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Efficacy and serum concentrations of perampanel for treatment of drug-resistant epilepsy in children, adolescents, and young adults: comparison of patients younger and older than 12 years

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ABSTRACT

Purpose: Perampanel (PER) is a selective, non-competitive antagonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor. In Japan, PER is approved for patients with epilepsy who are at least 12 years old for the adjunctive treatment of primary generalised tonic-clonic seizures and partial-onset seizures (with or without secondary generalization). We surveyed the efficacy, adverse effects, and serum concentrations of PER, focusing especially on patients younger than 12 years of age.

Methods: We retrospectively surveyed the clinical information of patients treated with PER and assessed the efficacy at 6 months after treatment initiation. We compared efficacy, adverse effects, and serum concentration in patients younger or older than 12 years of age. Responders were defined as those who experienced a ≥50% seizure reduction.

Results: Eighty-four patients were enrolled. The average age of the younger group was 7.1 ± 3.3 (standard deviation) years compared to 16.4 ± 3.7 years in the older group. The responder rate was 42.9% (36/84). The responder rate did not differ between the two age groups (< 12 years, 20/44, 45.4%; > 12 years, 16/40, 40.0%; p = 0.78). The younger age group had a significantly lower concentration-to-dose (CD) ratio than the older age group (< 12 years, 1849.8 ± 2209.3; > 12 years, 3076.3 ± 3352.2, p = 0.02). Treatment-emergent adverse events (TEAEs) were observed in 22.6% (19/84) of patients, with the most common being somnolence (8/84, 9.5%).

Conclusion: PER may be an alternative to treat seizures in paediatric drug-resistant epilepsy. Serum concentrations of PER might be lower in patients younger than 12 years than in older patients.

1. Introduction

Perampanel (PER) is a selective, non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist that was developed for the treatment of epilepsy [1]. PER has a novel and unique mechanism for epilepsy treatment, and once-daily administration is recommended because of its long half-life (53–136 h) [2]. One study using a rat model of status epilepticus indicated that PER provides a neuroprotective effect in addition to termination of seizures [3]. In Japan, PER is approved for patients with epilepsy aged ≥12 years for the adjunctive treatment of primary generalised tonic-clonic seizures (GTCS) and partial-onset seizures (with or without secondary generalization). Although clinical experience with PER continues to increase, there is insufficient data on treatment of epilepsy in children younger than 12 years of age. We hypothesized that PER can act as an effective alternative treatment for patients younger than 12 years of age with drug-resistant epilepsy.

We retrospectively investigated whether PER can serve as an alternative treatment for children, adolescents, and young adults with drug-resistant epilepsy. In particular, we focused on differences in efficacy, adverse effects, and serum concentrations of PER in patients younger than 12 years of age compared to patients older than 12 years of age.

Abbreviations: PER, perampanel; TEAE, treatment-emergent adverse events

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2. Methods

We retrospectively surveyed consecutive patients treated with PER at the Saitama Children's Medical Center from 2016 to 2018. Patients whose symptoms were observed to be resistant to treatment with at least 2 appropriate antiepileptic drugs and who were then administered PER as an add-on drug were enrolled. A total of 84 patients (49 boys, 35 girls) were included in this study. We divided the 84 patients into 2 groups based on whether patients were younger (44 patients) or older than 12 years of age (40 patients). We retrospectively collected the following clinical data: age at the onset of epilepsy, age at PER initiation, epilepsy syndromes, seizure types, seizure frequency before and after PER administration, adverse effects, and concomitant anti-epileptic drugs used at the start of PER treatment. PER was initially administered at 0.04 mg/kg/day and was increased at 2–4-week intervals. Epilepsy syndromes and seizure types were defined according to the International League Against Epilepsy classification [4]. Effectiveness was assessed by a paediatric neurologist who evaluated caregiver observations to compare the frequency of seizures during the 4 weeks before PER therapy was initiated (baseline) and a 4-week period 6 months after initiation. Concomitant antiepileptic drug doses, other than PER, were not changed in most of the cases. In this study, responders were defined as those patients who experienced a ≥50% seizure reduction and whose seizure frequency was more than one every two months at baseline. For patients with multiple seizure types, PER efficacy was valuated independently for each type [focal seizure, generalised tonic-clonic seizure (GTCS), generalised tonic seizure (GTS), myoclonic seizure, epileptic spasms, and absence seizure]. Aggravation of seizures was defined as a ≥25% increase in seizure frequency from baseline.

