Therapeutic drug monitoring of perampanel: Clinical utility and impact of co-medication on pharmacokinetic variability

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ABSTRACT

Background: Perampanel (PER) is a newly developed antiseizure medication (ASM). This study aimed to determine the utilization of therapeutic drug monitoring (TDM) for PER in a real-world clinical setting and investigate the influence of concomitant use of ASMs on the plasma concentration profile of PER.
Method: We analyzed data from the Chang Gung Research Database, which is the largest multi-institutional electronic medical records database in Taiwan. The main outcomes were the comparisons of PER plasma concentration and the ratio of concentration to the weight-adjusted dose (C/D; [ng/mL]/[mg/kg/d]) among patients received TDM of different clinical indication and among different ASM co-medication subgroups.
Results: Overall, 88 plasma samples were collected from 66 epilepsy patients treated with PER. The majority of patients (77.3 %) underwent PER TDM owing to poorly controlled seizures. There was a trend toward a higher plasma concentration and C/D ratio in those suspected of having PER toxicity owing to adverse events than of other indications. The PER concentration exhibited dose linearity. The mean PER plasma concentrations in patients co-medicated with enzyme-inducing ASMs were significantly lower than those in the patients who were not prescribed enzyme-inducing or enzyme-inhibiting ASMs, and co-medication with carbamazepine (CBZ) resulted in a significant reduction in the PER concentration.
Conclusion: PER concentration exhibited a linear regression relationship with PER dose, and the plasma concentration of the drug was highly susceptible to the drug's interactions with enzyme-inducing ASMs. TDM with clear indication could help determine the influence of ASMs used concomitantly on PER concentrations and guide clinical adjustments.

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1. Introduction

Perampanel (PER) is a newly developed antiseizure medication (ASM). It acts as a non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor on postsynaptic neurons [1–3]. The drug has been licensed for the adjunctive treatment for focal-onset seizures with or without evolution to bilateral tonic-clonic seizures and for generalized-onset tonic-clonic seizures in patients aged 12 years and higher [3,4].

The pharmacokinetic (PK) profile of PER has been well established in both healthy volunteers and a phase III clinical trial population [5,6]. PER has high protein-binding ratio (>95 %) and long half-life (~105 h) [5]. PER is primarily metabolized through cytochrome P450 CYP3A4/5 hepatic oxidation. Thus, drugs that inhibit or induce CYP3A4 can impact PER clearance. It has been reported that PER clearance was increased significantly by CYP3A4 enzyme-inducing ASMs, such as carbamazepine (CBZ), oxcarbazepine (OXC), and phenytoin (PHT) without affecting the slope of the exposure–efficacy relationship [5,7,8]. Further, PER clearance was unaffected by age and race. However, it was influenced by sex: clearance was slower in women than in men [7,9]. Conversely, the potential influence of enzyme inhibitors on PER metabolism is unclear [7,8,10].

Therapeutic drug monitoring (TDM) has been used as a tool to guide treatment decisions for patients with epilepsy for almost 60 years [11]. TDM of older generation ASMs has been widely accepted, whereas its benefits for the newer generations of ASMs, including PER, is controversial [12,13]. Although solid evidence for its usefulness in improving clinical outcomes is scarce, evidence from nonrandomized studies and everyday clinical experience indicates that measuring plasma concentrations of newer ASMs can have a valuable role in guiding patient management provided that concentrations are measured with a clear indication and interpreted critically considering the whole clinical context [14]. To date, few studies have reported the TDM of PER, while the correlation between PER dosage and blood concentrations has been reported. However, some studies failed to show a relationship between the blood concentrations of the drug and its clinical efficacy or toxicity. Phase III studies has suggested a significant correlation between PER plasma concentration, reduction in seizure frequency, and adverse effects (AEs) [6,15]. On the contrary, postmarketing studies revealed interindividual variability in the relationship between PER dosage, concentration, and matched clinical response [16–18]. Nevertheless, almost none of these studies mentions the indications to perform TDM for PER.

In Taiwan, TDM for newer ASMs is not covered by national health insurance; thus, most patients receive TDM with clear indications since they need to pay for it by themselves. This allows the study of the plasma concentrations of PER in different clinical circumstances. Thus, in this study, we investigated the TDM of PER in real-world clinical practice with clear clinical indications and drug interactions between PER and concomitantly used ASMs.

2. Materials and methods

2.1. Data collection

This study was conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional review board (IRB)/ethics committee of Chang Gung Memorial Hospital (CGMH), Linkou, Taiwan.

Electronic medical records and Chang Gung Research Database (CGRD) [19] of CGMH, Taiwan, were searched to identify all PER plasma level measurement requests sent for analysis as part of routine clinical management in seven medical institutes located in the area extending from the northeast to southern regions of Taiwan, during the period from September 2016 to May 2019.

Data collected from the medical records included medication prescribed and dose, epilepsy syndrome and seizure types, age at onset of epilepsy, body weight, monthly seizure frequency before and after TDM, AEs, co-medications, and laboratory test results. Furthermore, the nature of the sample (random or trough), documentation of indications, and test results were recorded. Patients with renal impairment, hepatic dysfunction or pregnancy were excluded.

