Effects of Phenytoin and Valproic Acid on Cognitive Functions of Thai Epileptic Patients: A Pilot Study

Thanakorn Sirisamut MSc*,**,
Yotin Chinvarun MD, PhD***, Mayuree H. Tantisira PhD*,****

** The Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand*
*** Siriraj Poison Control Center, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
**** PMK Comprehensive Epilepsy Program, Division of Neurology, Department of Internal Medicine, Pramongkutklao Hospital, Bangkok, Thailand*
***** The Faculty of Pharmaceutical Sciences, Burapha University, Chonburi, Thailand*

Effects of valproic acid (VPA) and phenytoin (PHT), as monotherapy, on cognitive functions and mood of Thai epileptic patients were investigated. Thai Mental Status Examination (TMSE) and Alcohol Use Disorder Identification Test (AUDIT) were used to screen for eligible subjects. Cognitive performance was assessed by neuropsychological tests including Stroop Color Word Test (SCWT), Wechsler Abbreviated Scale of Intelligence (WASI®) test, Profiles of Mood States (POMS®) and Adverse Event Profiles (AEP). Thirty epileptic patients, 15 taking PHT and 15 taking VPA, and 15 age and sex matched normal comparators were enrolled. In contrast to the effects of VPA, a statistically significant difference in T-score of WASI®-similarities and WASI®-matrix reasoning subtests was observed between PHT, and normal comparator group indicating poorer performance in intellectual functioning especially in executive function of the brain in patients taking PHT. Vigor is the only mood dimension that demonstrated significant difference between epileptic patients and normal comparators. VPA appears to be more appropriate than PHT when executive brain function is mostly concerned, however, further investigation is needed to gain better insight into the effects of AEDs on cognitive domain of the Thai epileptic patients.

Keywords: *Brain executive function, Valproic acid, Phenytoin, Epilepsy, Mood*

J Med Assoc Thai 2014; 97 (Suppl. 2): S77-S87
Full text. e-Journal: *http://www.jmatonline.com*

Epilepsy, defined by recurrent seizure, is the most common neurological disorder with prevalence of approximately 1%. Principally, pharmacotherapy is initiated with minimal effective dose of any AED as monotherapy then, stepwise increases may be required to achieve complete seizure control or else when maximal tolerated dose is reached. Failure of monotherapy would subsequently lead to polytherapy by numerous antiepileptic drugs (AEDs). As most of the patients have to take medication for life-time, adverse events from AEDs are unavoidable.

Among conventional AEDs, phenytoin was approved by USFDA, in 1938, to be used for partial seizure of all types, generalized tonic-clonic seizure (GTCS), juvenile myoclonic epilepsy (JME) and benign febrile convulsion of infancy; however, it is contra-indicated in absence seizure. Sodium valproate, a broad spectrum AED, was approved by USFDA for all types of seizure since 1978[1,2]. Both phenytoin and sodium valproate are widely known and extensively used AEDs in Thailand by the fact that they are available in both oral and parenteral dosage forms and physicians are familiar with their efficacy and adverse events[3-5]. Cognitive impairment is a frequently occurring secondary consequence of epilepsy[6,7]. The exact causes of cognitive impairment in epilepsy have not been fully explored, but three factors clearly are involved: etiology, the seizures, and the central side effects of the antiepileptic drugs treatment. Aldenkamp et al described that specific subgroups of the chronic central CNS-related side effects were the cognitive side effects such as drug-induced impairment of memory, attention or mental speed[8]. Many previous studies revealed cognitive adverse effects on mental or motor speed slowing as well as attention deficit in patients with epilepsy taking carbamazepine, phenytoin, and phenobarbital. Nevertheless, AEDs may impair cognitive function, but they also bring about advantages to cognitive function through their seizure suppression. Mental functioning of epileptic patients has long been concerned. During 1950 and 1965, only

Correspondence to:
Tantisira M, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.
Phone & Fax: 038-102-610
E-mail: tmayuree@chula.ac.th

0.2% of 17,771 published articles on epilepsy included measurement of intellectual function[9]. Nowadays, there are many studies reporting effects of AEDs on cognition and mood. Study design included comparison between monotherapy and polytherapy or between conventional and new AEDs. In general, conventional AEDs have demonstrated a negative effect more often than those of the new AEDs. However, some new AEDs exhibit unique negative adverse events[10-13]. A randomized double-blind crossover study was used to study adverse events (AEs) of phenobarbital, phenytoin and sodium valproate as monotherapy in 75 healthy volunteers for 1 month. It was found that phenobarbital demonstrated more negative effects on cognition than that resulted from sodium valproate that exerted a rather similar profile of AEs as phenytoin. Furthermore, monotherapy of carbamazepine was found to produce similar AEs as did phenytoin in 30 healthy volunteers. A randomized crossover design study had been reported in AEDs of carbamazepine and phenytoin monotherapy in 30 healthy volunteers[14,15]. In addition, deterioration of cognitive function was found to be well correlated with plasma level of AEDs especially in the concentration higher than therapeutic levels[16,17]. Furthermore, a study in seizure-free epileptic patients taking monotherapy of AEDs revealed adverse effects on cognitive function that were reversed after stopping AEDs[18].

Despite various reports of adverse events of AEDs, it is rational to strike a balance between seizure control and the potentially cognitive function adverse events in epilepsy management. Furthermore, it is generally appreciated that intellectual assessment plays an important part in clinical management of epilepsy[9,19,20]. Though there are over million Thai patients with epilepsy who are continuously taking AEDs, AED-related cognitive dysfunction has never been systematically explored. Therefore, it is of interest to investigate cognitive-related adverse events of phenytoin and sodium valproate that are strongly prescribed for Thai epilepsy patients.

