



CHAPTER V

DISCUSSION AND CONCLUSION

Epilepsy is a biomedical disturbance which involves an abnormal episodic bursts of electrical activity in certain neurons. Abnormal neuronal activity may have significantly impact on the normal cognitive processes and behavior of the affected individuals (Motamedi and Meador, 2003). As mentioned by Giordani (2002), antiepileptic drugs utilization is a part of various factors which affect coping and adaptive ability.

Many studies have demonstrated impact of AEDs on cognitive ability even though duration of drug exposure was only a month (Meador et al., 1991; Meador et al., 1995). However, in order to exclusively define AEDs- induced cognitive dysfunction, studying of cognitive decline from AEDs often performed in healthy population. Further study on the cognitive status of epileptic patients who always expose to AEDs remains to be carried out.

The present study was designed to assess cognitive and mood status of Thai epileptic patients receiving monotherapy of either valproate or phenytoin, using recommended neuropsychological tests namely Stroop Word color test, WASI[®] test and POMS (Psychological Corporation, 1999; Wymer, Rayls, and Wagner, 2003; Block, 2005). Age and sex matched normal volunteers were recruited according to the inclusion and exclusion criteria for the epileptic patients except for the absence of epilepsy and no consumption of AEDs. General characteristics of the subjects in normal volunteers, PHT and VPA groups are rather similar with regards to average age, TMSE and AUDIT scores. TMSE is the screening test, to identify active dementia status, presently practiced in Thailand (Train the Brain Forum Committee, 1993). From total score of 30, the average TMSE scores of the study population were 28.80 ± 1.26 , 28.13 ± 1.96 , and 29.07 ± 1.03 , and in normal volunteers, PHT, and VPA groups, respectively. 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. (Table 21) Dissimilarity among

the subjects was noted on the level of education in which the majority of normal volunteer group appeared to have higher education than both groups of epileptic patients.

Attention status of epileptic patients was evaluated by Stroop World Color Test which is generally known as the gold standard of research in attention (Block, 2005). It has been widely used in many randomized control trials to assess selective attention status and inhibition capacity of the brain (Baker and Marson, 2001). As inhibition is an executive function of the frontal lobe therefore, the score from this test reflect frontal lobe function (Andres and Von Der Linden, 2004). Based on the results that no significant difference in word test, color test and color-word test was noted among the 3 groups studies, attention- related performances of the 3 groups should be approximately of the same magnitude. Similar Stroop Test Score of PHT and VPA have been previously reported by Meador et al (1995) who conducted study comparing cognitive effects of PB, PHT and VPA in normal volunteers. PB produced the worse performance whereas PHT and VPA were not different from each other. However, in contrast to our finding, unwanted effect of PHT and VPA were noted when comparing with non-drug baseline. Different experimental design (parallel group vs. self control) could be one explanation. Alternatively, poor attention to perform the assigned task could possibly occur in the normal volunteer group in the present study as their interference score showed significant discrepancy between expected score and the score obtained. Therefore the small differences between normal volunteers and epileptic patients, if there is any, might not be revealed.

WASI[®], the neuropsychological tool, that was developed in an effort to establish a reliable short form of measuring intellectual functioning that was normed across life span (Axelrod, 2002). It has been used to assess cognition in traumatic brain injury, as well as in heart failure patients (Ryan et al., 2005; Wolfe et al., article in press). In the present study, no difference on VIQ (VC + SM) scores was noted among the 3 groups tested. As VIQ measures individual's expressive vocabulary, verbal knowledge as well as crystallized and general intelligence (Psychological Corporation, 1993), it is apparent that disturbances 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 (Table 29) whereas, significant difference was detected on SM (Table

31). 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 of information which are measured by VC. In contrast to our finding, the study of Roswall et al (2004), showed the decline of VIQ in presurgery pharmaco-resistant epileptic patients compared with normal population. Though, pharmaco-resistant patients are generally known to be almost always on polytherapy (Brodie and Kwan, 2002; McCorry, Chadwick, and Marson, 2004), unfortunately, no information on number of medications used by those patients, was reported thereby. Therefore, it is not justify comparing the results.