Indications for requesting PER TDM were grouped as follows: (1) understanding baseline or dose optimization; (2) uncontrolled seizures despite an apparently adequate dose; (3) suspected toxicity; (4) drug-drug interactions; (5) status epilepticus; and (6) elderly age.

The effects of daily PER dose, age, and concomitant ASM therapy on steady-state plasma PER concentrations were investigated. Blood samples were divided into subgroups according to the concomitantly administered ASM: group A, samples from those on PER monotherapy and not on enzyme-inducing ASMs (i.e., PHT, CBZ, OXC, or PHB) or enzyme-inhibiting ASMs (i.e., valproic acid [VPA]); group B, co-medication with enzyme-inducing ASMs; group C, co-medication with enzyme-inhibiting ASMs; and group D, co-medication with both enzyme-inducing and enzyme-inhibiting ASMs.

2.2. Measurement of PER plasma concentrations

PER plasma concentrations were measured with ultra-performance liquid chromatography/mass spectroscopy (UPLC-MS/MS; Waters XEVO TQ-S, Mundelein, IL) using a fully validated methodology in routine use in the Therapeutic Drug Monitoring Unit at the CGMH. The UPLC-MS/MS method was validated according to Clinical Laboratory Standards Institute guideline C62-A for LC-MS.

2.3. Statistical analysis

Statistical analyses and graphing were conducted with SPSS Statistics version 23 (IBM, Chicago, IL, USA), and data are expressed as

mean ± standard deviation. To analyze the effects of ASM regimens on the PK of each ASMs, correlations were evaluated by the Pearson correlation coefficient analysis. Comparisons of study variables among ASM co-medication subgroups were conducted by one-way analysis of variance (ANOVA) with Levene's statistic, followed by the Dunnett T3 or Bonferroni post hoc testing for multiple comparisons depending on variance significance. Sex distribution was compared among patient groups by using the chi-square test. Results were considered statistically significant when P-values were ≤0.05.

3. Results

3.1. Baseline demographic and clinical characteristics of patients

In the period study, 88 samples of plasma PER concentrations were collected from 66 patients with epilepsy (Table 1). Although some blood samples were collected at trough (i.e., just before the next dose), most were collected up to 3 h after PER ingestion (mean: 14.5 ± 5.4 h), and reflected everyday ASM TDM clinical practice. The PER concentration was below a detection limit (<5.2 ng/ml) in four samples, whereas the mean PER concentration in the remaining 84 samples was 219.0 ± 165.1 (range: 41.6–931.6) ng/ml (Table 1).

3.2. Association between PER concentration, dosage, and age

Pearson correlation analysis showed that the PER concentration exhibited dose linearity (r = 0.327, p = 0.002; Fig. 1A). However, there is no linear relationship between PER concentration-to-dose ratio (C/D ratio) and age (r = 0.179, p = 0.102, Fig. 1B). The C/D ratio was defined as PER plasma concentration (ng/mL) divided by the weight-adjusted daily dose (mg/kg/day).

3.3. Association between PER concentration, C/D ratio and concomitant ASM

Table 2 and Fig. 2 demonstrate the mean PER concentration and PER concentration-to-dose ratio (C/D ratio) in the four different co-medication groups. The mean PER C/D ratio were significantly different among the four groups (one-way ANOVA, p < 0.05).

Table 1
Clinical characteristic of patients received therapeutic drug monitoring for perampanel.

|	Total, n = 88 (%)
Gender, female	35 (39.8)
Age, y, mean ± SD	43.4 ± 17.6
Body weight, kg, mean ± SD	66.4 ± 15.3
Seizure onset age, y, mean ± SD	27.2 ± 23.4
Epilepsy duration, y, mean ± SD	16.2 ± 13.7
Seizure type	
Focal motor seizure with aware	5 (5.7)
Focal motor seizure with impaired awareness	6 (6.8)
Focal motor seizures with aware to bilateral tonic-clonic	6 (6.8)
Focal motor seizures with impaired awareness to bilateral tonic-clonic	5 (5.7)
Focal non-motor seizures with aware	0 (0)
Focal non-motor seizure with impaired awareness	7 (8.0)
Focal non-motor seizures with aware to bilateral tonic-clonic	1 (1.1)
Focal non-motor seizures with impaired awareness to bilateral tonic-clonic	43 (48.9)
Generalized motor	13 (14.8)
Unknown onset	2 (2.3)
Number of concomitant antiseizure medications	3 (0–6)
Monotherapy	2 (2.3)
Polytherapy	86 (97.7)
Carbamazepine	11 (12.5)
Clonazepam	21 (23.9)
Clobazam	16 (18.2)
Gabapentin	1 (1.1)
Lacosamide	35 (39.8)
Levetiracetam	56 (63.6)
Lamotrigine	12 (13.6)
Oxcarbazepine	26 (29.5)
Phenytoin	7 (8.0)
Pregabalin	2 (2.3)
Phenobarbital	6 (6.8)
Topiramate	27 (30.7)
Vigabatrin	1 (1.1)
Valproic acid	32 (36.4)
Zonisamide	14 (15.9)
Perampanel daily dose, mg, mean ± SD	7.0 ± 3.6
Perampanel plasma concentration, ng/mL, mean ± SD	219.0 ± 165.1
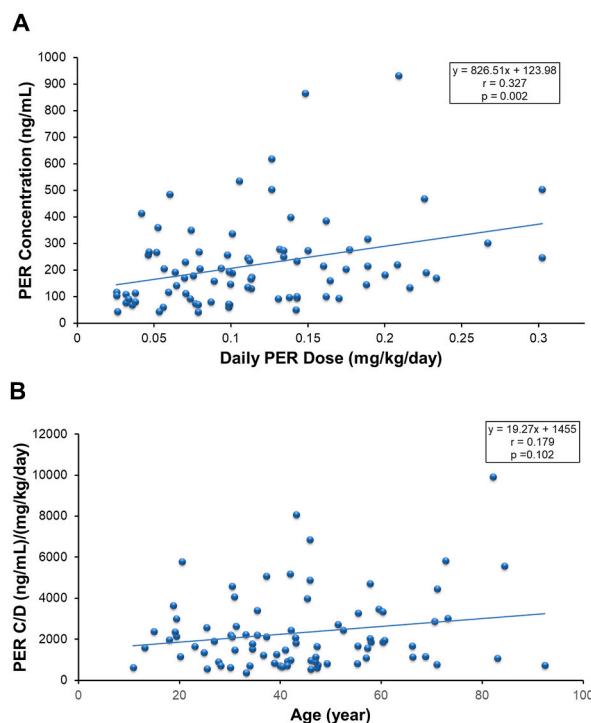
Fig. 1. Correlation between perampanel (PER) dose (in term of mg/kg/day) and PER plasma concentration (ng/ml) (1A); Correlation between age and perampanel (PER) plasma concentration to weight-adjusted daily dose ratio (C/D) (1B).

