CHAPTER I

INTRODUCTION

Background and Rationale

Phenytoin is an anticonvulsant drug frequently prescribed in adults and children. Phenytoin was first recognized to have high antiepileptic activity in the late 1930s. Phenytoin is considered to be the drug of choice for partial and generalized tonic-clonic seizures. Presently approved uses of phenytoin include : primary or secondary generalized tonic-clonic seizures , simple and complex partial seizures , mixed seizure types which include partial or generalized tonic-clonic seizures , and tonic-clonic status epilepticus.

The serum concentration of phenytoin is a better predictor of antiepileptic effect than the administered dosage due to variable disposition of phenytoin among individual patients. In particular, phenytoin undergoes dose dependent or saturable elimination following normal therapeutic doses therefore small increases in the daily phenytoin dose may result in unpredictably disproportionate increases in the average phenytoin serum concentration.

The interpretation of pharmacological activity based on total phenytoin concentrations in serum may be in appropriate because of interpatient variability in serum protein binding. This is particularly important in patients with hepatic or renal disease and in those taking drugs that displace phenytoin from serum proteins (ie., valproic acid). Because it is the free, unbound concentration of phenytoin that most closely correlates with pharmacological activity, the measurement of free concentrations may be more appropriate in these patient groups(Peterson, Khoo, and Witt, 1991 ; Berg, Ebert, Fincham, and Schottelius, 1987 ; Cai, Zhu, and Chen, 1993 ; Taylor and Diescaviness, 1986).

Phenytoin is a drug which therapeutic monitoring has been proved to be valuable because of the following reasons (Taylor and Diescaviness, 1986; Sadee and Beelen, 1980; Hudson and Walker, 1990; Evans, Schentag and Jusko, 1986):

1. Phenytoin has a narrow therapeutic index.
2. Phenytoin has non-linear pharmacokinetics.
3. The good correlation between serum phenytoin levels and both efficacy and toxicity.
4. The large variability in the dosage requirements of phenytoin.
5. Large interindividual pharmacokinetic variability.

However, very few studies of phenytoin monitoring was done in Thailand. This study was therefore designed to investigate serum drug levels and clinical responses of phenytoin therapy in Thai patients, to apply pharmacokinetic theories in adjusting for the appropriate dosage regimen in individual Thai patients by assessment from clinical responses and phenytoin serum level, and to compare the calculated drug levels from literature (predicted values) with the measured drug levels in blood (measured value).

Objectives

1. To assess whether the dosage regimen of phenytoin in the treatment of epileptic Thai patients is in therapeutic range, to assess incidence of adverse reactions and/or no beneficial effect of phenytoin, and to assess the correlation between phenytoin serum concentrations and clinical responses to phenytoin therapy for beneficial effects and adverse reactions of phenytoin in Thai patients treated with phenytoin.

2. To apply pharmacokinetic theories in adjusting for the appropriate dosage regimen in individual Thai patients when phenytoin serum concentrations are inappropriate by assessment from adverse reaction occuring and/or no beneficial effect of phenytoin in individual Thai patients.

3. To establish the pharmacokinetic parameter of phenytoin in Thai patients.

4. To compare the phenytoin serum concentrations obtained from the patients (measured values) with the calculated concentrations from pharmacokinetic parameters and equations from literature (predicted values).

The significance of the Study

1. This study will enable to justify whether the dosage regimen currently used by traditional physician can provide appropriate phenytoin serum level.

2. This study will provide the information of the correlation between phenytoin serum concentrations and clinical response to phenytoin therapy (e.g., beneficial effects and adverse reactions of phenytoin) in Thai patients.

3. This study will provide the information of clinical response improvement to phenytoin therapy after the appropriate phenytoin dosage regimen adjustment for individual Thai patients.

4. This study will determine whether the pharmacokinetic parameters and equations that are widely used in foreign countries can be used to predict phenytoin levels accurately in Thai patients. If so, this method shall be recommended for calculating dosage regimens of phenytoin for Thai patients.

5. This study will provide some pharmacokinetic parameters of phenytoin in Thai patients which may be used as the data for calculating the appropriate dosage regimen of each individual patient either manually or when computer program is applied.