Material and Method

An observational prospective method approved by The Institutional Review Board (IRB) of Royal Thai Army Medical Department (Approved No. Q035h/47) were used in the present study.

Enrollment of subjects

Subjects consisted of 30 epileptic patients who regularly visit Neurology Clinic of Pramongkutklao Hospital and 15 normal comparators from Pharmacy Department, Siriraj Hospital. All of them had no known history of psychiatric illness or drug abuse. Medical histories were obtained from medical records and interviews. They were enrolled with the following inclusion criteria: male or female age between 15-55 years old, normal value of clinical chemistry, hematology, and urinalysis as well as being literate person. Scores from the Thai Mental Status Examination (TMSE) were not less than 23 and scores from the Alcohol Use Disorders Identification Test (AUDIT) were not more than 8. Understanding study protocol and agree to participate in the study. In addition, for patients with epilepsy, they were receiving phenytoin (Dilantin Kapseal® or Dilantin infatab®) or valproic acid (Depakine® or Depakine Chrono®) at least 1 month before an enrollment.

Subjects were excluded from the study by the following conditions; color-blindness, history of severe head trauma (both before and after epilepsy onset), history of status epilepticus or thyroid-related diseases, known status of progressive neurological disorders, disability persons, pregnant or nursing mothers.

Neuropsychological tests

The following battery of five neuropsychological tests consisting yielding 17 variables was used to assess cognitive function of the subjects.

Selective attention

Stroop color word test (SCWT) standardized version which appears to pit an automatic process (word reading) against a controlled, conscious process (color naming)[21]. Subjects were requested to read word test cards, Color test card, and Color-word test card, respectively, down the column and across from the left column to the right column within 45 seconds. Only correct items of reading were recorded. The result of testing consisted of word score (W), color score (C), and color-word score (CW). A derived interference score, intended to measure 'pure' performance corrected for all speed, was then calculated (Equation 1-2). The negative value of the interference score indicates poor performance of selective attention.

Predicted CW = (C x W)/(C + W)_Equation 1

Interference score = CW (from testing)-Predicted CW_Equation 2

Cognitive performance

Wechsler Abbreviated Scale of Intelligence

(WASI®; a test consisting of four subtests vocabulary [VC], block design [BD], similarities [SM], and matrix reasoning [MR]) was used. Subjects were ordered to practice following the WASI® instruction under careful inspection of an investigator. The WASI® gives verbal and performance intelligence quotients (VIQ, PIQ)[22].

The WASI® VC subtest is a 42-item task. Test words were orally presented to subjects. The subjects orally defined definition. Raw score from this part was converted to vocabulary t-score.

The WASI® BD subtest is a set of 13 modeled or printed two-dimensional geometric patterns that the subjects were ordered to replicate within a specified time limit. Subjects who finished replication at an earlier time got high scores; raw scores from this part were converted to block design t-scores.

The WASI® SM subtest is a pair of words orally presented to the subjects to explain the similarity between the common objects or concepts of the two words presented. A raw score from this part was converted to similarities t-score.

The WASI® MR is a series of 35 incomplete gridded patterns that the subjects have to complete by pointing or stating the number of the correct response from five possible choices, a raw score from this part was converted to matrix reasoning t-score. Expression of subjects was also observed and recorded.

Mood and adverse event profile

Mood assessment

Profiles of Mood States (POMS®) (65-item, self-administering questionnaire of mood state) and Adverse Event Profile (AEP) (20-item, self-administering questionnaire of adverse event) were used. POMS® is a self-administering questionnaire which gives an information background of a 6 domains of mood status; tension [T], depression [D], anxiety [A], confusion [C], fatigue [F], and vigor [V].

Profile of Mood States (POMS®) is an adjective checklist to access mood. Subjects were ordered to select the choice that best described their mood in the blank of POMS®. After finished, a raw of POMS® score was carried to POMS® standard scoring grid to evaluate each mood dimension. It gives an individual six mood dimensions: Total Mood Disturbance (TMD) was calculated from this equation (Equation 3). The lower the score obtained in tension, depression, anxiety, confusion, fatigue, and TMD, the better the performance[23]. The questionnaires of POMS® was translated into Thai and also approved by Dr. Chulaporn Kongkaew, Language Institute, Chulalongkorn University.

TMD score = (Tension score + Depression score + Anxiety score + Confusion score + Fatigue score) - Vigor score_Equation 3

Assessment of adverse event profile

Originally, adverse event profile (AEP) is self-administering and contains 19 brief items that access the frequency of a different adverse effect using Liker scale[19]. AEP gives information related to drug-induced adverse effects especially from AEDs. For proper evaluation of adverse effects, paresthesia evaluation was added to an AEP format and the modified AEP was then objected to reliability test. For AEP, after finished testing, the number, which subjects chose, will be summed. The lower the score obtained in AEP, the better the performance.

Study protocol

Potential patients with epilepsy were recruited from Neurology Clinic, Pramongkutklao Hospital. Illness and medication history were obtained by an interview and from medical records. They underwent a thorough general physical examination (PE) by physician. TMSE and AUDIT were administered. Blood and urine samples were collected for laboratory investigation, eligible patients were selected according to inclusion and exclusion criteria and they were enrolled into the study after the completion of inform consent (D_0). On day 0, subjects were requested for AEs, PE was performed, blood and urine samples were collected for investigation. Battery of neuropsychological tests was administered to the subjects. The same protocol was applied to a normal comparator group of matched sex and ages. All processes were performed again on day 28 (visit 1) and day 56 (visit 2). Seizure recurrence counting was performed on baseline, day 28 and day 56. Radioimmunoassay (RIA) was used for the determination of plasma level of PHT and VPA.

