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Effect of phenytoin, phenobarbital and valproic acid on carbamazepine clearance and therapeutic out come: derived from routine therapeutic drug monitoring data at Prasat Neurological Institute

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Background : *Pharmacokinetics (PK) of carbamazepine (CBZ) are highly variable and further complicated by concomitant use of other antiepileptic drugs with induction or inhibition properties.*

Objective : *To determine the pharmacokinetics of CBZ when used as monotherapy or co-administrated with phenytoin (PHT), phenobarbital (PB) or valproic acid (VPA) along with the related therapeutic outcome.*

Design : *A descriptive study.*

Setting : *Prasat Neurological Institute, Bangkok.*

Patients : *Patients aged more than 13 years old with epilepsy or other neurological disease who used CBZ as monotherapy or co-administrated with PHT, PB or VPA and their therapeutic drug monitoring data (TDM) had been recorded and available were included into this study.*

Method : *Four-year retro-prospective data, August 2006 - August 2010, were collected from electronic database and medical records of the outpatient epilepsy clinic.*

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Result : *Data of 74 patients, 34 men and 40 women, were identified and used in this analysis; 71 were diagnosed with epilepsy while 3 had neuropathic pain. Their age were ranged from 13.87 to 82.05 years (mean = 40.13 ± 15.22). The median level - to - dose ratio of CBZ in patients who used CBZ as monotherapy (10.88 mcg/L/mg, N = 30) was significantly higher ($p < 0.001$) than those obtained after combination therapy with PHT (6.13 mcg/L/mg, N =15), PB (6.81 mcg/L/mg, N =14) or VPA (8.88 mcg/L/mg, N =15), even though the median daily dose of CBZ (13.36 VS 16.47, 16.88 and 16.02 mg/kg/day, respectively) was not significantly different ($p = 0.184$). The median clearance of CBZ in patients who used CBZ in combination with PHT (2.34 L/kg/day) or PB (1.49 L/kg/day) was significantly higher than that observed after CBZ monotherapy (1.09 L/kg/day) ($p < 0.001$ and $p = 0.013$, respectively). However, the median clearance of CBZ in patients who used CBZ in combination with VPA (1.34 L/kg/day) was not significantly different from that found after monotherapy ($p = 0.118$). Seventeen patients (24%) of the 71 epileptic patients participated had uncontrolled seizure while 4 patients (6%) had mild adverse effects.*

Conclusion : *The clearance of CBZ in patients who used CBZ as monotherapy was significantly lower than in those observed patients who used CBZ in combination with PHT or PB, but it was not significantly different from patients who used CBZ in combination with VPA.*

Keywords : *Pharmacokinetics, carbamazepine, phenytoin, phenobarbital, valproic acid, therapeutic drug monitoring.*

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บทนำ : *เภสัชจลนศาสตร์ของยาคาร์บามาซีพีนมีความแปรปรวนค่อนข้างสูง และเพิ่มความซับซ้อนมากขึ้นเมื่อมีการใช้ร่วมกับยากันชักชนิดอื่นที่มีคุณสมบัติเหนี่ยวนำหรือยับยั้งอัตราเร็วในการกำจัดยา*

วัตถุประสงค์ : *เพื่อศึกษาเภสัชจลนศาสตร์ของยาคาร์บามาซีพีนเมื่อใช้เป็นยาเดี่ยว และเมื่อใช้ร่วมกับยาเฟนิทอยน์ ฟีโนบาร์บิทาลหรือ วาลโพรอิกแอซิด ควบคู่ไปกับผลลัพธ์ในการรักษา*

รูปแบบการวิจัย : *การศึกษาแบบพรรณนา*

สถานที่ที่ทำการศึกษา : *สถาบันประสาทวิทยา กรุงเทพมหานคร*

ผู้ป่วยที่ได้ทำการศึกษา : *รวบรวมข้อมูลจากผู้ป่วยที่อายุมากกว่า 13 ปีที่เป็นโรคลมชักหรือโรคทางระบบประสาทที่ใช้ยาคาร์บามาซีพีนเป็นยาเดี่ยวหรือใช้ร่วมกับยาเฟนิทอยน์ ฟีโนบาร์บิทาลหรือวาลโพรอิกแอซิดที่มีข้อมูลการติดตามระดับยาในเลือด*

