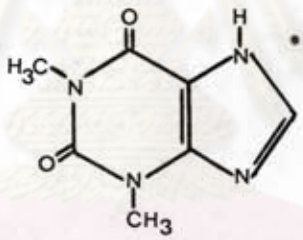
CHAPTER I

INTRODUCTION

Chemically, theophylline is a 1,3-dimethylxanthine that is a naturally occurring alkaloid. Although present in natural sources, theophylline is made available commercially by total synthesis. The structural formula of theophylline is as follows: (Cohen, 1975; Rall, 1985)



The therapeutic effect of theophylline has been known since 1930's. It has been used for treatment of bronchospasms. It is presently be used to prevent or allerviate asthma and acute exacerbation of obstructive airway disease in adults and children. (Rowe et. al., 1988). The concentration of theophylline in blood circulation which is necessary to produced therapeutic effect is in the range of 10-20 mcg./ml. and the concentrations correlate well with bronchodilator response and toxicity. (Jenne et. al.,1972;McDonald and Ladenson,1978) When plasma drug concentration greater than 20 mcg./ml., adverse effects commonly encountered causing nausea, vomiting, abdominal pain, gastro-intestinal bleeding, insomnia,

headache, anxiety, vertigo and palpitations. Severe overdosage or idiosyncrasy may also lead to maniacal behaviour, diuresis, dilirium, tachycardia, seizures, brain damage and death. (Jenne et. al., 1972; McDonald and Ladenson, 1978; Mathews, Schneiweiss and Cersosimo, 1986; Reynold, 1989; Wilson et. al., 1991)

The therapeutic failure when plasma theophylline concentration be in suboptimal therapeutic level or in supraoptimal therapeutic level is often observed with usual dose administered , due to the narrow therapeutic range of this drug. Second, the clinical usefulness of this drug may be distorted by patient compliance when the drug is prescribed in an outpatient setting, particularly in children.

The toxicity should be focused on children because they are more sensitive to the effect of xanthine drugs and their general reflex excitability is higher than adults. (Soifer, 1957)

The variation in rate of hepatic biotransformation is also the important factor which can shift the drug concentration from its therapeutic range. Since theophylline is primarily metabolized by the liver, the alteration of liver function from whatever causes (e.g.age, concurrent illness, aberrations in diet, intake of other drugs, and the differentiation of metabolizing enzyme efficiency) can alter the theophylline's elimination. (Leung, Kalisker and Bell, 1977; Hendeles, Massanari and Weinberger, 1986).

As already reported from either foreign or Thai patients (Bonham et.al.,1980; Hendeles, Weinberger and Johnson, 1983; Saming Kaojaroen,1988) plasma theophylline levels are mostly lower than 10 mcg./ml. or higher than 20 mcg./ml. This stimulates the necessitate of individualized monitoring of the dose used especially during chronic therapy.

Theophylline concentration can be determined by ultilyzing various techniques including ultraviolet spectrophotometry, (Schack and Waxler, 1949; Matheson, Bighley and Hendeles, 1977 and Schwertner, Wallace and Blum, 1978) gas chromatography,(Shah and Riegelman, 1974; Chrzanowski et al.,1974; Dusci, Hackett and McDonald, 1975; Least,Johnson and Solomon,1976) immunoassay,(Loomis and Frye, 1983; Habib et. al., 1987) and high performance liquid chromatography (Adams, Vandemark and Schmidt, 1976; Franconi et al.,1976; Evenson and Warren, 1976;Orcutt et al., 1977; Nelson et al., 1977; Soldin and Hill, 1977; Hill,1977; Butrimovitz and Raisys, 1979; Bock, Lam and Karmen, 1984). The classical application of the ultraviolet method of Schack and Waxler (1949) which have some disadvantages of using a large volume of sample, requiring a lengthy analysis time and lacking specificity; results were often falsely increased because of contribution from other xanthine compounds and other concurrent administered drug. Gas liquid chromatographic method provide greater selectivity than ultraviolet method, but extraction and derivatization steps are tedious time consuming. Moreover, and adequate internal standard is hardly available (Piafsky and Ogilvie, 1975). Immunoassay methods are convenience for routine measurement

of theophylline, but the cross reactivity of theophylline antibody with its own metabolites have to be highly concentrated especially in samples obtaining from renal failure patient. (Rowe et al, 1988)

The high-performance liquid chromatography technique is accepted as an outstanding analytical method appropriately for theophylline analysis in research laboratory and clinical services. (Piafsky and Ogilvie, 1975; Hendeles et. al.,1983) It is acceptable for its sensitivity and specificity with the rapid procedure. (Orcutt et. al.,1977; Nelson et. al.,1977; Bock et. al.,1984) Therefore, the high-performance liquid chromatography was selected to be the analytical method of theophylline in this study.