Compared with those who were not prescribed enzyme-inducing or enzyme-inhibiting ASMs (group A), the mean PER C/D ratio in patients co-medicated with enzyme-inducing ASMs (group B) were significantly lower ($p < 0.05$). On the other hand, the mean PER C/D ratio in those co-medicated with VPA, a known CYP-enzyme inhibitor (group C), were not significantly different from those in the patients who were not co-medicated with enzyme-inducing or enzyme-inhibiting ASMs (group A). The mean PER C/D ratio in patients co-medicated with enzyme-inducing ASMs (group B) were lower than those in the patients co-medicated with enzyme-inhibiting ASMs (group C), although the intergroup difference was not significant. The presence of both enzyme-inducing and enzyme-inhibiting ASMs (group D) resulted in significantly lower mean PER C/D ratio, compared with those in the patients who were not co-medicated with enzyme-inducing or enzyme-inhibiting ASMs (group A) ($p < 0.05$) (Table 3).

To investigate the specific effects of individual ASMs on PER plasma concentrations, the samples were further sub-grouped according to which single enzyme-inducing or enzyme-inhibiting ASM was co-prescribed. If patients were co-medicated with more than one enzyme-inducing ASM, they were excluded from the analysis. Fig. 3 and Table 4 show the mean PER C/D ratio were no significantly different among the six groups (one-way ANOVA, $p = 0.052$). However, patients co-medicated with CBZ had the lowest PER

Table 2
Participant characteristics in the different groups (n = 84).

	Group A	Group B	Group C	Group D	P value
Sample number	25	29	15	15	
Patient number	23	28	13	14	
Age, year	45.2 ± 20.3	45.0 ± 15.3	50.0 ± 18.1	29.8 ± 10.0	0.008*
Sex, male/female	16/9	16/13	7/8	12/3	0.255
Weight, kg	69.9 ± 17.9	65.4 ± 14.0	62.7 ± 15.6	65.1 ± 15.3	0.518
PER dose, mg	6.6 ± 3.5	7.2 ± 3.9	7.3 ± 4.1	7.6 ± 2.6	0.856
PER dose, mg/kg/day	0.099 ± 0.056	0.115 ± 0.061	0.129 ± 0.092	0.121 ± 0.053	0.507
PER plasma concentration, ng/mL	288.2 ± 239.6	159.2 ± 110.4	234.2 ± 102.8	182.8 ± 98.0	0.025*
PER C/D ratio (ng/mL)/(mg/kg/day)	3302.1 ± 2244.1	1781.1 ± 1672.8	2469.1 ± 1455.1	1578.2 ± 547.8	**0.004***

