Original article

Epileptic Disord 2020; 22 (4): 455-61

Changes in serum perampanel concentration profile after discontinuation of carbamazepine

Sumitha Murugesu [1], Kiminobu Okayama [2], Yoshiaki Yamamoto [2], Kiyohito Terada [2], Yukitoshi Takahashi [2]

[1] Pediatric Neurology Unit, Kuala Lumpur Woman and Children Hospital, Kuala Lumpur, Federal Territory of Kuala Lumpur, Malaysia
[2] Department of Clinical Research, NHO, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

Received December 15, 2019; Accepted May 02, 2020

ABSTRACT – *Aim.* To evaluate changes in the pharmacokinetics of perampanel after discontinuation of carbamazepine.
Methods. We enrolled 13 patients receiving perampanel who discontinued carbamazepine therapy between June 2016 and December 2018. Data on serum concentrations were obtained from the therapeutic drug monitoring database of the National Epilepsy Center (Shizuoka, Japan). To compare the pharmacokinetics of perampanel before and after discontinuation of carbamazepine, we determined the concentration/dose (CD) ratio of perampanel (serum level [ng/mL] divided by the dose [mg/kg]). The follow-up period was set to eight weeks following the discontinuation of carbamazepine therapy.
Results. The mean baseline CD ratio of perampanel was 1,247 ng/mL/mg/kg which increased markedly over time after discontinuation of carbamazepine, with a mean CD ratio at Weeks 1-2, Weeks 3-4, and Weeks 5-8 of 2,683, 3,914, and 4,220, respectively. At eight weeks, the mean CD ratio of perampanel had increased by 276%. Eleven patients developed adverse events, including dizziness, somnolence, irritability, and ataxia. Five of these 11 patients required perampanel dose reduction within eight weeks after discontinuation of carbamazepine. Two patients achieved seizure-free status at Weeks 5-8.
Conclusion. The serum perampanel concentration began to increase from one week after discontinuation of carbamazepine, and continued to rise for eight weeks. Based on these findings, we recommend frequent monitoring of serum perampanel concentration for at least eight weeks after stopping carbamazepine therapy. Monitoring is required as a guide for dose adjustment in order to achieve a safe and effective therapeutic dose of perampanel.

Key words: perampanel, carbamazepine, enzyme-inducing antiepileptic drugs, de-induction, therapeutic drug monitoring

Correspondence:
Yukitoshi Takahashi
Department of Clinical Research,
NHO Shizuoka Institute of Epilepsy and Neurological Disorders,
886 Urushiyama, Aoi-ku,
Shizuoka, 420-8688, Japan
<takahashi-ped@umin.ac.jp>

doi:10.1684/epd.2020.1182

Perampanel (PMP) is a novel adjunctive antiepileptic drug (AED) with established efficacy as monotherapy and adjunctive treatment for both partial and secondary generalized seizures. PMP is mainly metabolized by cytochrome P450 3A4 (CYP3A4) (Rogawski and Hanada, 2013; Patsalos, 2015). The activity of this enzyme is strongly

influenced by concomitant administration of enzyme-inducing AEDs (EIAEDs), such as carbamazepine (CBZ), oxcarbazepine, phenobarbital, and phenytoin (PHT) (Brodie *et al*., 2013; Zaccara and Perucca, 2014). Recently, Hole *et al*. reported that PHT and CBZ show approximately two-fold greater CYP3A4-inducing potency compared to that of phenobarbital (Hole *et al*., 2018). Thus, PHT and CBZ enhance metabolism of PMP by induction of CYP3A4 and reduce the serum PMP concentration (Patsalos *et al*., 2016; Yamamoto *et al*., 2017; Ishikawa *et al*., 2019; Steinhoff *et al*., 2019). Among the various EIAEDs, concomitant administration of CBZ has been reported to markedly reduce the serum PMP concentration by approximately 70% (Patsalos *et al*., 2016; Yamamoto *et al*., 2017). While previous reports have established the induction effect of EIAEDs on serum PMP concentration, there are no published reports on the reverse process of de-induction after EIAED withdrawal.

