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# Plasma concentration and clinical effects of perampanel—The Kork experience

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ABSTRACT

*Purpose:* To investigate the correlation between steady-state plasma concentrations of perampanel (PER) with efficacy and tolerability in adult patients with difficult-to-treat epilepsy.

*Methods:* PER plasma concentrations were assessed at steady-state conditions in 92 adult patients (57% female, 43% male, mean age 39,5 years, age range 20–73 years). All patients had been treated with PER at a stable dose for at least 3 weeks. Clinical efficacy was assessed on the day of measuring the plasma concentrations by a retrospective analysis of the seizure frequency and adverse effects.

*Results:* The mean overall plasma concentration was 323,5 ng/ml (range 19 ng/ml – 2436 ng/ml). The corresponding mean dose was 7,5 mg (range 2 mg – 12 mg). PER dose and plasma concentration showed a close linear correlation. Plasma levels and doses varied widely concerning both efficacy and tolerability of PER. The differences between plasma levels of responders and non-responders were not statistically significant. Therefore a clinically useful general reference range could not be defined.

*Conclusion:* Our data do not indicate a reliable therapeutic range for PER plasma concentrations. Individual reference ranges varied widely. Therapeutic drug monitoring (TDM) may still be helpful in certain clinical situations.

## 1. Introduction

Therapeutic drug monitoring (TDM) is an established method to improve the quality of antiepileptic drug (AED) therapy. Especially with traditional AEDs such as carbamazepine, phenytoin, or ethosuximide, therapeutic ranges were defined and are still widely used. On the other hand, clinically reliable and useful ranges are still not defined for many new agents, including perampanel (PER) [1].

The so-called therapeutic, or reference range describes a drug-specific span between lower and upper limits, which defines the range of probable antiseizure efficacy without dose-related adverse events [2]. Recently the importance of an absolute reference range has been questioned. It was proposed to use a more individualized therapeutic range instead [1].

PER is the first in-class, selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid (AMPA) receptor antagonist used in epilepsy therapy [3–5] that was introduced to the German market in 2012 [2]. Because of its pharmacokinetic profile with an elimination half-life of up to 105 h, once daily dosing at bedtime is recommended [3–12]. Potent cytochrome (CYP)3A4 inducers, such as carbamazepine, phenytoin, or oxcarbazepine, may markedly accelerate the elimination half-life time to approximately 25 h and decrease plasma concentrations of PER [3,5,7–13]. This resulted in less efficacy in the pivotal phase III trials as an adjunct, although still statistically significant superiority over placebo was apparent [14]. Contrary to the initial pivotal phase III studies [4,14], in a recent phase III study from the Asian-Pacific area, it could not be justified that adjunct 4 mg was superior to placebo [15]. It has been argued that the higher percentage of enzyme-inducing AEDs may have had an impact on these findings [16]. Therefore it has been recommended to consider dose increments if the baseline medication consists of potent enzyme inducers [3,5,9]. Real-world experience, as shown in several studies, indicates that, at least in some instances, patients clearly benefitted from even low doses (i.e., 4 mg of PER irrespective of the underlying AED therapy [4,9].

Although reference ranges for PER have been proposed based on the data of the pivotal pilot phase III studies [7] or recommendations of the Dianalund Danish Epilepsy Center [17] it is unclear whether a reliable therapeutic range exists. A linear dose-concentration relationship has been reported earlier [7,12,13] and might suggest such a predictable range. However, in a study from Japan serum concentrations varied widely in PER responders [13]. Thus our interest was to further