A: PER monotherapy and those neither on enzyme-inducing ASMs or enzyme-inhibiting ASMs.
B: co-medication of enzyme-inducing ASMs (CBZ, PHT, OXC, PHB).
C: co-medication of enzyme-inhibiting ASMs (VPA).
D: co-medication of both enzyme-inhibiting and enzyme-inhibiting ASMs.
One-way ANOVA, *$p < 0.05$.
PS: Age: Bonferroni post-hoc, group D *vs.* group A, $p = 0.037$; *vs.* group B, $p = 0.032$; *vs.* group C, $p = 0.009$.
PER, perampanel; ASM, anitiseizure medication; CBZ, carbamazepine; PHT, phenytoin; OXC, oxcarbazepine; VPA, valproic acid.
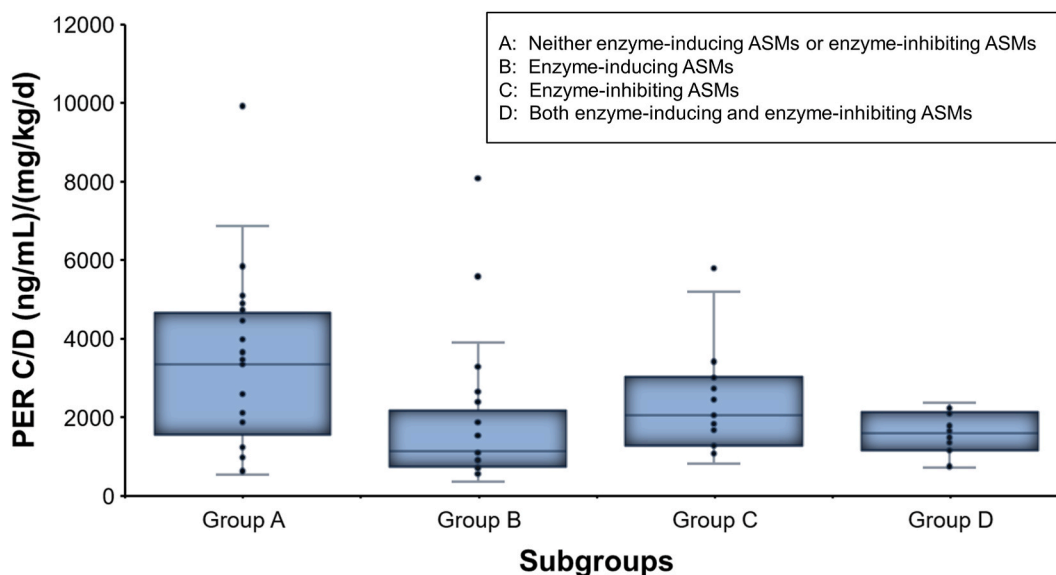
Fig. 2. Box plot of plasma concentration to weight-adjusted daily dose ratio (C/D) of perampanel (PER) by subgroups of co-administered antiseizure medications (ASMs). The horizontal line shows the mean value. The overall significance of comparison among the four groups by one-way analysis of variance (plasma concentration, p = 0.028; and C/D ratio, p = 0.004).

Table 3
Mean PER concentrations and PER concentration versus dose ratios in the different groups (n = 84).

Group	Number	Mean PER concentration (ng/ml)	Group comparison	Mean PER concentration difference (ng/ml)	P value
A	25	288.2 ± 239.6	A vs. B	129.0	**0.022***
B	29	159.2 ± 110.4	A vs. C	54.0	1.000
C	15	234.2 ± 102.8	A vs. D	105.4	0.268
D	15	182.8 ± 98.0	B vs. C	−75.1	0.838
			B vs. D	−23.6	1.000
			C vs. D	51.4	1.000
Group	Number	Mean PER CDR (ng/mL)/(mg/kg/day)	Group comparison	Mean PER CDR difference (ng/mL)/(mg/kg/day)	P value
A	29	3103.0 ± 2151.1	A vs. B	1520.9	**0.045***
B	29	1781.1 ± 1672.8	A vs. C	6833.0	0.639
C	15	2469.1 ± 1455.1	A vs. D	1723.9	**0.006***
D	15	1578.2 ± 547.8	B vs. C	−688.0	0.648
			B vs. D	202.9	0.991
			C vs. D	890.9	0.201

A: PER monotherapy and those neither on enzyme-inducing ASMs or enzyme-inhibiting ASMs.
B: co-medication of enzyme-inducing ASMs.
C: co-medication of enzyme-inhibiting ASMs.
D: co-medication of both enzyme-inhibiting and enzyme-inhibiting ASMs.
One-way ANOVA, Dunnett T3 post-hoc, *$p < 0.05$.
CDRs, concentration versus dose ratios; PER, perampanel; ASM, antiseizure medication.

plasma concentration, and the mean PER C/D ratio in these patients was significantly lower than that in the patients who were not prescribed enzyme-inducing or enzyme-inhibiting ASMs (control, i.e., group A) (*p* < 0.05) (Table 5).

