Epilepsy & Behavior Reports 29 (2025) 100743

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Usefulness of perampanel as initial monotherapy in children with non-lesional focal epilepsy

Hideaki Kanemura [a,b,*], Yoshihiro Miyasato [a], Yutaro Tomi [a], Fumikazu Sano [b]

[a] Department of Pediatrics, Toho University Medical Center Sakura Hospital, Sakura, Chiba 285-8741, Japan
[b] Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Chuo, Yamanashi 409-3898, Japan

ARTICLE INFO

Keywords:
PER, perampanel
focal epilepsy
Antiseizure medication, ASM
IED, interictal epileptiform discharge
Child
initial monotherapy

ABSTRACT

This study aimed to compare carbamazepine (CBZ) and perampanel (PER) in terms of the efficacy against clinical seizures and electroencephalographic abnormalities such as interictal epileptiform discharges (IEDs) and safety as initial monotherapy in children with non-lesional focal epilepsies. This retrospective review included participants recruited from among epilepsy outpatients treated at the authors' hospital between January 01, 2000, and December 31, 2019 in the CBZ group and between January 01, 2020, and December 31, 2022 in the PER group. The inclusion criterion in both groups was ≥12 months of follow-up. Responders were identified as participants demonstrating complete disappearance (100 % reduction in seizures or IEDs) or response (>50 % reduction in seizure frequency or IEDs). Safety primary outcome was defined as appearance rate of AEs. The study group comprised 247 participants treated with CBZ and 46 participants treated with PER. Total efficacy rate for clinical seizures was significantly higher with PER than with CBZ ($p = 0.0148$). Moreover, the rate of complete disappearance was significantly higher with PER than with CBZ ($p = 0.0133$). Total efficacy rate for IED was again significantly higher with PER than with CBZ ($p < 0.0001$). The appearance of adverse events was significantly lower with PER than with CBZ ($p = 0.023$). PER may be useful as initial monotherapy in children with non-lesional focal epilepsies.

1. Introduction

In the therapeutic approach to children with epilepsy, seizure control and the risk of adverse events (AEs) from antiseizure medications (ASMs) should be balanced. Because many seizures in epileptic children are benign and childhood epilepsies are often readily treatable with easy remission, the choice of ASM must be carefully considered to minimize the risk of AEs. The consensus first-choice treatment for focal epilepsies (FEs) in both children and adults has been carbamazepine (CBZ). Randomized controlled trials and a Cochrane review have recommended CBZ as a first choice for FEs including self-limited epilepsies [1–3]. However, several ASMs have recently entered the market. Insufficient data have been accumulated concerning the effectiveness of new ASMs, including perampanel (PER). On the other hand, AEs are not uncommon in epileptic patients administered CBZ [4]. Dermatological reactions can be severe, leading to CBZ discontinuation. Skin rash is seen as an AE of CBZ in approximately 10 % of cases [5,6]. Moreover, CBZ may lead to seizure exacerbation and electroencephalographic abnormalities. In contrast, new ASMs may be less toxic and may result in fewer AEs compared to conventional ASMs [7]. This would make new ASMs advantageous for use as initial monotherapy.

PER is a highly selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist [8], and in 2020 was approved for use as a monotherapy in children ≥ 4 years old for focal-onset seizures in Japan. PER tends not to lead to severe AEs, such as the skin rash, thrombocytopenia, or abnormality in

Abbreviations: AE, adverse event; ASM, antiseizure medication; FE, focal epilepsy; CBZ, carbamazepine; PER, perampanel; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EEG, electroencephalogram; IED, interictal epileptiform discharge; SeLECTS, self-limited epilepsy with centrotemporal spikes; SeLEAS, self-limited autonomic seizures; MRI, magnetic resonance imaging; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition; ID, intellectual disability; FSIQ, full-scale intelligent quotient; FLE, frontal lobe epilepsy; SBS, secondary bilateral synchrony; FMS, focal motor seizure; FIAS, focal impairment awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure.

* Corresponding author at: Department of Pediatrics, Toho University Medical Center Sakura Hospital, Sakura, Chiba 285-8741, Japan.
E-mail addresses: hideaki.kanemura@med.toho-u.ac.jp (H. Kanemura), yoshihiro.miyasato@med.toho-u.ac.jp (Y. Miyasato), yutaro.tomi@med.toho-u.ac.jp (Y. Tomi), fsano@yamanashi.ac.jp (F. Sano).

https://doi.org/10.1016/j.ebr.2025.100743
Received 7 December 2024; Received in revised form 26 January 2025; Accepted 26 January 2025
Available online 30 January 2025

hepatic function seen with CBZ or valproate sodium [9–11]. PER is also associated with fewer AEs such as dermatological or hypersensitivity reactions [10,11]. PER may thus be appropriate as initial monotherapy for children with FE. However, PER may present AEs such as serious psychiatric and behavioral reactions [12], whereas these AEs are remotely related with CBZ. CBZ may thus be appropriate as initial monotherapy in this respect. The utility of PER as initial monotherapy has not been sufficiently evaluated in children with FE.