Statistical analysis

To assure the reliability of test conducting, verifying of reliability of SCWT, WASI®, POMS®, AEP was operated. The test-retest technique was used to verify the reliability of SCWT and WASI® test conducting. The internal consistency technique, Cronbach's alpha, was used to verify the reliability of POMS®, and AEP test conducting.

The primary analysis was direct comparison between PHT-treating group versus normal comparator and VPA-treating group versus normal comparators

group. A secondary analysis was also performed comparing PHT-treating versus VPA-treating group. In consideration of a small sample size (<30) in all treatment groups, significant differences of cognitive function between or among them were made by non-parametric statistical analysis namely Kruskal-Wallis one-way ANOVA test (Kruskal-Wallis H test)[24,25]. The *p*-value ≤0.05 was considered statistical significant.

Results

Subjects

Thirty patients with epilepsy and 15 age and sex were matched with healthy volunteers (normal comparators) and enrolled in the study. Subjects consisted of 27 males and 18 females. The average age of the subjects were 31.13±10.52, 28.13±10.64, and 31.60±8.17 years for normal volunteers, epileptic patients receiving sodium valproate (VPA group), and epileptic patients taking phenytoin (PHT group), respectively. Fifteen patients were taking valproic acid in the dose range of 250-2,000 mg/day (average 1,020±501.36 mg/day); 15 patients were taking phenytoin in the dose range of 250-300 mg/day (average 296.67±44.19 mg/day). Almost all (90%) of epileptic patients were seizure-free during enrollment; moreover the average blood levels of PHT and VPA were within therapeutic range (13.44±9.31 mcg/mL for PHT and 76.39±33.67 mcg/mL for VPA). There was no significance in TMSE and AUDIT scores among normal comparators and epileptic patients taking either valproic acid or phenytoin. Dissimilarity among the subjects was noted on the level of education in which the majority of normal comparators group appeared to have higher education than both groups of epileptic patients (Table 1).

Reliability of testing

To assure the consistency and validity of neuropsychological testing, statistical analysis of results was performed. The data of neuropsychological testing among three groups in each visit was pooled and analyzed. The data obtained from analysis exhibited high reliability in every neuropsychological testing (Table 2).

Neuropsychological and mood states

Stroop color word test: No statistical significance in word score, color score or color-word score was observed among the three groups but for interference score, there was statistically significant difference between VPA group and comparators.

WASI®: According to four T scores of

Table 1. Demographic data of 45 subjects

Description	Normal comparators (n = 15)	Valproic acid (n = 15)	Phenytoin (n = 15)
Sex: male/female	9/6 (60%)	10/5 (66.67%)	8/7 (53.33%)
Age[1] (year) mean ± SD	33.13±10.52	28.13±10.64	31.60±8.17
Education			
Bachelor degree	4	10	11
Bachelor degree or higher	11	5	4
Epilepsy type			
Generalized-related	-	3	5
Localized-related	-	6	8
Unspecified or N/A	-	6	2
TMSE score (mean ± SD)	28.80±1.26	29.07±1.03	28.13±1.96
AUDIT score (mean ± SD)	0.47±1.81	0.47±1.81	0±0
Serum levels of sodium valproate[1] and phenytoin[2] (mean ± SD)			
Baseline	-	75.99±36.37	13.25±9.03
Visit 1	-	75.50±33.06	14.11±10.10
Visit 2	-	77.68±33.85	12.95±9.37
Average	-	76.39±33.67	13.44±9.31

TMSE = Thai mental status examination; AUDIT = alcohol use disorder identification test

[1] Therapeutic range 50-100 mcg/mL

[2] Therapeutic range 10-20 mcg/mL

Table 2. Results of reliability test of neuropsychological tests

Test	Baseline-visit 1	Visit 1-visit 2	Baseline-visit 2
Stroop-word test#	0.920	0.935	0.936
Stroop-color test#	0.884	0.867	0.890
Stroop-color word test#	0.770	0.716	0.835
WASI®-VC subtest#	0.988	0.985	0.994
WASI®-BD subtest#	0.865	0.935	0.861
WASI®-SM subtest#	0.892	0.946	0.876
WASI®-MR subtest#	0.769	0.833	0.757
POMS® test*	0.9465	0.9499	0.9505
AEP test*	0.8712	0.8304	0.8580

WASI = wechsler abbreviated scale of intelligence; VC = vocabulary; BD = block design; SM = similarities; MR = matrix reasoning; POMS = profiles of mood state; AEP = adverse events profile

verified by test-retest reliability technique, results shown as Pearson's product moment

* verified by Internal consistency technique, results shown as standardized item alpha

(Data obtained from baseline, visit 1 and visit 2 were pooled data of normal comparator, valproic acid and phenytoingroups in each visit)

subtests of WASI®, there were only two subtests (SM and MR) exhibited the statistically significant in T scores among three groups. In SM subtest, VPA and PHT group exhibited statistically significant difference in T scores compared with normal comparators. For MR subtest, PHT group exhibited statistically significant difference in T scores compared with VPA group and comparators.

