CHAPTER I

INTRODUCTION

Rationale and Background

A seizure is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system neurons (1). Depending on the distribution of discharges, this abnormal central nervous system activity can have various manifestations, ranging from dramatic convulsive activity to experiential phenomena not readily discernible by an observer.

Epilepsy is a condition in which a person has recurrent seizures due to a chronic, underlying process (1). Epilepsy refers to a clinical phenomenon rather than a single disease entity, since there are many forms and causes of epilepsy. Epilepsy is a broad category of symptom complexes arising from a number of disordered brain functions. According to international classification of epilepsies and epileptic syndromes, epilepsy is classified by seizure origin into four types, i.e. 1) localization-related epilepsy 2) generalized epilepsy 3) epilepsies and syndromes undetermined as to whether focal or generalized, unclassified epilepsy and 4) special syndromes (2).

Epilepsy is one of the most common disorders of the brain (3). One of every ten people will have at least one epileptic seizure during a normal lifespan, and a third of these will develop epilepsy. According to a World Health Organization survey, epilepsy accounts for 1% of the global burden of disease, a figure equivalent to breast cancer in women and lung cancer in men (4). Age-adjusted prevalence per 1,000 population reported widely from 2.7 to more than 40, however, most studies showed a range from 4 to 8 (5).

Epilepsy is a common world-wide health problem. It is more common in developing countries than developed countries. Its life time prevalence in Thailand is approximately 1.3 percent that means nearly one million Thai people suffer from epilepsy

(6). Antiepileptic drug (AED) has been a standard treatment of epilepsy for a century. Despite modern therapeutic options being developed, e.g. epilepsy surgery, vagal nerve stimulation, deep brain stimulation, ketogenic diet therapy, sex hormone therapy, behavioral therapy, etc. AED is still the mainstay management. Epilepsy is a chronic illness. Discontinuation of AED can be justified after achieving a seizure-free period of, at least, two years or more (7). In practical, 3-year seizure free is more wildly applicable. However, approximately, 20-30% of epileptic patients will have chronic active epilepsy (7). These chronic active epileptic patients need to take AED for such a long time or even lifelong. Thus, these patients may suffer from some adverse effects of long-term AED therapy such as alopecia, gingival hyperplasia, hirsutism, cerebellar atrophy, impaired cognitive function, decreased bone mineral density (BMD), etc.

The adverse effect of AED on BMD in epileptic patients has been documented for more than 30 years (8). Increasingly decreased BMD will eventually lead to osteopenia-osteoporosis which is a major fracture risk. However, a small amount of physicians have paid attention on this issue (9). In addition, there is no guideline, recommendation or even consensus on prevention and intervention for adverse effect on BMD from long-term AED therapy yet.

BMD is affected by many factors. Age and gender are among major influencing factors. Thai population, as other countries, have decreased bone mass with advancing age. The rate of decline is greater in women particularly after 60 years old (10). It is realized that menopause is one of major risk factors of osteoporosis in women and the major important prevention measure of postmenopausal osteoporosis is to keep bone mass as high as possible before menopause. Recently, there is evidence-based recommendation for prevention of osteoporosis and osteoporotic fractures in postmenopausal women (11, 12). If long-term AED therapy can cause significant decreased BMD, medical attention should be paid on this issue and appropriate intervention for prevention of osteopenia-osteoporosis particularly in female is crucial. If AED can cause significant decreased BMD in Thai pre-menopausal epileptic patients,

then efficacy of application of the different osteopenia-osteoporosis prevention and management may be further evaluated.

Although there is some evidence that AED can decrease BMD, most of these data were carried on in Western countries. BMD is influenced by various factors, e.g. calcium, phosphorus and vitamin D intake, sunlight exposure, weight-bearing activity, etc. Vitamin D predominantly affects homeostasis of calcium and BMD in different ways. Human have vitamin D from food such as milk. Additionally, vitamin D is synthesized from 7-dehydrocholesterol by skin ultraviolet radiation. Sunlight exposure is, therefore, one of much important environmental factors strongly influent on BMD. Unlike most Western countries, Thailand is in the tropical zone where there is a high amount of sunlight all year round. However, Thai people do not drink as much milk that contains both calcium and vitamin D as Western people. Furthermore, it was found that calcium intakes for males and females in Ubon Ratchathani and Bangkok were lower than Thai recommended dietary allowances (RDA), that is 524.6 ± 259.9, 379.9 ± 111.4 and 366.5 ± 150.5, 286.7 ± 68.7 mg/day respectively (13). In addition, different genetics may partly have an effect on drug metabolism differently. Therefore, effect of long-term AED therapy on BMD in Thai epileptic patients should be explored.

BMD is dynamic. Bone resorption and formation occur simultaneously throughout life. After negative factors being resolved, bone formation can catch up usual BMD. Most epileptic patients who finally achieve seizure-free and discontinue AED in a few years may not subject to osteopenia. Therefore, the study concentrate on epileptic patients who need long-term AED that is 3 years or more.

If long-term AED use has negative effect on BMD, female epileptic patients are more prone to osteoporotic fracture than male epileptic patients especially when they turn to post-menopausal age. Moreover, modern preventive measures for osteopenia and osteoporosis have been studied in Thai female, female epileptic patients are focused on. Since BMD is dynamic in relation to age, pre-menopausal female epileptic patients aged 20-50 years are the preliminary focus of the study.

BMD varies among ethnic group, age and reproductive status. There is no normal BMD reference in Thai female yet. Comparing BMD of patients with normal reference of other ethnic group may not be accurate and from the methodological perspective, the study decides to compare the study group with normal Thai pre-menopausal female in the same age range.

To date, there is no adequate data in term of adverse effect on BMD from long-term AED therapy in Thai pre-menopausal epileptic patients available for the decision of prevention and intervention recommendation. Bone markers are intermediate variables of bone change whereas BMD is the final measurable bone change outcome. Therefore, BMD, not bone markers, should be used for outcome evaluation of effect of AED on osteopenia and osteoporosis. Moreover, BMD can be accurately measured by available non-invasive technology. Therefore, BMD is selected for primary outcome measurement in the study.