Antiepileptic polypharmacy is often inevitable in patients with refractory epilepsy, but this increases the risk of drug interactions involving EIAEDs. Accordingly, therapeutic drug monitoring for PMP is routinely performed at the National Epilepsy Center (Shizuoka, Japan), and this has revealed a marked increase in the serum concentration of PMP after discontinuation of EIAEDs. Gidal *et al*. found that the seizure reduction rates in patients taking PMP with EIAEDs were lower than those in patients using EIAEDs (Gidal *et al*., 2015). In contrast, there was a positive correlation between the serum concentration of PMP and adverse events, including dizziness, somnolence fatigue, and irritability (Gidal *et al*., 2013). PMP has a long half-life of around 53-136 hours (Rogawski and Hanada, 2013). Consequently, when monitoring the de-inducing effect, it is essential to do so over a sufficiently long period.

Therefore, it is clinically relevant to determine how long the de-induction effect of EIAED discontinuation acts on PMP concentration before it reaches a steady state. Accordingly, this study was performed to examine the pharmacokinetics of PMP after discontinuation of CBZ therapy, since understanding the magnitude and time course of the pharmacokinetic changes is expected to be useful for optimizing PMP therapy.

Methods

Subjects

The protocol of this study was approved by the ethics committee of our hospital (Protocol No. 2016-28). We retrospectively reviewed patients aged 12 years or older using CBZ and PMP concomitantly in whom measurement of the serum PMP concentration was performed between June 2016 and December 2018. Because patients had refractory seizures, most were receiving multiple AEDs. We defined CBZ and PHT as EIAEDs, while all other AEDs were classified as non-EIAEDs. Only sodium valproate (VPA) has a slight inhibitory effect on CYP3A4, while topiramate has a weak enzyme-inducing effect. Because there was no influence of these AEDs on the pharmacokinetics of PMP in a previous study, we classified both drugs as non-EIAEDs (Yamamoto *et al*., 2017).

During the study period, 678 serum samples were obtained for analysis from 179 patients receiving CBZ. We employed the following criteria to select patients for this study:

– Patients aged ≥ 12 years on treatment with CBZ and PMP+/- other AEDs.

– Patients receiving a stable dose of PMP for a minimum of three weeks before stopping CBZ therapy (10-19 days are required to achieve steady-state pharmacokinetics of PMP[2]).

– Patients not using PHT or phenobarbital, oxcarbazepine, or other CYP3A4 inducers/inhibitors (*e.g*. rifampicin, clarithromycin, azole antifungals, and protease inhibitors).

Based on these criteria, 13 patients (47 samples) were enrolled for analysis (*table 1*).

Additionally, to evaluate the influence of CBZ dose on the concentration/dose ratio (CD ratio) of PMP, we recruited 133 patients (73 men and 60 women; age range: 13 to 64 years) treated with CBZ but not taking either PHT or phenobarbital.

Blood collection and measurement of PMP

Blood samples were collected at 12-16 hours after administration of PMP the previous evening and centrifuged at 1800*g*. The serum concentration of PMP was measured by liquid chromatography-tandem mass spectrometry, as reported previously (Mano *et al*., 2015), and the detection limit of the assay for PMP was 10 ng/mL.

Data analysis

The date of CBZ therapy discontinuation was defined as Day 0, and the baseline period was determined as the eight weeks before discontinuation of therapy. If two or more serum samples were obtained from a patient during the baseline period, we used the earlier value.

Initially, we evaluated the pharmacokinetic change in PMP within an eight-week period following discontinuation of CBZ therapy. In addition, we retrospectively assessed the clinical response and adverse events by reviewing the clinical records. The observation period was set at 52 weeks. To assess the pharmacokinetics of PMP after discontinuation of CBZ, we calculated the CD ratio as follows:

Table 1. Patient characteristics.

