CHAPTER I

INTRODUCTION

Background and Rationale

Theophylline is commonly used in pediatrics for treatment of asthma and other cause of reversible airway obstruction (Wrenn et al., 1991). In recent years, the use of theophylline has tended to decrease because of narrow therapeutic index combined with having many factors affected on drug metabolism (McFadden, 1991 ; Stoloff, 1994 ; Troger and Mayer, 1995). Consequently, adverse drug reactions from the use of theophylline have frequency been reported (Baker, 1986 ; Gill et al, 1995).

However, the use of theophylline has remained a standard part of therapy to treat a variety of respiratory problems related to prematurity. In neonates with apnea, theophylline has been shown to decrease the number of apneic episodes and to decrease the need for and duration of mechanical ventilation (Aranda and Turmen, 1979). In infants with bronchopulmonaly dysplasia (BPD), theophylline decreases airway resistance, improves lung compliance, and shortens the duration of mechanical ventilation (Rooklin et al, 1979). Theophylline also has been shown to prevent post-extubation respiratory failure in small premature infants (Durand et al, 1987 ; Viscardi et al, 1985).

From pharmacokinetic studies in neonates found that theophylline clearance is very slow secondary to an immature cytochrome P-450 (C-P450) system. Consequently, the drug 's half-life is prolonged about 30 hours (Aranda et al, 1992). The results in intrapatient and interpatient variation have led to the same dose in any patient, the different drug serum level. Previous studies recommended the optimal dosage regimens in infants and developed the equations to predict individualize dosage regimen which led to therapeutic level based on pharmacokinetic studies (Giacoia et al, 1976 ; Jones and Billie, 1979). However, these guidelines were empiric used and none was best for the patients. So that, they have been evaluated to produce the optimal guideline in the future (Bhatt-Mehta et al, 1995 ; Bhatt-Mehta et al, 1996).

From these reasons, theophylline serum level monitoring combined with clinical monitoring may be a good method to monitor efficiency of theophylline used in infants, decrease the number of the patients who had the dug concentration within subtherapeutic level which causes inadequate clinical response or treatment failure and avoid toxicity or adverse reaction from overtherapeutic level.

This study was designed to investigate theophylline serum level in patients after first dose or loading dose which was called the non-steady state serum concentration, to apply pharmacokinetic theones to adjust for the appropriate dosage regimen based on the serum level during non-steady state. This method lead to decrease the time to wait for the steady state which too long ranged from 3 - 5 half life and prevent toxicity before the drug was accumulated to go beyond therapeutic level. Also, this study wanted to evaluate reliability and precision of the prediction of theophylline serum level during steady state based on the drug serum level during non-steady state, the appropriateness of the loading dose and the correlation between the drug serum level and clinical response in the patients.

Objectives

1. To adjust for appropriate theophylline dosage regimen in preterm infants based on the drug serum level during non-steady state.

2. To evaluate the reliability and precision of using the drug serum level during non-steady state to predict the steady state serum level in preterm infants.

3. To evaluate the appropriateness of the loading dose in preterm infants.

4. To evaluate the correlation between theophylline serum concentration and clinical responses both efficiency or beneficial effect and adverse drug reaction in preterm infants.

The Sigificance of the Study

1. This study will provide the answer about the reliability and precision for prediction of the steady state theophylline serum concentrations based on pharmacokinetic parameters which are calculated from the non-steady state serum concentrations by using basic equations.

2. This study will apply pharmacokinetic method for rapid adjustment of the dosage regimen in preterm infants before the steady state serum concentration is reached, results in adequate clinical response and avoiding adverse reaction or toxicity from overtherapeutic level.

3. This study will provide the answer about appropriateness of traditional theophylline loading dose in preterm infants which lead to adjust for the appropriate loading dose in the future.

4. This study should be an initiation of the possible method for calculation of the maintenance dose in preterm infants before the steady state serum concentration is reached.