Pharmacotherapy must ultimately be judged in accordance with data obtained from clinical research and experience. The aims of this study were to evaluate efficacy against clinical seizures and abnormalities on the electroencephalogram (EEG) such as interictal epileptiform discharges (IEDs), and safety as an initial monotherapy in children with non-lesional FE, comparing CBZ as a conventional ASM with PER as a new ASM.

2. Materials and methods

2.1. Participants

Eligible participants were those diagnosed with FEs including self-limited epilepsy with centrotemporal spikes (SeLECTS) or self-limited autonomic seizures (SeLEAS). In addition, FE children not fitting any defined syndrome were also included if no structural or underlying metabolic cause of epilepsy was present. Thus, participants with magnetic resonance imaging (MRI) abnormalities such as mesial temporal abnormalities or focal cortical abnormalities were not included.

Participants were classified into two groups based on the results of initial monotherapy by CBZ or PER. Participants in the CBZ group had been seen in our hospital between January 01, 2000, and December 31, 2019. Participants in the PER group had been seen between January 01, 2020, and December 31, 2022. All patients were reviewed retrospectively and were included if follow-up was $\geq$ 12 months. Exclusion criteria were as follows: 1) unreliable information from parents/caregivers regarding seizure frequency and AEs; 2) poor compliance with attending necessary visits; 3) inability to set the baseline of clinical manifestations including seizure frequency; 4) need for any medication other than ASM due to the presence of severe medical and/or progressive neurological disorders; 5) less than one seizure in the 12 months prior to ASM initiation; 6) poor adherence to pharmacotherapy; 7) evidence of using $>$ 1 ASM; or 8) presence of non-epileptic seizures or other chronic disorders.

Demographic data, epileptic syndrome, seizure type, and seizure frequency before and after ASM administration for each participant were reviewed. For all participants in both groups, blood biochemistry before ASM initiation was obtained as baseline data.

Among PER group participants $>$ 6 years old, cognitive scores measured using the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV) were monitored before and 12 months after ASM initiation. Intellectual disability (ID) was defined as a full-scale intelligent quotient (FSIQ) $<$ 70 from the WISC-IV.

2.2. Strategy for ASM administration

2.2.1. CBZ group

The dose titration schedule for CBZ was based on the clinical practice, summarized as follows. Participants started CBZ at a dose of 3 mg/kg/day. Doses were increased by 3 mg/kg/day per visit if seizures were still present, and maintained if seizure disappearance had been obtained. Doses could also be decreased if AEs were present. Based on the judgement of the attending clinician, the dose of CBZ could be increased up to 20 mg/kg/day.

2.2.2. PER group

PER administration was performed in accordance with the therapeutic strategy based on the clinical practice, summarized as follows. The starting PER dose was 0.5 mg/day in children $<$8 years old or 1 mg/day in children $\geq$8 years old, maintained for the first 2 weeks. Based on the judgement of the attending clinician, PER dose was increased by 0.5 mg/day per 2 weeks, up to 12 mg/day. Dose of PER was unchanged if seizure disappearance was obtained and could be decreased if AEs were present. The treatment goal in the present study was $\geq$50 % seizure reduction without AEs. The final PER dose was kept stable during the first 3 months of the monitoring period. Modification was then possible in cases of inappropriate seizure control or presence of AEs.

2.2.3. EEG procedures

Electroencephalographic examinations were performed in a similar manner to our previous report [13]. Briefly, EEGs were recorded every 3 months as a regular schedule. The duration of each EEG tracing was at least 20 min. In principle, EEGs were recorded in both awake and sleep states without drug sedation.

EEG data were analyzed by two or three epileptologists or pediatric neurologists blinded to the information of the participant. Reader agreement with respect to the presence of IEDs was needed for participant inclusion.

2.2.4. Clinical seizure analysis

Baseline data concerning seizure frequency, type, and duration were recorded by the parents and caregivers of participants prior to ASM initiation. Information about the frequency of seizures both at home and during the day at nursery/kindergarten/school was obtained from the parents, caregivers, and teachers of participants. Seizure frequency was defined as the mean number of seizures per month. The presence or absence of AEs and their symptoms were also obtained from an epilepsy diary completed by parents and/or caregivers.

Seizure response to ASMs was divided into the categories defined in our previous report [14]: complete disappearance, 100 % reduction in seizure frequency; response, $\geq$50 % but $<$100 % reduction in seizure frequency; minimal response, $\geq$25 % but $<$50 % reduction in seizure frequency; no response, $<$25 % reduction to $<$50 % increase in seizure frequency; or exacerbation, $\geq$50 % increase in seizure frequency. Responders in terms of clinical seizures were identified as those participants presenting with either complete disappearance or response.