วิธีการศึกษา : *รวบรวมจากฐานข้อมูลคอมพิวเตอร์และเวชระเบียนที่คลินิกผู้ป่วยนอกโรคลมชักระหว่างเดือนสิงหาคม 2549 - สิงหาคม 2553*

ผลการศึกษา : *ข้อมูลได้มาจากผู้ป่วย 74 ราย ซึ่งเป็นเพศชาย 34 รายและเพศหญิง 40 ราย เป็นผู้ป่วยโรคลมชัก 71 รายและอีก 3 รายมีอาการปวดปลายประสาท อายุของผู้ป่วยอยู่ระหว่าง 13.87 ถึง 82.05 ปี (ค่าเฉลี่ย 40.13 ± 15.22) ค่ามัธยฐานของสัดส่วนระดับยาต่อขนาดยาคาร์บามาซีพีนในกลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนเป็นยาเดี่ยว (10.88 ไมโครกรัม/ลิตร/มิลลิกรัม, ผู้ป่วย 30 ราย) สูงกว่ากลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนร่วมกับยาเฟนิทอยน์ (6.13 ไมโครกรัม/ลิตร/มิลลิกรัม, ผู้ป่วย 15 ราย) ฟีโนบาร์บิทาล (6.81 ไมโครกรัม/ลิตร/มิลลิกรัม, ผู้ป่วย 14 ราย)หรือ วาลโพรอิกแอซิด (8.88 ไมโครกรัม/ลิตร/มิลลิกรัม, ผู้ป่วย 15 ราย) อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) แม้ว่าค่ามัธยฐานของขนาดยาคาร์บามาซีพีนต่อวันในแต่ละกลุ่ม (13.36 เทียบกับ 16.47, 16.88 และ 16.02 มิลลิกรัม/กิโลกรัม/วัน ตามลำดับ) จะไม่แตกต่างกัน*

วิจารณ์และสรุป : *อย่างมีนัยสำคัญทางสถิติ (p = 0.184) ค่ามัธยฐานของอัตราการกำจัดยาคาร์บามาซีพีนในกลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนร่วมกับยาเฟนิทอยน์ (2.34 ลิตร/กิโลกรัม/วัน) หรือฟีโนบาร์บิทาล (1.49 ลิตร/กิโลกรัม/วัน) สูงกว่าในกลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนเป็นยาเดี่ยว (1.09 ลิตร/กิโลกรัม/วัน) อย่างมีนัยสำคัญทางสถิติ (p < 0.001 และ p = 0.013 ตามลำดับ) อย่างไรก็ตามค่ามัธยฐานของอัตราการกำจัดยาคาร์บามาซีพีนในกลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนร่วมกับยาวาลโพรอิกแอซิด (1.34 ลิตร/กิโลกรัม/วัน)นั้นไม่แตกต่างจากกลุ่มที่ใช้ยาคาร์บามาซีพีนเป็นยาเดี่ยวอย่างมีนัยสำคัญทางสถิติ (p = 0.118). ผู้ป่วย 17 ราย (24%) ในจำนวน 71 รายของผู้ป่วยโรคลมชักยังควบคุมอาการชักไม่ได้ ผู้ป่วย 4 ราย (6%) มีผลข้างเคียงเล็กน้อยจากการใช้ยา อัตราการกำจัดยาคาร์บามาซีพีนในกลุ่มผู้ป่วยที่ใช้คาร์บามาซีพีนเป็นยาเดี่ยวจะต่ำกว่าในกลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนร่วมกับยาเฟนิทอยน์หรือฟีโนบาร์บิทาลอย่างมีนัยสำคัญทางสถิติ แต่ไม่แตกต่างจากกลุ่มผู้ป่วยที่ใช้ยาคาร์บามาซีพีนร่วมกับยาวาลโพรอิกแอซิด*

คำสำคัญ : *เภสัชจลนศาสตร์, คาร์บามาซีพีน, เฟนิทอยน์, ฟีโนบาร์บิทาล, วาลโพรอิกแอซิด, การติดตามระดับยาในเลือด.*

