CHAPTER V

CONCLUSION

Fifty four patients were completely followed up for their treatment with phenytoin, the results from this study were concluded as follow:

1. dermographic data

1.1 Educational background of the epileptic patients participated in this study.

Most patients finished primary school (40.74%) and high school (24.07%).

1.2 The occupation of the epileptic patients participated in this study.

The patients are employee (27.78%), commercial (16.67%), officer (12.96%), student (12.96%) and some of them are unemployed (14.81%).

1.3 Income of the patients participated in this study.

Majority of the the patients have low income (37.04%) , either don't have any income at all (37.04%) or have income which is less than 5,000 baht/month (37.04%).

1.4 The history of seizure of the other members in their family.

Four out of fifty-four patients have history of seizure in their family.

1.5 Cause of first seizure of these epileptic patients.

The causes was usually unknown (55.56%) while fever was the most common known cause of first seizure (24.07%).

1.6 Concomitant disease.

Most of the epileptic patients joined in this study do not have any other concomitant disease (97.30%).

1.7 Smoking and alcohol drinking patients.

83.33 percent of the patients were not smoking while 83.33 percent of the patients were not drinking.

2. Therapeutic monitoring of phenytoin

2.1 In this study, 15 patients (27.78%) were treated with phenytoin alone, and 39 patients (72.22%) were treated with phenytoin along with other antiepileptic drugs (phenobarbital, carbamazepine, valproic acid, clonazepam). The antiepileptic drug most oftenly used along with phenytoin was phenobarbital (42.59%).

2.2 Phenytoin serum concentration correlated well with seizure control and central nervous system adverse drug reaction.

2.3 Higher percentage of patients showed the absolutely seizure control beneficial effect when their phenytoin serum concentrations were in overtherapeutic range , therapeutic range and subtherapeutic range, respectively. However, higher percentage of patients showed partially seizure control beneficial effect when their phenytoin serum concentrations were in subtherapeutic range and in therapeutic range. The seizure could not be controlled in 24.24% of the patients and 39.39% of the patients showed central nervous system adverse drug reaction.

2.4 The incidence of phenytoin adverse reactions (general and central nervous system side effects) in the group of patients treated with phenytoin together with other antieleptic drugs occured more often (46.00%) than the group of patients treated with phenytoin alone (20.00%).

2.5 The general adverse drug reactions observed most often was gum hypertrophy (31.82%). Gum hypertropy was found in every range of phenytoin concentrations. The central nervous system adverse drug reactions (Nystagmus, ataxia, drowsiness, dizziness, diplopia and headache) were found in 52.31% of the patient. Nystagmus was the most commonly found central nervous system adverse drug reaction. Nystagmus occured in patients with phenytoin serum concentrations higher than 20 μg/mL and ataxia occured in patients wtih phenytoin serum concentrations higher than 30 μg/mL. Central nervous system side effects do correlate with serum concentration.

2.6 Phenytoin dosage regimen adjustment improved clinical responses. The adverse drug reactions of 4 patients were decreased and the seizure of 6 patients were better controled after the new dosage were administered.

2.7 Good correlation between phenytoin serum concentration and phenytoin saliva concentration (R^2 = 0.88) was found. Saliva phenytoin concentration may represent the serum phenytoin serum concentration. Serum phenytoin concentration and saliva phenytoin concentration ratio was 12.61.

3. Comparison between the measured and the predicted phenytoin serum concentrations.

3.1 The mean measured and predicted phenytoin serum concentrations were 14.73 ± 12.15 and 11.29 ± 9.36 μg/mL, respectively. The mean difference between measured and predicted values was 8.25 ± 9.18 while the mean percentage of difference between measured and predicted values was 129.81 ± 293.15 (mean ± SD). The percent coefficient of variation was 225.83. Predicted phenytoin serum concentration using population pharmacokinetic parameters differed greatly from the measured concentrations. However, coefficient of variation between the predicted and measured phenytoin serum concentration was lower when the serum concentrations were in the range of 10–35 μg/mL as compared to the coefficient of variation obtained when the serum concentrations were higher or lower than this range. Predicted

phenytoin serum in this range may be more reliable than other range of phenytoin serum concentrations.

3.2 Comparison between measured and predicted phenytoin serum concentrations in the patients receiving phenytoin alone.

The mean measured and predicted phenytoin serum concentrations were 17.34 ± 13.54 μg/mL and 14.63 ± 13.25 μg/mL respectively, and the mean difference between measured and predicted values was 11.02 ± 11.88 , the mean percentage of difference between measured and predicted values was 84.48 ± 98.56. The percent coefficient of variation was 116.67.

3.3 Comparison between measured and predicted phenytoin serum concentrations in the patients receiving phenytoin along with others antiepileptic drugs.

The percent coefficient of variation of phenytoin serum concentrations when patients recieving phenytoin alone was 116.67 while the percent coefficient of variation of phenytoin serum concentrations when patients receiving phenytoin along with other antiepileptic drugs were 225.79 (no factors adjusting) or 272.31 (used factors adjusting). This indicated that when patients receiving phenytoin with other antiepileptic drugs the prediction of phenytoin serum concentrations may be less reliable.

The percent coefficient of variation when patients receiving phenytoin with phenobarbital were 171.46 (no factor adjusting) or 166.01 (used factor adjusting). This indicated that phenobarbital may affect the validity of phenytoin serum concentrations prediction.

The percent coefficient of variation between measured and predicted phenytoin serum concentrations when patients receiving phenytoin with phenobarbital and carbamazepine were 56.34 (no factor adjusting) or 76.09 (used factor adjusting). However, since only six patients were categorized in this group, the validity of this result could not be confirmed until further studies in more patients have been done.

3.4 Comparison between the measured values to the predicted value calculated by different methods (calculated by using population pharmacokinetic parameters, wagner method, calculated by fixing $K_m = 4$, and calculated by fixing $V_{max} = 7$).

The percent coefficient of variation of the method which calculated by fixing $K_m = 4$ was lowest (63.59%). Therefore, this method was suggested to be used to calculate predicted phenytoin serum concentration when only one dose and its corresponding serum concentration were known.

3.5 Comparison between measured and predicted phenytoin serum concentrations which calculated by used individual pharmacokinetic parameters (K_m and V_{max}).

Only four patients whose dosage were adjusted twice and three steady state serum concentrations corresponding to the dose were known. After the individual pharmacokinetic parameters were calculated using data obtained from the first two doses. Their K_m and V_{max} were then used to predict the serum concentration of the third dose compared to its measured value. The mean percentage of differences of one patients was 25.49±29.32. This method showed tendency to predict phenytoin serum concentration more accurate than any other methods. However, since only four patients were included in this study further studies are required.

4. Pharmacokinetic Parameters of Phenytoin in Thai Patients.

4.1 The K_m obtained ranged from 1.34 to 45.18 mg/kg/d and the mean was 12.86 ± 14.25 (mean ± SD) while the V_{max} obtained ranged from 6.34 to 13.58 μg/mL and the mean was 8.76 ± 2.62 (mean ± SD).

4.2 The pharmacokinetic parameters of patients that calculated by using one of the population pharmacokinetic parameters were K_m equal to 6.23 ± 6.98 (mean± SD) and V_{max} equal to 7.06 ± 1.77 (mean± SD).

5. General comment.

For inpatients, adjustment of phenytoin dosage may require the measurement of non-steady state serum phenytoin concentration because inpatients stayed in hospital in a short period and usually the condition of the patients was so bad that the symptom should be controlled as soon as possible.