No.	Age	Sex	BW (kg)	Epilepsy syndrome	Etiology	Seizure types	Age of onset (year)	Seizure frequency	Concomitant AEDs and other drugs
1	43	F	49	FLE	Unknown	SPS, CPS, and GTC	0 (6 months)	Weekly	CBZ (600 mg), TPM (125mg), and pregabalin
2	39	F	102	SPE	Unknown	SPS, CPS, and GTC	0 (3 months)	Weekly	CBZ (1100 mg), VPA (120 mg), and LTG (150 mg)
3	41	F	51	FLE	Unknown	CPS	6	Weekly	CBZ (300 mg), VPA (800 mg), LTG (200 mg), and famotidine
4	38	F	49	FLE	Encephalitis	SPS, CPS, GTC, and tonic	23	Weekly	CBZ (400 mg) and CLB (5 mg)
5	22	F	47	FLE	Encephalitis	SPS, CPS, and GTC	6	Weekly	CBZ (600 mg), CLB (10 mg), and LCM (200 mg)
6	35	F	42	SPE	Schizencephaly	SPS, CPS, and GTC	22	Monthly	CBZ (700 mg) and LEV (250 mg)
7	13	F	40	SPE	Encephalitis	CPS and MYC	1	Daily	CBZ (500 mg), LTG (125 mg), and pranlukast
8	28	M	52	SPE	Encephalitis	SPS and GTC	16	Daily	CBZ (1200 mg), VPA (800 mg), LEV (1000 mg), LTG (400 mg), pranlukast, and olanzapine
9	37	F	78	SPE	Encephalitis	CPS	26	Weekly	CBZ (800 mg) and CLB (10 mg)
10	15	M	54	SPE	Genetics	SPS, CPS, and GTC	6	Weekly	CBZ (400 mg), VPA (1100 mg), and LTG (150 mg)
11	14	M	44	SPE	Unknown	SPS and CPS	2	Weekly	CBZ (600 mg)
12	19	F	58	TLE	Tumor	SPS and CPS	6	Daily	CBZ (6000 mg) and LTG (300 mg)
13	19	F	72	SPE	Encephalitis	SPS, CPS, and GTC	15	Daily	CBZ (200 mg), VPA (800 mg), CZP (1.5 mg), and lansoprazole

BW: body weight; CBZ: carbamazepine; CLB: clobazam; CPS: complex partial seizures; CZP: clonazepam; FLE: frontal lobe epilepsy; GTC: generalized tonic-clonic seizures; LEV: levetiracetam; MYC: myoclonic seizures; LCM: lacosamide; LTG: lamotrigine; SPE: symptomatic partial epilepsy; SPS: simple partial seizures; VPA: sodium valproate.

$$CD\ ratio\ of\ PMP\ \left(ng/mL/mg^{-1}/kg^{-1}\right) = \frac{Serum\ concentration\ of\ PMP\ \left(ng/mL\right)}{Body\ weight-adjusted\ dose\ of\ PMP\ \left(mg/kg\right)}$$

In addition, we reviewed the clinical records to investigate adverse events associated with discontinuation of CBZ. To compare CD ratios before and after stopping CBZ therapy, analysis of variance was employed with a post-hoc Dunnett's test. Correlation between CBZ dose and CD ratio of PMP was assessed by Pearson's correlation coefficient analysis. The unpaired t-test was used to compare the two CBZ dose groups. Results are expressed as the mean ± standard error. Statistical analyses were conducted with IBM SPSS Statistics Ver. 25 (IBM Japan), and the level of significance was set at $p<0.05$.

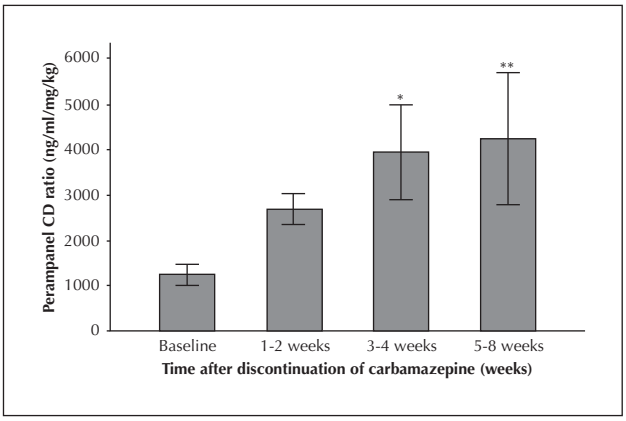

Figure 1. Mean CD ratio of perampanel before and after discontinuing carbamazepine therapy.
Significance was determined by ANOVA ($p<0.01$).
*Dunnett's test; *$p<0.05$ versus baseline, **$p<0.01$ versus baseline.

