Epilepsy & Behavior 94 (2019) 82–86

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Clinical profiles associated with serum perampanel concentrations in children with refractory epilepsy

Nobutsune Ishikawa [a,b,*], Yuichi Tateishi [a,b], Hiroo Tani [a,b], Yoshiyuki Kobayashi [a,b], Masao Kobayashi [a]

[a] Department of Pediatrics, Hiroshima University Hospital, Japan
[b] Epilepsy Center, Hiroshima University Hospital, Japan

ARTICLE INFO

Article history:
Received 18 January 2019
Revised 2 February 2019
Accepted 4 February 2019
Available online 18 March 2019

Keywords:
Perampanel
Efficacy
Treatment-emergent adverse events
Serum concentration
Concentration-to-dose
Children

ABSTRACT

Background: Perampanel (PER) is a new antiepileptic drug (AED) with a novel mechanism of action. Investigations of the efficacy and safety of PER in pediatric and adult patients have increased recently. Although the clinical usefulness and pharmacokinetics of PER have been investigated in adolescent and adult populations, similar studies have not been performed in children.

Patients and methods: We retrospectively reviewed the medical records of patients treated with PER for more than 6 months in the Department of Pediatrics, Hiroshima University Hospital, between September 2016 and November 2018. We obtained demographic and clinical data including age, sex, epilepsy type, seizure type, seizure frequency before and after treatment initiation, adverse events, reasons for discontinuing PER treatment, doses at evaluation points, serum concentrations, concomitant AEDs, intellectual status, and epilepsy etiology. Seizure types and epilepsy syndromes were classified according to the criteria of the International League Against Epilepsy.

Results: The study included 44 patients (22 males) between the ages of 6 months and 16 years. Of those, 10 patients discontinued PER therapy. The 50% response rate was 52.3% in patients treated with PER, and four patients achieved complete seizure control. Perampanel was highly effective in patients with generalized and focal epilepsy (50% responder rates, 52.9% and 50.0%, respectively). Favorable response rates were observed for tonic–clonic, focal nonmotor, and absence seizures with 50% response rates of 54.5%, 50.0%, and 66.7%, respectively. The 50% responder rate was 31.3 for epileptic spasms (ES). Treatment-emergent adverse events (TEAEs) included somnolence ($n = 8$), irritability ($n = 2$), ataxia ($n = 2$), and one case each of dizziness, compulsiveness, and enuresis. Serum concentrations of PER were compared in patients taking concomitant enzyme-inducing antiepileptic drugs (EIAEDs; carbamazepine, phenytoin, and phenobarbital) and those taking concomitant non-EIAEDs. Serum PER concentrations were correlated with dose per body weight in both groups (EIAED: $r = 0.765$, $p = 0.00000212$; non-EIAED: $r = 0.71$, $p = 0.0000158$). The mean concentration-to-dose (CD) ratio was 2398.4 ng mL^{-1} mg^{-1} kg^{-1} (range: 800–4524.7) in the non-EIAED group and 693.7 ng mL^{-1} mg^{-1} kg^{-1} (range: 344–1309.7) in the EIAED group. Serum PER levels were lower in the EIAED group than in the non-EIAED group. All patients with serum PER concentrations above 400 ng/mL experienced somnolence.

Conclusions: Perampanel is effective against various types of seizures, including ES, in pediatric patients with refractory epilepsy. Furthermore, PER has good tolerability when the dose is adjusted based on serum concentrations. The PER CD ratio was lower in pediatric patients than in adolescents and adults; therefore, clinicians must consider the CD ratio when treating children with PER.

1. Introduction

Despite the development of new antiepileptic drugs (AEDs) with excellent efficacy and good tolerability in recent years, refractory epilepsy remains a significant clinical problem. Therefore, AEDs with satisfactory efficacy and tolerability, and novel mechanisms of action, are urgently needed. Furthermore, because the manifestations of epilepsy and the factors considered to constitute an epileptic syndrome differ between adult and pediatric patients, that is, peculiar epileptic syndromes including age-dependent epileptic encephalopathy occur during childhood, alteration of seizure type by aging is often observed, genetic cause can lead to onset of epilepsy during early period of life, etc., separate studies in children are necessary.

