# CHAPTER V

# CONCLUSION

Thirty-three preterm infants admitted at Queen Sirikit National Institute of Child Health ( 17 males,16 females ) were included and completed the study. The mean age at the beginning of theophylline therapy was 5.58 ± 4.84 days (range 2 - 27 days). The results obtained in this study were concluded as follow :

1. The present theopylline dosage regimen used in preterm infants at Queen Sirikit National Institute of Child Health resulted in subtherapeutic theophylline serum concentrations in most patients. 66.67% of the patients had theophylline serum concentrations lower than the recommended therapeutic range at 6 hours after the loading dose. The maintenance doses of 8 patients were adjusted before the steady state serum concentration was reached and the clinical response was improved after adjustment of the maintenance dose in most patients. From the study, the equations used for calculation of the aminophylline loading dose and maintenance dose which produced the serum concentration at the $12^{th}$ hour after the loading dose to be 6 mcg/ml and the steady state serum concentration to be 8 mcg/ml, respectively, were generated. The generated equations were as follow :

   LD (mg/kg) = 6.16 + 0.62PNA in wks.
   MD (mg/kg/day) = 3.5 + 0.91 PNA in wks

2. Reliability and precision of prediction of the steady state serum concentrations based on the serum concentration during non-steady state

   Reliability and precision of prediction of the steady state serum concentrations based on the serum concentration during non-steady state were evaluated by 7 methods. The results obtained could be concluded that all methods had reliability but lacked of precision for prediction of the steady state theophylline serum concentration ( $\alpha$ = 0.05 ). The methods which calculated the steady state serum concentration by using pharmacokinetic parameters, i.e., elimination rate constant (Ke), volume of distribution (Vd) and clearance (Cl), which was each individually calculated from the non-steady state

concentration data had less precision for prediction of the steady state serum concentration than the methods which calculated the steady state serum concentration by using only the individual Ke calculated from the non-steady state data together with the population Vd or Cl. In addition, the methods which calculated the steady state serum concentration by using the individual Ke calculated from the non-steady state data and the population Vd had more precision for prediction of the steady state serum concentration than the method which calculated the steady state serum concentration by using the population Cl. Among the different method, the best method for prediction of the steady state serum concentration was the method which calculated the steady state serum concentration by using the individual Ke calculated from the two non-steady state serum concentrations and the population Vd (0.858 L/kg) and applied to the simplified equation. Apply in this method, 52.63% of the predicted steady state concentration was within 20% difference of the observed values compared to less than 40% obtained from the other methods.

1. Correlation between theophylline serum concentration and clinical response

This study found that most patients got benefit effect when the serum concentration was within the therapeutic range. Benefit effect was found in 66.67% of the patients when the drug concentrations were within therapeutic range. Nevertheless, the benefit effects were often obtained when other treatments were used along with theophylline treatment, especially when the drug concentration was less than the therapeutic range. When theophylline was used alone, 71.43% of the patients with therapeutic serum concentrations got benefit effect , whereas only 53.33% of the patients with subtherapeutic serum concentrations got benefit effect when theophylline was used alone. The correlation between theophylline serum concentration and benefit effect could be found when theophylline was used to manage apnea, however, this correlation was less obvious when theophylline was used as an adjuvant to weaning. The highest incidence of adverse reaction was found when the serum concentration was overtherapeutic. Tachycardia more than 180 beats per minute was the only type of theophylline adverse reaction found in this study.

The results obtained from this study indicated that therapeutic drug monitoring could help to improve the patients' care. When the patients need rapid adjustment of the maintenance dose before the steady state is reached, the method which predicted the steady state serum concentration by using the individual Ke calculated from the non-steady state data and the population Vd (0.858 L/kg) is the method of choice for use in the preterm infants. However, caution use of this method is suggested because only

approximately 50% of the predicted steady state serum concentrations were within 20% difference of the observed value. For the institute which theophylline serum concentration measurement is not the routine part of the patients care, we suggest that the aminophylline loading dose should be 6.5 mg/kg and the maintenance dose should be 4.0 mg/kg/day for the patients use the drug during the first week of life or aminophylline loading dose should be 7.0 mg/kg and the maintenance dose should be 4.75 mg/kg/day for the patients use the drug during the second week of life or the loading dose and the maintenance dose could be calculated from the equations as follow :

$$\text{LD (mg/kg)} = 6.16 + 0.62\text{PNA in wks}$$

$$\text{MD (mg/kg/day)} = 3.50 + 0.91\text{PNA in wks}$$

Age of the patients may be a condition when applying these equations since they were generated from the data of the preterm infants with the age less than 1 month. However, these equations should be evaluated in the larger group of Thai preterm infants and performed in the prospective study to confirm this result.