CHAPTER V

CONCLUSION

Sixty-nine patients were observed in this study , the results obtained were concluded as follow :

The data proved that in steady-state conditions and in the normal function of liver and kidney , patients age from 1 month up to 15 years , the serum level dose ratio for phenobarbital has a statistically significant increase with the increase of the patient's age. The patients could be classified into four age groups with different level dose ratios. The equation from linear regression analysis is L/D = 3.59 + 0.25 age, r = 0.727 , $P<0.001$. So we can calculate the phenobarbital dosage (mg/kg/day) required to produce a desired serum level by either one of the two methods :-

First, Using the mean level dose ratio of the age group of the patients :

$$\text{Phenobarbital dosage (mg/kg/day)} = \frac{\text{Required serum level (µg/ml)}}{\text{L/D of the age group of the patient}}$$

Second , Using the equation obtained from linear regression analysis

$$\text{Phenobarbital dosage (mg/kg/day)} = \frac{\text{Required serum level (µg/ml)}}{3.59 + 0.25 \text{ age (years)}}$$

The phenobarbital level dose ratio increased with the increased age may be explained by a progressive reduction of hepatic drug metabolism with age. Variations of volume of distribution with age

may also contribute to these changes. The younger children may have a far greater metabolic capacity to eliminate phenobarbital than adults and may require higher dosage (mg/kg/day). In this study, since the average dosage (mg/kg/day) of the younger children were higher than the older children and adult , even though the level dose ratio of younger children were lower than the older children and adult , the average phenobarbital serum concentrations in each age group were nearly equal.

The recommended therapeutic range used for phenobarbital concentrations in adults (10 - 40 μg/ml) is based largely on studies which included only adults or with relatively few paediatric patients (13, 24). This range is widely used in children as a practical approach to initial individualization of therapy. Paediatric neurology clinic, Chulalongkorn hospital also use this range in practical treatment as could be seen from the results. If therapeutic range was recommended to be 10 - 40 μg/ml , the percentage of the patients who had serum level within therapeutic range would be high(85.5%). If therapeutic range was recommended to be 10 - 20 μg/ml (as Morselli recommended for infant and children), the percentage of the patients who had serum level within therapeutic range would be much lower (24.6%).

Most patients whose seizures were completely controlled had their phenobarbital serum levels within therapeutic range if the therapeutic range was considered to be 10 - 40 μg/ml (91.8%). However , if the therapeutic range was determined to be 10 - 20 μg/ml , the percentage of controlled patients whose serum levels were within therapeutic range was much lower (26.5%). The mean concentrations in each age group are about 24 to 27 μg/ml since pediatrists in this clinic

determined the target serum level to be 10 to 40 μg/ml , they prescribed the doses for their pediatric patients according to this target. Further prospective studies are required for the therapeutic range of 10 - 20 μg/ml as recommended by Morselli and monitor the clinical response closely before any conclusion about the therapeutic range for the young patients could be made.

The drug interaction between phenobarbital and valproic acid was probably one of the clinically most significant interactions as it occurred predictably in the majority of patients taking these two drug together due to the mechanism by which valproic acid inhibits phenobarbital metabolism. In this study all 3 patients who received phenobarbital concurrently with valproic acid had higher level dose ratio than the mean level dose ratio of the same age group. Two patients who concomittantly used diazepam and phenobarbital had their level dose ratios which were lower than the mean level dose ratio of the same age group. However , since no pharmacokinetic interaction between phenobarbital and diazepam had ever been reported and the number of patients in this study were too few , further studies are required before any conclusion could be made.

Percentage of side effect did not increase with the increased serum level. The side effects found in this study included hyperactivity , sedative, ataxia , and aggressive. All of these side effects were the neurological side effect. Hyperactivity was the most frequently found side effect. Hyperactivity was reported more frequently for patients in school age than the other ages , the reason might due in part from that at this age group the side effect was reported either from teacher to their parents or their parents found it by themselves.

In patients whose age were higher than 15 years , there was no incidence of hyperactivity. Sedative was found in higher percentage among patients age more than 15 years. We found low incidence of aggressive behavior since this side effect is more serious , if it occurs, the physician tend to decrease or stop the medication.

As all of our subjects are out - patients, there might be some uncertainty about the compliance of the patients either caused by themselves or by their parents. Therefore the variability of our data may be in part due to the irregular administration of the medication in some children.