IQ scores: From four T scores of WASI® subtest, VIQ, PIQ, FSIQ-4 and FSIQ-2 score were obtained. VIQ score was a summation of T score of VC and SM. Whereas, PIQ score was a summation of T score of BD and MR. In addition, FSIQ-4 score was obtained by a summation of VIQ and PIQ score but, FSIQ-2 score was obtained by a summation of T score of VC and MR. In the present study, there was statistically significant difference in PIQ, FSIQ-4 and FSIQ-2 scores between PHT group and normal comparator (p = 0.001, p = 0.004, and p = 0.012, respectively). Moreover, the PIQ score of PHT group was even statistically lower than that of VPA group (p<0.05). Unlike PHT group, VPA group did not exhibit any significant differences to normal comparators with regard to VIQ, PIQ, FSIQ-4, and FSIQ-2.

POMS® score: Among the 3 groups, there were no significant differences in any of the dimensions of mood tested except vigor in which the scores obtained by VPA and PHT group were statistically significant lower than of normal comparators (p<0.05). However, the TMD score, which is the net effect of all mood dimensions, was rather similar among the three groups tested (Table 3).

Adverse events evaluation

Modified form of adverse event profile (AEP) was used as a tool to evaluate adverse events of subjects during study. The higher the AEP score, the poorer were the adverse events. There was no statistical significance in AEP scores among the three groups. However, there were statistically significant differences in four sub-items among the three groups in sub-item analysis (Table 4).

Discussion

Although there are several new generations of antiepileptic drugs (AEDs) available, conventional AEDs are mostly prescribed as a first-line agent for Thai epileptic patients. In consideration of the lack of data of cognitive dysfunction, which is one of major concern, especially in long-term seizure control, the present study was designed to assess cognitive and mood status of Thai epileptic patients receiving monotherapy of PHT or VPA, using recommended neuropsychological tests namely Stroop Color Word Test (SCWT), WASI® test and POMS® test.

Age and gender-matched normal comparators were recruited according to the inclusion and exclusion criteria for the epileptic patients except for the absence of epilepsy and AEDs. General characteristics of the subjects in normal comparators, PHT and VPA groups are rather similar with regard to average age, TMSE, and AUDIT scores. TMSE is a screening test, to identify

Table 3. Neuropsychological and mood status of normal comparators and patients taking valproate or phenytoin (n = 15 in each group)

Test	Normal comparator (n = 15)	Valproic acid (n = 15)	Phenytoin (n = 15)
Word score of SCWT	94.73±9.46	92.87±9.69	90.04±15.51
Color score of SCWT	72.91±13.02	70.42±11.94	66.76±14.71
Color-word score of SCWT	39.16±8.67	42.67±8.38	38.40±13.9.21
Interference score of SCWT	-1.64±6.04	2.86±4.64	0.36±5.60
T score of VC	51.22±12.86	47.71±16.21	48.33±15.98
T score of BD	49.60±10.00	50.87±9.18	46.71±10.07
T score of SM	48.91±9.59	42.20±11.74	42.13±10.59
T score of MR	49.51±9.93	44.33±12.04	37.91±12.63
VIQ	100.18±17.27	92.67±19.64	93.71±18.82
PIQ	99.18±11.43	95.69±12.92	88.31±14.81
FSIQ-4	99.62±13.38	94.60±16.20	89.93±16.67
FSIQ-2	101.29±15.91	94.29±18.24	89.98±19.11
Tension score	14.76±5.60	13.40±0.78	13.67±5.72
Depression score	16.87±13.77	13.42±8.16	19.38±12.12
Anxiety score	14.78±10.39	14.13±10.41	15.11±8.45
Confusion score	12.36±6.15	10.87±3.76	12.53±5.58
Fatigue score	9.24±7.02	9.38±6.36	11.40±6.46
Vigor score	20.51±4.46	17.49±4.29	15.62±4.69
TMD score	47.49±42.68	42.78±28.49	56.36±32.25

SCWT = stroop color word test; VC = vocabulary; BD = block design; SM = similarities; MR = matrix reasoning; VIQ = verbal IQ; PIQ = performance IQ; FSIQ = full scale IQ; TMD = total mood disturbance

active dementia status, presently practiced in Thailand[26]. Therefore, the mental status of each group is rather similar and so is the status of alcohol consumption as indicated by approximately the same score of AUDIT.

Attention status of epileptic patients was evaluated by Stroop Word Color Test which is generally known as the gold standard of research for attention[27]. It has been widely used in many randomized control trials to assess selective attention status and inhibition capacity of the brain. Inhibition capability is an executive function of the frontal lobe. Therefore, the score from this test reflect frontal lobe function. Based on the results that there were no significant differences in word tests, color tests and color-word tests, was noted among the three groups studied; attention-related performances of the three groups should be approximately of the same magnitude. Meador and colleagues who conducted study comparing cognitive effects of phenobarbital (PB), PHT and VPA in normal volunteers, have previously reported similar SCWT scores of PHT and VPA. PB produced the worst performance, whereas PHT and VPA were not different from each other[15]. WASI® is a neuropsychological tool, which was developed in an effort to establish a reliable short form of measuring intellectual functioning across lifespan[28]. It has been used to access cognition in traumatic brain injury (TBI), as well as in heart failure patients[29,30]. In the present study, no difference in VIQ (VC+SM) scores was noted among the three groups tested. As VIQ measures individual's expressive vocabulary, verbal knowledge as well as crystallized and general intelligence[22], it is apparent that disturbance of PHT and VPA on these parameters is minimal. VIQ is composed of VC and SM. VC was the component, which was rather similar across the three groups tested whereas significant difference was detected on SM. Therefore, it is implied that difference in SM subtest, which measures abilities to see similarities between objects and situations, could be offset by ability to express vocabulary, and fund information, which is measured by VC. Decline of VIQ in pre-surgery pharma-co-resistant patients with epilepsy compared with normal population has been reported by Roswell et al[31]. Though pharma-co-resistant patients are generally known to be almost always on polytherapy[32,33], unfortunately, no information on number of medications used by those

