

# Slow Carbamazepine Clearance in a Nonadherent Malay Woman With Epilepsy and Thyrotoxicosis

Li-Ling Yeap, BPharm (Hons),\* Kheng-Seang Lim, MBBS, MRCP,‡ Ching-Ching Ng, PhD,†  
Amy Hui-Ping Khor, BSc (Hons),† and Yoke-Lin Lo, PhD\*

**Abstract:** The authors describe a case of a 37-year-old Malay lady with an unusually slow carbamazepine clearance, which may be related to genetic polymorphisms of drug metabolizing enzymes and transporters. When given a small daily dose of 200 mg immediate-release carbamazepine, this patient experienced drowsiness. Subsequently, she reduced her carbamazepine dose to 200 mg twice a week (on Mondays and Fridays), resulting in poor seizure control. At the same time, the patient was diagnosed with hyperthyroidism and was given carbimazole and propranolol. Hyperthyroidism and the concurrent use of these antihyperthyroid agents may have further slowed down the metabolism of carbamazepine. Therapeutic drug monitoring of carbamazepine was carried out, and a slow carbamazepine clearance of  $1.45 \text{ L} \cdot \text{h}^{-1}$  per 70 kg was observed. Genotyping of selected genetic variants in *CYP3A4*, *CYP3A5*, *EPHX1*, *ABCB1*, and *ABCC2* revealed that she has *CYP3A5*\*3/\*3 and *ABCB1* 3435-CC genotypes. Both genotypes have been shown to be associated with higher adjusted mean serum carbamazepine concentration in Chinese and Korean patients with epilepsy. Physicians should be vigilant about the risk of adverse effects among patients with a slow carbamazepine clearance, especially in Malays. Simulations of carbamazepine dosing regimen based on the pharmacokinetic parameters of this patient were performed to allow individualization of drug therapy.

**Key Words:** carbamazepine, therapeutic drug monitoring, pharmacokinetics, nonadherence, genetic polymorphisms

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## CLINICIAN

A 37-year-old Malay woman was diagnosed with occipital lobe epilepsy since 14 years of age. She has been in seizure remission for the past 6 years and since then she has been maintained on monotherapy of daily 200 mg immediate-release carbamazepine (CBZ). (Tegretol 200; Novartis, Torre Annunziata, Italy). Nonetheless, she started having 5 episodes

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From the \*Department of Pharmacy, Faculty of Medicine; ‡Division of Neurology, Faculty of Medicine; and †Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia.

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Correspondence: Yoke-Lin Lo, PhD, Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia (e-mail: yllo@um.edu.my).

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of epileptic attacks in a month since 5 months ago. The episodes were manifested as visual aura of seeing flickering lights over both visual fields, dizziness, followed by generalized clonic seizure and postictal drowsiness.

One month before her seizure relapse, the patient experienced symptoms of palpitation, hot flushes, unexplained weight loss, and exophthalmus. Her free thyroid hormone (FT4) was elevated to 43.9 pmol/L (reference range, 11.5–23.2), and thyroid stimulating hormone was suppressed to  $<0.01 \mu\text{IU/mL}$  (reference range, 0.40–5.50). She was then diagnosed with Graves disease with hyperthyroidism and was treated with carbimazole 15 mg daily and propranolol 10 mg thrice a day. In a recent neurology clinic visit, her FT4 had reduced to 21.2 pmol/L, whereas thyroid stimulating hormone remained low at  $<0.01 \mu\text{IU/mL}$ . The dose of carbimazole was subsequently titrated to 20 mg daily and propranolol 10 mg twice a day.

Is it likely that her seizure relapse is a result of hyperthyroidism or the concurrent use of carbimazole and/or propranolol?