Results

Patients

Table 1 shows the demographic details of the patients. There were 18 patients initially, but five patients were excluded because of insufficient data (two patients; lack of body weight) or failure to meet the inclusion criteria (three patients). The 13 patients consisted of 10 males and three females with a mean age of 27.9 years, and they were all of Japanese ethnicity. Most of the patients had symptomatic focal epilepsy and a third of them had post-encephalitic seizures. All patients had been treated with at least four different types of AEDs over time reflecting the pharmacoresistant nature of their epilepsy. PMP therapy was introduced due to uncontrolled seizures for over five years. After PMP titration up to a permissible dose, the CBZ dose was tapered or stopped due to insufficient impact.
Table 2 summarizes the maximum PMP concentration and adverse events after discontinuation of CBZ therapy. Eleven of the 13 patients developed adverse events associated with an increase of PMP concentration after stopping CBZ. Common adverse events were dizziness, somnolence, irritability, and ataxia, while other events included problems with vision and speech. In five out of 11 patients, reduction of the PMP dose was required within eight weeks of CBZ discontinuation. The interval up to the onset of adverse events was between one and eight weeks after stopping CBZ, with events commonly occurring in Weeks 1, 2, 5 and 8. Accordingly, stringent monitoring of the PMP concentration for eight weeks is crucial. Two patients (Patient 1 and 11) achieved seizure-free status at Weeks 5-8.
A follow-up survey was conducted after eight weeks. Although Patient 1 showed a good response within 24 weeks, she chose to discontinue PMP therapy due to adverse events. Patients 2 and 13 also discontinued PMP therapy due to adverse events and insufficient efficacy, respectively. Finally, four patients (Patients 6, 8, 9, and 11) achieved good clinical responses (seizure-free or 50% seizure reduction) after eight weeks. The remaining six patients (Patients 3, 4, 5, 7, 10, and 12) had a partial response (<50% decrease in seizures), and therefore they continued PMP therapy.

CD ratio of PMP

Figure 1 displays the mean CD ratio of perampanel before (baseline) and after discontinuation of CBZ. The mean baseline CD ratio was 1,247±224 and increased markedly after discontinuation of CBZ; the mean CD ratio in Weeks 1-2, Weeks 3-4, and Weeks 5-8 was 2,683 ± 343, 3,914 ± 1,042, and 4,220 ± 1,447, respectively. In comparison with baseline, the mean CD ratio was significantly higher in Weeks 3-4 and Weeks 5-8. There was a steady increase of the PMP level until it peaked at two or four weeks after CBZ termination, with the CD ratio of PMP increasing markedly by 3.5-fold from baseline. This suggests that the one-month period after stopping CBZ is most crucial for monitoring PMP. After four weeks, the PMP level tended to decline gradually, before slowly rising again at eight weeks. Thus, serum PMP levels were elevated for at least eight weeks after discontinuation of CBZ.

Influence of CBZ dose

Figure 2 shows the relationship between the CBZ dose and the CD ratios of PMP. CBZ significantly reduced the CD ratio in a dose-dependent manner ($r = –0.34$; $p<0.001$). The mean CD ratio was significantly higher for CBZ doses less than 5 mg/kg/day compared to CBZ

Table 2. Clinical course after discontinuation of carbamazepine therapy.

Patient No.	Baseline			After CBZ discontinuation (first 8 weeks)				After CBZ discontinuation (after 8 weeks)			
	PMP dose	PMP level	CBZ tapering	Week	PMP level	Change (%)	Adverse events	Week	PMP dose	PMP level	Clinical outcomes
1	12	179	No	2	1060[1)]	492	Dizziness, psychosis, and irritability	36	0	-	Discontinuation of PMP therapy
2	10	162	No	8	1170[1)]	622	Irritability	10	0	-	Discontinuation of PMP therapy
3	2	60	Yes	8	250	317	-	36[2)]	4	307	
4	6	197	Yes	5	532[1)]	170	Dizziness, somnolence, and speech problems	32[2)]	4	325	
5	6	189	Yes	5	513	171	-	52	8	496	
6	12	121	No	1	511[1)]	322	Ataxia, dizziness, and irritability	52	4	461	Seizure free
7	6	192	Yes	8	504	163	Dizziness	52	5	611	
8	8	175	Yes	1	461	163	Irritability	52	8	443	50% seizure reduction
9	8	168	Yes	5	629[1)]	274	Irritability and agitation	52	8	513	50% seizure reduction
10	4	93	Yes	2	182	96	Somnolence	52	6	492	
11	6	215	Yes	7	347	61	Dizziness and vision problems	28[2)]	10	592	50% seizure reduction
12	6	97	Yes	1	349	260	Dizziness	12[2)]	7	500	
13	8	248	Yes	4	456	84	Somnolence	28	0		Discontinuation of PMP

[1)] The reduction of PMP dose was required due to adverse events. [2)] Patients were transferred to other hospitals and the follow-up survey at 52 weeks could not be completed.
CBZ: carbamazepine; PMP: perampanel.

