation: İ.E., C.G., Literature Search: İ.E., C.G., Writing: İ.E., C.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Haas LF. Hans Berger (1873-1941), Richard Caton (1842-1926), and electroencephalography. *J Neurol Neurosurg Psychiatry*. 2003;74(1):9. [Crossref]
2. Galderisi S, Sannita WG. Pharmaco-EEG: a history of progress and a missed opportunity. *Clin EEG Neurosci*. 2006;37(2):61-65. [Crossref]
3. Salinsky MC, Oken BS, Storzbach D, Dodrill CB. Assessment of CNS effects of antiepileptic drugs by using quantitative EEG measures. *Epilepsia*. 2003;44(8):1042-1050. [Crossref]
4. Salinsky MC, Binder LM, Oken BS, Storzbach D, Aron CR, Dodrill CB. Effects of gabapentin and carbamazepine on the EEG and cognition in healthy volunteers. *Epilepsia*. 2002;43(5):482-490. [Crossref]
5. Salinsky MC, Spencer DC, Oken BS, Storzbach D. Effects of oxcarbazepine and phenytoin on the EEG and cognition in healthy volunteers. *Epilepsy Behav*. 2004;5(6):894-902. [Crossref]
6. Meador KJ, Loring DW, Abney OL, et al. Effects of carbamazepine and phenytoin on EEG and memory in healthy adults. *Epilepsia*. 1993;34(1):153-157. [Crossref]
7. Seneviratne U, Mohamed A, Cook M, D'Souza W. The utility of ambulatory electroencephalography in routine clinical practice: a critical review. *Epilepsy Res*. 2013;105(1-2):1-12. [Crossref]
8. Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. *Neurology*. 1996;47(1):260-264. [Crossref]
9. Stefan H, Hopfengärtner R. Epilepsy monitoring for therapy: challenges and perspectives. *Clin Neurophysiol.* 2009;120(4):653-658. [Crossref]
10. Loughman A, Seneviratne U, Bowden SC, D'Souza WJ. Epilepsy beyond seizures: predicting enduring cognitive dysfunction in genetic generalized epilepsies. *Epilepsy Behav*. 2016;62:297-303. [Crossref]
11. Browne TR, Dreifuss FE, Penry JK, Porter RJ, White BG. Clinical and EEG estimates of absence seizure frequency. *Arch Neurol*. 1983;40(8):469-472. [Crossref]
12. Sivakumar S, Zutshi D, Seraji-Bozorgzad N, Shah AK. Effects of Marijuana on Ictal and Interictal EEG Activities in Idiopathic Generalized Epilepsy. *J Clin Neurophysiol*. 2017;34(1):e1-e4. [Crossref]
13. Binnie CD. The use of the inter-ictal EEG in the study of antiepileptic drugs. *Electroencephalogr Clin Neurophysiol Suppl.* 1982;36:504-512. [Crossref]
14. Milligan N, Richens A. Methods of assessment of antiepileptic drugs. *Br J Clin Pharmacol*. 1981;11(5):443-456. [Crossref]
15. Eriksson AS, Knutsson E, Nergårdh A. The effect of lamotrigine on epileptiform discharges in young patients with drug-resistant epilepsy. *Epilepsia*. 2001;42(2):230-236. [Crossref]
16. Rocamora R, Wagner K, Schulze-Bonhage A. Levetiracetam reduces frequency and duration of epileptic activity in patients with refractory primary generalized epilepsy. *Seizure*. 2006;15(6):428-433. [Crossref]
17. Seneviratne U, Boston RC, Cook M, D'Souza W. EEG correlates of seizure freedom in genetic generalized epilepsies. *Neurol Clin Pract*. 2017;7(1):35-44. [Crossref]
18. Powell TE, Harding GF. Twenty-four hour ambulatory EEG monitoring: development and applications. *J Med Eng Technol.* 1986;10(5):229-238. [Crossref]
19. French JA, Krauss GL, Wechsler RT, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy A randomized trial. *Neurology*. 2015;85(11):950-957. [Crossref]
20. Goldsmith D, Minassian BA. Efficacy and tolerability of perampanel in ten patients with Lafora disease. *Epilepsy Behav*. 2016;62:132-135. [Crossref]