## THERAPEUTIC DRUG MONITORING CONSULTANT

CBZ is an antiepileptic drug (AED) with a narrow therapeutic index and its disposition may be altered by various illnesses or drug–drug interactions.<sup>1,2</sup> A recent study reaffirms that medication adherence can be a problem among patients with epilepsy.<sup>3</sup> Nonadherence to AEDs often has a detrimental effect on seizure control.<sup>4,5</sup>

Drug interactions involving CBZ are common and often clinically important. CBZ is metabolized mainly via CYP1A2, CYP2B6, CYP2C8, CYP3A4, CYP3A5, and CYP3A7. CBZ is also a potent inducer of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, and uridine diphosphate-glucuronosyl transferase. On the other hand, CBZ inhibits the activities of isoenzymes CYP1A2 and CYP2C19.<sup>6–8</sup> Blood concentrations of CBZ may be altered by its autoinduced metabolism and also by inducers or inhibitors of enzymes involved in CBZ biotransformation. Common inducers of the biotransformation of CBZ include phenytoin, phenobarbitone, primidone, oxcarbazepine, and rifampin. Concurrent use with amiodarone, cimetidine, cyclosporine, danazol, diltiazem, protease inhibitors such as ritonavir; antifungals such as fluconazole, itraconazole, ketoconazole, miconazole, macrolides (not including azithromycin); nefazodone, omeprazole, quinidine, and verapamil may inhibit the metabolism of CBZ and lead to CBZ toxicity.<sup>1,9–11</sup>

After oral administration, carbimazole is rapidly hydrolyzed to methimazole. Methimazole is not a substrate for cytochrome P450 enzymes but it is an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.<sup>6</sup> Propranolol is a substrate of CYP1A2, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP3A7 as well as an inhibitor of CYP1A2 and CYP2D6.<sup>6</sup> Theoretically, the concurrent use of these drugs with CBZ increases serum CBZ concentrations. CBZ may, in turn, decrease the therapeutic effect of propranolol<sup>6</sup> and increase the risk of carbimazole-induced agranulocytosis.<sup>12</sup>

To date, there is no study or report on the causal relationship between hyperthyroidism, augmented CBZ metabolism, and increased seizure occurrence. On the contrary, results of *in vitro* studies demonstrate that triiodothyronine reduces the activity and the expression of CYP3A4.<sup>13,14</sup> Thyroid hormone may reduce CYP3A activity<sup>15</sup> and hyperthyroidism, particularly Graves disease may cause hepatic dysfunction<sup>16</sup> that may dampen down the metabolism of CBZ, a low hepatic extraction ratio drug.<sup>17</sup>

The postulated drug–drug interactions and the presence of hyperthyroidism, however, still fall short of explaining seizure relapse in this patient. Presuming good medication adherence in this patient, an investigation of CBZ serum concentrations for therapeutic drug monitoring (TDM) before a dosage adjustment may be helpful.<sup>2,18</sup>

### CLINICIAN

A blood sample for TDM was collected 5 hours after an oral CBZ 200 mg dose. The assay result showed a CBZ serum concentration of 6.10 mg/L, which is within the targeted therapeutic range of 4–12 mg/L. In view of seizure recurrence, the dosage of CBZ was titrated up to 200 mg twice daily.

### THERAPEUTIC DRUG MONITORING CONSULTANT

Usually total (unbound and bound) CBZ serum concentrations are determined by homogenous enzyme immunoassay technique (ARCHITECT ci4100 Integrated System; Abbott Diagnostic, IL) in the hospital. The established CBZ reference range of 4–12 mg/L for optimal seizure control refers to the total drug concentrations.<sup>2</sup>

Ideally, TDM samples for AEDs should be collected at the end of a dosing interval or immediately before the next dose.<sup>2,18</sup> A random CBZ level may not necessarily represent a trough concentration.<sup>18</sup> A slow rate of dissolution and the anticholinergic properties of CBZ that suppress gut motility may result in an erratic and unpredictable absorption process.<sup>19–22</sup> The time to reach the peak plasma concentration following a single oral dose of an immediate-release CBZ tablet is between 2 and 9 hours,<sup>2</sup> but time as late as 24 hours has been observed.<sup>19</sup> The pharmacokinetics of CBZ is often marked by a large intraindividual and interindividual variability.<sup>21,22</sup> Therefore, CBZ may still be in its distribution phase at the fifth hour after dose, and a blood sample taken at that time may not necessarily reflect CBZ clearance (CL).

Practice guideline from International League Against Epilepsy (ILAE)<sup>2</sup> recommends that dose adjustments should never be made on the basis of serum drug concentrations alone, but should be primarily justified by careful assessment of a patient's clinical state. This is because the reference range is built on retrospective and observational studies. There are patients who have good seizure control when CBZ serum concentrations are below the lower limit of the range. On the contrary, the upper limit of the range may vary from one patient to another. Therefore, dosage should not be modified in patients who achieve sustained seizure freedom at serum CBZ concentrations below the reference range or in those who are doing clinically well at concentrations above this range.