Perampanel (PER) is an orally active selective noncompetitive α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor antagonist [1]. This novel mechanism of action is indicated for the treatment of partial-onset seizures with and without secondary generalization and for primary generalized tonic–clonic seizures. Early investigations

* Corresponding author at: Department of Pediatrics, Hiroshima University Hospital, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan.
E-mail address: ishikan@hiroshima-u.ac.jp (N. Ishikawa).

https://doi.org/10.1016/j.yebeh.2019.02.004
1525-5050/

of PER efficacy were performed in patients aged 12 years and older [2–5]; however, recent findings suggest that the drug is safe and effective in pediatric patients [6–9]. A previous study found a significant association between elevated plasma PER concentrations and reduced seizure frequency in patients older than 12 years old [2]. However, the same study found that increased PER plasma concentrations were potentially associated with an increase in the rate of adverse events [2]. The systemic clearance for various AEDs is higher in infants and children than in adults after normalization for differences in body weight [10–12]. Given potential pharmacokinetic differences between adults and children, blood concentration data of pediatric patients are needed to assess and manage accurately the efficacy and the safety of PER in this population.

In light of these findings, we measured serum concentrations in pediatric patients treated with PER to investigate the relationship of efficacy/safety with the pharmacokinetics of the drug in children.

2. Patients and methods

We retrospectively reviewed the medical records of patients treated with PER for more than 6 months in the Department of Pediatrics, Hiroshima University Hospital, Hiroshima, Japan, between September 2016 and November 2018. Perampanel is an approved adjunct treatment for focal seizures in patients older than 12 years in Japan. Written informed consent to the use of PER was obtained from both parents, as in use in our Hospital for off-label drugs. All patients had been treated with more than two AEDs and observed for more than 6 months from the initiation of PER to the last visit. We obtained demographic and clinical data including age, sex, epilepsy type, seizure type, seizure frequency before and after treatment initiation, adverse events, reasons for discontinuing PER treatment, PER doses at clinical evaluation points, serum concentrations, concomitant AEDs, intellectual status, and epilepsy etiology. Seizure types and epilepsy syndromes were classified according to the current criteria of the International League Against Epilepsy [13]. Intellectual/developmental status was assessed using a variety of well-established tools including the Wechsler Intelligence Scale for Children, third or fourth edition, the Kyoto Scale of Psychological Development, and the Enjoji Scale of Infant Analytical Development, all of which are widely used in Japan.

The incidence of treatment-emergent adverse events (TEAE) was based on reports from parents, school teachers, and caregivers. Seizure frequency was determined from the patients' seizure diaries commonly used in our hospital. Efficacy was assessed by comparing seizure frequency during the 4 weeks prior to treatment initiation with that 4 weeks after the acceptable maximum dose of PER was achieved. For children with a low seizure frequency (less than one per month), seizure frequency during the 3-month period before the initiation of PER treatment was compared with that after the acceptable maximum PER dose was achieved.

Efficacy, functional status, and adverse events were monitored regularly during monthly visits to our hospital.

The statistical tests were performed using the R statistical package (ver. 3.2.2; available at http://www.r-project.org). Numerical variables were compared using the Mann–Whitney *U*-test. p-Values <0.05 were considered to indicate statistical significance. Differences between independent groups were assessed using the Kruskal–Wallis and Fisher's exact tests for categorical variables.

This study was approved by the Hiroshima University Institutional Review Board.

3. Results

3.1. Patients' characteristics

The study included 44 patients (22 males) between the ages of 6 months and 16 years. In total, 36 patients exhibited intellectual impairment/developmental delay, which was classified as mild in nine patients, moderate in nine, and severe in 18 patients. The epilepsy seizures were classified as focal in 22 cases, generalized in 17 cases, as combined generalized and focal in four cases, and one case classified as unknown. The main seizure types were epileptic spasms (ES, n = 16) and focal nonmotor-onset seizures (n = 12). The majority of patients (n = 22, 50%) had been treated with three concomitant AEDs; 11 (25%) patients had been treated with two AEDs, and 10 (22.7%) patients had received enzyme-inducing AEDs (EIAEDs; carbamazepine, phenytoin, and phenobarbital; Table 1).