Carbamazepine (CBZ) is a first-line antiepileptic drug (AED) for partial and generalized tonic–clonic seizures.[1-5] It is used as monotherapy or co-administration with other AEDs for instance phenytoin (PHT), phenobarbital (PB) or valproic acid (VPA).[5-7] Additionally, it is commonly used for other neurological diseases, for instance, pain relief in trigeminal neuralgia, bipolar disorder.[8] CBZ is 99% metabolized by the liver; *CYP3A4* and *CYP3A5* are the most importance enzymes.[8-12] CBZ induces its own metabolism (autoinduction), the clearance of which increases on continued dosing. Autoinduction begins 3 to 5 days after the initiation of therapy and takes 3-5 weeks to complete. The result of the autoinduction is that the clearance of CBZ will increase whereas its half-life becomes shorter.[10, 11] The serum concentration of CBZ that is reported to be accepted therapeutic range is 4-12 mg/L when the drug is used for the treatment of seizures. However, the range for psychiatric disorders and trigeminal neuralgia is assumed to be the same.[9] This range is intended as a guideline and not as absolute protocol, because of the variables in the amount of free drug, the contribution of the CBZ 10, 11-epoxide (active metabolite) and the interindividual variability in response. The target concentration for each patient should be determined by response and occurrence of side effects.[10] Prediction of the appropriate dosage regimens for patients treated with CBZ is difficult because of its erratic absorption, autoinduction, active metabolite, diurnal fluctuations, and narrow therapeutic range. In addition, anticonvulsant therapy can be further complicated by concomitant use of other AEDs with induction or inhibition properties. Clinical experience has proved that individualized dose adjustment by the aid of therapeutic drug monitoring (TDM) can significantly improve the treatment with CBZ and other narrow therapeutic range AEDs.[13] The purpose of this study was to determine the clinical PK of CBZ when used as monotherapy or co-administration with classical AED, PHT, PB or VPA and investigate other related therapeutic outcomes.

Patients and Methods

Study design

A descriptive study design was used. The protocol has been approved by Institutional Review Board (IRB) /Independent Ethics Committee, Prasat Neurological Institute (Bangkok, Thailand). Four-year retro-prospective data, during August 2006 - August 2010 were reviewed using electronic database and medical records.

Patients

Outpatients at the epilepsy clinic aged more than 13 years old with epilepsy or neurological disease who used CBZ as monotherapy or co-administration with PHT, PB or VPA whose TDM data were recorded were recruited. Both CBZ and VPA were in the form of controlled-release tablet (Tegretol CR or Zeptol CR and Depakine chrono, respectively). The patients were on a stable dosage regimen for at least 6 weeks. Hence, the steady-state was assumed and autoinduction was complete. The following data were collected from electronic database: 1) demographic data; 2) CBZ, PHT, PB and VPA dosing regimen; 3) CBZ, PHT, PB and VPA plasma concentrations. The body weight and therapeutic outcome were collected from the medical records. Patients with hepatic

disease or kidney disease were excluded. Additionally, patients who concomitantly used the following drugs that may interfere with CBZ PK were excluded, namely: verapamil, diltiazem, haloperidol, theophylline, ticlopidine, cimetidine, omeprazole, trazodone, fluoxetine, risperidone, clarithromycin, erythromycin, rifampicin, isoniazid, isotretrinion, gemfibrozil, and metronidazole. [14-16]

Blood Sampling and Assay

Blood samples were obtained as a part of a routine TDM. All blood samples were drawn in the morning before drug intake (trough level). Total CBZ, PHT, PB and VPA concentrations in the serum were determined using an immuno-turbidimetry assay method with an automate analyzer (Synchron LX® Systems, Beckman Coulter Inc., Fullerton, California).

Pharmacokinetic Parameter Calculation

CBZ elimination parameter was calculated using the following equation: [8, 9]

$$\text{Clearance} = (S)(F)\,\text{Dose} / (\tau)(C_{ss\,ave})$$

Where S is the salt fraction of CBZ (S = 1); F is the CBZ bioavailability (assumed to be 0.7 for controlled-release tablet); τ is the dosing interval; and, $C_{ss\,ave}$ is the measured serum CBZ concentration at steady state.

Data Analysis

Calculation PK data by Microsoft Excel sheet and statistical analyses were determined by using the SPSS version 17.0 (SPSS Co., Ltd., Bangkok Thailand). The level of significance was set at an $\alpha = 0.05$. Continuous variables were determined for normal distribution using Kolmogorov–Smirnov test and determined for homogeneity of variance by Levene's test.