### CLINICIAN

The individual therapeutic range has not been established for this patient. The patient presented to the clinic 3 days later with complaints of light-headedness. Her vital signs were normal with blood pressure at 121/82 mm Hg and heart rate at 82 bpm. No other symptoms related to hyperthyroidism were reported. Carbimazole dosage remained at 20 mg daily and propranolol 10 mg twice daily. She was also on day 3 of her increased CBZ dosage of 200 mg twice a day.

### THERAPEUTIC DRUG MONITORING CONSULTANT

The observed symptoms may be attributed to a sudden dosage increment of CBZ. Other commonly observed concentration-related adverse effects include nausea, vomiting, lethargy, drowsiness, headache, blurred vision, diplopia, unsteadiness, ataxia, and incoordination. When the CBZ dosage remains constant, patients often show adaptation effect after some days.<sup>23</sup>

Serum CBZ levels may be measured when a new steady state is established after a dosage modification. A recent dosage increment of CBZ may instigate the dose-dependent autoinduction process,<sup>24–29</sup> and blood samples taken during autoinduction process may result in overestimating the steady-state serum concentrations.<sup>2</sup>

TDM samples, however, may be assessed as soon as a patient presents with clinical suspicion of CBZ toxicity.<sup>2,18</sup> It is worth noting that if autoinduction process is still in progress, the pharmacokinetic parameters of CBZ can be estimated using a nonlinear regression algorithm that incorporates components of Bayes' theorem. Because of the complexity of autoinduction pharmacokinetics, at least 4 CBZ levels are needed to generate acceptable estimations of the pharmacokinetic parameters.<sup>30</sup> Complete blood counts, liver function, and renal function should also be assessed to rule out altered pharmacokinetics due to organ dysfunctions or changes in protein binding.

### CLINICIAN

Serial serum CBZ concentrations after the administration of a 200 mg dose were measured. The observed CBZ levels were 15.50 mg/L (predose), 18.20 mg/L (1-hour postdose), 16.90 mg/L (2.5-hour postdose), 16.00 mg/L (4-hour postdose), and 15.40 mg/L (5-hour postdose). No clinically significant

abnormalities in the patient's renal function, liver function, or hematologic findings were detected.

### THERAPEUTIC DRUG MONITORING CONSULTANT

An elevated predose and postdose CBZ serum concentration above 12 mg/L may explain the concentration-dependent neurological side effects. The CBZ concentrations–time profile of this patient was studied using NONMEM 7. 2 (NONMEM Project Group, San Francisco, CA). The pharmacokinetics of CBZ can be described using a 1-compartment open model with first-order absorption and first-order elimination. The absolute bioavailability (F) was not determined nor assumed as there is no injectable CBZ formulation and no precise datum exists on the absolute bioavailability of CBZ.<sup>24–26</sup> Therefore, the pharmacokinetic parameters such as CL and volume of distribution (V) were interpreted as CL/F and V/F, respectively, where F is the bioavailability.

The estimated CL is 1.45 L·h<sup>-1</sup> per 70 kg (using allometric scaling), V is 46.2 L per 70 kg, and the absorption rate constant (Ka) is 30 per h. The estimated V value of 46.2 L per 70 kg is smaller than that of the published average value (70.0–133.0 L per 70 kg).<sup>2,31</sup> Nonetheless, a Vd as small as 25.9 L per 70 kg has been reported.<sup>27</sup> The estimated CL value of 1.45 L·h<sup>-1</sup> per 70 kg, however, is much lower than those previously reported (3.36–7.56 L·h<sup>-1</sup> per 70 kg).<sup>27,32–34</sup> The elimination half-life (T<sub>1/2</sub>) is estimated to be 22.1 hours. The estimated time to the peak plasma concentration of 0.22 hours was found to be very rapid when compared with the published data of 2–9 hours.<sup>2</sup> When the values of CBZ concentrations of 6.10 mg/L and 15.40 mg/L at the 5-hour postdose time point of 2 different occasions were compared, discrepancies were noted and a possible explanation would be nonadherence to the prescribed dosage. It is prudent to further investigate this patient's medication adherence before an ensuing clinical decision is made.