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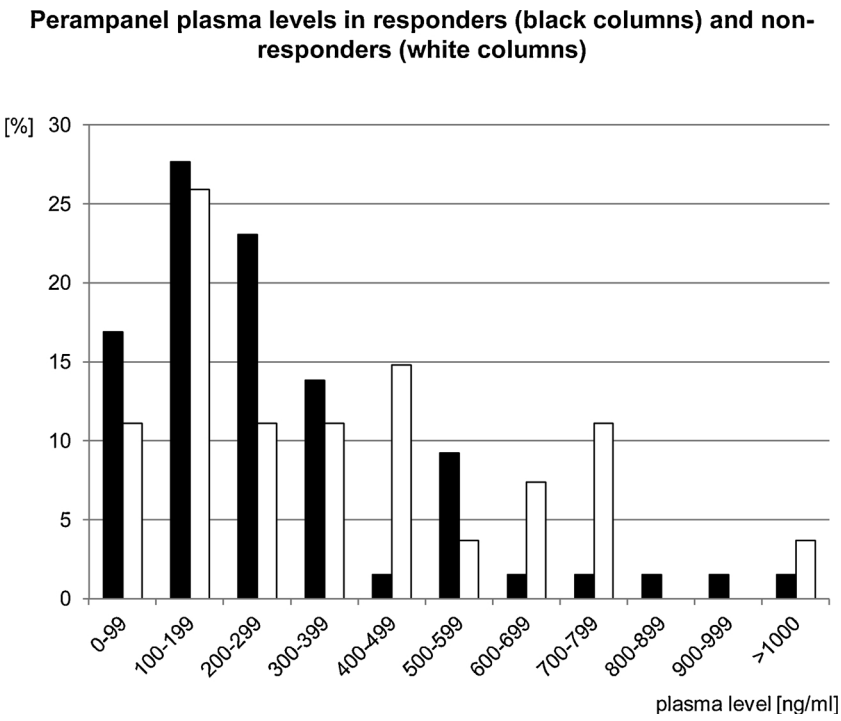


**Fig. 1.** Individual plasma levels of perampanel in responders and non-responders. Because of marked differences between the group strengths of responders and non-responders each column shows the percentage of responders (white columns) versus non-responders (black columns) represented in each plasma level group beginning with 0–99 ng/ ml up to > 1000 ng/ml.

investigate this unsolved problem by measuring PER trough plasma levels in 92 in-patients treated with add-on PER at our centre and correlating these levels with the clinical efficiency.

## 2. Material and methods

PER plasma concentrations were measured only inpatients. All patients took PER according to a once daily dosing schedule between 9 and 10 o'clock in the evening. Plasma samples were drawn between 7.30 and 7.45 o'clock the next morning under fasting conditions. Because of the long half-life of approximately 105 h without the influence of enzyme-inducing drugs that reduce the elimination half-life markedly, [3,5,7–13] PER plasma concentrations were measured only if the PER dose had been stable for at least 3 weeks. A stable plasma steady state is reached within 10–19 days after increases or decreases of the PER dose [7].

Plasma concentrations were measured in our own certified TDM laboratory by means of liquid chromatography mass spectrometry (LCMS). PER plasma concentrations show a linear distribution between 10 and 2000 ng/ml in this essay, with an accuracy of < 4.2% and a precision < 2.1%.

At the time of measuring the PER plasma concentration, the additional medication, the tolerability, and the seizure situation were assessed. Both seizure situation was evaluated based on the written notes of our experienced staff in the patient charts.

Because the individual period of a stable PER dose varied, the efficacy for the individual period of the last change of the PER dose, which varied between 3 weeks and several months, was assessed. The seizure frequency during this period was compared with that of 3 months before the initiation of PER. If the last stable PER period was shorter than 3 months, the seizure frequency during this period was extrapolated to 3 months. For example, if a patient had three seizures during the last stable PER period of 30 days, the extrapolated seizure frequency per 3 months was 9 compared with the 3-month period before the onset of PER treatment. The assessment of tolerability was performed on the day of plasma concentration measurement by means of a direct interview and a clinical examination.

The study was approved by the local ethical committee at the University of Freiburg, Germany.

## 3. Theory/Calculation

For the statistical analysis of a difference between plasma levels in responders and non-responders we used a two-tailed *t*-test at a 005 significance level for two independent means the prerequisites for using a *t*-test were tested by means of the Kolmogorov-Smirnov-test for a normal distribution and by means of the F-test a difference in variance. Otherwise descriptive statistics were used.

## 4. Results

PER plasma concentrations at steady-state conditions were collected in 92 adult patients (57% female, 43% male, mean age 39,5 ± 137 years, age range 20–73 years). The mean PER dose was 7,5 mg ± 2,8 mg (range 2 mg – 12 mg). The mean plasma concentration was 323,5 ng/ml ± 309,5 ng/ml (range 19 ng/ml – 2436 ng/ml).