2.2.5. EEG analysis

Frequency of IEDs on EEGs was analyzed as briefly outlined below. Frequency of IEDs was calculated in sleep stages 1 and 2 for at least 15 min and identified as the number of epileptiform discharges per minute. IEDs present on bipolar montage were counted, and the correlation between EEG score and treatment response was evaluated. The frequency of IEDs prior to ASM initiation was used as the baseline score. Comparisons of IED frequency for each participant were performed within the same sleep stage. Treatment response was evaluated 12 months after starting ASM administration. In comparison with baseline score, EEG response was divided into four groups according to our previous report [15]: complete disappearance, 100 % reduction in IED frequency; response, $\geq$50 % reduction in IED frequency; no response, $<$50 % reduction to $<$50 % increase in IED frequency; or exacerbation, $\geq$50 % increase in IED frequency. EEG responders were identified as those participants presenting with complete disappearance or response.

2.2.6. Analysis of tolerability and AEs

Safety primary outcome was defined as the appearance rate of AEs. Tolerability and presence of AEs were evaluated by self-reports or laboratory examinations. AEs were divided into categories of major or minor according to content and severity. Major AEs were identified as events resulting in discontinuation of ASMs. Tolerable AEs resulting in dose modification or necessity for any management were identified as minor AEs. Participant adherence was evaluated by self- or parent-report and serum concentrations of ASMs.

2.2.7. Statistical analysis

The various statistical analyses in the present study were performed using SPSS statistical software (version 19; IBM, New York, USA). Data such as continuous variables are presented as mean ± standard deviation. Group differences in variables were analyzed using the chi-square test or Fisher's exact test, as appropriate, and continuous variables were analyzed using analysis of variance with Bonferroni correction. Statistical significance was determined at the level of $p < 0.05$.

2.2.8. Ethics committee approval

The present study was carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee at Toho University Medical Center Sakura Hospital (approval no. S23069). Research information was posted on the hospital website and potential participants were given the opportunity to decline to be included in the study (opt-out).

3. Results

The CBZ group comprised 271 children treated between January 01, 2000 and December 31, 2019. Among these, 24 were excluded because of loss to follow-up. The remaining 247 children were included in this study. The PER group comprised 48 children treated between January 01, 2020 and December 31, 2022. Among these, 2 were excluded because of loss to follow-up. The remaining 46 children (mean age, 7.1 years) were included in this study. Clinical manifestations for participants from both groups are shown in Table 1. Mean ages at onset were 5.4 years (range, 1.8–10.4 years) in the CBZ group and 5.2 years (range, 3.9–8.1 years) in the PER group, showing no significant difference (p = 0.39). No significant difference in sex distributions was evident between groups, with 128 boys (51.8 %) in the CBZ group and 24 boys (52.2 %) in the PER group (p > 0.99). ID was present in 25 children (10.1 %) in the CBZ group and 5 children (10.9 %) in the PER group. Twenty-eight children (11.3 %) in the CBZ group and 6 children (13.0 %) in the PER group presented with a psychiatric history, including autism spectrum disorder. No significant differences in frequency of ID or psychiatric history were seen between groups (p = 0.80 each).

When classified by epileptic seizures with overlapping, 46 children (18.6 %) in the CBZ group and 8 children (17.4 %) in the PER group showed focal motor seizures. Two hundred and five children (83.0 %) in the CBZ group and 39 children (84.8 %) in the PER group had focal impairment awareness seizure. One hundred and forty-eight children (59.9 %) in the CBZ group and 31 children (67.4 %) in the PER group had focal to bilateral tonic-clonic seizures. No significant differences in the proportions of seizure types were evident between groups (p > 0.99, p > 0.99, and p = 0.41, respectively).

When classified according to electroclinical syndromes, 41 children (16.6 %) in the CBZ group and 7 children (15.2 %) in the PER group had SeLECTS. Twenty-three children (9.3 %) in the CBZ group and 4 children (8.7 %) in the PER group had SeLEAS. Twenty children (8.1 %) in the CBZ group and 7 children (15.2 %) in the PER group had frontal lobe epilepsy (FLE). One hundred and thirty-one children (53.0 %) in the CBZ group and 25 children (54.3 %) in the PER group had unclassified FEs. No significant difference in the proportions of electroclinical syndromes was evident between groups (p = 0.94).

Mean dosages and concentrations in the CBZ group were 5.9 ± 2.1 mg/kg/day (range, 3.9–8.1 mg/kg/day) and 6.7 ± 1.0 μg/mL (range, 4.2–9.1 μg/mL). Mean dosages and concentrations in the PER group were 3.4 ± 1.2 mg/day (range, 1.5–6 mg/day) and 319.6 ± 89.4 ng/mL (range, 114–524 ng/mL), respectively.

Clinical efficacy of each ASM is shown in Table 2. Overall, 134 children (54.2 %) in the CBZ group showed complete disappearance of seizures at the end of 12 months of treatment. Moreover, another 12 children (4.9 %) showed a seizure response. In the PER group, 34 children (73.9 %) showed complete disappearance of seizures at the end of 12 months of treatment, and another 4 children (8.7 %) showed a seizure response. The frequency of seizure responders was significantly higher in the PER than in the CBZ group (p = 0.0148). Moreover, the rate of complete disappearance of seizures was significantly higher in the PER group than in the CBZ group (p = 0.0133).