3.4. Association between PER concentration, C/D ratio and indication of TDM

Most of the patients (n = 68, 77.3 %) received PER TDM owing to poorly controlled seizures, including nine patients with status epilepticus (Fig. 4A). Suspected alterations in PK owing to drug-drug interactions and concentration-related PER toxicity were the second and third leading factors because of which TDM was requested for PER in our cohort. Fig. 4B and **C** demonstrate the mean PER C/D ratio in the subgroup with various PER TDM indications. There was a trend toward a higher C/D ratio in those suspected of having PER toxicity owing to adverse events than in those with poorly controlled seizures (C/D ratio: 3191.8 ± 3843.1 [ng/mL]/[mg/kg/d] vs. 2307.8 ± 1743.1 [ng/mL]/[mg/kg/d]). However, the intergroup difference was not significant.
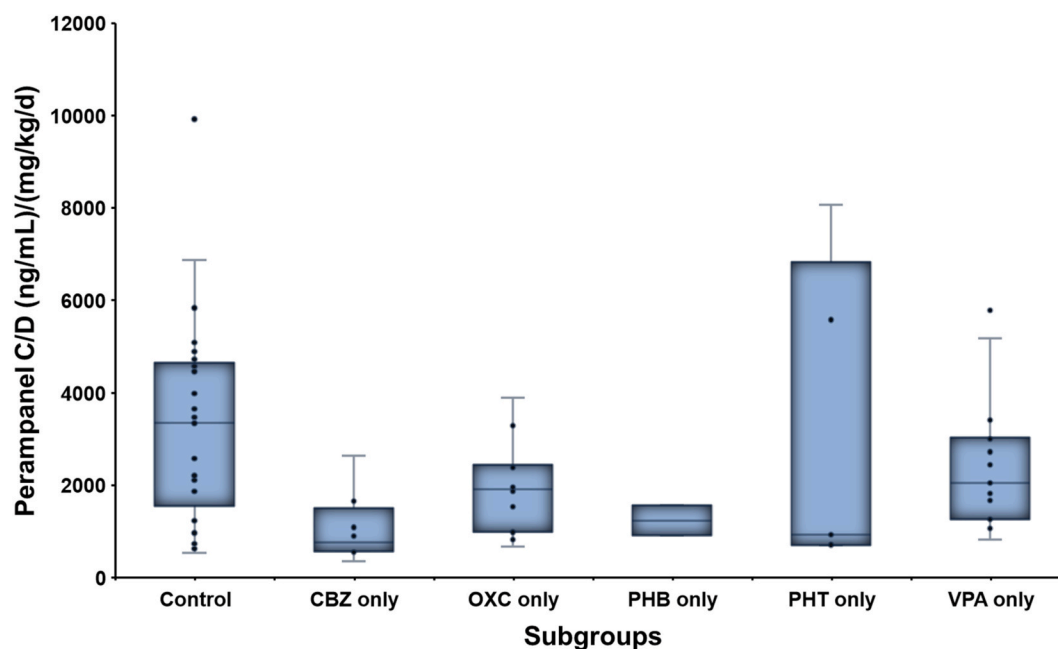
Fig. 3. Box plot of plasma concentration to weight-adjusted daily dose ratio (C/D) plasma concentration of perampanel (PER) by subgroups of individual co-administered antiseizure medications (ASMs). The horizontal line shows the mean value.

Table 4
Participant characteristics in the different ASMs (n = 66).

	Control	CBZ	OXC	PHB	PHT	VPA	P value
Sample number	25	8	11	2	5	15	
Patient number	23	8	11	2	4	12	
Age, year	45.2 ± 20.3	37.4 ± 11.5	42.4 ± 14.4	52.1 ± 7.3	50.0 ± 19.2	50.0 ± 18.1	0.617
Sex, male/female	16/9	5/3	7/4	2/0	1/4	7/8	0.385
Weight, kg	69.9 ± 17.9	64.8 ± 12.1	68.6 ± 17.4	63.9 ± 5.5	60.6 ± 17.0	62.7 ± 15.6	0.732
PER dose, mg	6.6 ± 3.5	6.5 ± 3.2	6.2 ± 3.7	12.0 ± 0	5.2 ± 1.8	7.3 ± 4.1	0.317[@]
PER dose, mg/kg/day	0.099 ± 0.056	0.104 ± 0.051	0.093 ± 0.054	0.188 ± 0.016	0.092 ± 0.041	0.129 ± 0.092	0.309
PER plasma concentration, ng/mL	288.2 ± 239.6	92.0 ± 69.6	160.0 ± 102.0	229.1 ± 66.7	202.4 ± 174.0	234.2 ± 102.8	0.099
PER C/D ratio (ng/mL)/(mg/kg/ day)	3302.1 ± 2244.1	1050.6 ± 756.5	1975.7 ± 1002.3	1235.0 ± 460.0	3195.7 ± 3427.1	2469.1 ± 1455.1	0.052

A: PER monotherapy and those neither on enzyme-inducing ASMs or enzyme-inhibiting ASMs.
ASM, antiseizure medication; PER, perampanel; CBZ: carbamazepine; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; VPA, valproic acid.
One-way ANOVA.
[@] PHB group was excluded for comparisons in term of PER dose (mg) because of 0 variance.

4. Discussion

In general, newer ASMs are considered more favorable for clinical use than older ASMs due to their more predictable pharmacokinetics and less potential of drug-drug interactions [20]. As a result, TDM of newer ASMs has been considered unnecessary. However, our study found that TDM of PER, in case where there is a clear indication for it, has proven to be clinically useful. For example, we observed a trend toward higher plasma concentration and C/D ratio in patients suspected of PER toxicity due to adverse events compared to those receiving the drugs for other indications. Since it can be difficult to recognize signs of toxicity based on clinical grounds alone in most cases [14], our clinical experiences align with non-randomized studies that suggest TDM may be useful for both older and newer ASMS in optimizing and individualizing ASM treatment, as long as blood concentrations are measured with a clear indication and with a careful clinical interpretation [14,20].

