CHAPTER I

INTRODUCTION

Background and Rationale

Cognition can be defined as the capacity of the brain to process information accurately and to program adaptive behavior. Cognition involves the ability to solve problems, to memorize information, or to focus attention. On a higher level, it involves dealing with complex situations creatively by transcending from the immediate circumstances to anticipate future acting (Aldenkamp, 1997)

Cognitive function or cognitive ability is composed of many changeable factors. Furthermore, cognitive ability can be decreased or increased by many factors. Hence, cognitive function is a dynamic process of organisms.

Epilepsy is the most common neurologic disorder with a prevalence of approximately 0.8%. About 50% of patients continue to experience seizures despite optimized treatment with modern antiepileptic drugs (Majak and Pitkänen, 2004).

Deterioration of quality of life (QoL) of epileptic patients is well recognized. Recurrent seizure may occur anytime in daily life if being provoked by precipitating factors such as lack of sleep, stress, alcohol etc. Nowadays, many antiepileptic drugs (AEDs) have been used to control seizure. However, by the fact that patients have to take medication as long-term prophylaxis, adverse events from AEDs are unavoidable.

Pharmacotherapy of epilepsy depends on type of epilepsy as some drugs may aggravate the frequency of seizure activity e.g. phenytoin may worsen absence seizure. Principle of drug therapy is starting with minimal effective dose of monotherapy then, stepwise increases may be required to achieve complete seizure control or else when maximal tolerated dose is reached (Schmidt and Gram, 1995; Leppik, 2000; Löscher, 2002).

Among conventional AEDs, phenytoin has been approved by USFDA since 1938 to be used for all types of partial seizure, generalized tonic-clonic seizure (GTCS), juvenile myoclonic epilepsy (JME) and benign febrile convulsion of infancy, but it is contraindicated in absence seizure. Sodium valproate, a broad spectrum AED, has been approved by USFDA since 1978 for all types of seizure (Leppik, 2001).

Both phenytoin and sodium valproate are the well known and widely used AEDs in Thailand by the fact that they are available in both oral and parenteral dosage forms and prescribers are familiar with their efficacy and adverse events (Pratyasanti, Srisomboon, and Rattanajinda, 1997; Shoolerd, Wongsasuluk, and Rungapiromnan, 2004; Fun, 2005)

AEDs mainly act on the central nervous system (CNS) to control seizure for a long period thus, many cognition-related adverse events (AEs) may subsequently occur. The concerning over the mental functioning of epileptic patients has a long history (Ossetin, 1988). During 1950 and 1965, only 0.2% of 17,771 articles published on epilepsy included measurement of intellectual function (Penry, 1976 cited in Ossetin, 1988). 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. Conventional AEDs have demonstrated a negative effect more often than those of the new AEDs. However, some new AEDs exhibit a unique negative adverse event (Martin et al., 1999; Mula et al., 2003). A randomized double-blind crossover study was used to study AEs of phenobarbital, phenytoin and sodium valproate as monotherapy in 75 healthy volunteers for 1 month. It was found that phenobarbital demonstrated more negative effect on cognition than that resulted from sodium valproate which exerted 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 have been reported AEs of carbamazepine and phenytoin monotherapy in 30 healthy volunteers (Meador, Loring, Allen et al., 1991; Meador, Loring, Moore et al., 1995).

In addition, deterioration of cognitive function was found to be well correlated with plasma level of AEDs especially in the concentration higher than therapeutic level (Thompson and Trimble, 1983; O'Dougherty et al., 1987).

There are many reports from western countries with regard to AEs of AEDs. Thus, it is rationale to 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 (Vermeulen and Aldenkamp, 1995; Ossetin, 1988; Ortinsky and Meador, 2004). Though there are over million Thai epileptic patients who are continuously taking AEDs, AEDs-related cognitive dysfunction have never been systematically explored (Pratyasanti, Srisomboon, and Rattanajinda, 1997; WHO, 1998; Shoolerd, Wongsasuluk, and Rungapiromnan, 2004) Therefore, it is interesting to investigate cognitive-related AEs of phenytoin and sodium valproate which are highly prescribed for epileptic patients in Thailand (Pratyasanti, Srisomboon, and Rattanajinda, 1997; Shoolerd, Wongsasuluk, and Rungapiromnan, 2004).

Hypothesis

Phenytoin-treated and sodium valproate- treated epileptic patients have poor cognition status when compare with normal population.

Objective

To evaluate adverse events of phenytoin or sodium valproate monotherapy on cognition and mood of Thai epileptic patients.

Expected outcome

Preliminary information of adverse events from phenytoin and sodium valproate monotherapy on cognition and mood in Thai epileptic patients would be beneficial for management of epileptic patients and provide a basis for further studies.