21. Potschka H, Trinka E. Perampanel: Does it have broad-spectrum potential? *Epilepsia*. 2019;60(Suppl 1):22-36. [Crossref]
22. Santamarina E, Alpuente A, Maisterra O, et al. Perampanel: A therapeutic alternative in refractory status epilepticus associated with MELAS syndrome. *Epilepsy Behav Case Rep*. 2019;11:92-95. [Crossref]
23. Tsai JJ, Wu T, Leung H, et al. Perampanel, an AMPA receptor antagonist: From clinical research to practice in clinical settings. *Acta Neurol Scand*. 2018;137(4):378-391. [Crossref]
24. Huang CW, Brown S, Pillay N, Campo MD, Tellez-Zenteno J, McLachlan RS. Electroencephalographic and electrocardiographic effect of intravenous lacosamide in refractory focal epilepsy. *J Clin Neurophysiol.* 2018;35(5):365-369. [Crossref]
25. Goncharova II, Alkawadri R, Gaspard N, et al. The relationship between seizures, interictal spikes and antiepileptic drugs. *Clin Neurophysiol*. 2016;127(9):3180-3186. [Crossref]
26. Ayala GF, Dichter M, Gumnit RJ, Matsumoto H, Spencer WA. Genesis of epileptic interictal spikes. New knowledge of cortical feedback systems suggests a neurophysiological explanation of brief paroxysms. *Brain Res.* 1973;52:1-17. [Crossref]
27. WARD AA Jr. The epileptic spike. *Epilepsia*. 1960;1:600-606. [Crossref]
28. Gotman J. Relationships between interictal spiking and seizures: human and experimental evidence. *Can J Neurol Sci.* 1991;18(Suppl 4):573-576. [Crossref]
29. de Curtis M, Avanzini G. Interictal spikes in focal epileptogenesis. *Prog Neurobiol.* 2001;63(5):541-567. [Crossref]
30. Avoli M, Biagini G, de Curtis M. Do interictal spikes sustain seizures and epileptogenesis? *Epilepsy Curr.* 2006;6(6):203-207. [Crossref]
31. Gunawan C, Seneviratne U, D'Souza W. The effect of antiepileptic drugs on epileptiform discharges in genetic generalized epilepsy: a systematic review. *Epilepsy Behav*. 2019;96:175-182. [Crossref]
32. Seneviratne U, Boston RC, Cook M, D'Souza W. Temporal patterns of epileptiform discharges in genetic generalized epilepsies. *Epilepsy Behav*. 2016;64(Pt A):18-25. [Crossref]
33. Karoly PJ, Freestone DR, Boston R, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. *Brain*. 2016;139(Pt 4):1066-1078. [Crossref]
34. Lanzone J, Ricci L, Tombini M, et al. The effect of perampanel on EEG spectral power and connectivity in patients with focal epilepsy. *Clin Neurophysiol.* 2021;132(9):2176-2183. [Crossref]
35. Liguori C, Spanetta M, Izzi F, et al.
36. Perampanel increases cortical EEG fast activity in child and adult patients affected by epilepsy: a quantitative EEG study. *Clin EEG Neurosci.* 2021;52(5):360-370. [Crossref]
37. Kanemura H, Sano F, Sugita K, Aihara M. Effects of levetiracetam on seizure frequency and neuropsychological impairments in children with refractory epilepsy with secondary bilateral synchrony. *Seizure*. 2013;22(1):43-47. [Crossref]
38. Marciani MG, Gigli GL, Stefanini F, et al. Effect of carbamazepine on EEG background activity and on interictal epileptiform abnormalities in focal epilepsy. *Int J Neurosci*. 1993;70(1-2):107-116. [Crossref]
39. Frost JD Jr, Hrachovy RA, Glaze DG, Rettig GM. Alpha rhythm slowing during initiation of carbamazepine therapy: implications for future cognitive performance. *J Clin Neurophysiol*. 1995;12(1):57-63. [Crossref]
40. Clemens B, Ménes A, Piros P, et al. Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings. *Epilepsy Res*. 2006;70(2-3):190-199. [Crossref]