The effect of ASMs on the frequency of IEDs differed between groups. In 31 of the 247 children (12.6 %) treated with CBZ, a > 50 % decrease was observed in IED frequency. Among responders in CBZ group, complete disappearance of IEDs was observed in only 4 children (12.9 % of responders; 1.6 % of total CBZ recipients). In contrast, 30 (65.2 %) of the 46 children in the PER group were considered as EEG responders.

Table 1
Clinical characteristics of participants in the present study.

Characteristics	CBZ(n = 247)	PER(n = 46)	p-value
Sex			
Male	128	24	>0.99
Female	119	22	
Age at onset (yrs)	5.4 ± 1.7	5.2 ± 1.2	0.39
Presence of Intellectual disability	25	5	0.8
Presence of prior psychiatric history	28	6	0.8
Epileptic seizure			
FMS	46	8	>0.99
FIAS	205	39	>0.99
FBTCS	148	31	0.41
Total			0.89
Epileptic syndrome			
SeLECTS	41	7	>0.99
SeLEAS	23	4	>0.99
FLE	20	7	0.56
Unclassified	131	25	>0.99
Total			0.94
Drug serum concentration	6.7 ± 1.0	319.6 ± 89.4	

CBZ, carbamazepine; PER, perampanel; FMS, focal motor seizure; FIAS, focal impairment awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; SeLECTS, self-limited epilepsy with centrotemporal spikes; SeLEAS, self-limited epilepsy with autonomic seizure; FLE, frontal lobe epilepsy.

Table 2
Clinical efficacy and adverse events in each treatment group.

Treatment response	CBZ(n = 247)	PER(n = 46)	p-value
Seizure response			
Complete disappearance	134	34	0.0133
Responder	12	4	0.293
Total responder	146	38	0.0148
Responders rate by epilepsy syndrome type (%)			
SeLECTS	34/41 (82.9)	7/7 (100)	0.5725
SeLEAS	21/23 (91.3)	4/4 (100)	>0.9999
FLE	6/20 (30.0)	6/7 (85.7)	0.0237
Others	85/163 (52.1)	21/28 (75.0)	0.0381
EEG response			
Complete disappearance	4	18	<0.0001
Responder	27	12	0.0055
Total responder	31	30	<0.0001
Responders rate by epilepsy syndrome type (%)			
SeLECTS	1/41 (2.4)	7/7 (100)	<0.0001
SeLEAS	1/23 (4.3)	4/4 (100)	0.0003
FLE	2/20 (10.0)	6/7 (85.7)	0.0006
Others	27/163 (16.6)	13/28 (46.4)	0.0009
AE			
Major	18	1	0.327
Total	72	6	0.023

CBZ, carbamazepine; PER, perampanel; EEG, electroencephalogram; AE, adverse event; SeLECTS, self-limited epilepsy with centrotemporal spikes; SeLEAS, self-limited epilepsy with autonomic seizure; FLE, frontal lobe epilepsy.

Moreover, 18 of these children demonstrated complete disappearance of IEDs (60.0 % of responders; 39.1 % of total PER recipients). The frequency of IEDs responders was significantly higher in the PER group than in the CBZ group ($p < 0.0001$). Moreover, the rate of complete IED disappearance was significantly higher in the PER group than in the CBZ group ($p < 0.0001$). All EEG responders were also seizure responders in both groups.

AEs were identified in 72 children (29.1 %) treated with CBZ and 6 children (13.0 %) treated with PER. Major AEs were observed in 18 children (7.3 %) in the CBZ group, comprising: skin rash (13 children, 5.3 %), neutropenia (3 children, 1.2 %), and severely elevated levels (>100 IU/L) of aspartate aminotransferase/alanine aminotransferase (2 children, 0.8 %). Other minor AEs consisted of drowsiness (35 children), learning difficulties (6 children), mildly elevated levels of aspartate aminotransferase/alanine aminotransferase (6 children), nausea and anorexia (4 children), fatigue (4 children), and transient auditory cognitive impairment (2 children). Meanwhile, a major AE was observed in one child (2.2 %) treated with PER. The cause of ASM discontinuation in this participant was severe drowsiness. The dose and concentration of PER in this participant were 5.5 mg/day and 514 ng/mL, respectively. Other minor AEs were mild drowsiness in 5 children (10.9 %) and lightheadedness in 1 child (2.2 %). Mean dosage and concentrations of PER in these participants were 3.3 mg/day (range, 1.5–4.5 mg/day) and 339.8 ng/mL (range, 197–454 ng/mL), respectively. In addition, mean FSIQs in the 12 participants in the PER group for whom this information was available before and 12 months after PER initiation were 85.6 and 86.3, respectively. No declines in cognitive functions were observed in this study. Similarly, no children in the PER group presented with behavioral problems during the entire treatment period. The frequency of AEs was significantly lower in the PER group than in the CBZ group ($p = 0.023$).

