CHAPTER I

INTRODUCTION

Background and Rational

Phenobarbital was first introduced as an Anti-epileptic drug in 1912 by Hauptmann (1). The drug had previously been used as hypnotic and a tranquilizer. Hauptmann prescribed phenobarbital at a daily dosage of 200 - 300 mg in bromide-resistant patients and patients suffering from heavy bromide side effects (2). It is the most effective of all the barbiturates for long-term treatment of seizure disorders.

Until recently, there are many new antiepileptic drugs but Phenobarbital is still widely used and remains at the top of the list of essential drugs in the treatment of epilepsy in developing countries including Thailand. Its major advantage is that it has the longest half-life of all the standard antiepileptic drugs, permitting once-a-day dosing possible which is convenience for patients compliance (3). In addition, Phenobarbital is the most inexpensive antiepileptic drug, it is available from multiple routes of administration, and broad-spectrum efficacy (4). It is commonly used for generalized tonic-clonic seizure, simple partial seizures, and complex partial seizures (1),(5). In children, Phenobarbital is the drug of choice for the treatment of infantile and neonatal seizures, which is advantageous due to several available routes of administration as well as the relatively predictable pharmacokinetics (4).

Phenobarbital has been proven effective in preventing febrile seizures.A febrile convulsion recurrence rate of 13% was found in Phenobarbital -treated group compared to 26% in the control group (6). A survey of current

practice and phenobarbital usage in USA, phenobarbital is used for preventing complex febrile seizure 89% and preventing simple febrile seizure 43% (7).

In Thailand, phenobarbital was reported as the most common prescribed antiepileptic drugs (44% of all antiepileptic drugs) (8) in Srinakarin hospital Khon-Khan. At neurology clinic, paediatric department, Chulalongkorn hospital, there are about 38% of all patients in this clinic used Phenobarbital(9).

The incidence of epilepsy disease in USA is about 0.5-2% of the population, about 50% of patients have seizures in age below 18 years and most of the new patients are the patients in age below 5 years (10).

Phenobarbital is a long-acting barbiturate with narrow therapeutic index (10- 40 μg/ml in adults (11), 15-25 μg/ml in neonates, and 10-20 μg/ml in infants and children (12)). There is considerable interindividual variation in the relationship between control of seizures and the serum antiepileptic drug concentration. Age of onset, type of seizures, etiology, and pretreatment frequency of seizures all have significant influences on the response to treatment (13).

Phenobarbital has gained considerable attention as an antiepileptic drug in paediatric patients. Paediatric patients have different rate of absorption, metabolism and elimination. The gastric fluid of neonates, infants, and young children contain high pH value which is changing with the maturation of acid secreting system bioavailability of phenobarbital that has acid property increases. In neonates enzyme capacity is not fully function so phenobarbital half life is longer (130-500 hours in neonates) than adults. Half life of the drug is shorter (30-60 hours in infants, 25-70 hours in children (12)) and then will increase with the increasing age (90-100 hours in adults) (14, 15). So infants and neonates required higher dose per kilogram than adults.

Several investigators have described the pharmacokinetics of phenobarbital in children and adults (16). However, there may be striking variation among patients in phenobarbital's serum level/dose relationship due to considerable interpatient variation. The phenobarbital dosage necessary to reach the same plasma level is higher in children than in adults, it seems that the younger the child, the greater the phenobarbital dosage needed to reach the same plasma level (15).

Svensmark and Buthal found that the serum level/dose ratio was significantly higher at 10-14 years (6.9 ± 0.3) than at 1-6 years (4.8 ± 0.2) (15). However, one research mentioned that the rate of increasing of plasma level/dose ratio shown to increase relatively high in the first year of life and become less markedly thereafter (17).

The study here justify the level-dose ratio in patients of different ages, treated with Phenobarbital in monotherapy and polytherapy at the different dosage regimens of Thai paediatric patients.

Objective

1. To determine level dose ratio in Thai paediatric patients of different ages.

2. To determine the percentage of patients whose serum phenobarbital levels were within the therapeutic range , in subtherapeutic range and over therapeutic range.

3. To justify the relationship between serum phenobarbital level and clinical results such as seizure frequency and side effect.

Significance of the study

1. From this study, it will be justify whether the dosage regimens presently used in Thai paediatric patients could provide a suitable serum therapeutic level.

2. The level dose ratio obtained could be used as basic data for adjusting dosage of phenobarbital in Thai paediatric patients in each age group.

3. Some common side effect of phenobarbital in Thai paediatric patients and its relationship with serum level will be determined.

4. Relation of serum level to seizure control in Thai paediatric patients will be investigated.