Most of the patients in this study received TDM for PER owing to poorly controlled seizures, concerns of drug-drug interactions and suspected toxicity. In this study, we found a linear relationship between PER dose and plasma PER levels. This result is in line with those of a previous phase III clinical trial [6] and other real-world studies [7,8,21,22]. A phase III clinical trial studies revealed lower PER oral clearance in female patients than in male patients [9]. However, Patsalos et al. reported neither sex- nor age-related differences in PER plasma concentration [7]. Because of age-related changes in physiological functions and alterations in blood flow, the clearance of many ASMs is presumed to decrease in the elderly, and the plasma concentrations can thus be expected to increase. In

Table 5
Mean PER concentrations and PER concentration versus dose ratios in the different ASMs (n = 66).

ASM	Number	Mean PER concentration (ng/ml)	Group comparison	Mean PER concentration difference (ng/ml)	P value
Control	25	288.2 ± 239.6	Control vs. CBZ	196.2	**0.014***
CBZ	8	92.0 ± 69.6	Control vs. OXC	128.2	0.348
OXC	11	160.0 ± 102.0	Control vs. PHB	59.2	0.989
PHB	2	229.1 ± 66.7	Control vs. PHT	85.8	0.991
PHT	5	202.4 ± 174.0	Control vs. VPA	54.0	0.995
VPA	15	234.2 ± 102.8	CBZ vs. OXC	−68.0	0.722
			CBZ vs. PHB	−137.1	0.496
			CBZ vs. PHT	−110.4	0.886
			CBZ vs. VPA	−142.3	**0.012***
			OXC vs. PHB	−69.1	0.899
			OXC vs. PHT	−42.4	1.000
			OXC vs. VPA	−74.3	0.653
			PHB vs. PHT	26.7	1.000
			PHB vs. VPA	−5.2	1.000
			PHT vs. VPA	−31.8	1.000

Group	Number	Mean PER CDR (ng/mL)/(mg/kg/day)	Group comparison	Mean PER CDR difference (ng/mL)/(mg/kg/day)	P value
Control	29	3302.1 ± 2244.1	Control vs. CBZ	2251.5	**0.002***
CBZ	8	1050.6 ± 756.5	Control vs. OXC	1326.4	0.238
OXC	11	1975.7 ± 1002.3	Control vs. PHB	2067.1	0.070
PHB	2	1235.0 ± 460.0	Control vs. PHT	106.4	1.000
PHT	5	3195.7 ± 3427.1	Control vs. VPA	833.0	0.906
VPA	15	2469.1 ± 1455.1	CBZ vs. OXC	−925.0	0.355
			CBZ vs. PHB	−184.4	1.000
			CBZ vs. PHT	−2145.1	0.872
			CBZ vs. VPA	−1418.5	0.075
			OXC vs. PHB	740.6	0.743
			OXC vs. PHT	−1220.1	0.996
			OXC vs. VPA	−493.5	0.992
			PHB vs. PHT	−1960.7	0.918
			PHB vs. VPA	−1234.1	0.376
			PHT vs. VPA	726.6	1.000

Control: PER monotherapy and those neither on enzyme-inducing ASMs or enzyme-inhibiting ASMs.
One-way ANOVA, Dunnett T3 post hoc, $*p < 0.05$.
PER, perampanel; ASM, antiseizure medication; CDR, concentration versus dose ratio; CBZ, carbamazepine; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; VPA, valproic acid.

concordance with the previous studies [6,7], in this study we also found an absence of a liner regression correlation between age and the PER C/D ratio; the PER plasma concentration was unaffected by sex. It is important to note, however, that these results may be influenced by differences in co-medications.

Although PER at a high concentration induced CYP3A4 activity four-fold in vitro, it is neither a potent inhibitor nor an inducer of CYP or UDP-glucuronosyltransferase isoenzymes at clinically relevant concentrations. Consequently, PER is not expected to cause significant PK interactions. However, because PER is metabolized primarily via CYP3A4, an isoenzyme that can be readily induced and inhibited, it will be the target of drugs that affect this isoenzyme [3,4]. In agreement with previous studies, we found that PER concentration is susceptible to concomitant ASMs. Patients co-medicated with enzyme-inducing ASMs had low PER concentrations. Regarding the effects of individual ASMs, patients co-medicated with CBZ had the lowest PER concentration. In a population PK analysis of three pooled phase III studies in patients with partial-onset seizures, CBZ, OXC, and PHT increased PER clearance three-, two-, and two-fold, respectively, and subsequently reduced area under the curve by approximately 67 %, 50 %, and 50 %, respectively [23]. As systemic exposure to PER increases, so does efficacy. Patsalos et al. reported similar results by using a TDM database, that CBZ, OXC, and PHT reduce PER concentrations by approximately 69 %, 37 %, and 13 %, respectively [5]. In our study, patients co-medicated with TPM have no significant difference in C/D ratio compared to those co-mediated neither on enzyme-inducing ASMs or enzyme-inhibiting ASM (3429.9 ± 1408.0 vs. TPM only 2897.5 ± 2210.4, $p = 0.470$, as shown in Fig. 5). These data corroborate the published population data in which, TPM, considered as a weak enzyme-inducing ASM, did not significantly decreased the PER concentration [5,7]. Conversely, the possible PK interaction between PER and VPA remains unclear. Contin et al. reported that PER concentration increased in patients who were concomitantly treated with VPA [10]. However, in our patient population, the mean plasma PER concentrations in those who were co-medicated with VPA were not significantly different from those in the patients who were not co-medicated with enzyme-inducing or inhibiting ASMs. A similar observation was reported by Patsalos et al. in their retrospective study [7]: PER concentration is unaffected by VPA co-administration.