3.2. Drug doses

In patients older than 4 years, the initial dose of PER was 2 mg/day once daily, increasing to 4 mg/day after 2 weeks and to 6 mg/day after a further 2 weeks. During this period, the PER dose could be increased to a maximum of 12 mg/day based on the clinician's judgment. Perampanel was started at a dose of 1 mg in nine patients older than 4 years. Patients younger than 4 years were started on PER at lower doses, adjusted according to age and body weight. Perampanel was initiated at a dose of 1 mg in five patients between the ages of 1 and 4 years. Two patients younger than 1 year received initial doses of 0.4 mg and 0.5 mg per day, respectively. Perampanel doses were increased to the point of a seizure response (>50% seizure reduction) or the disappearance of seizures without adverse events. The PER doses were reduced in patients who experienced TEAEs.

Table 1
Patient demographic and clinical characteristics.

	Total (n = 44)
Mean age (SD), years	8.9 (4.9)
Female, n (%)	22 (50)
Onset age (SD), years	3.4 (3.2)
Intellectual/developmental status, n (%)	
Borderline to normal (IQ or DQ > 75)	8 (18.2)
Mild delay (75 > IQ or DQ > 50)	9 (20.5)
Moderate delay (50 > IQ or DQ > 35)	9 (20.5)
Severe delay (35 > IQ or DQ)	18 (40.9)
Mean maximum dose of PER (SD), mg	5.3 (3.1)
Median maximum dose of PER, mg	5.5
Mean duration of PER treatment (SD), months	7.4 (5.9)
Median duration of PER treatment, months	5.5
Type of epilepsy, n (%)	
Focal	22 (50.0)
Generalized	17 (38.6)
Combined generalized and focal	4 (9.1)
Unknown	1 (2.3)
Type of seizure, n (%)	
Focal nonmotor onset	12 (27.3)
Focal tonic	6 (13.6)
Focal to bilateral tonic–clonic	5 (11.4)
Focal clonic	2 (4.5)
Generalized onset tonic–clonic	3 (6.8)
Generalized tonic	6 (13.6)
Epileptic spasms	16 (36.4)
Myoclonic	3 (6.8)
Absence	3 (6.8)
Median concomitant AEDs at baseline, n	3
Number of concomitant AEDs at baseline, n (%)	
1	4 (9.1)
2	11 (25.0)
3	22 (50.0)
4 or more	7 (15.9)
Enzyme-inducing AEDs, n (%)	
Carbamazepine	4 (9.1)
Phenytoin	4 (9.1)
Phenobarbital	2 (4.5)
Nonenzyme-inducing AEDs, n (%)	34 (77.3)

IQ, intellectual quotients; DQ, developmental quotients; PER, perampanel; AEDs, antiepileptic drugs; SD, standard deviation.

Table 2
PER efficacy according to various subgroups.

	Patients, n	Aggravation, n	50–99% response, n	Seizure-free, n	All responders, n (%)
Etiology					
Structural	20	1	13	1	14 (70.0)
Genetic	2	0	0	1	1 (50.0)
Immune	1	0	0	0	0 (0.0)
Unknown	21	3	6	2	8 (38.1)
Intellectual/Developmental status					
Borderline to normal	8	0	3	2	5 (62.5)
Mild delay	9	0	5	1	6 (66.7)
Moderate delay	9	2	3	0	3 (33.3)
Severe delay	18	2	8	1	9 (50.0)
Epilepsy syndrome					
Focal	22	2	9	3	11 (50.0)
Generalized	17	1	9	1	9 (52.9)
Combined generalized and focal	4	1	1	0	1 (25.0)
Unknown	1	0	0	0	0 (0.0)
Type of seizure					
Focal nonmotor onset	12	1	3	3	6 (50.0)
Focal tonic	6	0	1	1	2 (33.3)
Focal to bilateral tonic–clonic	5	0	2	1	3 (60.0)
Focal clonic	2	0	2	0	2 (100)
Generalized tonic–clonic	3	0	1	1	2 (66.7)
Generalized tonic	6	0	3	0	3 (50.0)
Epileptic spasms	16	1	5	0	5 (31.3)
Myoclonic	3	1	1	0	1 (33.3)
Absence	3	0	2	0	2 (66.7)