Results

Demographic data

Data used for analysis included from 74 patients; 71 were diagnosed as epilepsy, and 3 neuropathic pain. Of the 71 epileptic patients, 13 had a generalized seizure, and 58 had a localized seizure. Among these, 30 patients used CBZ as monotherapy, 15 patients used CBZ in combination with PHT; 14 patients used CBZ in combination with PB and 15 patients used CBZ in combination with VPA. The details are shown in Table 1.

Table 2 . CBZ pharmacokinetic parameters from the total patients included into the study.

Table 3. The comparisons of patient's characteristics and PK parameters of CBZ when categorized patients into 4 groups based on other AEDs used in combination with CBZ; CBZ monotherapy, CBZ combination with PHT (CBZ+PHT), CBZ combination with PB (CBZ+PB), and CBZ combination with VPA (CBZ+VPA). Patient's age, body weight, CBZ daily dose per body weight were not significantly different among these 4 groups, but the CBZ daily dose, CBZ level, CBZ level-to-dose ratio and CBZ clearance were significantly different among the 4 groups.

Multiple comparisons of the pharmacokinetic parameters of CBZ among the 4 groups of different drug treatments, in order to identify which group was different from other groups, are shown in details in Table 4. The result indicated that the CBZ level-to-

dose ratio in CBZ monotherapy group was significantly higher than all of the other groups, and this parameter in the CBZ+PHT group was significantly lower than that observed in the CBZ+VPA group. Comparisons of the median of CBZ clearance among the 4 groups indicated that the CBZ monotherapy group had significantly lower CBZ clearance as compared to the CBZ+PHT and CBZ+PB groups, but this CBZ clearance was not significantly different from the CBZ clearance obtained from the CBZ+VPA group. At the same time, the median CBZ clearance of the CBZ+PHT group was significantly higher than that of the CBZ+VPA group.

The parameters of the other classical AEDs which used in combination with CBZ are shown in Table 5.

Table 1. Demographic data of patients.

Descriptive data	**N**	**%**
Number of patients	74	100
Age (years)		
Mean ± SD = 40.13 ± 15.22		
Range = 13.87 – 82.05		
Weight (kgs)		
Median = 60		
Range = 37-104		
Gender		
Male	34	45.9
Female	40	54.1
Indication of CBZ used		
Epilepsy	71	96
Neuropathic pain	3	4
Type of epilepsy		
Generalized seizure	13	18.3
Localized seizure	58	81.7
Combination therapy		
CBZ monotherapy	30	40.5
CBZ+PHT	15	20.3
CBZ+PB	14	18.9
CBZ+VPA	15	20.3

CBZ+PHT: carbamazepine combination with phenytoin, CBZ+PB: carbamazepine combination with phenobarbital, CBZ+VPA: carbamazepine combination with valproic acid.

Table 2. Pharmacokinetic parameters of CBZ from total patients included.

PK parameters (N = 74)	Minimum	Maximum	Mean ± SD or Median
CBZ dose (mg/day)	200	2,000	800
(mg/kg/day)	3.33	32.33	15.20 ± 6.80
CBZ level (mg/L)	2.10	11.90	7.57 ± 2.44
(mcg/L/mg)	3.50	29.00	9.69 ± 4.46
CBZ clearance (L/hr)	1.01	18.10	3.23
(L/day)	24.14	434.48	77.48
(L/kg/hr)	0.0168	0.2586	0.0560
(L/kg/day)	0.40	6.21	1.34

Kg: kilogram, mg: milligram, L: litre, mcg: microgram.

Table 3. Comparisons of some patient's characteristics and pharmacokinetic parameters of CBZ among CBZ monotherapy and difference combination therapy groups.