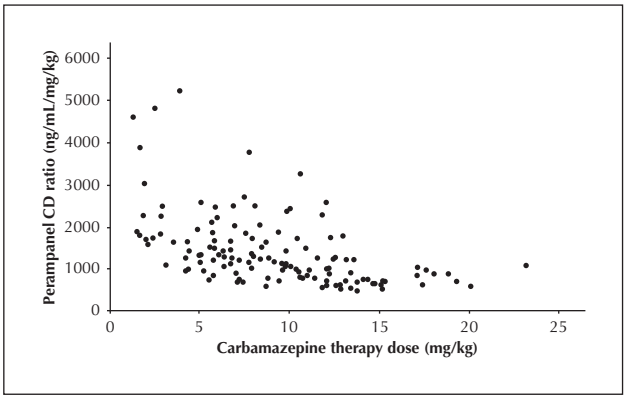

Figure 2. Relationship between carbamazepine dose and CD ratios of perampanel.
CD ratio: concentration/dose ratio.

doses at 5-15 mg/kg/day ($p<0.001$; 2154 ± 1192 vs. 1226± 626).

Discussion

This study was performed to investigate the time required for the serum level of PMP to reach a new steady state after cessation of CBZ therapy, thus providing data to develop a PMP monitoring regimen.

AED polypharmacy is required in a significant number of patients with refractory epilepsy to achieve seizure control. However, concomitant use of EIAEDs markedly reduces the concentrations of CYP3A4 substrates, such as clobazam, topiramate, and PMP. Unfortunately, there is limited information about changes in the concentrations of these AEDs after patients discontinue EIAEDs. Drug interactions may further complicate the management of epilepsy, making it important to understand the pharmacodynamics of these AEDs.

In this study, we evaluated the PMP concentration profile within eight weeks of discontinuing CBZ therapy. To our knowledge, there is no published information on the time course of serum PMP concentrations after cessation of CBZ. Our study showed a significant de-induction effect on PMP when CBZ was discontinued (*figure 1*), and we found that the serum PMP concentration increased by two- to three-fold within two weeks of stopping CBZ.

Inui *et al*. examined the pharmacokinetics of midazolam (a CYP3A substrate) to determine the changes of CYP3A4 activity after discontinuation of rifampicin (a strong CYP3A4 inducer) (Inui *et al*., 2013). They found that CYP3A activity remained elevated at four days after discontinuation of rifampicin, but returned to baseline (without rifampicin) by eight days after discontinuation. Similar results were obtained when discontinuation of St John's wort (a strong CYP3A4 inducer) was investigated (Imai *et al*., 2008). These studies support our findings and suggest that the inducing effect of CBZ would disappear by one week after withdrawal. Although PMP has a long half-life (53-136 hours), it was greatly affected by EIAEDs. Moreover, the half-life of PMP was reported to be reduced by 56% when patients took CBZ (Patsalos, 2015). Conversely, discontinuation of CBZ prolongs PMP half-life. Consistent with this, the PMP concentration increased after two weeks in our study.

Five of the 13 patients (38.4%) developed adverse events in this period. In our study, a total of 11 patients (84.6%) had adverse events after stopping CBZ, but eight of them were using CYP3A4 and/or UDP-glucuronosyltranferase (UGT) substrates (lamotrigine and clobazam). The concentration of these other AEDs can increase by about two-fold after discontinuation of EIAEDs, which may lead to adverse events.

Theoretically, our findings imply that the dose of PMP should be reduced by a third or half relative to the baseline dose when CBZ is stopped. As the peak CD ratio of PMP was found within one month after stopping CBZ, we propose monitoring the PMP concentration at weekly intervals for the first month and then once a fortnight for the second month until the level becomes stable. In addition, the serum concentration should be measured at any time if clinical signs suggest an onset of PMP toxicity.

When patients discontinued CBZ without tapering, acute elevation of the serum PMP concentration led to the development of adverse events (Patients 1, 2, and 6) (*table 2*). Our study demonstrates that CBZ significantly reduces the CD ratio in a dose-dependent manner (*figure 2*). Thus, if a patient discontinues CBZ therapy, a slow tapering schedule should be considered.