In 80 patients (87%) the last stable PER dose period was shorter than 3 months so that we extrapolated the seizure frequency for a 3-month period in these cases according to the methodological approach mentioned above. Of the 92 adult patients, 27 (29%) were responders with a reduction of seizure frequency by at least 50%. In these patients the mean PER plasma concentration was 425,5 ng/ml ± 270,6 ng/ml with a range between 52 and 2436 ng/ml. The mean PER dose was 6,5 mg ± 2,6 mg (range 2 mg – 12 mg). The percentage of responders with plasma levels above the mean of all patients (323,5 ng/ml) was 48%.

Twelve patients were completely seizure-free (13%). Mean plasma levels in these cases were 506,1 ± 358,9 ng/ml (range 88–2436 ng/ml). The doses ranged between 4 mg and 12 mg (mean 6,5 mg ± 2,4 mg). The lowest plasma concentration with beneficial therapeutic response was 52 ng/ml for responders and 88 ng/ml for seizure-free patients, respectively. The highest plasma concentration we measured was 2436 ng/ml and this was not associated with adverse events. 54% had higher plasma levels than the mean level of all patients.

In non-responders (n = 65 [71%]) the mean plasma concentration was 281,1 ng/ml ± 217,8 ng/ml with a range between 19 and

1136 ng/ml, which corresponded to a mean dose of 7,9 mg ± 2,6 mg (range 4–12 mg). Fig. 1 shows the individual plasma levels in responders and non-responders.

For statistical testing the outlaying plasma level of 2436 ng/ml was excluded from the statistics. In the Kolmogorov-Smirnov-test distribution of plasma levels of responders and non-responders did not differ significantly from a normal distribution (D = 0,20246, p = 0,19032 versus D = 0,2047, p = 0,19672). F-test showed no evidence on a significance level of 005 for a difference in variance between the plasma levels of responders and non-responders (f = 1,156). Using a two-tailed *t*-test for two independent means no significant difference between the plasma levels of responders and non-responders was found on a significance level of 0,05 (t = −1,31263, p = 0,19).

Adverse events (AEs) occurred in 30 patients (33%), with somnolence being the leading one (n = 12 [13%]) followed by dizziness. In 10 patients, altered mood was reported, which comprised a variety of symptoms such as irritability, aggression, impulsive behaviour, and depressed mood. In single or almost three cases cognitive decline, ataxia, blurred vision, weight loss, increased appetite, or weight gain occurred. Plasma concentrations did not differ between patients with and without tolerability problems. The mean plasma level was 329,5 ± 192,9 ng/ml (range 19–911 ng/ml) at a mean dose of 7,7 mg ± 2,8 mg (range 2–12 mg). In patients without apparent adverse effects (n = 62 [67%]) a mean plasma concentration of 319,5 ± 203,8 ng/ml (range 52–2436 ng/ml) was measured. The corresponding mean dose was 7,3 mg ± 2,5 mg (2–12 mg).

Table 1 summarizes the serum concentrations and doses of our patients dependent from response and tolerability.

There was an evident linear relationship between dose and plasma concentrations (The correlation coefficient r between dose and plasma level was both 0,93 in patients with without enzyme-inducing antiepileptic drugs) with markedly lower plasma concentrations in those 48 patients (52%) on enzyme-inducing AEDs as baseline medication (Fig. 2). Enzyme-inducing AEDs comprised carbamazepine, oxcarbazepine, eslicarbazepine acetate, phenytoin, and phenobarbital.

Under a baseline therapy with enzyme-inducing AEDs, 35 of 48 patients (73%) had no adverse events compared with 27 of 44 patients without enzyme-inducing co-medication (61%). The responder rate in patients with enzyme-inducing AEDs was 17% compared with 43% in patients without enzyme-inducing AEDs. However, some of the patients on enzyme-inducing AED therapy were dramatic responders who became seizure-free: Two patients were on 4 mg (plasma levels 88 ng/ml and 185 ng/ml) and one each on 8 mg (182 ng/ml) and 12 mg (183 ng/ml).