### CLINICIAN

The patient disclosed to have reduced her CBZ dosage to 200 mg twice per week, that is, on Mondays and Fridays only, for the past 2 years. She claimed feeling dizzy when taking 200 mg CBZ daily and expressed her concerns about long-term treatment with CBZ. She, however, decided to adhere to the newly prescribed CBZ 200 mg twice a day dosing regimen after she had agreed to serial blood sampling for TDM.

### THERAPEUTIC DRUG MONITORING CONSULTANT

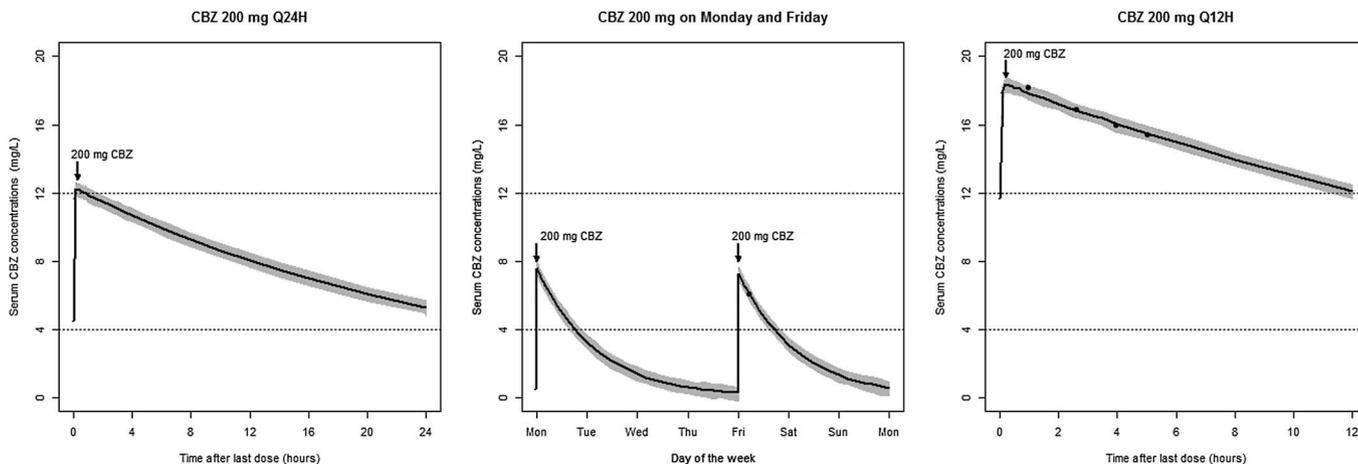
Based on the CBZ pharmacokinetic parameters of this patient, simulations were performed for the dosing regimens previously taken by the patient, that is, 200 mg once daily, 200 mg on Mondays and Fridays, and 200 mg twice daily. The side effects reported by the patient with CBZ 200 mg daily can be correlated with peak CBZ levels higher than the reference range (Fig. 1, left pane). The 200 mg twice per week dosing regimen may cause serum CBZ levels to plummet way below the reference range of 4–12 mg/L in between dosing intervals (Fig. 1, middle pane), thus resulting in poor seizure control. On the other hand, CBZ 200 mg twice daily dosing regimen may result in serum CBZ concentrations being perpetually above the reference range (Fig. 1, right pane) resulting in the neurological adverse effects observed in the patient.

### CLINICIAN

What are the other possible causes for the low CL of CBZ in this patient?

### THERAPEUTIC DRUG MONITORING CONSULTANT

Altered pharmacokinetics processes (absorption, distribution, metabolism, and elimination) of CBZ may be



**FIGURE 1.** Plots of serum CBZ concentrations versus time after last dose when immediate-release CBZ tablets are given at various dosing regimens. The filled circles (●) symbolize observed CBZ concentrations. The solid lines (—) are the median serum CBZ concentrations, the shaded areas (■) represent the 95th-percentile intervals after 200 simulations, and the dotted lines (---) denote the reference range of 4–12 mg/L.

attributed to variants in metabolism enzymes expressed in both enterocytes and hepatocytes<sup>35,36</sup> or possibly variants in drug transporters in intestinal lumen.<sup>36</sup> Some of the *ABCB1* and *ABCC2* polymorphisms affect the expression of intestinal drug transporters, MDR1 and MRP2, respectively. Therefore, these polymorphisms are possible determinants of CBZ blood levels and dose requirement in patients with epilepsy.<sup>36</sup> Seo et al<sup>37</sup> reported that *ABCB1* polymorphisms might influence the AED responsiveness and/or the P-glycoprotein activity.<sup>37</sup> Nevertheless, the effects of the polymorphisms may vary among races.