According to the Phase III trials of PMP, patients with response to PMP had serum concentrations ranging from 180 to 980 ng/mL. In our previous study, the patient group who achieved a better response with PMP therapy had a mean serum PMP concentration of 450 ng/mL (Yamamoto *et al*., 2017). In the present study, four patients achieved good clinical responses and had serum concentrations ranging between 400 to 600 ng/mL, which are consistent with the findings of previous studies.

During the study period, six patients discontinued PHT therapy. The mean baseline CD ratio of PMP was 1,619 ng/ml/mg/kg, and after discontinuation of PHT increased by 127.7% (mean CD ratio: 3,754; data not shown). Thus, when discontinuing phenytoin, serum PMP concentration should be monitored carefully.

This study had several limitations. As the study was performed retrospectively, we were unable to assess the level of compliance with PMP therapy. In addition, monitoring of PMP concentrations was not performed at standardized intervals, therefore the data available

for each week varied. This limitation, along with the small sample size, contributed to variation in the estimated duration of PMP elevation. However, the mean CD ratio of PMP was 1,247±224 during CBZ therapy and 3,914 ± 1,042 after three to four weeks without CBZ, which are similar values to the results of previous studies.

Conclusion

When discontinuing CBZ therapy, a slow tapering schedule should be considered. The serum PMP concentration increased within a week of stopping CBZ therapy and was still elevated after eight weeks. We recommend therapeutic monitoring of PMP every one to two weeks, up to eight weeks after discontinuation of CBZ. Both careful monitoring and PMP dose adjustment are needed during this period to minimize the risk of adverse events. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
We thank all physicians involved in management of the patients reported here.
None of the authors have any conflict of interest to declare.

References

Brodie MJ, Mintzer S, Pack AM, *et al*. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 2013; 54(1): 11-27.

Gidal BE, Ferry J, Majid O, *et al*. Concentration-effect relationships with perampanel in patients with pharmacoresistant partial-onset seizures. *Epilepsia* 2013; 54(8): 1490-7.

Gidal BE, Laurenza A, Hussein Z, *et al*. Perampanel efficacy and tolerability with enzyme-inducing AEDs in patients with epilepsy. *Neurology* 2015; 84(19): 1972-80.

Hole K, Wollmann BM, Nguyen C, *et al*. Comparison of CYP3A4-inducing capacity of enzyme-inducing antiepileptic drugs using 4β-hydroxycholesterol as biomarker. *Ther Drug Monit* 2018; 40(4): 463-8.

Imai H, Kotegawa T, Tsutsumi K, *et al*. The recovery time-course of CYP3A after induction by St John's wort administration. *Br J Clin Pharmacol* 2008; 65(5): 701-7.

Inui N, Akamatsu T, Uchida S, *et al*. Chronological effects of rifampicin discontinuation on cytochrome P450 activity in healthy Japanese volunteers, using the cocktail method. *Clin Pharmacol Ther* 2013; 94(6): 702-8.

Ishikawa N, Tateishi Y, Tani H, *et al*. Clinical profiles associated with serum perampanel concentrations in children with refractory epilepsy. *Epilepsy Behav* 2019; 94: 82-6.

Mano Y, Takenaka O, Kusano K. High-performance liquid chromatography-tandem mass spectrometry method for the determination of perampanel, a novel α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist in human plasma. *J Pharm Biomed Anal* 2015; 107: 56-62.

Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. *Epilepsia* 2015; 56(1): 12-27.

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(3): 358-64.

Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. *Acta Neurol Scand Suppl* 2013; 197: 19-24.

Steinhoff BJ, Hübers E, Kurth C, *et al*. Plasma concentration and clinical effects of perampanel-The Kork experience. *Seizure* 2019; 67: 18-22.

Yamamoto Y, Usui N, Nishida T, *et al*. Therapeutic drug monitoring for perampanel in Japanese epilepsy patients: influence of concomitant antiepileptic drugs. *Ther Drug Monit* 2017; 39(4): 446-9.

Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord* 2014; 16(4): 409-31.

TEST YOURSELF

(1) How long does it take for perampanel to reach a new steady state after discontinuation of carbamazepine?

(2) How often and how long should perampanel drug concentrations be monitored after carbamazepine withdrawal?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".