## 5. Discussion

Reports on the blood level reference range of PER are scarce. In the pivotal phase III trials [9] the plasma levels in responders ranged between 180 and 980 mcg/l (corresponding to ng/ml which was used as a unit in this paper) [1,7]. In a Japanese study the mean PER serum level in responders was 450 ± 361 ng/ml with a range of 85 to 1500 ng/ml [13]. Based on a personal communication from the Dianalund Epilepsy Center in Denmark, a Norwegian report recently proposed a reference range between 86 and 1000 ng/ml [17]. Comparing these reference ranges with our results, our study had one patient with higher plasma concentrations, a good therapy response, and no adverse events at a level of 2436 ng/ml. The next highest serum concentration among seizure-free patients was 731 ng/ml. Looking at responders, only one other patient had a plasma level above 980 or 1000 ng/ml, respectively (1136 ng/ml and no adverse effects). In fact, both mean serum concentration and the wide variability of serum levels in responders were almost identical to the results of Yamamoto et al. [13]. Thus 96% of the responders and 92% of the seizure-free patients had PER plasma levels below the upper limit of the proposed reference ranges [17]. Looking at the lower proposed limits, 22% (n = 6) showed levels below the ranges according to the phase III trials [1,7] and 4% (n = 1) below the Scandinavian recommendations [17]. Therefore we question whether the definition of a lower limit is justified. Even more, we saw a similar phenomenon concerning tolerability: 23% (n = 7) of patients with adverse events showed plasma levels below 180 ng/ml and 7% (n = 2) showed plasma levels below 86 ng/ml. The most common adverse events with PER are somnolence and dizziness [3–5,8,10,11,14]. If somnolence occurred, it was observed at levels between 133 ng/ml and 744 ng/ml. Dizziness occurred at plasma levels between 129 ng/ml and 395 ng/ml. Conversely, we saw many patients with higher plasma levels and without these leading adverse events. Thus we do not believe that our data suggest a specific range beyond which the typical side effects become probable. The unique mode of action of PER may be a reason for this finding. In most instances of AED levels beyond which adverse events with neurotoxic symptoms such as dizziness occur, the underlying mechanism is different, namely the blockade of voltage-sensitive sodium channels [2].

It was previously reported that a specific subgroup of patients may react markedly at very low doses and, at low plasma levels, either positively (seizure-free at 4 mg even in combination with enzyme-inducing AEDs) or negatively (adverse events) [4,9], It is tempting to speculate that both groups may reflect sensitive reactions to the unique mode of action of PER [4]. Our data suggest that such subgroups exist which contradicts the hypothesis of an absolute lower reference range limit although the majority, namely 64% and 87% of our patient data lay within the reference ranges mentioned in the literature [1,7,17].

The only trend seen was towards higher plasma concentrations in responders (see Figs. 1 and 2) and especially in seizure-free patients compared with non-responders. This indicates that in some patients it may be helpful to increase the dose.

In line with previous reports of others [12,13] our data clearly support the linear correlation between dose and plasma levels both in patients with and without enzyme-inducing co-medication (see Fig. 2). We did not differentiate between the several AEDs with potential enzyme-inducing properties because this would have led to very small subgroups. If the patient has good tolerability, especially in patients on enzyme-inducing AEDs it may be meaningful to increase the PER dose to achieve higher plasma levels and better clinical results [3,9,13] and to overcome efficacy issues that have been partly described in patients at low doses and under enzyme-inducing AED treatment [15,16].

Compared to other so-called real-life observational survey including reports from our center [4,9–11,18–20] the responder rates were relatively low and the incidence of adverse events relatively high. The easiest explanation for this discrepancy is that in the cohort investigated here we only included in-patients where in most other observational surveys out-patients predominated. Patients who are referred to our hospital as in-patients most probably represent an even more refractory population. Secondly, the assessment of efficacy may have included too short periods of observation in order to identify true and sustained responders, since we tried to address PER response appropriately by extrapolating the 3-month seizure frequency in patients with a shorter period of the last dose modification. In patients with longer and stable PER doses presumably the percentage of responders