From many previous reports, whole blood, plasma and serum can be used for thephylline concentration monitoring but these medias need invasive method in withdrawing samples. This sample collecting method is not justified in some conditions; as in massive bleeding patients, elderly or neonate patients.

The use of theophylline concentrations in saliva for monitoring theophylline therapy in children was first suggested by Levy, Ellis and Koysooko. (1974) Many other studies confirming the concept of substituting saliva for plasma in theophylline concentration monitoring have been known. (Johnson, Dechtiaruk and Solomon, 1975; Eney and Goldstein, 1976; Galant et al., 1977; Ohmori, 1986; Aviram et al, 1987) Additionally, The summary of some distinct advantages of saliva over the invasive medias was stated in Danhof and Bremer (1983).

For example :

- Saliva can be collected by non-invasive technique and many samples can be obtained without exposing patients to discomfort, skin irritation and infection risk. This is of special importance for children and elderly patients.

- There are indications that the concentration of some drug in saliva is equal to the free or protein-unbound concentration in plasma, which is more closely related to activity of the drug than is the total plasma concentration. Therefore, the measurement of drug concentrations in saliva may be of greater therapeutic meaning than that of plasma concentrations.

To substitute saliva for plasma samples, the saliva-plasma theophylline concentration ratio is needed for conversing saliva theophylline concentration to plasma concentration. Many differance saliva-plasma theophylline concentration ratio values have been reported from various investigators, ranging from 0.42-0.67. (Johnson, Dechtiaruk and Solomon, 1975; Eney and Goldstein, 1976; Galent et. al.,1977; Ohmori et. al.,1986; Aviram et. al.,1987) In Thailand, one study on relationship between the theophylline concentration in saliva and plasma of 10 Thai asthmatic children reported the proportionality factor of saliva to serum to be 0.62. (Montri Tuchinda et.al.,1987) Galent et.al.(1977) has suggested that the value of saliva-plasma concentration ratio determined in each individual place with each different patient's condition should be only suitably used in their own. Some studies have been tried to determine the saliva-plasma ratio in healthy adult volunteers as the represent value for any patient. (Koysooko,Ellis and

Levy, 1974; Cohen, Johnson and Osvaldo, 1975; Culig, Johnston and Turner, 1982; Ohmori et.al.,1986) However at present, there are still no reports or research subjects determining the saliva-plasma ratio in Thai healthy volunteers. Additionally, it has already reported that the elimination half-life of caucasian asthmatic children (6-17 years of age) ranging from 1.4 to 7.9 hours (mean 3.7 hours). (Ellis, Koysooko, and Levy, 1976) which was different to those detected in Thai asthmatic children (8-13 years of age), ranging from 6.8 to 17 hours. (Montri Tuchinda et. al.,1984) Although the value of saliva-plasma ratio is not affected by elimination half-life, it is still led to question that the saliva-plasma concentration ratio of Thais may differ from the previous foreign ratios.

It is therefore interested in determination of the representative value of saliva-plasma theophylline concentration ratio in Thais in which it would be possible be generalized to individual Thai patients with or without specific conditions in future.

Objectives

1. To determine the saliva-plasma concentration ratio of theophylline in healthy Thai volunteers.

2. To study the possibiity of using this ratio in predicting plasma theophylline concentration in asthmatic patients from theophylline saliva concentration.

The Significance of the Study

1. This study will provide the saliva-plasma concentration ratio of theophylline in healthy Thais.

2. This study will reveal the possibility of theophylline monitoring in Thai patient via salivary level measurements.

3. The information obtained could apply to other drugs, which should be monitored by following this studied pattern.