In the majority (27 participants, 87.1 %) of the 31 seizure-and-EEG responders in the PER group, the effective dosage of PER was ≤ 4 mg/day. The mean effective dose of PER was 3.0 mg/day (range, 1.5–5.5 mg/day). Similarly, in the majority (26 participants, 76.5 %) of the 34 participants with complete disappearance of seizures, the effective dosage of PER was < 4 mg/day. However, a relatively high (≥5 mg/day) effective dosage was required in 4 responders. No correlation was noted between PER dose and seizure/IED responder status ($p = 0.9615$ and $p = 0.2349$, respectively) (Fig. 1). Moreover, no correlation was identified between blood concentration of PER and seizure/IED responder status ($p = 0.3933$ and $p = 0.1146$, respectively) (Fig. 2).

4. Discussion

The pharmacological mechanism of action for PER is new and unique among ASMs. PER acts as a non-competitive antagonist of the AMPA glutamate receptor, which can lead to positive effects for clinical seizures and IEDs on EEG [8,16]. In adults with epilepsy, PER monotherapy has been shown to be effective [17]. However, little is known about the efficacy of PER as initial monotherapy for children with epilepsy.

The purpose of this study was to evaluate the efficacy and safety of PER as initial monotherapy in children with non-lesional FE in comparison with CBZ. Our findings confirmed good response for clinical seizures, IEDs on EEG and the safety profile of PER in FE children. Our study also showed that treatment with PER was more effective and better tolerated in comparison with CBZ. Previous studies have indicated that novel ASMs offer non-inferior efficacy and similar tolerability in comparison with conventional ASMs [18]. However, our findings showed the usefulness of PER for children with FE. This positive finding supports the consideration of PER as initial monotherapy for non-lesional FE children.

Children presenting with uncontrolled seizures are at greater risk of unfavorable functioning in daily life, even in cases of self-limited FE in childhood. Prompt and adequate treatment can prevent cognitive declines and behavioral impairments in children with FE [19]. However, paradoxical responses in the form of increased seizures or EEG abnormalities may also be induced by ASM treatment [20,21]. In patients with SeLECTS, CBZ sometimes caused an increase in IEDs and negative myoclonus [20]. In addition, seizure and EEG exacerbations were occasionally induced by CBZ in cases of SeLEAS [21]. Accordingly, CBZ is not recommended in cases with generalized or extensive spike-and-wave discharges on EEG [20,22]. In contrast, previous findings have indicated that PER could reduce the frequencies of both seizures and secondary bilateral synchrony (SBS) on EEG [16]. Moreover, PER monotherapy showed good retention, seizure-free and responder rates among children with focal-onset seizures [23]. These findings indicate that PER may represent a favorable option in the treatment of children with FE.

In this study, IEDs completely disappeared in about 53 % of children who achieved complete seizure disappearance in the PER group. All participants with complete IED disappearance were also found to be seizure responders. This finding may indicate that children with early EEG normalization are more likely to achieve seizure improvement. Reductions in IED could be associated with seizure improvements in various epilepsies [13,16,24].

The suppression of interictal IEDs on EEG may lead to the prevention of neuropsychological impairments such as cognitive and behavioral deterioration in at least some children with epilepsy [19]. Among the various ASMs, treatment with PER may lead to a reduction in IEDs. PER could decrease duration of after-discharge and the degree of synchronized discharges in postsynaptic neurons of the primary motor cortex [25,26]. Our previous study demonstrated that among 8 seizure responders of 14 epileptic children presenting with SBS on EEG by treatment with PER, 6 children were considered responders for EEG and

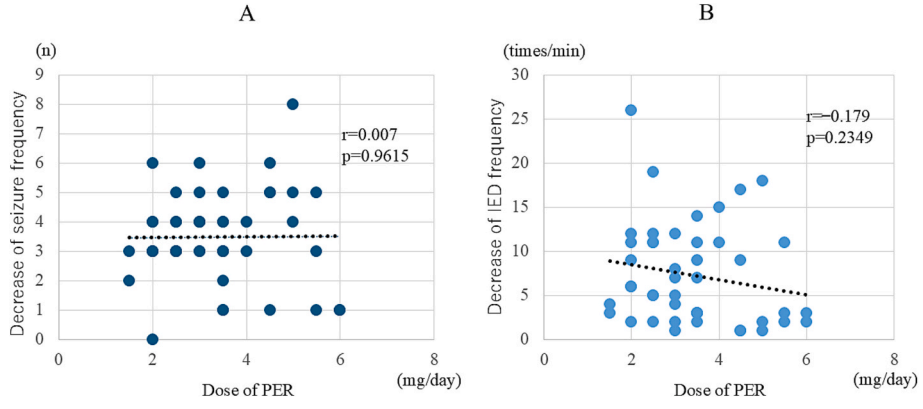

Fig. 1. Relationships between PER dose and seizure reduction (A) and IED reduction (B). No correlation was present between PER dose and seizure/IED responder status ($p = 0.9615$ and $p = 0.2349$, respectively). PER, perampanel; IED, interictal epileptiform discharge.