3.3. Efficacy and tolerability

Perampanel was discontinued within the first 3 months in six patients, between 3 and 6 months in three patients, and between 6 and 12 months in one patient. The reasons for discontinuation were lack of efficacy in 9.1% (n = 4) of the patients (last doses, 3–8 mg), intolerable adverse effects in 4.5% (n = 2), and seizure aggravation in 9.1% (n = 4) of the patients. The 50% responder rate was 52.3% for PER treatment. In total, four patients experienced complete seizure control (seizure-free for 6 months before the follow-up visit). Patients with a structural etiology had a high 50% responder rate (70%). The 50% responder rate was not significantly different between the mild developmental delay and normal development groups or between the moderate and severe developmental delay groups (47.1% and 40.7%, respectively; p = 0.76). Although PER was highly effective in patients with severe intellectual impairment/developmental delay (50% responder rate of 50%), all four cases of seizure aggravation occurred in the moderate and severely delayed groups. The 50% responder rates were high in patients with generalized epilepsy (52.9%) and focal epilepsy (50.0%). Furthermore, the responses were favorable for tonic and tonic–clonic seizures (50% responder rate, 54.5%), focal nonmotor seizures (50.0%), and absence seizures (66.7%). The 50% responder rate was 31.3% in patients with ES (Table 2).

The TEAEs included somnolence in eight cases, irritability in two cases, ataxia in two cases, and one case each of dizziness, compulsiveness, and enuresis. One patient experienced somnolence, ataxia, and dizziness and another experienced somnolence and enuresis. Perampanel was discontinued because of somnolence in one patient and compulsiveness in another, both of which developed within 1 month after starting treatment. However, all of the remaining patients with TEAEs were able to continue treatment at a reduced dose.

3.4. Serum concentrations

Serum concentrations were measured at 28 evaluation points in 10 patients taking EIAEDs (carbamazepine, phenytoin, and phenobarbital; EIAED group) and at 29 evaluation points in 17 patients taking non-EIAEDs (non-EIAED group). Serum PER concentrations were correlated with dose per body weight in both groups (EIAED: r = 0.765, p = 0.00000212; non-EIAED: r = 0.71, p = 0.0000158; Figs. 1 and 2). The

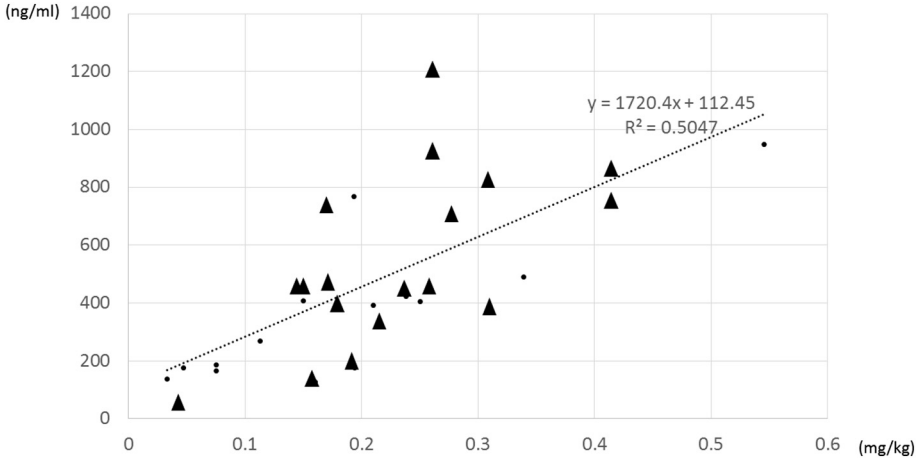

Fig. 1. Serum PER concentrations (mg per body weight [kg]) in patients taking concomitant nonenzyme-inducing antiepileptic drugs (EIAEDs). A significant correlation was found between serum PER levels and dose per body weight (r = 0.71, p = 0.0000158). Dots represented ones measured serum concentrations. Solid triangles indicate 50% responders.

