CHAPTER VI
CONCLUSION

This study was performed in patients receiving valproic acid monotherapy and the necessary pharmacokinetic parameters were calculated, then, precisely define the relationship between unbound and total valproic acid concentrations, the effects of daily dose, age, weight, albumin and valproic acid concentrations on valproic acid disposition. Stepwise multiple linear regression analysis lead to independent examination of the effect of daily dose, weight, serum albumin, and trough concentration on valproic acid pharmacokinetics. The conclusion of this study were

1. There were marked relationships between total and unbound valproic acid concentrations, the unbound concentration could therefore be predicted either from total concentration or free fraction.

2. The equations to predict unbound concentration from total concentrations could be derived from this study:

unbound concentration = -6.01 + 0.18(total concentration) (r^2=0.776, $p<0.001$)

unbound concentration =-4.82 + 0.166(total concentration)(r^2=0.757, $p<0.001$)
; concentration <100 μg/mL)

unbound concentration = -6.73 + 0.192(total concentration)(r^2=0.321, $p<0.05$)
; concentration ≥100 μg/mL)

The unbound concentration was more accurately predicted when the total concentration was lower than 100 μg/mL.

3. In this study, the free fractions were divided into three groups according to three different levels of total valproic acid concentrations which were <50 μg/mL, 50-100 μg/mL and >100 μg/mL. These free fractions were significantly different among the three groups which the values equaled to 7.1,

9.8 and 13.46%, respectively. The equation that might be applied to predict the free fraction (ff) were as follow:

$$ff = 0.035 + 0.0008(\text{total concentration}) \quad (r^2 = 0.46, p<0.001)$$

4. The variation of free fraction by albumin was greater at higher concentration. Valproic acid trends to undergo saturated protein binding within the concentration of therapeutic range. As a result, the unbound concentration of VPA is much more variable than that of the total. This may have important implications in correlation between efficacy and/or toxicity with unbound concentrations. Patients with hepatitis, hypoalbuminemia or renal disease may have a free-fraction that was higher than patients who do not have these conditions.

5. The kinetics of unbound valproic acid showed great differences from those of the total valproic acid in the present study, such as larger V_d and clearance and shorter terminal half-life.

5.1 There were no differences in pharmacokinetic parameters by sex.

5.2 The total and unbound clearances of Chrono dosage form showed no significant differences from those obtained from solution dosage form.

5.3 Elimination rate constant of unbound drug could be predicted from that of the total drug by the equation: $K_{e\ unbound} = -0.0413 + 2.113(K_{e\ total})$ ($r^2=0.563$)

5.4 Clearance, volume of distribution and half life showed low relationship between the total and unbound correspondent pharmacokinetic parameters.

6. Relationship between pharmacokinetic parameters and demographic data

6.1 Total concentrations depend mostly on daily dose, unbound concentrations depends on daily dose and albumin concentration.

6.2 Total clearance depends mostly on daily dose and the weight of the patient. Clearance of the unbound VPA was much less correlated.

6.3 The half-life of total valproic acid varied with age, whereas that of unbound valproic acid was not, it depended mostly on daily dose but was much less correlated.

7. Prediction of pharamacokinetic parameters from valproic acid concentrations: when trough concentration was known and combined to the prediction models, the pharmacokinetic parameters (K_e, Cl, V_d, $t_{1/2}$) were all better predicted (r^2 were increased for both total and unbound VPA)

8. No adverse effect of any type could be recorded from the patients participated in this study including the patients whose total concentrations were high above 100 μg/mL.

An accurate method for prediction of free valproic acid concentration based on more easily determined total serum concentration of the drug plus the concentration of serum albumin, should be of clinical importance in the management of patients with epilepsy. The models obtained from this study could be applied for patients treated with valproic acid in routine clinical situations. The result, which showed variation in binding at different valproic acid concentration levels also is importance, it indicated that binding of valproic acid to plasma protein trend to become saturated within the concentrations of therapeutic range.

This study demonstrated the difference between total and unbound VPA pharmacokinetic parameters. Therefore, the pharmacokinetics of unbound valproic acid are considered to be of special interest in therapeutic drug monitoring in the future, since it is the fraction of a drug in the blood which access to the central nervous system. This study tried to achieve some information about valproic acid pharmacokinetic parameter based on demographic data of the patients, which is quite helpful in clinical decision.

In present study, the subjects comprised of patients taken valproic acid as monotherapy with normal levels of serum albumin. The investigations of more complex situations should be further accomplished in order to completely describe the pharmacokinetics of valproic acid in children.