PIQ (BD + MR) measures individual's ability to mentally manipulate abstract symbols, perceptual organization, general intelligence, and to perceive the relationship among them while, FSIQ-4 (VC + BD + SM + MR) represents complete dimension of performance VIQ and PIQ. In addition, FSIQ-2 (VC + MR) represents only some dimension of VIQ and PIQ (Psychological Corporation, 1993). In the present study, we found that PHT group exhibited poorer performances in PIQ, FSIQ-4 and FSIQ-2 than normal volunteer 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 volunteers 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 comparable intellectual score. In the present study, statistically significant difference between normal volunteers and PHT was found on MR task which is the component shared by PIQ, FSIQ-4, and FSIQ-2 thus, performance on MR seemed to be the domain that obviously affected by PHT. MR subtest of WASI[®] has been suggested to be the test that can detect deficit of working memory dual task processing which is a part of executive function of the brain (Mckinnon, 2001). Therefore, it is suggestive that intellectual function adversely affected by PHT involves executive function of the brain. Lower performance in the cognitive domain of speed motor which could involve higher cortical information processing system has been reported in epileptic patients receiving PHT (Aldenkamp et al., 1994; Trimble, 1987). In addition, PHT has been found to disrupt spatial working memory of the animals in water-maze paradigm and

hippocampal function was suggested to be the one that was affected (Churchill et al., 1998, 2003 cited in Samuelson, 2005).

Mood disorders especially as a comorbid finding in epileptic patients have become increasingly recognized as a serious health concern (Krishnamoorthy, 2001; Barry, 2003; Gilliam, Hecimovic, and Sheline, 2003). 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 (Reijs, Aldenkamp, and De Krom, 2004). Using POMS[®] which is one of most frequently used neuropsychological test to assess mood, Meador et al (1991) and Meador et al (1995) demonstrated mood dimension that differed between normal volunteers with and without AEDs. 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 volunteers 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 correlate with mood, therefore differences in performance observed might be attributable to differences in the study population or operating mood. In the present study, VPA which demonstrated significant difference in vigor score from normal volunteers exhibited no differences in VIQ, PIQ, FSIQ-4, and FSIQ-2 of WASI[®], in comparison to normal volunteers. It is likely that operational mood when the study was conducted did not strongly affect the results observed in WASI[®].

Analysis of sub items of AEP indicated that PHT demonstrated significant higher score in restlessness and memory problems than normal volunteers whereas, VPA significantly exhibited tremor (shaky hands). Surprisingly, normal volunteers had more problems on weight gain than both groups of epileptic patients.

Though, the total score of adverse events which were assessed by AEP showed no significant difference among 3 groups, the present study did demonstrate the adverse effects of PHT on cognitive function when assessed by WASI[®]. Therefore, more attention is required if cognitive function is the major concern in treating epilepsy. Based on the results obtained, VPA is the drug to choose than PHT when cognitive function is an

important consideration. This is in line with previous reports of Gillham et al (1990) and Guerrini (2006).

In the present study, the average dose of PHT used by the patients was rather high (296.67 ± 44.19 mg/day) whereas, the average dose of VPA was rather low ($1,020 \pm 501.36$ mg/day) and this might affect the performances observed (Klasco, 2004.). Therefore, similar dose range should be taken into consideration for further studies.

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 epileptic patients receiving PHT than in the general population. Comparatively, PHT was found to adversely affected intelligence especially those dealing with executive function than did VPA. Cognitive deficits are multifactorial in etiology, ranging from biologic factors, such as type of epilepsy, age of onset, and therapeutic interventions that may adversely affect epileptic patients. 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 well matched population to gain further insight into the changing of cognitive ability and mood status of Thai epileptic patients.