Table 4. Sub-items ofadverse event profiles of normal comparators and patients taking valproate or phenytoin

Average score of sub-items (mean ± SD)	Normal comparators (n = 15)	Valproic acid (n = 15)	Phenytoin (n = 15)	*p*-value
Unsteadiness	1.78±1.06	1.87±0.97	1.73±0.99	0.720
Tiredness	2.33±0.98	2.40±1.07	2.27±1.12	0.824
Restlessness	2.47±1.14	2.09±0.92	1.64±0.96	<0.001
Feeling of aggression	1.78±0.97	1.67±0.90	1.89±0.96	0.464
Nervousness and/or agitation	1.58±0.78	1.29±0.55	1.47±0.66	0.174
Headache	1.91±0.97	1.76±0.93	1.80±0.89	0.719
Hair loss	1.56±0.92	1.29±0.59	1.27±0.65	0.044
Skin problems e.g. rash, acne	1.91±1.20	1.36±0.71	1.44±0.81	0.044
Double or blurred vision	1.62±0.94	1.33±0.77	1.22±0.42	0.053
Upset stomach	1.62±0.68	1.78±0.88	1.44±0.66	0.147
Difficulty in concentrating	2.11±0.80	2.49±1.14	2.27±1.18	0.331
Trouble with mouth or gum	1.84±1.04	1.44±0.72	1.44±0.66	0.096
Shaky hands	1.31±0.63	2.47±1.29	1.82±1.11	<0.001
Weight gain	1.58±0.92	1.27±0.62	1.18±0.49	0.028
Dizziness	1.56±0.81	1.56±0.81	1.33±0.56	0.416
Sleepiness	2.16±1.00	2.58±1.14	2.38±1.07	0.203
Depression	1.53±0.73	1.71±0.97	1.69±0.87	0.737
Memory problems	2.09±0.79	2.40±1.03	2.69±1.04	0.018
Disturbed sleep	1.84±1.11	1.96±1.17	1.84±0.95	0.899
Paresthesia	1.18±0.39	1.33±0.74	1.29±0.69	0.791

patients was reported thereby. Hence, it is not justified to compare the results.

PIQ (BD+MR) measures individual's ability to manipulate mentally abstract symbols, perceptual organization, general intelligence, and to perceive the relationship among them while, FSIQ-4 (VC+BD +SM+MR) represents complete dimension of VIQ and PIQ. In addition, FSIQ-2 (VC+MR) represents only some dimension of VIQ and PIQ[22]. In the present study, we found that PHT group exhibited poorer performances in PIQ, FSIQ-4 and FSIQ-2 than normal comparators group. Furthermore, the PIQ score of PHT group was even statistically lower than that of VPA group. Unlike PHT group, VPA group did not demonstrate any significant differences to normal comparators with regard to PIQ, FSIQ-4, and FSIQ-2. Apparently, intellectual function seemed to be adversely affected by the administration of PHT than VPA, which exhibited intellectual scores comparable to those of normal comparators. In the present study, statistically significant differences between normal comparators and PHT was found on Matrix Reasoning (MR) task which is the component shared by PIQ, FSIQ-4, and FSIQ-2 thus, performance on MR seemed to be the domain that was obviously affected by PHT. MR subtest of WASI® has been accepted as the test that can detect a deficit in working memory dual task processing, which is a part of executive function of the brain[34]. Therefore, it is suggestive that the intellectual function adversely affected by PHT involves executive function of the brain. Lower performance in the cognitive domain of speed motor, which could involve a higher cortical information processing system has been reported in patients with epilepsy receiving PHT[8,35]. In animal models, there were much evidence to demonstrate disruption in spatial working memory of the animals in a water-maze paradigm and hippocampal function was suggested to be the one that was affected or cause disturbance on learning and memory of the animals in the elevated plus maze model. Moreover, in the same study PHT exhibited induction of oxidative stress as evaluated by brain malondialdehyde. PHT-induced cognitive dysfunction may be the summation of various disruptions in the brain[36,37]. In human, there was a case report about adverse cognitive effects of PHT in severe brain injury and cognitive deficits (e.g. time and place disorientation, very poor semantic episodic and anterograde memory) were improved dramatically following withdrawal of PHT[38,39]. Mechanisms of action of AEDs may be a contributing factor in AEDs-induced cognitive dysfunction. AEDs, which involve in GABA enhance-

ment, are known to cause cognitive dysfunction e.g. short-term benzodiazepines taking in healthy volunteers which produced sedation, psychomotor slowing, anterograde amnesia and difficulties in learning new materials; however, various confounding factors can influence this phenomenon[7].