We also retrospectively reviewed all data on serum PER concentration collected from 2016 to 2018. PER concentration had been measured 130 times in 54 patients during the study period. Blood samples were collected 12–18 h after administration of PER. PER concentration measurements were performed at least four weeks after each patient reached a stable dose of PER, and every 6–12 months while PER was administered. If the dose of PER was changed secondary to the patient's seizure condition, we remeasured the PER concentration. Therefore, some patients had their concentrations measured several times according to how many times the PER dose was changed. Serum concentrations of PER were measured using liquid chromatography-tandem mass spectrometry [5]. Because of the substantial number of paediatric patients included in this study, we calculated the concentration-to-dose (CD) ratio (ng/ml per mg/kg) in order to correct for body weight. We compared patients based on whether they were or were not administered enzyme-inducing antiepileptic drugs (EIAEDs). For this study, EIAEDs were defined as carbamazepine, phenytoin, phenobarbital, or topiramate. The CD ratio was compared in patients who had been treated with EIAEDs versus those who had not. We then compared the CD ratio between patients younger and older than 12 years in order to assess paediatric PER concentration.

Informed consent was obtained from the parents or guardians of each patient. For patients < 12 years of age, we explained the nature of the study and obtained age-appropriate assent. This study was approved by the Saitama Children's Medical Center Institutional Review Board [2018-03-05].

Data were analysed using SPSS (SPSS Inc., Chicago, IL) software for statistical analysis. Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Differences were defined as significant at a probability level of less than 0.05.

3. Results

The clinical data of the 84 patients included in the present study are shown in Table 1. The age of onset of epilepsy ranged from 0 months to 15 years [mean ± standard deviation (SD), 3.0 ± 3.6]. The age at which PER treatment was initiated ranged from 7 months to 28 years (mean ± SD, 11.4 ± 5.9). There was no significant between-group difference in the number of antiepileptic drugs that the patients had previously tried (< 12 years, median 4 drugs, range 2–9 drugs; > 12 years, median 4 drugs, range 2–8 drugs; p = 0.77). The 50% responder rate was 42.9% (36/84). Seven patients (8.3%) were seizure-free following PER treatment. There was no significant difference in responder rate in patients younger or older than 12 years of age (< 12 years, 20/44, 45.4%; > 12 years, 16/40, 40.0%; p = 0.78).

Table 1
Clinical profile of patients.

	Overall (n = 84)[a]	< 12 years old (n = 44)[b]	> 12 years old (n = 40)[c]
Age when PER was initiated, years (SD)	11.4 (6.0)	7.1 (3.3)	16.4 (3.7)
Age at onset of epilepsy, years (SD)	3.0 (3.6)	1.5 (2.1)	4.5 (4.3)
Female, n (%)	35 (41.7)	22 (50.0)	13 (32.5)
Seizure type, n (%)			
Focal seizures	55 (65.5)	25 (56.8)	30 (75.0)
Generalised tonic clonic seizures	9 (10.7)	3 (6.8)	6 (15.0)
Generalised tonic seizures	11 (7.1)	10 (22.7)	1 (0.3)
Myoclonic seizures	10 (11.9)	5 (11.4)	5 (12.5)
Epileptic spasms	10 (11.9)	10 (22.7)	0 (0.0)
Absence seizures	1 (1.2)	1 (2.3)	0 (0.0)
Epilepsy type, n (%)			
Focal	71 (84.6)	35 (79.5)	36 (90.0)
Generalized	13 (15.5)	9 (20.5)	4 (10.0)
No. of concomitant AEDs, n (%)			
One	16 (19.0)	10 (22.7)	6 (15.0)
Two	25 (29.8)	12 (27.3)	13 (32.5)
Three	20 (23.8)	10 (22.7)	10 (25.0)
Four or more	23 (27.4)	12 (27.3)	11 (27.5)
Concurrent EIAED treatment, n (%)	39 (46.4)	18 (40.9)	21 (52.5)
No concurrent EIAED treatment, n (%)	45 (53.6)	26 (59.1)	19 (47.5)

AED = Anti-epileptic drug, EIAED = enzyme-inducing anti-epileptic drug, PER = perampanel.
[a] 8 patients had 2 seizure types, 2 patients had 3 seizure types.
[b] 6 patients had 2 seizure type, 2 patients had 3 seizure types.
[c] 2 patients had 2 seizure type.

In terms of outcomes according to seizure type, 33.3% (3/9) of GTCS patients and 36.4% (4/11) of generalised tonic seizure (GTS) patients were observed to respond to PER, as well as 43.6% (24/55) of patients with focal motor with or without secondary generalised seizure, 50.0% (5/10) of patients with myoclonic seizures, 40.0% (4/10) of patients with epileptic spasms, and no (0/1) patients with absence seizures (Table 2). There were no significant differences in responder rate between patients younger or older than 12 years with respect to any of the seizure types.