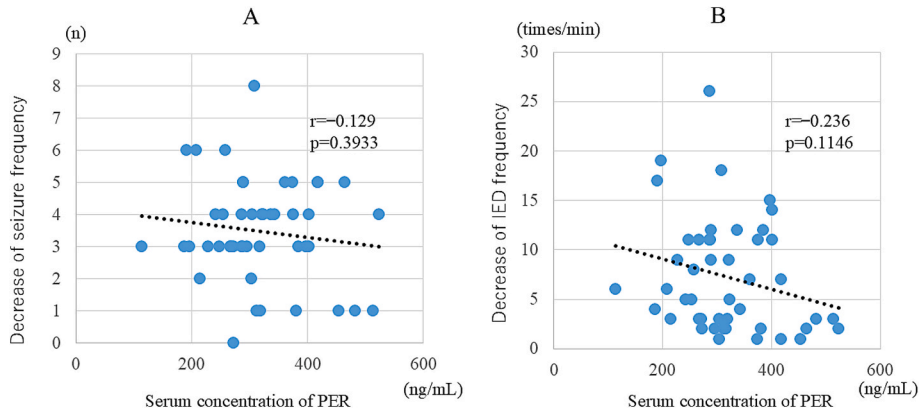

Fig. 2. Relationships between PER concentration and seizure reduction (A) and IED reduction (B). No correlation was present between serum concentration of PER and seizure/IED responder status ($p = 0.3933$ and $p = 0.1146$, respectively). PER, perampanel; IED, interictal epileptiform discharge.

behavioral problems [16]. Thus, PER may prove effective in reducing IEDs.

The efficacy of PER against IEDs may be associated with the dosage. Wu et al. reported that the efficacy of PER on the threshold of after-discharge depended on the dosage [25]. Moreover, our previous study demonstrated that EEG responders in patients presenting with SBS were treated using comparatively high doses [16]. However, participants in the present study were treated using comparatively low doses of PER. The early initiation of PER may lead to prompt improvements in seizures and EEG findings; however, no definitive conclusions can be drawn from the present study. Further investigations with larger samples are needed to clarify this aspect.

Epileptic patients with sleep-related seizures have reportedly obtained higher rates of seizure disappearance after PER monotherapy [23]. Our recent study showed that atypical evolution of SeLECTS, which is considered a sleep-related epilepsy, achieved greater benefits from PER [16]. In addition, PER may have a preferential effect on clinical seizures and IEDs in FLE [27], which is also considered a sleep-related epilepsy. In the present study, PER monotherapy showed efficacy in 6 of 7 children with FLE, and 5 of these 6 responders became seizure-free. Children with FLE thus obtained higher benefit from PER monotherapy. In addition, all 7 children with SeLECTS treated using PER were seizure/EEG responders. These findings may indicate that PER has a positive effect in children with sleep-related epilepsies.

In this study, the tolerability of PER was good without reported or expected safety issues. ASM treatment can cause various AEs, including drug eruption or abnormal laboratory findings. No children treated with PER displayed such AEs in the present study. ASMs can also cause various types of neuropsychiatric impairments, including somnolence, irritability and aggressiveness. Only one participant in the PER group of the present study discontinued treatment due to the appearance of somnolence. Severe neuropsychiatric impairments including behavioral reactions are listed as AEs of PER. Meanwhile, neuropsychiatric disorders including epilepsy are considered to involve pathophysiological mechanisms contributing to inhibitory/excitatory imbalances due to AMPA receptor dysfunctions. Moreover, anxious behavior could be prevented with non-competitive AMPA receptor antagonists. AMPA receptor antagonists could thus show an anxiolytic effect [28]. In addition, AMPA receptor antagonists could modulate neuronal activity, avoiding the excitotoxicity resulting from glutamate excess [29]. PER may also reduce behavioral problems related to improvements in EEG and clinical seizures [16,27]. However, many studies have reported psychiatric symptoms and behavioral problems in some patients treated with PER. Even in patients with seizure responders, behavioral symptoms could appear [30]. Further research with larger samples will be needed to clarify behavioral effects by PER treatment.

The dose of PER may affect the appearance of AEs. In one meta-analysis, PER doses of 4 and 8 mg/day appeared tolerable in patients ≤12 years old [11]. The same dose of PER can be administered to patients of all ages without requiring dose adjustment [11]. Thus, the pharmacokinetics of PER are considered independent of age and weight. The initial and maintenance doses reported in several studies were 1–2 mg/day and 8–12 mg/day, respectively [23]. On the other hand, 56.1 % of responders presented with serum concentrations in the range of 180.0–610.0 ng/mL, with AEs occurring in only a small proportion of children [31]. That study indicated a serum concentration of PER of 180.0–610.0 ng/mL may be adequate in epileptic children. In another study of 44 Japanese children, all participants with serum PER concentrations >400 ng/mL experienced AEs such as somnolence [32]. Our study showed mean PER doses and serum concentrations of 3.4 mg/day and 319.6 ng/mL, respectively. The PER dose was comparatively lower than in other studies and serum PER concentrations were within the reference range identified by above previous studies, potentially contributing to the high responder rate and low incidence of AEs. In addition, this low incidence of AEs might have been facilitated by the relatively slow titration. However, the present results showed no correlation between PER dose/concentration and seizure/IED reduction. These findings indicate that adequate dosages and serum concentrations of PER may differ between individual children with FE.