Mood disorders especially as a co-morbid finding in epileptic patients have become increasingly recognized as a serious health concern[40-42]. In addition to their effects on cognitive function, most AEDs are considered to have a mood-modulating effect and some are currently used in mood affective disorder. Theoretically, VPA is considered to have negligible negative effects on mood in epileptic patients. Conversely, PHT may provoke behavioral problems other than depression, such as schizophrenia-like psychosis at high serum levels and in the context of a toxic syndrome[43,44]. Using POMS®, which is one of most frequently used neuropsychological test to assess mood, Meador et al demonstrated mood dimension that differed between normal comparators with and without AEDs[14,15]. Anger, vigor, fatigue, and confusion were the dimensions that differed whereas tension and depression are rather similar. However, the present study found that vigor score was the only mood dimension that differed among the three groups. Normal comparators had vigor score better than both groups of epileptic patients, whereas, vigor score of PHT and VPA groups were not statistically different from each other.

According to previous work of Elixhauser et al (1999), attention and language have been found to be affected by mood[45]. In the present study, VPA, which demonstrated significant difference in vigor scores from normal volunteers, exhibited no differences in VIQ, PIQ, FSIQ-4, and FSIQ-2 of WASI® in comparison to normal volunteers. It is, thus, likely that operational mood, when the study was conducted, did not strongly affect the results observed in WASI®. However, numerous limitations on methodological issues of evaluating mood effects of AEDs do exist and that may account for controversial or inconclusive outcomes of some studies as well as disparity of the results between different studies[46]. Though the total score of adverse events, which were assessed by AEP, showed no significant difference among the three groups, the present study did demonstrate the adverse effects of PHT on cognitive function when assessed by WASI®. Analysis of sub-items of AEP indicated that PHT demonstrated significant higher scores in restlessness and memory problems than normal comparators, whereas VPA significantly exhibited tremor (shaky hands). Surprisingly, normal comparators had more problems with weight gain than both groups of epileptic patients.

Therefore, more attention is required in prescribing AEDs if cognitive function is the major concern in treating epilepsy. Based on the results of the present study, VPA is the drug to choose rather than PHT when cognitive function is an important concern. This finding is in line with previous reports[47,48]. On the other hand, it should be noted that the average dose of PHT used by the patients in the present study was rather high (296.67$\pm$44.19 mg/day), whereas the average dose of VPA was rather low (1,020$\pm$501.36 mg/day) and might affect the performances observed[49]. Though cognitive adverse effects of AEDs is a great concern for patients taking AEDs for a long period of time, AEDs, which negatively affected cognitive performances such as PB, was commonly used in low- and middle-income countries depending on risk to benefit ratio of their respective available AEDs[50,51].

Taken all together, the present study demonstrated that while no significant effect of PHT and VPA was observed on attention and verbal knowledge, cognitive deficits are more common in Thai epileptic patients receiving PHT than in the general population. Comparatively, PHT was found to have adversely affected intelligence especially those dealing with executive function than did VPA. Cognitive deficits are multi-factorial in etiology, ranging from biologic factors, such as type of epilepsy, age of onset, and therapeutic interventions that may adversely affect epileptic patients[7,35]. Although epilepsy per se may cause cognitive problems, treating epilepsy is necessary and by itself may resolve or alleviate the cognitive and behavioral deficits of the disease. Therefore, epileptic treatment should be tailored to the individual patient with potential risks in mind. The superior method of assessment of AEDs-induced cognitive dysfunction and mood disorder is before and after study design. However, there are many limitations such as timing, costs, newly diagnosed epileptic patients, and an appropriate matched normal volunteer availability. Therefore, the method which mentioned above cannot be conducted. As a first study of its kind, the results of the present study call for further investigation with before and after prospective study design with a well matched population to gain further insight into cognitive ability and mood status of Thai epileptic patients taking certain AEDs.

Conclusion

The present study is the first report on the effects of VPA and PHT on cognitive performances and mood status of Thai epileptic patients. In comparison to normal comparator, VPA or PHT had no effect on selective attention or attention-related performances of epileptic patients. However, while VPA showed rather similar profile of cognitive performances to those of normal comparator group, significantly poorer intellectual functioning especially brain executive function was demonstrated in PHT group. Vigor is the only mood dimension that demonstrated significant difference between epileptic patients and normal comparator. VPA appears to be more appropriate than PHT when executive brain function is mostly concerned; however, further investigation is needed to gain better insight into the effects of AEDs on cognitive domain of the Thai epileptic patients.

Acknowledgement

The authors are sincerely thankful to the Division of Neurology, Department of Internal Medicine, and Department of Clinical Pathology, Pramongkutklao Hospital for the sympathy and sincere help during our research. The authors deeply express their sincere gratitude to Assistant Professor Supakit Wongwiwatthananukit, PhD and Capt. Associate Professor Jayanton Patumanond, PhD for their valuable advice in statistical analyses methodology, Professor Kimford J. Meador, PhD for his kind offering of neuropsychological tests. Last but not least, we also deeply expressed our sincere gratitude to the Graduate School, Chulalongkorn University for research grants.

Potential conflicts of interest

None.