Treatment-emergent adverse events (TEAEs) were observed in 22.6% (19/84) of patients. The most common TEAE was somnolence (8/84, 9.5%), followed by aggravation of seizure (6/84, 7.1%), and irritability (3/84, 3.6%). Respiratory failure, dizziness, and appetite loss were each observed in 1.2% (1/84) of our sample. In total, 15.5% (13/84) of patients discontinued treatment with PER because of TEAEs. There was no significant difference in the incidence of TEAEs in patients older than 12 years of age versus those younger than 12 years of age (10/44, 22.7% vs. 9/40, 22.5%, respectively; p = 0.81).

PER serum concentration results are shown in Figs. 1 and 2. In total, 130 samples from 54 patients were analysed during the study period. The mean ± SD for PER serum concentration was 269.2 ± 290.5 ng/ml, with a CD ratio of 2414.6 ± 2845.9 ng/ml per mg/kg. We also

Table 2
Efficacy and adverse effects of perampanel.

	Overall (n = 84)	< 12 years (n = 44)	> 12 years (n = 40)	p value
Responder rate, n (%)	36 (42.9)	20 (45.5)	16 (40.0)	0.78
Seizure-free rate, n (%)	7 (8.3)	3 (6.8)	4 (10.0)	0.90
Responder rate by seizure subtype				
Focal seizures, n (%)	24 (43.6)	13 (52.0)	11 (36.7)	0.38
Generalised tonic clonic seizures, n (%)	3 (33.3)	1 (33.3)	2 (33.3)	0.45
Generalised tonic seizures, n (%)	4 (36.4)	3 (30.0)	1 (100.0)	0.77
Myoclonic seizures, n (%)	5 (50.0)	2 (40.0)	3 (60.0)	1.00
Epileptic spasms, n (%)	4 (40.0)	4 (40.0)	n.d.	n.d.
Absence seizures, n (%)	0 (0.0)	0 (0.0)	n.d.	n.d.
Treatment-emergent adverse events	19 (22.6)	10 (22.7)	9 (22.5)	0.81

n.d. = no data.

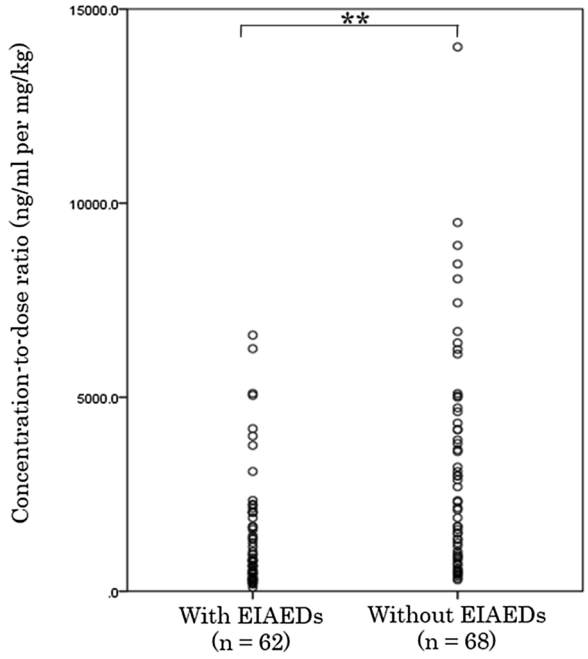

Fig. 1. Serum concentrations of perampanel.
Comparison of patients by administration of enzyme-inducing anti-epileptic drugs. ** indicates p-value < 0.01.

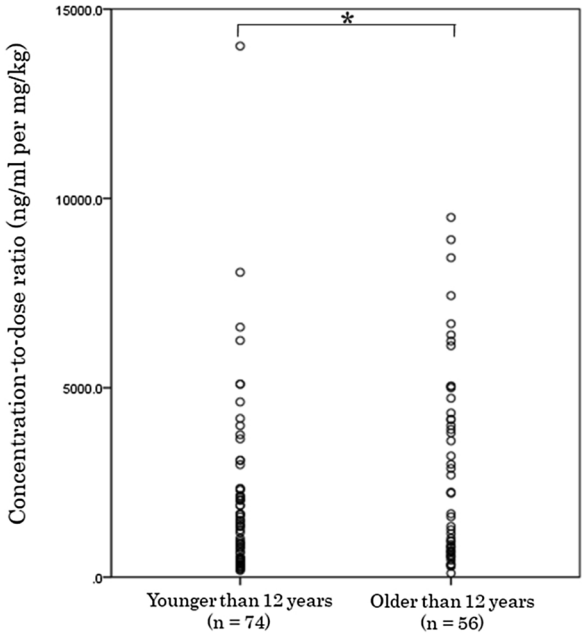

Fig. 2. Serum concentration of perampanel.
Comparison of patients by age group (younger than 12 vs older than 12). * indicates p value under 0.05.