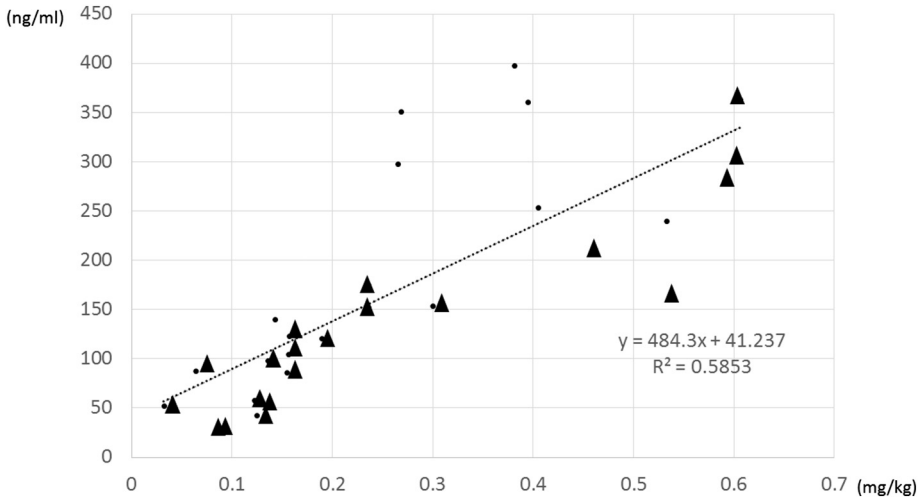

Fig. 2. Serum PER concentrations (mg per body weight [kg]) in patients taking concomitant enzyme-inducing antiepileptic drugs (EIAEDs). A significant correlation was found between serum PER levels and dose per body weight ($r = 0.765$, $p = 0.00000212$). Dots represented ones measured serum concentrations. Solid triangles indicate 50% responders.

mean concentration-to-dose (CD) ratio was 2398.4 ng mL^{-1} mg^{-1} kg^{-1} (range: 800–4524.7) in the non-EIAED group and 693.7 ng mL^{-1} mg^{-1} kg^{-1} (range: 344–1309.7) in the EIAED group. Serum PER levels were lower in EIAED than in the non-EIAED group. The 50% responders were widely distributed across serum PER concentrations in both concomitant drug groups; thus, we were not able to establish a dose-dependent effect (Table 3). All patients with serum PER concentrations above 400 ng/mL experienced somnolence (Fig. 3).

4. Discussion

The overall 50% responder rate was 52.3% in our study, although seizure freedom was achieved in four cases (9.1%). All of the patients enrolled in our study had pharmacoresistant seizures that were refractory to more than two AEDs. Given this criterion, our findings support previous studies showing that PER has good efficacy in pediatric patients with refractory epilepsy [6–9]. Perampanel reduced seizure frequency in children who have intellectual impairment/developmental delay suggesting that its effect is independent of intellectual/developmental status, which is consistent with previous findings [14]. Moreover, we found that PER was effective against various seizure types. Perampanel may reduce seizure frequencies in pediatric patients with intractable motor and nonmotor seizures. The major seizure type in our cohort was ES, a common intractable seizure type in children with refractory epilepsy. We found that PER was effective against pharmacoresistant ES (50% responder rate of 31.3%).

Previous studies have shown that serum concentrations of various AEDs at the same dose per body weight vary according to age [15,16]. Yamamoto et al. [17] measured serum PER concentrations in Japanese patients with epilepsy older than 12 years and found that the mean CD ratio was 3963 ng mL^{-1} mg^{-1} kg^{-1} (range: 1793–13,299) in the nonenzyme inducer group and 1760 (range: 892–3090), 2256 (range: 700–4703) and 1120 (range: 473–1853) ng mL^{-1} mg^{-1} kg^{-1} in patients taking concomitant phenytoin, phenobarbital, and carbamazepine, respectively. Patsalos et al. [16] reported that sex and age did not influence serum concentrations of PER in adult patients with epilepsy.

Table 3
Efficacy and serum PER concentrations according to concomitant drug therapy.