In our study, the mean PER plasma concentration in 66 patients was 219.0 ± 165.1 ng/ml (range: 41.6–965.7 ng/ml). Among the responders in phase III trials, the PER concentration ranged from 180 to 980 ng/ml [5,6], which is comparable to our data. However, the optimum therapeutic concentration range for PER has not been established. On the other hand, the interindividual relationship between PER concentration and matched clinical response varied widely. Krauss et al. reported a significant relationship between PER
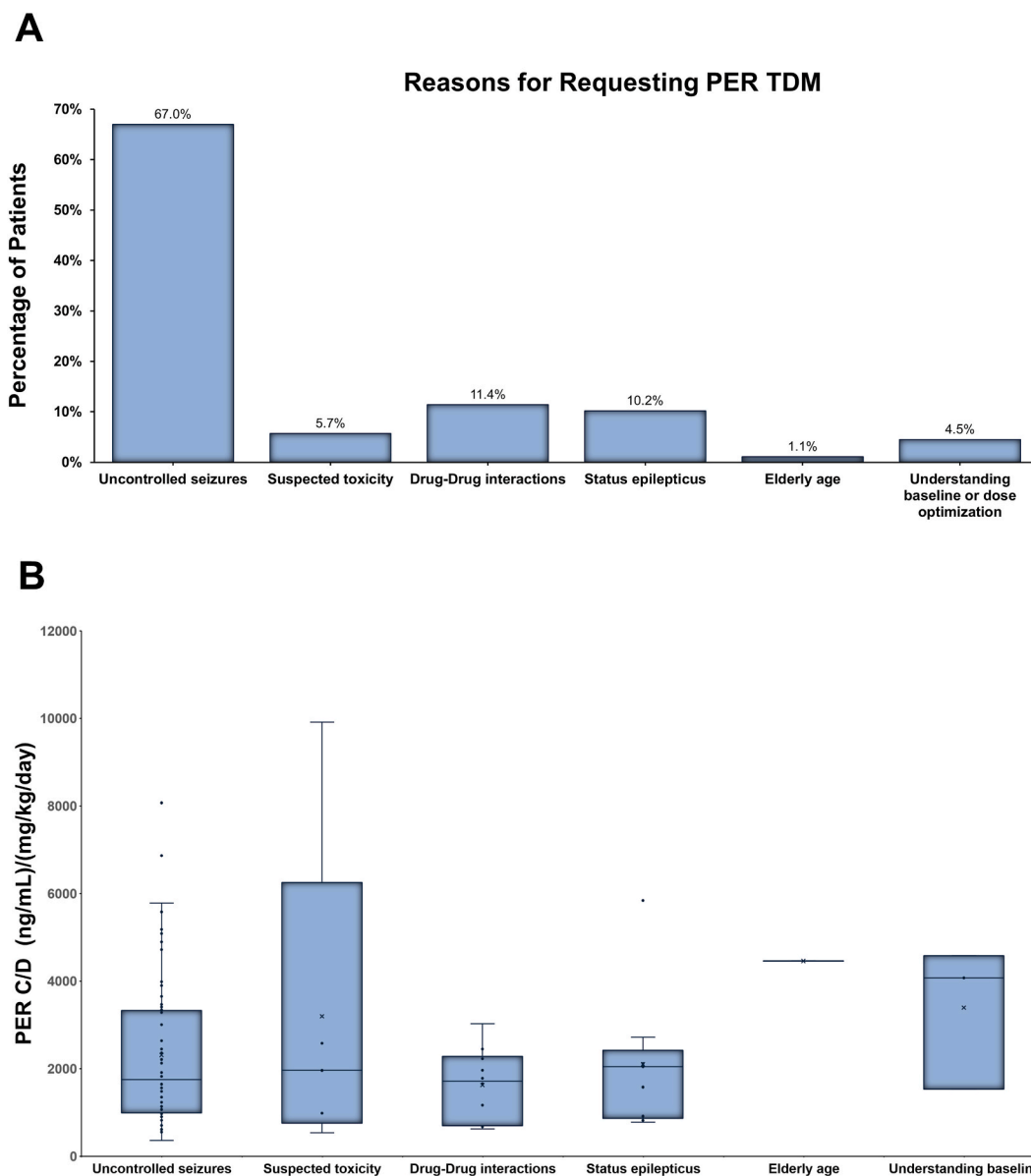
A

B

Fig. 4. (A) Reasons for requesting therapeutic drug monitoring (TDM) for perampanel (PER); Box plot of plasma concentration to weight-adjusted daily dose ratio (C/D) by subgroups with different indications. The horizontal line shows the mean value. CBZ, carbamazepine; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; VPA, valproic acid.