Our findings also indicate that PER may not have negative influences on cognitive function. Operto reported that PER never affected executive functions negatively [33]. Treatment with PER may be tolerated in terms of cognitive function in children with FE.

The frequency of IEDs can be influenced by the sleep state during EEG recording. EEG examinations were performed during awake and asleep state in this study. In addition, a comparison of IED frequencies was performed in the same sleep stage in each participant. Thus, our findings for EEG might not have been influenced by sleep state.

The results of this study provide new insights into the efficacy and safety of PER in children with non-lesional FE based on clinical experience. However, ASMs were selected by clinicians according to their experience. Thus, selection bias regarding ASMs could have been present for individual participants. Baseline data were retrospectively obtained from medical records for the CBZ group. However, the therapeutic protocol before the initiation of ASM therapy has been standardized in our hospital, including baseline laboratory examinations, EEG, neuroradiological examinations, and follow-up visits. Clinicians obtained information on the appearance of AEs as reported by the child or their parents on every visit. In addition, the treatment and evaluation periods of the present study were comparatively short, and the PER group was small. PER has recently started to see use in the initial treatment of FEs in children in Japan, and therefore, this significant difference in the sample size between 2 groups was caused. This might obscure the ability of present study to identify differences of treatment

effects between ASM groups, and no definitive conclusions can be drawn. Moreover, the absence of assessments of other conventional and new ASMs was another limitation to our study. The efficacy and tolerability of PER should be compared with those of other new ASMs in children with FE. Further research is needed to clarify these issues.

5. Conclusions

The present study provides information on the utility of PER as initial monotherapy in children with non-lesional FE. PER appears to have preferential efficacy for seizure reduction and EEG improvement and a lower risk of AEs in comparison with CBZ. Our results suggest that administering PER as initial monotherapy may represent a useful therapeutic strategy in children with non-lesional FE.

6. Statement regarding the use of generative artificial intelligence (AI)

The authors have not used generative artificial intelligence (AI) in preparation of the manuscript.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Hideaki Kanemura: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yoshihiro Miyasato:** Project administration, Data curation. **Yutaro Tomi:** Project administration, Data curation. **Fumikazu Sano:** Formal analysis.

Ethics approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Hideaki Kanemura has received speaker's fees from Eisai Co., Ltd. None of the other authors have any conflicts of interest to disclose.

Acknowledgments

The authors thank FORTE Science Communications (https://www.forte-science.co.jp/) for English language editing.