Parameters	Mean ± SD or Median				
	CBZ (N = 30)	CBZ+PHT (N = 15)	CBZ+PB (N = 14)	CBZ+VPA (N = 15)	P value
Age (years) [a]	45.71 ± 14.42	34.25 ± 16.32	39.15 ± 13.87	35.74 ± 14.35	0.052
(range)	(16.53 – 82.05)	(14.13 – 64.90)	(13.87 – 61.69)	(18.35 – 65.51)	
Body weight (kgs) [a]	59.97 ± 10.15	61.05 ± 14.78	62.41 ± 10.25	66.23 ± 14.55	0.438
(range)	(40.10 – 89.00)	(37.00 – 82.00)	(47.30 – 82.00)	43.30 – 104.00)	
CBZ dose (mg/day) [b]	800	900	1,000	1,000	0.035 *
(range)	(200 – 1,600)	(300 – 2,000)	(400 – 1,600)	(400 – 1,600)	
(mg/kg/day)	13.36	16.47	16.88	16.02	0.184
(range)	(3.33 – 29.09)	(5.19 – 27.91)	(6.23 – 30.77)	(7.08 – 32.33)	
CBZ level (mg/L) [b]	8.85	4.90	7.40	8.50	0.001 *
(range)	(3.70 – 11.90)	(2.10 – 9.20)	(3.80 – 10.80)	(3.70 – 10.90)	
(mcg/L/mg)	10.88	6.13	6.81	8.88	0.000 *
(range)	(6.17 – 29.00)	(3.50 – 16.11)	(3.80 – 13.50)	(5.81 – 13.83)	
CBZ clearance (L/hr) [b]	2.68	5.22	4.28	3.29	0.000 *
(range)	(1.01 – 4.73)	(2.22 – 18.10)	(2.16 – 7.68)	(2.11 – 5.02)	
(L/day)	64.38	125.37	102.76	78.87	0.000 *
(range)	(24.14 – 113.51)	(53.26 – 434.48)	(51.85 – 184.21)	(50.60 – 120.43)	
(L/kg/hr)	0.0455	0.0973	0.0619	0.0558	0.004 *
(range)	(0.0168 – 0.0824)	(0.0361 – 0.2586)	(0.0346 – 0.1391)	(0.0273 – 0.110)	
(L/kg/day)	1.09	2.34	1.49	1.34	0.004 *
(range)	(0.40 – 1.98)	(0.87 – 6.21)	(0.83 – 3.34)	(0.66 – 2.66)	

* Statistical significant difference ($p < 0.05$), [a] one way ANOVA test, [b] Median Test.

Table 4. Multiple comparisons of the pharmacokinetic parameters of CBZ between CBZ monotherapy and combination therapy.

CBZ level (mg/L) [a]	Group	CBZ	CBZ+PHT	CBZ+PB	CBZ+VPA
	CBZ				
	CBZ+PHT	0.000*			
	CBZ+PB	0.203	0.014*		
	CBZ+VPA	0.448	0.000*	0.348	
	Median	8.85	4.90	7.40	8.50
CBZ level/dose (mcg/L/mg) [a]	Group	CBZ	CBZ+PHT	CBZ+PB	CBZ+VP
	CBZ				
	CBZ+PHT	0.000*			
	CBZ+PB	0.004*	0.123		
	CBZ+VPA	0.017*	0.017*	0.331	
	Median	10.88	6.13	6.81	8.88
CBZ Clearance [a]	Group	CBZ	CBZ+PHT	CBZ+PB	CBZ+VPA
	CBZ				
	CBZ+PHT	0.000*			
	CBZ+PB	0.004*	0.029*		
	CBZ+VPA	0.011*	0.005*	0.527	
(L/hr)	Median	2.68	5.22	4.28	3.29
(L/day)	Median	64.38	125.37	102.76	78.87
CBZ Clearance [a]	Group	CBZ	CBZ+PHT	CBZ+PB	CBZ+VP
	CBZ				
	CBZ+PHT	0.000*			
	CBZ+PB	0.013*	0.061		
	CBZ+VPA	0.118	0.003*	0.275	
(L/kg/hr)	Median	0.0455	0.0973	0.0619	0.0558
(L/kg/day)	Median	1.09	2.34	1.49	1.34

* Statistical significant differences, [a] Mann-Whitney U test.

Table 5. Parameters of the other classical AEDs which used in combination with CBZ.

Parameters	Minimum	Maximum	Mean ± SD or Median
CBZ+PHT (N=15)			
PHT dose (mg/day)	200.00	400.00	298.33 ± 69.09
PHT dose/BW (mg/kg/day)	3.33	6.67	5.01 ± 1.07
PHT level (mg/L)	4.50	32.20	15.32 ± 8.61
CBZ+PB (N=14)			
PB dose (mg/day)	30	150	90
PB dose/BW (mg/kg/day)	0.54	2.68	1.45 ± 0.68
PB level (mg/L)	7.00	32.80	16.38 ± 7.62
CBZ+VPA (N=15)			
VPA dose (mg/day)	500	1,750	1,000
VPA dose/BW (mg/kg/day)	8.85	39.26	19.28 ± 7.95
VPA level (mg/L)	12.70	95.20	62.17 ± 21.60

Kg: kilogram, BW: body weight, mg: milligram, L: litre.

