SIMULTANEOUS SALIVA & PLASMA THEOPHYLLINE CONCENTRATION LEVELS IN ASTHMATIC PATIENTS

THESIS

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(CHEST DISEASES)

BY

SOBHY HASSAN SAYED EL GENDY

M.B., B.Ch.

UNDER SUPERVISION OF

Prof. Dr. MOHAMED AWAD TAG EL-DIN

Prof of Chest Diseases

Ain Shams University

Dr. SAMIHA SAYED ASHMAWI

Lec of Chest Diseases

Ain Shams University

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

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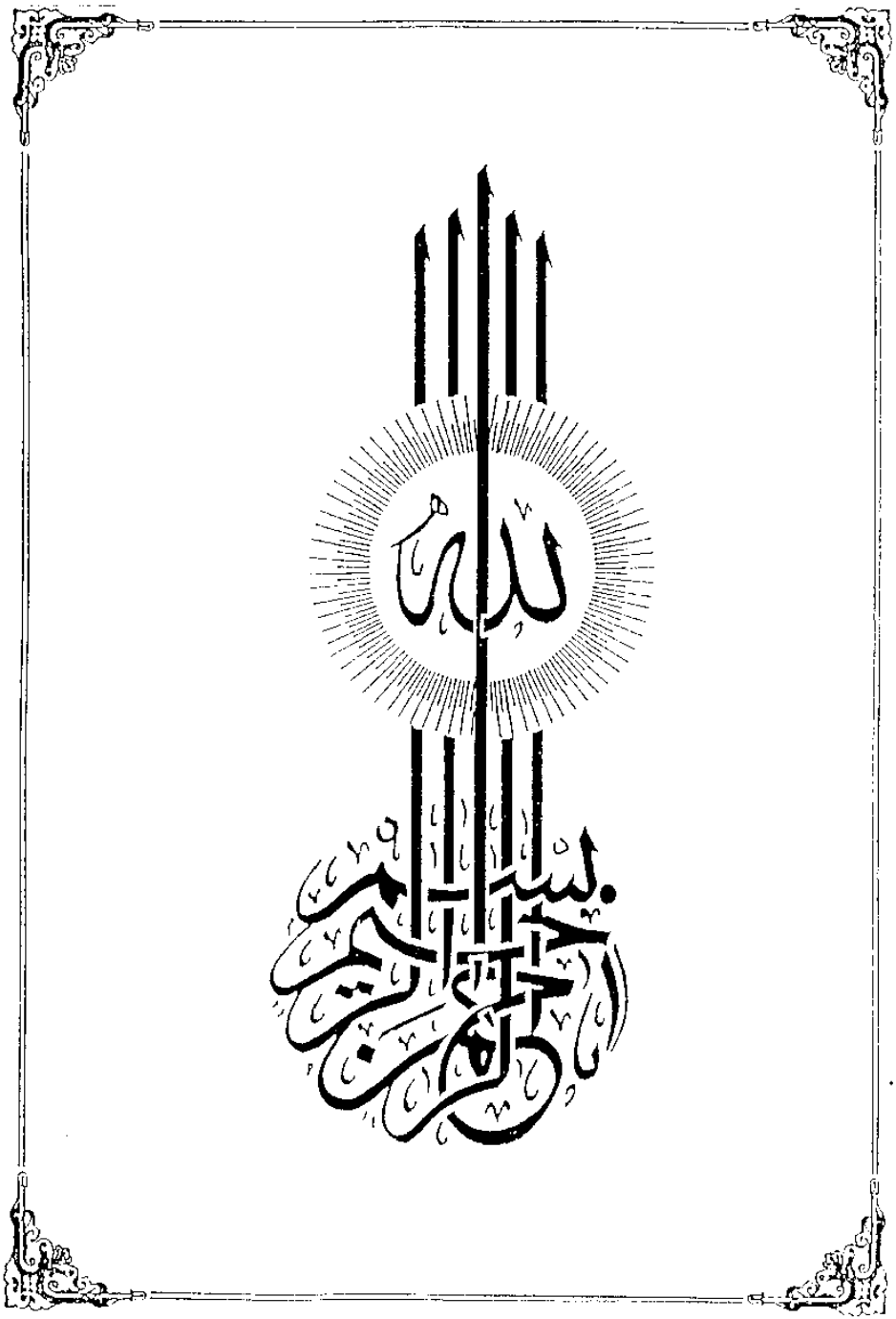
بسم الله الرحمن الرحيم