References

[1] Fejerman N, Caraballo RH, Bernardina BD. Benign childhood epilepsy with centrotemporal spikes. In: Fejerman N, Caraballo RH, editors. Benign focal epilepsies in infancy, childhood and adolescence. Montrouge: John Libbey Eurotext; 2007. p. 77–113.
[2] Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. Cochrane Database Syst. Rev. 2019; 10: Ed000142. 10.1002/14651858.ed000142.
[3] Cheng W, Yang Y, Chen Y, Shan S, Li C, Fang L, et al. Anti-seizure medication treatment of benign childhood epilepsy with centrotemporal spikes: A systematic review and meta-analysis. Front Pharmacol 2022;13:821639.
[4] Carbamazepine SM. In: The treatment of epilepsy. 2nd ed. Blackwell Science Ltd: Massachusetts; 2004. p. 345–57.
[5] Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kalviainen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54: 551–63.
[6] Carbamazepine LP. Clinical efficacy and use in epilepsy. In: Levy RH, Mattson RH, Meldrum BS, editors. Antiepileptic Drugs. 5th ed. Philadelphia PA: Lippincott Williams & Wilkins; 2002. p. 262–72.
[7] Kanemura H, Sano F, Ohyama T, Sugita K, Aihara M. Effect of levetiracetam monotherapy in nonlesional focal childhood epilepsy. Neuropediatrics 2018;49: 135–41.
[8] Rogawski MA. Revisiting AMPA receptors as an antiepileptic drug target. Epilepsy Curr 2011;11:56–63.
[9] French JA, Krauss GL, Wechsler RT, Wang XF, DiVentura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial. Neurology 2015;85:950–7.
[10] Omatsu H, Watanabe T, Kira R, Ishiba K, Patten A, Takase T, et al. Open-label study to investigate the safety and efficacy of adjunctive perampanel in pediatric patients (aged 4 to <12 years) with inadequately controlled focal-onset seizures: Japanese subgroup analysis. Seizure 2023;110:109–16.
[11] Sun S, Li X, Liu X. Efficacy, tolerability and safety of perampanel in children and adolescents with epilepsy: Systematic review and meta-analysis. Brain and Development 2023;45:260–9.
[12] Steinhoff BJ, Ben-Menachem E, Rvylin P, Shorvon S, Kramer L, Satlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. Epilepsia 2013;54:1481–9.
[13] 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;22:43–7.
[14] Kanemura H, Sano F, Tando T, Sugita K, Aihara M. Efficacy and safety of add-on levetiracetam in refractory childhood epilepsy. Brain and Development 2013;35: 386–91.
[15] Kanemura H, Sano F, Ohyama T, Sugita K, Aihara M. Effect of levetiracetam on behavioral problems in pervasive developmental disorder children with epilepsy. Eur J Paediatr Neurol 2014;18:482–8.
[16] Kanemura H, Sano F, Hoshino H, Takayama K, Aihara M. Effects of perampanel on secondary bilateral synchrony and behavioral problems in adolescents with epilepsy showing insufficient response with levetiracetam. Seizure 2020;80:131–7.
[17] Villanueva V, Garces M, Lopez-Gonzalez FJ, Rodriguez-Osorio X, Toledo M, Salas-Puig J, et al. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: The FYDATA study. Epilepsy Res 2016;126:201–10.
[18] Yılmaz U, YılmazTS DG, Akıncı G, Güzel O, Tekgül H. Efficacy and tolerability of the first antiepileptic drug in children with newly diagnosed idiopathic epilepsy. Seizure 2014;23:252–9.
[19] Kanemura H. Therapeutic strategies in children with epilepsy: a quality-of-life-related perspective. J Clin Med 2024;13:405.
[20] Nanba Y, Maegaki Y. Epileptic negative myoclonus induced by carbamazepine in a child with BECTS. Pediatr Neurol 1999;21:664–7.
[21] Kikumoto K, Yoshinaga H, Oka M, Ito M, Endoh F, Akiyama T, et al. EEG and seizure exacerbation induced by carbamazepine in Panayiotopoulos syndrome. Epileptic Disord 2006;8:53–6.
[22] Fejerman N. Early-onset benign childhood occipital epilepsy (Panayiotopoulos type). In: Engel Jr J, Pedley TA, editors. Epilepsy: a comprehensive textbook. 2nd ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2008. p. 2379–86.
[23] Xu S, Xu ZVR, Zheng Y, Miao P, Feng J, Guo Y. Efficacy and safety of perampanel monotherapy in patients with focal-onset seizures: A real-world experience in eastern China. Seizure 2023:231–7.
[24] Specchio N, Boero G, Michelucci R, Gambardella A, Giallonardo AT, Fattouch J, et al. Effects of levetiracetam on EEG abnormalities in juvenile myoclonic epilepsy. Epilepsia 2008;49:663–9.
[25] Wu T, Ido K, Ohgoh M, Hanada T. Mode of seizure inhibition by sodium channel blockers, an SV2A ligand, and an AMPA receptor antagonist in a rat amygdala kindling model. Epilepsy Res 2019;154:42–9.
[26] Oi K, Neshige S, Hitomi T, Kobayashi K, Tojima M, Matsuhashi M, et al. Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex. Clin Neurophysiol 2019;130:1804–12.
[27] Kanemura H, Sano F, Hoshino H, Aihara M. Efficacy of perampanel in epilepsy patients with autism spectrum disorder. Epilepsy Res 2021;170:106550.
[28] Kapus GL, Gacsalyi I, Vegh M, Kompagne H, Hegedus E, Leveleki C, et al. Antagonism of AMPA receptors produces anxiolytic-like behavior in rodents: effects of GYKI 52466 and its novel analogues. Psychopharmacology (Berl) 2008; 198:231–41.
[29] Tanaka K. Antibiotics rescue neurons from glutamate attacks. Trends Mol Med 2005;11:259–62.
[30] De Liso P, Vigevano F, Specchio N, De Palma L, Bonanni P, Osanni E, et al. Effectiveness and tolerability of perampanel in children and adolescents with refractory epilepsies-an Italian observational multicenter study. Epilepsy Res 2016; 127:93–100.
[31] Li Y, Dong N, Qin YX, Dai HR, Hu YH, Zhao YT, et al. Therapeutic drug monitoring of perampanel in children diagnosed with epilepsy: Focus on influencing factors on the plasm concentration-to-dose ratio. Epilepsia Open 2022;7:737–46.
[32] Ishikawa N, Tateishi Y, Tani H, Kobayashi Y, Kobayashi M. Clinical profiles associated with serum perampanel concentrations in children with refractory epilepsy. Epilepsy Behav 2019;94:82–6.
[33] Operto FF, Pastorino GMG, Mazza R, Di Bonaventura C, Matricardi S, Verrotti A, et al. Perampanel tolerability in children and adolescents with focal epilepsy: effects on behavior and executive functions. Epilepsy Behav 2020;103(PtA): 106879.