A study by Maekawa et al<sup>38</sup> found that variant protein CYP3A4.16 may result in a lower CBZ CL than that of CYP3A4.1. The distribution of *CYP3A4\*16* allele was reported to exhibit large ethnic differences<sup>39</sup> with a frequency of 0.2% in Korean<sup>40</sup>; between 1.4% and 5% in Japanese<sup>41</sup>; and 5% in Mexican<sup>42</sup> populations. Other studies in Chinese and Korean populations found that CYP3A5 nonexpressors

(*CYP3A5\*3/\*3*) have a higher mean serum concentration of CBZ even though a lower dose of CBZ was given.<sup>43,44</sup> The effects of CYP3A5 nonexpression, however, were not apparent in Japanese patients with epilepsy who were coadministered with enzyme inducers of CYP3A4.<sup>45</sup> Variants in *EPHX1* have also been reported to be associated with altered CBZ metabolism. Certain haplotypes of *EPHX1*: Y113H and *EPHX1*: H139R show increased and decreased plasma CBZ-diol/CBZ-epoxide ratios in vivo in Japanese patients with epilepsy.<sup>46</sup>

Genetic variability in CBZ pathway genes among different racial groups and its implication on drug disposition may explain the patient's previous seizure control with small doses of CBZ, although none of the previous pharmacogenomic studies mentioned above was performed in a Malay population. Selected genetic variants in 3 major genes involved in biotransformation of CBZ (*CYP3A4*, *CYP3A5*, and *EPHX1*) and 2 drug transporter genes (*ABCB1* and

**TABLE 1.** Genotypes of Selected *CYP3A4*, *CYP3A5*, *EPHX1*, *ABCB1*, and *ABCC2* SNPs in the Patient

Gene	SNP rs ID	Nucleotide Changes (Effect)	Genotype	
<i>CYP3A4</i>	rs67666821 (insA; -)	c.1461-1462insA (488frameshift)	—	
	rs4986913	c.1399C>T (Pro467Ser)	CC	
	rs4986910	c.1334T>C (Met445Thr)	TT	
	rs4986909	c.1247C>T (Pro416Leu)	CC	
	rs12721629	c.1117C>T (Leu373Phe)	CC	
	rs67784355	c.1088C>T (Thr363Met)	CC	
	rs2242480	g.20230 G>A	GA ( <i>CYP3A4*1/*1G</i> )	
	rs28371759	c.878T>C (Leu293Pro)	TT	
	rs4646438 (insA; -)	c.830_831insA (277 frameshift)	—	
	rs55785340	c.664T>C (Ser222Pro)	TT	
	rs55901263	c.653C>G (Pro218Arg)	CC	
	rs113667357	c.600A>T (Gln200His)	AA	
	rs4987161	c.566T>C (Phe189Ser)	AA	
	rs12721627	c.554C>G (Thr185Ser)	TT	
	rs35599367	g.15389C>T	CC	
	rs4986908	c.520G>C (Asp174His)	GG	
	rs4986907	c.485G>A (Arg162Gln)	GG	
	rs57409622	c.484C>T (Arg162Trp)	CC	
	rs72552798	c.508G>A (Val170Ile)	GG	
	rs72552799	c.389 G>A (Arg130Gln)	GG	
	rs55951658	c.352A>G (Ile118Val)	AA	
	rs56324128	c.167G>A (Gly56Asp)	GG	
	rs12721634	c.44T>C (Leu15Pro)	TT	
	rs2740574	-392A>G	AA	
	rs59715127	g.26206C>A	CC	
	<i>CYP3A5</i>	rs776746	g.6986A>G (Splicing defect)	GG ( <i>CYP3A5*3/*3</i> )
	<i>EPHX1</i>	rs1051740	c.337T>C (Tyr113His)	TC (Tyr/His)
rs2234922		c.416A>G (His139Arg)	AA	
<i>ABCB1</i>	rs1128503	c.1236C>T	CT	
	rs2032582	c.2677G>,T A (Ser893Ala/Thr)	GG	
	rs1045642	c.3435C>T	CC	
<i>ABCC2</i>	rs17222723	c.3563T>A (Val1188Glu)	TT	
	rs8187710	c.4544 G>A (Cys1515Ala)	GG	
	rs2273697	c.1249 G>A (Val417Ile)	GA (Val/Ile)	
	rs717620	c.-24C>T	CC	