plasma concentration, efficacy, and tolerability [15]. On the contrary, several post-marketing studies did not find a significant correlation between PER concentration, therapeutic response, and AEs [17,18,22]. The role of routine monitoring of TDM in the management of epilepsy has been debated for many years. In fact, the National Institute for Health and Care Excellence (NICE) epilepsy clinical guidelines do not recommend routine drug monitoring for all patients with epilepsy [24]. However, a tendency toward using TDM as a routine test without due consideration, rather than as an aid in resolving clinical problems is still noted in clinical settings. Such indiscriminate use of monitoring is undesirable, because it may lead to unnecessary therapeutic action and sometimes to therapeutic misadventure. However, TDM may still be helpful to guide decision making in clinical situations. Our patients received PER TDM according to the recommendations in the NICE [24] and International League Against Epilepsy [25] guidelines, and poorly controlled seizures were the most common cause for requesting PER TDM, followed by concerns regarding drug-drug interactions and suspected toxicity. Interestingly, we found that patients in whom PER TDM was requested because of suspected PER toxicity due to adverse events had higher plasma concentrations and C/D ratio than did patients with other indications. Our finding is in agreement with those of a phase III clinical trial, in which Gidal et al. reported a significant relationship between increases in PER plasma concentration, reduction in seizure frequency, and risk of AEs [6]. Nevertheless, large interpatient variability was observed in the PER
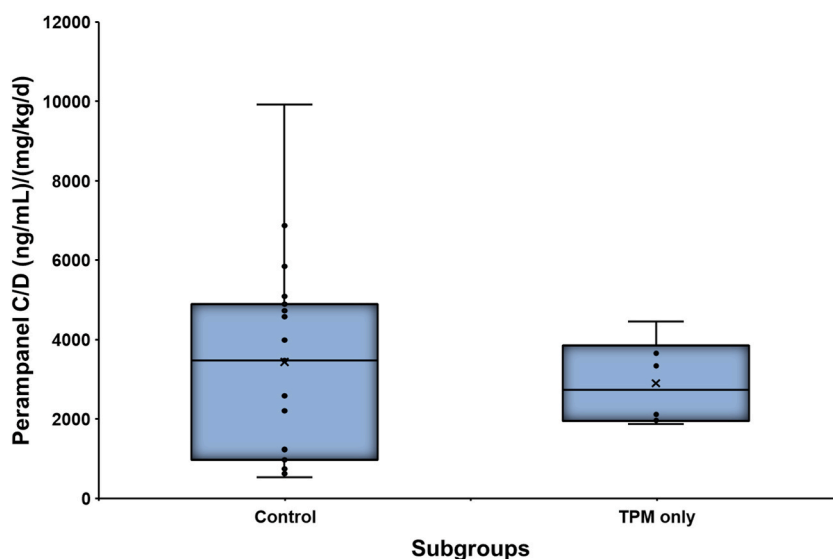
Fig. 5. Box plot of plasma concentration to weight-adjusted daily dose ratio (C/D) plasma concentration of perampanel (PER) by subgroups of controls neither on enzyme-inducing ASMs or enzyme-inhibiting (n = 19) and those with topiramate (TPM) only (n = 6). The horizontal line shows the mean value.

plasma concentration–adverse events relationship in real-world studies.

Our study has several limitations. First, this was a retrospective study with data collection from a relatively small number of patients, which did not allow significant comparison among plasma samples grouped according to individual ASM co-administration, and the impact of varying dosages of these co-administered ASMs could not be adequately assessed. Additionally, owing to this restricted sample size, we were unable to compare the effects of mono-enzyme inducing ASM regimens on PER C/D ratio, despite previous work by Yamamoto et al. establishing a dose-dependent reduction in PER concentration induced by these enzymatic inducers [26]. Further, we enrolled 70 patients, and in most of them, PER concentration was checked only once and there was no follow-up, and lack of standardization of blood drawings with respect to time of dose ingestion, fasting or feeding condition due to retrospective nature of our study. It is noteworthy that we did no publish the validation procedure for the LC-MS/MS analysis of PER within our laboratory. However, it is imperative to underscore that the LC-MS/MS methodology employed was rigorously validated in accordance with the Clinical Laboratory Standards Institute guideline C62-A for LC-MS. Additionally, a previous investigation has already established the development of LC-MS/MS assay for the quantification of PER concentrations in plasma [27]. Further extensive studies in a higher number of patients and a longer period of observation are needed to validate the results of this study.

5. Conclusions

We demonstrated a linear regression relationship between PER concentration and PER dosage. Furthermore, PER plasma concentration is highly susceptible to interactions with enzyme-inducing ASMs, such as CBZ. TDM with clear indication could be helpful in determining the influence of co-medication with ASMs on PER concentrations and guide clinical decision-making.

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CRediT authorship contribution statement

Chih-Yin Lin: Data curation, Formal analysis, Methodology, Writing – original draft. **Chun-Wei Chang:** Data curation, Software, Validation, Writing – review & editing. **Wei-En Johnny Tseng:** Data curation, Formal analysis, Methodology. **Tony Wu:** Data curation, Methodology, Validation. **Mei-Yun Cheng:** Data curation, Formal analysis. **Chih-Hong Lee:** Data curation, Formal analysis. **Hsing-I Chiang:** Data curation, Formal analysis. **Wey-Ran Lin:** Methodology, Software, Validation. **Chia-Ni Lin:** Investigation, Methodology. **Chun-Jing Liu:** Data curation, Formal analysis. **Po-Ru Chen:** Data curation. **Hui-Fen Cheng:** Data curation. **Siew-Na Lim:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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