**Table 1**
Perampanel dosing and plasma concentrations and clinical response.

| | Mean perampanel plasma level (ng/ml) | Mean perampanel daily dose (mg) | n (%) |
|---|---|---|---|
| Responders | 425,5 ± 270,6 | 6,5 ± 2,6 | 27 (29) |
| Seizure-free patients | 506,1 ± 358,9 | 6,5 ± 2,4 | 12 (13) |
| Non-responders | 281,1 ± 217,8 | 7,9 ± 2,6 | 65 (71) |
| Adverse events | 329,5 ± 192,9 | 7,7 ± 2,8 | 30 (33) |
| No adverse events | 319,5 ± 203,8 | 7,3 ± 2,5 | 62 (67) |
| Total | 323,5 ± 309,5 | 7,5 ± 2,8 | 92 (100) |

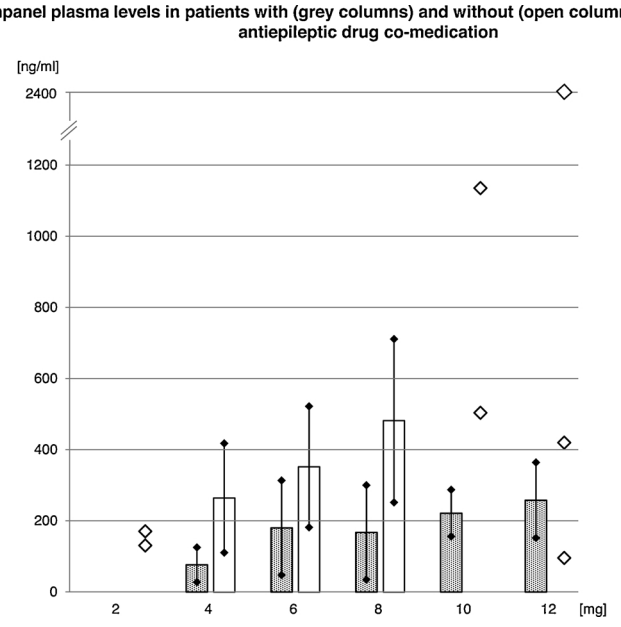


**Fig. 2.** Linear correlation of perampanel dose and plasma concentration in patients with and without enzyme-inducing antiepileptic drugs. Enzyme-inducing antiepileptic drugs comprised carbamazepine, oxcarbazepine, eslicarbazepine acetate, phenytoin and phenobarbital. If the number of patients was sufficient to calculate means and standard deviations these are displayed as grey (patients with enzyme-inducing antiepileptic drugs) or white (patients without enzyme-inducing antiepileptic drugs) columns. If the number of patients was 2 or 3 only, the individual levels are displayed as white diamonds. The correlation coefficient r between dose and plasma level was both 0,93 in patients with without enzyme-inducing antiepileptic drugs.

might be higher. In order to overcome this potential methodological drawback and since the pharmacokinetics of PER do not necessarily require trough level measuring in the morning due to the minimal diurnal oscillations of the serum concentration [12] it should be possible to collect additional data in out-patients with stable PER doses over longer periods than in our study.

Our investigation has several other methodologic drawbacks that have to be emphasized: Data would be more reliable if a prospective design would have been applied. Furthermore, although our staff documented all apparent seizures, still some seizures may have been overlooked. Finally, objective methods of measuring adverse events would have increased the diagnostic accuracy concerning tolerability. Future studies should consider this.

TDM of PER levels may still be helpful in appropriate clinical situations [1], for example, if baseline medication is changed towards enzyme-inducing AEDs [12,13], in patients under special conditions like hepatic or renal impairment or just to define the individual reference range [1].

## 6. Conclusions

In 92 adult patients it was shown that PER plasma levels correlate strongly with dose levels. Under the influence of AEDs with enzyme-inducing properties, PER plasma levels are reduced. Still, a variety of patients were PER responders or reported tolerability problems at low plasma levels and doses. Because the individual therapeutic ranges varied widely, a clinically useful absolute or general reference range for PER cannot be proposed.

## Declaration of conflicts of interest

BJS has received speaker's honoraria from Al-Jazeera, Desitin, Eisai, GW, Hikma, Novartis and UCB. He was a member of advisory boards of or has consultancy agreements with B. Braun, Eisai, GW, Idorsia, and UCB.

CK has received speaker's honoraria from Desitin. He was a member of advisory boards of or has consultancy agreements with GW.

EH and UJ have no conflicts of interest to declare.

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