analysed CD ratio according to whether patients received EIAEDs or not and observed a significantly lower mean CD ratio in patients who received EIAEDs (n = 62) than in those who did not (n = 68) (1494.7 ± 1552.7 vs. 3265.9 ± 3456.7, respectively; p < 0.01, Fig. 1). The ratio of the patients who received EIAEDs was not significantly different between the two age groups (patients < 12 years of age, 16/31; patients > 12 years of age, 16/23; p = 0.29). The ratio of responders was also not significantly different between the two age groups (patients < 12 years of age, 14/31; patients > 12 years of age, 10/23; p = 0.90). We observed that patients younger than 12 years of age (n = 74) showed a significantly lower mean CD ratio than patients older than 12 years of age (n = 56) (1849.8 ± 2209.3 vs. 3076.3 ± 3352.2, respectively; p = 0.02, Fig. 2). The CD ratio was not significantly different between responders (n = 62) and non-responders (n = 68) (2106.3 ± 2116.1 vs. 2708.9 ± 3390.9, respectively; p = 0.23).

4. Discussion

In this retrospective cohort study, PER was an effective drug-resistant epilepsy treatment for patients younger than or older than 12 years of age. A 50% responder rate (i.e., at least 50% seizure reduction following initiation of PER treatment) was observed in 36 of the 84 patients (42.9%) included in the present study, while seizures were completely resolved in 7 patients (8.3%). Prior studies have reported that the efficacy (50% responder rate) of PER in drug-resistant epilepsy patients with primary GTCS is 64.2% in those 12 years and older [6] and 37.5% in those under the age of 18 [7]. The patients enrolled in the present study were being treated with at least two anti-epileptic drugs prior to initiation of PER, meaning that they exhibited relatively drug-resistant epilepsy. In the current study, 52.4% (44/84) of patients were younger and 47.6% (40/84) were older than 12 years of age. We found no differences between the age groups (> 12 years vs < 12 years) in terms of PER effectiveness, suggesting that PER might be an effective treatment for drug-resistant epilepsy in paediatric patients.

Previous studies in rat models indicate that PER has anti-ictogenic and anti-epileptogenic properties in both mature and immature animals [8]. Thus, we sought to determine the clinical effectiveness of PER in children. We did not observe any difference between the age groups according to the type of seizure. Previous studies have suggested that PER might be particularly effective for patients with myoclonic seizures [9–11]. Our study supports these previous results, as we observed a relatively high responder rate in patients with myoclonic seizures (50%, 5/10) in the total patient group.

The adverse effects of PER reported in previous studies were usually mild or moderate in severity [12]. In our study, TEAEs were present in

22.6% (19/84) of patients, and most of these cases did not require further treatment. We regard the sedative effects of PER to be mild. All TEAEs resolved soon after discontinuation of PER. Previous reports have indicated that TEAEs related to PER are less likely to occur in patients who are younger than 12 years of age [13,14]. In our report, there was no significant difference in the incidence of TEAEs in patients older than or younger than 12 years of age (10/44, 22.7% vs. 9/40, 22.5%, respectively; $p = 0.81$).

The pharmacokinetic profile of oral PER is characterised by slow elimination (long half-life), and PER clearance can be markedly increased by the CYP3A4 enzyme inducers carbamazepine, phenytoin, phenobarbital, or topiramate [2,15,16]. Yamamoto et al. [17] reported that PER concentrations in a Japanese sample were lower than had been reported in other populations, possibly reflecting the low frequency of CYP3A5*3/*3 in Japanese compared to Caucasian populations. The average CD ratio in the current study tended to be lower than the ratios previously reported in Caucasian patients [18]. Serum concentrations of PER have been shown to be highly variable, suggesting that they are dependent on age, sex, and body weight [17]. Therefore, we investigated age-specific tendencies in PER concentrations and found that patients younger than 12 years old showed lower PER concentrations than those older than 12 years. One past study reported that PER administered concurrent with EIAEDs resulted in a lower responder rate compared to administration without EIAEDs [19], and a phase III study of PER has clearly demonstrated a positive dose-response relationship with 4 mg and 8 mg/day doses [20]. These reports suggest that EIAEDs may lead to lowering of PER concentrations and that higher PER concentrations may be necessary for effective treatment. Therefore, higher dosages of PER may be needed for children with drug-resistant epilepsy compared to adolescents and young adults.

A limitation of this study is the small number of patients from a single institution. In addition, evaluation of PER efficacy was limited to the subjective assessments of seizure frequency based on caregiver observations. Seizure frequency data were collected retrospectively based on case notes. Therefore, the results of this study should be interpreted with caution. Future, prospective studies should examine the efficacy of PER in children.

In conclusion, PER could serve as an alternative for seizure treatment in paediatric drug-resistant epilepsy and appears to be relatively safe. Serum concentrations of PER might be lower in patients who are younger than 12 years of age compared to those older than 12 years.

Declarations of interest

None.

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