*ABCC2*) were analyzed by direct sequencing of the PCR amplicons, and the patient's genotypes are shown in Table 1.

The patient has *CYP3A4*\*1/\*1*G* and *CYP3A5*\*3/\*3 (nonexpressor) genotypes. Although she has 1 copy of *CYP3A4*\*1*G* allele, the impact of the A-variant in intron 10 on CBZ CL is unclear. The result is consistent with the idea that polymorphisms affecting *CYP3A4* activity are rare. Conversely, *CYP3A5*\*3 has been shown to cause alternative splicing and protein truncation which strongly decreases *CYP3A5* activity. She is heterozygous for the *EPHX1* 337T>C (Y113H) in which 113H variant is suggested to affect protein stability leading to a decreased enzyme level in vitro.<sup>47</sup> In contrast, individuals with 113H are reported to have increased plasma CBZ-diol/CBZ-epoxide ratios.<sup>46</sup>

For the *ABCB1* single nucleotide polymorphism (SNP) analyzed, she is 1236-CT, 2677-GG, and 3435-CC. Puranik et al<sup>48</sup> reported that patients with at least 1 *ABCB1* 1236-T allele had significantly higher CBZ CL in African Americans but not whites. Conflicting results have been reported regarding the association between *ABCB1* 3435C>T polymorphism and plasma level of CBZ. Individuals with 3435-CC genotype had higher plasma CBZ concentrations compared to those with 3435-TT genotype in Chinese patients<sup>43</sup> but lower CBZ levels in patients from the Republic of Macedonia.<sup>49</sup> The discordant effect of the polymorphism may be attributed to different haplotype structures or racial backgrounds. With respect to the *ABCC2* SNPs, the patients are heterozygous for the 1249G>A (V417I). Although 1249-AA and GA patients were shown to be associated with higher CBZ CL in whites but not among African Americans,<sup>48</sup> the relationship of this SNP and CBZ level in Asians remains to be elucidated. The combined effect of the above genetic variants coupled with incomplete autoinduction process, carbimazole/

propranolol-related inhibition of metabolizing enzymes and also triiodothyronine-related reduction in *CYP3A4* may contribute to her slow CL of CBZ.

### CLINICIAN

What would be an appropriate CBZ dose for this patient at this point?