References

1. Das N, Dhanawat M, Shrivastava SK. An overview on antiepileptic drugs. Drug Discov Ther 2012; 6: 178-93.
2. Leppik IE. Monotherapy and polypharmacy. Neurology 2000; 55 (11 Suppl 3): S25-9.
3. Pratyasanti J, Srisomboon J, Rattanajinda S. Study of antiepileptic drugs utilization in out-patients of Prasat Neurological Institute [Senior Project for Bachelor of Pharmacy]. Bangkok: Chulalongkorn University; 1997
4. Shoolerd S, Wongsasuluk P, Rungapiromnan W. Phenytoin utilization in inpatients at Police General Hospital [Senior Project for Bachelor of Pharmacy]. Bangkok: Chulalongkorn University; 2004.
5. Fun LW, editor. MIMS Thailand. 100th ed. Bangkok: CMP Medica; 2005.
6. Cornaggia CM, Beghi M, Provenzi M, Beghi E. Correlation between cognition and behavior in epilepsy. Epilepsia 2006; 47 (Suppl 2):34-9.
7. Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. CNS Drugs 2009; 23: 121-37.
8. Aldenkamp AP, Alpherts WC, Diepman L, van 't Slot B, Overweg J, Vermeulen J. Cognitive side-effects of phenytoin compared with carbamazepine in patients with localization-related epilepsy. Epilepsy Res 1994; 19: 37-43.
9. Ossetin J. Methods and problems in the assessment of cognitive function in epileptic patients. In: Trimble MR, Reynolds EH, editors. Epilepsy, behaviour, and cognitive function. Chichester: Jonh Wiley & Sons; 1988: 9-26.
10. Martin R, Kuzniecky R, Ho S, Hetherington H, Pan J, Sinclair K, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology 1999; 52: 321-7.
11. Mula M, Trimble MR, Thompson P, Sander JW. Topiramate and word-finding difficulties in patients with epilepsy. Neurology 2003; 60: 1104-7.
12. Bootsma HP, Aldenkamp AP, Diepman L, Hulsman J, Lambrechts D, Leenen L, et al. The Effect of Antiepileptic Drugs on Cognition: Patient Perceived Cognitive Problems of Topiramate versus Levetiracetam in Clinical Practice. Epilepsia 2006; 47 (Suppl 2): 24-7.
13. Gomer B, Wagner K, Frings L, Saar J, Carius A, Harle M, et al. The influence of antiepileptic drugs on cognition: a comparison of levetiracetam with topiramate. Epilepsy Behav 2007; 10: 486-94.
14. Meador KJ, Loring DW, Allen ME, Zamrini EY, Moore EE, Abney OL, et al. Comparative cognitive effects of carbamazepine and phenytoin in healthy adults. Neurology 1991; 41: 1537-40.
15. Meador KJ, Loring DW, Moore EE, Thompson WO, Nichols ME, Oberzan RE, et al. Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. Neurology 1995; 45: 1494-9.
16. Thompson PJ, Trimble MR. Anticonvulsant serum levels: relationship to impairments of cognitive functioning. J Neurol Neurosurg Psychiatry 1983; 46: 227-33.
17. O'Dougherty M, Wright FS, Cox S, Walson P.

Carbamazepine plasma concentration. Relationship to cognitive impairment. Arch Neurol 1987; 44: 863-7.
18. Hessen E, Lossius MI, Reinvang I, Gjerstad L. Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. Epilepsia 2006; 47: 2038-45.
19. Vermeulen J, Aldenkamp AP. Cognitive side-effects of chronic antiepileptic drug treatment: a review of 25 years of research. Epilepsy Res 1995; 22: 65-95.
20. Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav 2004; 5 (Suppl 1):S60-5.
21. The Stroop color and word test [package insert]. Illinois: Stoelting; 2003.
22. Wechsler abbreviated scale of intelligence [package insert]. San Antonio, TX: The Psychological Corporation; 1999.
23. McNair DM, Lorr M, Heuchert JWP, Droppleman LF. POMS: Profile of mood states. Ontario: Multi-Health Systems (MHS); 2003.
24. Train the Brain Forum Committee. Thai mental status examination. Siriraj Hosp Gaz 1993; 45: 359-74.
25. Block J. The Stroop effect: its relation to personality. Pers Indiv Differ 2005; 38: 735-46.
26. Axelrod BN. Validity of the Wechsler abbreviated scale of intelligence and other very short forms of estimating intellectual functioning. Assessment 2002; 9: 17-23.
27. Ryan JJ, Carruthers CA, Miller LJ, Souheaver GT, Gontkovsky ST, Zehr MD. The WASI matrix reasoning subtest: performance in traumatic brain injury, stroke, and dementia. Int J Neurosci 2005; 115: 129-36.
28. Wolfe R, Worrall-Carter L, Foister K, Keks N, Howe V. Assessment of cognitive function in heart failure patients. Eur J Cardiovasc Nurs 2006; 5: 158-64.
29. Andersson-Roswall L, Engman E, Samuelsson H, Sjoberg-Larsson C, Malmgren K. Verbal memory decline and adverse effects on cognition in adult patients with pharmacoresistant partial epilepsy: a longitudinal controlled study of 36 patients. Epilepsy Behav 2004; 5: 677-86.
30. Brodie MJ, Kwan P. Staged approach to epilepsy management. Neurology 2002; 58 (8 Suppl 5): S2-8.
31. McCorry D, Chadwick D, Marson A. Current drug treatment of epilepsy in adults. Lancet Neurol 2004; 3: 729-35.
32. McKinnon L. Working memory dual task processing in children with traumatic brain injury [Thesis]. Texas: *University* of *Texas* at *Dallas*; 2001.
33. Trimble MR. Anticonvulsant drugs and cognitive function: a review of the literature. Epilepsia 1987; 28 (Suppl 3):S37-45.
34. Samuelson DL, Arnold LL, Mowery TM, Mesnard NA, Garraghty PE. The effects of phenytoin on the performance of rats in a delayed match-to-place task. Integr Physiol Behav Sci 2005; 40: 17-27.
35. Reeta KH, Mehla J, Gupta YK. Curcumin is protective against phenytoin-induced cognitive impairment and oxidative stress in rats. Brain Res 2009; 1301:52-60.
36. Pandey AK, Gupta S. Psychiatric symptomatology, scholastics, and phenytoin. Indian J Psychiatry 2012; 54: 286-7.
37. Pinder C, Young C. Adverse cognitive effects of phenytoin in severe brain injury: a case report. Brain Inj 2011; 25: 634-7.
38. Krishnamoorthy ES. Treatment of depression in patients with epilepsy: problems, pitfalls, and some solutions. Epilepsy Behav 2003; 4 (Suppl 3):S46-54.
39. Barry JJ. The recognition and management of mood disorders as a comorbidity of epilepsy. Epilepsia 2003; 44 (Suppl 4):30-40.
40. Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health, and function in epilepsy. Epilepsy Behav 2003; 4 (Suppl 4):S26-30.
41. Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. Drug Saf 2007; 30: 555-67.
42. Reijs R, Aldenkamp AP, de Krom M. Mood effects of antiepileptic drugs. Epilepsy Behav 2004; 5 (Suppl 1):S66-76.
43. Elixhauser A, Leidy NK, Meador K, Means E, Willian MK. The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. Epilepsy Res 1999; 37: 13-24.
44. Piedad J, Rickards H, Besag FM, Cavanna AE. Beneficial and adverse psychotropic effects of antiepileptic drugs in patients with epilepsy: a summary of prevalence, underlying mechanisms and data limitations. CNS Drugs 2012; 26: 319-35.
45. Gillham RA, Williams N, Wiedmann KD, Butler E, Larkin JG, Brodie MJ. Cognitive function in adult