Therapeutic outcome

Therapeutic outcomes were organized from the evaluations of physicians that they put in the medical records. Among the 30 patients of CBZ monotherapy group, 3 patients used CBZ for neuropathic pain while 27 patients used for epilepsy. Within these 27 epileptic patients, 4 patients (15%) had uncontrolled seizure even though their CBZ levels were within the therapeutic range. A second drug had been added to 3 patients, namely: topiramate to 2 patients, and the remainder received VPA. Their seizures improved later. Because of the precipitating factor (fever); one patient still received the same dosage of CBZ. None of the patients in CBZ monotherapy group showed any sign of noticeable adverse effect. (Table 6)

Among the 15 patients of CBZ+PHT combination therapy group, 4 patients (27%) still had seizure; the dosages of CBZ were increased in 2 patients and the dosages of PHT were increased in one patient; their seizures improved later. One patient still received the same dosages of CBZ+PHT, since the seizure was due to precipitating factor (sleep late). There were 5 patients who had their PHT levels above the therapeutic range; 2 of them had adverse effects: nystagmus and ataxia, and their PHT dosages were decreased. (Table 6)

Among the 14 patients of CBZ+PB combination therapy group, 2 patients (14%) still had seizure. The dosage of CBZ was increased in one patient, while the other received the same dosages of CBZ+PB since her seizure was due to precipitating factor (perimenstruation period). One patient noticed mild dizziness. (Table 6)

Among the 15 patients of CBZ+VPA combination therapy group, 7 patients (47%) still had seizure. The dosage of VPA was increased in one patient and the third drug (topiramate or lamotrigine)

Table 6. Therapeutic outcome of patients.

Therapeutic levels	Efficacy				Adverse effect
	Controlled seizure		Uncontrolled seizure		
CBZ monotherapy (N = 27)					
Subtherapeutic range (CBZ level < 4mg/L)	1		-		-
Therapeutic range (CBZ level 4-12 mg/L)	22		4		-
Above therapeutic range (CBZ level > 12 mg/L)	-		-		-
CBZ+PHT (N = 15)					
	CBZ	PHT	CBZ	PHT	
Subtherapeutic range (CBZ level < 4mg/L and/or PHT <10 mg/L)	1	3	2	3	-
Therapeutic range (CBZ level 4-12 mg/L and PHT 10-20 mg/L)	3	3	1	1	-
Above therapeutic range (CBZ level > 12 mg/L and/or PHT > 20 mg/L)	-	5	-	-	2
CBZ+PB (N = 14)	CBZ	PB	CBZ	PB	
Subtherapeutic range (CBZ level < 4mg/L and/or PB <10 mg/L)	1	3	-	-	-
Therapeutic range (CBZ level 4-12 mg/L and PB10-40 mg/L)	8	8	2	2	1
Above therapeutic range (CBZ level > 12 mg/L and/or PB > 40 mg/L)	-	-	-	-	-
CBZ+VPA (N = 15)					
	CBZ	VPA	CBZ	VPA	
Subtherapeutic range (CBZ level < 4mg/L and/or VPA <50 mg/L)	1	3	-	1	1
Therapeutic range (CBZ level 4-12 mg/L and VPA 50-100 mg/L)	5	5	6	6	-
Above therapeutic range (CBZ level > 12 mg/L and/or VPA > 100 mg/L)	-	-	-	-	-

were added in 2 patients; their seizures improved later; the other 4 patients still received the same dosages of CBZ+VPA since their seizures were due to precipitating factors (sleep late, stress, perimenstruation period). One patient had mild tremor. (Table 6)

Discussion

The mean daily dose of CBZ calculated from the total patients included in this study was 15.20 ± 6.80 mg/kg/day which was within the recommended dose range of 15 – 25 mg/kg/day for seizure control.[9] Even though the daily dose of CBZ used in several patients was lower than that of the recommendation, especially in patients who used CBZ as monotherapy, but most of the patient's CBZ levels were within the therapeutic range. The mean daily dose of PHT from the patients who used CBZ in combination with PHT was 5.01 ± 1.07 mg/kg/day which was within the recommended dose range of 4 – 7 mg/kg/day.[17] The mean daily dose of PB from the patients who used CBZ in combination with PB was 1.45 ± 0.68 mg/kg/day which was within the recommended dose range of 1.1 – 2.0 mg/kg/day. [18] The mean daily dose of VPA from the patients who used CBZ in combination with VPA was 19.28 ± 7.95 mg/kg/day, while the recommended dose range of VPA in the absence of enzyme inducer drug is 7 – 18 mg/kg/day. [19] This indicated that when VPA was used concurrently with CBZ which is an enzyme inducer, the VPA dose was increased. The median level - to - dose ratio of CBZ in patients who used CBZ as monotherapy was