	50% responder	Non-50% responder	p-Value
Overall, ng/mL	325.2 ± 290.2 (211)	341.6 ± 217.9 (284)	0.332
EIAEDs, ng/mL	135.4 ± 97.3 (105)	274.5 ± 95.1 (276)	0.0054
Non-EIAEDs, ng/mL	505.6 ± 298.7 (443)	395.3 ± 274.7 (332)	0.367

EIAEDs, enzyme-inducing antiepileptic drugs.

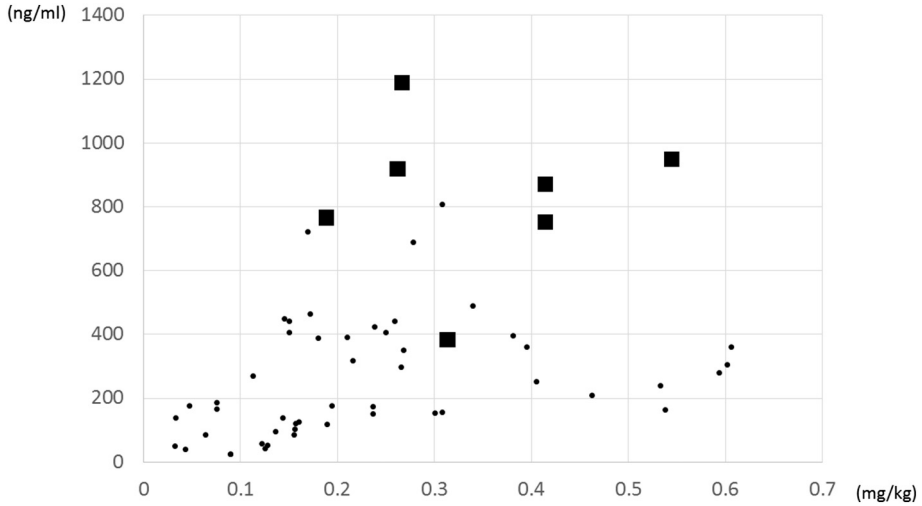

Fig. 3. The effect of serum PER concentrations (mg per body weight [kg]) on somnolence. Dots represented ones measured serum concentrations. Solid squares indicate somnolence cases.

Table 4
Treatment-emergent adverse events according to concomitant drug treatments.

	EIAEDs, (n = 10)	Non-EIAEDs, (n = 34)	Total, 44
TEAE cases, n (%)	2 (20.0)	8 (23.5)	10 (22.7)
Dose reduction	2	6	8
Discontinuation	0	2	2
Incidence of individual TEAEs (dose reduction/discontinuation)			
Somnolence	2 (2/0)	6 (3/1)	8 (5/1)
Irritability	0	2 (2/0)	2 (2/0)
Dizziness	0	2 (0/0)	2 (0/0)
Ataxia	0	1 (1/0)	1 (1/0)
Compulsiveness	0	1 (0/1)	1 (0/1)
Enuresis	0	1 (1/0)	1 (1/0)

EIAEDs, enzyme-inducing antiepileptic drugs.

We found that the serum concentrations of PER in our cohort of children <12 years old differed from those of older patients and had a lower CD ratio than those reported in older patients with epilepsy [16,17].

Gidal et al. [2] found concentration–effect relationships with PER in patients with focal epilepsy. The authors reported that seizure frequency decreased linearly as predicted PER average steady-state plasma concentration increased. Our study focused on the association between 50% responders and serum concentrations of PER. In the EIAED group, serum PER concentrations were higher in patients who did not achieve a 50% response than in the 50% responders, suggesting that some pediatric patients were refractory to PER at high doses, whereas the drug was effective in others at low-doses.

Treatment-emergent adverse events occurred in 10 patients (22.7%). Of those, only two discontinued treatment with PER, demonstrating good tolerability of the drug. Somnolence, the most frequent TEAE in our cohort, was observed in 18.2% of the patients. All of the patients with TEAEs, except one who withdrew shortly after starting PER therapy, were able to continue treatment on lower doses of the drug. Although serum PER concentrations above 400 ng/mL caused somnolence, patients were able to continue PER therapy on a lower dose of the drug. Thus, TEAEs can be managed by careful monitoring and adjusting PER serum levels (Table 4).