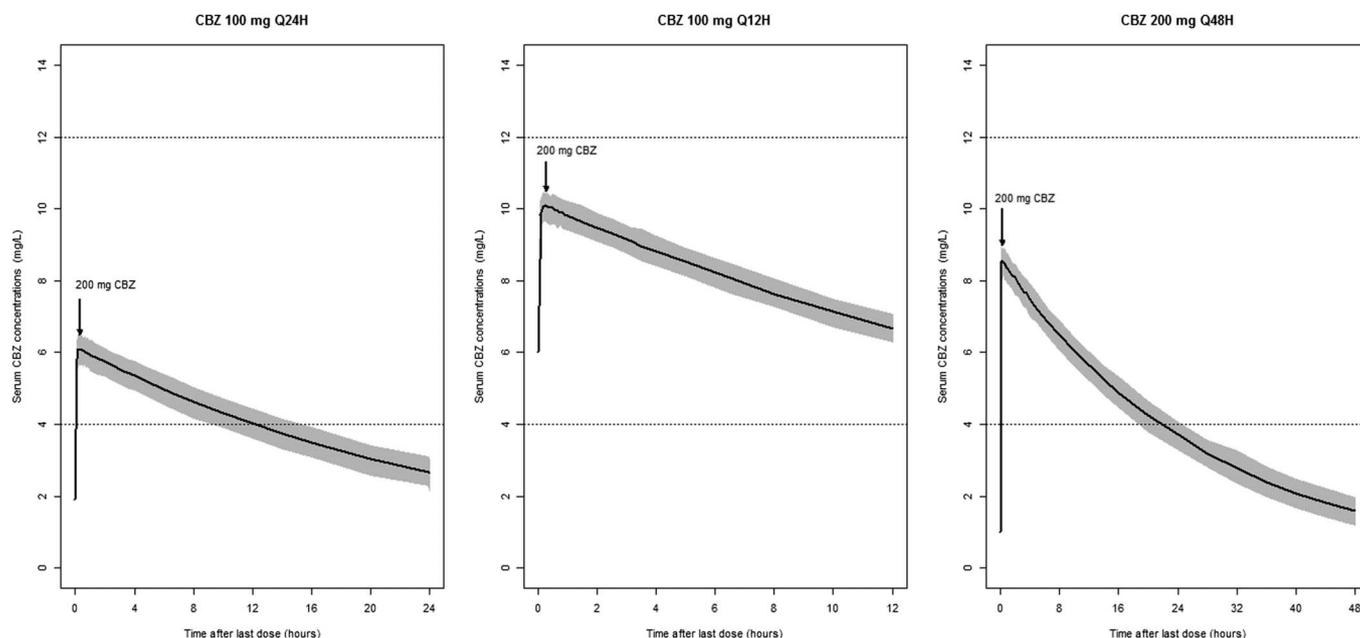
### THERAPEUTIC DRUG MONITORING CONSULTANT

Simulations using different dosing regimens were performed based on the pharmacokinetic parameters estimated for this patient. Dosage regimens of CBZ tested include 100 mg once a day, 100 mg twice a day, and also 200 mg on alternate days.

In view of the efficacies and toxicities of CBZ, the criteria for a recommended dosage regimen are as follow: predicted CBZ serum concentrations fall within 4–12 mg/L with a minimum fluctuation of serum CBZ levels between dosing intervals. Simulation results show that a dosage regimen of CBZ 100 mg twice a day fulfills the criteria (Fig. 2). The therapeutic effects and steady-state CBZ serum concentrations can be assessed 2–3 weeks later and CBZ dosage can then be titrated accordingly, if necessary.

### CLINICIAN

The patient was counseled on the safety of CBZ therapy. She was also encouraged to discuss with her doctor or pharmacist symptoms that bother her when taking her medication. The new CBZ dosing regimen of 100 mg twice



**FIGURE 2.** Plots of serum CBZ concentrations versus time after last dose for various dosing regimens of immediate-release CBZ tablets after 200 simulations. The solid lines (—) are the median serum CBZ concentrations, the shaded areas (■) represent the 95th-percentile intervals, and the dotted lines (---) denote the reference range of 4–12 mg/L.

a day was proposed. The importance of medication adherence was emphasized to the patient.

### THERAPEUTIC DRUG MONITORING CONSULTANT

It may be assumed that seizure relapse in this patient was mainly due to poor medication adherence. Avoidance of medication adverse effects is one of the main contributing factors to poor adherence.<sup>50</sup> CBZ-related adverse effects are positively related to elevated serum drug concentrations, the swiftness of serum concentration surge, or the fluctuations of serum levels between dosing intervals.<sup>23</sup> These unwanted effects may be avoided or minimized by giving smaller CBZ doses at more frequent intervals or by replacement with sustained- or controlled-release formulations.<sup>51</sup>

Epilepsy treatment with CBZ is indeed complex and challenging. The inconsistency in treatment outcome can be attributed to the inherent narrow therapeutic window of CBZ, its autoinductive metabolism behavior, a wide range of potential drug–drug interactions or drug–disease interactions and sometimes, patient-related issues such as communication barriers, poor medication adherence, or genetic polymorphisms. Education and reassurance to patients from healthcare providers are important. A trusted patient–physician relationship or patient–pharmacist relationship should be established to encourage open discussions pertaining to drug-related issues to improve medication adherence.<sup>5</sup> Attending physicians should be vigilant and request TDM service judiciously, so that the dosage of CBZ can be adjusted promptly for maximum seizure control with minimum adverse effects. Pharmacogenomic studies on CBZ patients of various races may be helpful in identifying individual with a slow CBZ CL.

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