significantly higher than those obtained after combination therapy with PHT, PB or VPA, even though the median daily dose of CBZ was not significantly different. This indicated that when CBZ was used with PHT, PB or VPA the dose of CBZ was not changed, even though the level of CBZ was decreased, especially when used CBZ with PHT which is the strongest inducer.

The CBZ clearance in patients who used CBZ in combination with PB was 40% increased, which was consistent with some previous studies who reported the increment of CBZ clearance to be within the range of 16 - 44% when concurrently used with PB. [20-23] The CBZ clearance in patients who used CBZ in combination with PHT was 115% increased, while previous studies reported the increment to be 42 - 45 %.[20, 21] A previous study reported CBZ clearance in patients who used CBZ as polytherapy (in combination therapy with enzyme-inducing AED, for instance PHT, PB) to be 0.1 L/kg/hr. [9] The median of CBZ clearance in patients who used CBZ in combination with PHT in this study was 0.0973 L/kg/hr which was close to those reported in a previous study. However, the median of CBZ clearance in patients who used CBZ in combination with PB was lower than that reported previously (0.0619 L/kg/hr). There are conflicting results on the effect of VPA on CBZ clearance: increase, decrease, or no change. [10, 11, 16, 20, 22, 23] In this study, we found that CBZ when used in combination with VPA, the clearance of CBZ, after accounted for the body weight of the patients, did not significantly change. The mean daily dose of VPA was greater than 18 mg/kg which had been claimed by a previous study that this high dose could increase CBZ clearance by 21%.[20] The average CBZ clearance in patients who received CBZ as monotherapy in this study was lower than those reported by some previous studies (Table 7). This can be attributed to the reasons that CBZ clearance might be decreased with increasing age, while in contrary CBZ clearance might be increased with the size of the dose. [20, 22, 23]

Table 7. Overview of CBZ clearance estimations from CBZ monotherapy reported by different ethnicity.

Population	CBZ clearance (L/kg/hr)	Characteristics		
		Age (yrs)	Weight (kg)	Dose (mg/kg/day)
Chinese [20]	0.0539	23.6	52.3	9.47
American [21]	0.0611	35.0	75.0	12.90
Japanese [23]	0.0554	14.0	39.3	7.36
Singaporean [24]	0.0636	12.5	34.9	16.70
Omani [25]	0.0540	27.8	60.8	9.70
Thai [26]	0.0610	34.5	51.75	17.03
Thai (This study)	0.0455	45.7	59.9	13.36

There were 17 patients (24%) of the 71 epileptic patients who had uncontrolled seizures and 4 patients (6%) had mild adverse effects. Patients with uncontrolled seizure without any precipitating factors, the doses of AEDs were adjusted or the second or third AED were added. For instance, topiramate, lamotrigine which are the newer AEDs with different mechanism of actions; then, the seizures were better controlled. When considered the levels of AEDs, we found that majority of the patients had their drug levels within the therapeutic ranges (51 of the 71 patients, 72%); 15 patients (21%) had their drug levels lower than the therapeutic ranges, while the other 5 patients (7%) had their PHT levels upper than the therapeutic ranges. Recommended therapeutic ranges serve as good guidelines especially when the drug is used as monotherapy; however, when AEDs were used in combination, the therapeutic ranges might be decreased since the seizures could be controlled with lower therapeutic levels of each drug and adverse effect could be found even at subtherapeutic or therapeutic range.

Conclusion

The CBZ clearance in patients who used CBZ as monotherapy was significantly lower than that in patients who used CBZ with PHT or PB, but was not significantly different from patients who used CBZ with VPA. Therapeutic ranges are the good guidelines especially in monotherapy. However, these recommended ranges should be adjusted when the drugs are used in combination. TDM of the classical AEDs has the role to identify an individual's optimum concentrations and thus establish a reference level in patients.

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