Our study has several limitations. First, it was a retrospective observational study conducted in a relatively small, heterogeneous sample of pediatric patients. Other potential limitations include the absence of a control group for PER treatment and the lack of a fully unified titration regimen for PER. Despite these limitations, our study is the first to demonstrate the efficacy and safety of PER in the treatment of intractable seizures, such as ES, and the safety of PER as an adjunct therapy in children. Further large-scale studies are needed to clarify the concentration effect in infants and children.

5. Conclusions

Perampanel is effective against various types of seizures, including ES, in pediatric patients with refractory epilepsy. Perampanel has good tolerability with dose adjustment based on serum concentrations. Serum PER concentrations were lower in patients receiving concomitant EIAEDs than in those taking non-EIAEDs. However, the 50% responders were widely distributed across serum concentrations in both groups. The CD ratio of PER was lower among pediatric patients than adolescent and adult patients. Therefore, the CD ratio must be considered when treating pediatric patients with PER.

Acknowledgments

None.

Funding

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

Conflict of interest

None of the authors has any conflict of interest to disclose.

References

[1] Plosker GL. Perampanel as adjunctive therapy in patients with partial-onset seizures. CNS Drugs 2012;26:1085–96.
[2] Gidal BE, Ferry J, Majid O, Hussein Z. Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures. Epilepsia 2013;54:1490–7.
[3] French JA, Krauss G, Biton V, Squillacote, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures. Randomized phase III study 304. Neurology 2012;79:589–96.
[4] French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Neurology 2013;54:117–25.
[5] Krauss GL, Serratosa JM, Villanueva N, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306. Adjunctive perampanel for refractory partial-onset seizures. Neurology 2012;78:1408–15.
[6] Swiderska N, Tan HJ, Rajai A, Silwal A, Desurkar A, Martland T. Effectiveness and tolerability of perampanel in children, adolescents and young adults with refractory epilepsy: a UK national multicenter study. Seizure 2017;52:63–70.
[7] Lin K, Lin J, Chou M, Hung P, Hsieh M, Chou I, et al. Efficacy and tolerability of perampanel in children and adolescents with pharmacoresistant epilepsy: the first real-world evaluation in Asian pediatric neurology ckinics. Epilepsy Behav 2018;85:188–94.
[8] Heyman E, Lahat E, Levin N, Epstein O, Lazinger M, Berkovitch M, et al. Tolerability and efficacy of perampanel in children with refractory epilepsy. Dev Med Child Neurol 2017;59:441–4.
[9] 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 epilepsy—An Italian observational multicenter study. Epilepsy Res 2016;127:93–100.
[10] Rosati A, Ilvento L, Lucenteforte E, Pugi A, Crescioli G, McGreevy KS, et al. Comparative efficacy of antiepileptic drugs in children and adolescents: a network meta-analysis. Epilepsia 2018;59:297–314.
[11] May TW, Boor R, Rambeck B, Jürgens U, Kom-Merker E, Brandt C. Serum concentrations of rufinamide in children and adults with epilepsy: the influence of dose, age, and comedication. Ther Drug Monit 2011;32:214–21.
[12] Wallander KM, Ohman I, Dahlin M. Zonisamide: pharmacokinetics, efficacy, and adverse events in children with epilepsy. Neuropediatrics 2014;45:362–70.
[13] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[14] Snoeijen-Schouwenaars FM, Van Ool JS, Tan IY, Schelhaas HJ, Majoie MHJM. Evaluation of perampanel in patients with intellectual disability and epilepsy. Epilepsy Behav 2017;66:64–7.
[15] Van Dijkman SC, Rauwé WM, Danhof M, Della Pasqua O. Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children. Br J Clin Pharmacol 2018;84:97–111.
[16] Patsalos PN, Gougoulaki M, Sander JW. Perampanel serum concentrations in adults with epilepsy: effect of dose, age, sex, and concomitant anti-epileptic drugs. Ther Drug Monit 2016;38:358–64.
[17] Yamamoto Y, Usui N, Nishida T, Tkahashi Y, Imai K, Kagawa Y, et al. Therapeutic drug monitoring for perampanel in Japanese epilepsy patients: influence of concomitant antiepileptic drugs. Ther Drug Monit 2017;39:446–9.