epileptic patients established on anticonvulsant monotherapy. Epilepsy Res 1990; 7: 219-25.
46. Guerrini R. Valproate as a mainstay of therapy for pediatric epilepsy. Paediatr Drugs 2006; 8: 113-29.
47. Klasco RK, DRUGDEX® System. Vol. 122 Expire [12/2004]. Greenwood Village, Colorado: *Thomson* Reuters *Micromedex*; 2004.
48. Zhang LL, Zeng LN, Li YP. Side effects of phenobarbital in epilepsy: a systematic review. Epileptic Disord 2011; 13: 349-65.
49. Brodie MJ, Kwan P. Current position of phenobarbital in epilepsy and its future. Epilepsia 2012; 53 (Suppl 8):40-6.

การศึกษาเบื้องต้นถึงผลของฟีนัยโตอินและวาลโพรอิคแอซิดต่อเชาวน์ปัญญาของผู้ป่วยโรคลมชักชาวไทย

ธนกร ศิริสมุทร, โยธิน ชินวลัญช์, มยุรี ตันติสิระ

จากการศึกษาผลของฟีนัยโตอิน (PHT) และโซเดียมวาลโพรเอต (VPA) ต่อเชาวน์ปัญญาและอารมณ์ ของผู้ป่วยโรคลมชักชาวไทยที่ได้รับยาดังกล่าวเพียงชนิดเดียวโดยใช้ Thai Mental Status Examination (TMSE) และ Alcohol Use Disorder Identification Test (AUDIT) ในการคัดกรองเบื้องต้นใช้แบบทดสอบ Stroop Color Word Test (SCWT), Wechsler Abbreviated Scale of Intelligence (WASI®) test ในการประเมินเชาวน์ปัญญาและใช้แบบทดสอบ Profiles of Mood State (POMS®) และ Adverse Event Profile (AEP) ในการประเมินอารมณ์และอาการไม่พึงประสงค์ของกลุ่มตัวอย่าง ซึ่งเป็นกลุ่มผู้ป่วยโรคลมชักจำนวน 30 คน ที่ได้รับยา PHT และ VPA อย่างละ 15 คน และกลุ่มอาสาสมัครสุขภาพดี 15 คนที่มีเพศและวัยใกล้เคียงกับกลุ่มผู้ป่วยโดยใช้เกณฑ์การคัดเลือกเดียวกัน พบว่ามีความแตกต่างอย่างมีนัยสำคัญทางสถิติในค่า T score ของ WASI®-similarities กับค่า T score ของ WASI®-matrix reasoning subtest ระหว่างกลุ่มที่ได้รับ PHT กับอาสาสมัครสุขภาพดี ซึ่งเป็นการบ่งชี้ถึงการมีเชาวน์ปัญญาที่ต่ำกว่าอาสาสมัครสุขภาพดีโดยเฉพาะในด้าน executive function ในผู้ป่วยที่ได้รับ PHT ในขณะที่ไม่พบความแตกต่างเช่นนี้ในกลุ่มที่ได้รับ VPA สำหรับในด้านอารมณ์นั้นอารมณ์กระตือรือร้น (vigor) เป็นอารมณ์ด้านเดียวที่มีความแตกต่างอย่างมีนัยสำคัญเมื่อเปรียบเทียบกันระหว่างกลุ่มผู้ป่วยโรคลมชักที่ได้รับยากันชักดังกล่าวกับกลุ่มอาสาสมัครสุขภาพดีดูเหมือนว่า VPA จะมีความเหมาะสมมากกว่า PHT ในการใช้กับผู้ป่วยหากคำนึงถึงผลที่ตามมาทางด้าน executive function เป็นเบื้องแรกอย่างไรก็ตามจำเป็นอย่างยิ่งที่จะต้องมีการศึกษาเพิ่มเติม ในรายละเอียดต่อไปเกี่ยวกับผลของยากันชักที่มีต่อเชาวน์ปัญญาในผู้ป่วยโรคลมชักชาวไทย