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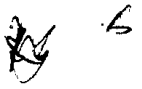

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T H E O P H Y L L I N E

REVIEW OF LITERATURE

THEOPHYLLINE

INTRODUCTION

Theophylline is an old drug that, over the years, has been used as a diuretic, a bronchodilator and respiratory stimulant. It has been used clinically for heart failure, cheyne-stoke respiration, infantile apnoea and asthma.

Long recognised as a potent bronchodilator for relief of acute symptoms of asthma, in recent years: It has also become a major prophylactic agent for controlling the symptoms and signs of chronic asthma.

This advance has resulted largely from the application of new knowledge of the pharmaco-dynamic and pharmaco-kinetic characteristics of this drug and the availability of rapid and specific methods for assaying of theophylline in serum (Weinberger M. & Hendeles L., 1983)

AIM OF THE STUDY :

Theophylline concentration in the plasma should be maintained within the range of 10-20 ug/ml. to achieve maximum therapeutic benefit with minimum adverse effect. so, it is advisable to monitor the plasma concentration of theophylline at appropriate intervals to facilitate the safe and

effective use of this drug.

Determination of plasma concentration of theophylline requires frequent blood sampling which involves considerable inconvenience to patients and medical personnel.

Koysooko et al, 1974, observed that theophylline determination in saliva may be convenient, painless and noninvasive method for routine monitoring of theophylline levels.

The principle aim of this study is to evaluate the relationship between theophylline concentration in serum and saliva.

Theophylline is a dimethylated xanthine similar in structure to coffeine and theobromine.

(Weinberger M. & Hendeles L., 1983).

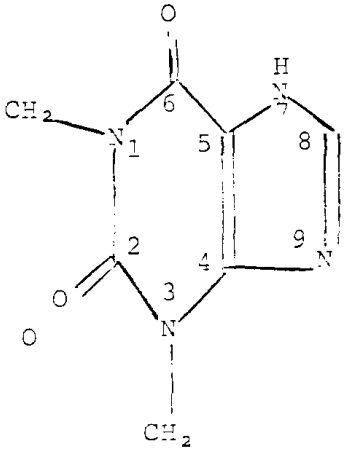
CHEMICAL HISTORY OF XANTHINES :-

Xanthine belong to the group of purine compounds. Purine were first isolated by Von Scheele in 1776. In 1820 Runge managed to isolate caffeine from caffee. There was then some confusion as to the purine content of tea leaves. Tea leaves contain a considerable amount of coffeine,which was isolated and for some years called thein, until its identify was clarified by Berzelius et al. In 1888 Kossel

successfully isolated asmall amount of dimethylxanthine from tea and named it THEOPHYLLINE.

Emil Fischer was anioneer in his work on the synthesis and determination of the chemical structure of caffeine and theophylline. A significant further step was taken by Traube, who devised a verstile method for synthesis of different xanthines derivatives.

(Carl G. A. Persson, 1986) ⓐ



1,3 Dimethylxanthine

MEDICAL HISTORY OF XANTHINES :-

Theophylline was prescribed as diuretic drug. Increasing doses were employed and serious adverse effects were soon noticed. In 1904 Allard described the seizure induced capacity of theophylline inpatient.

In 1912 Trendelenburg showed that xanthines relax airway smooth muscles. Ten years later Hirsch used theophylline in asthmatic subjects, and at the end of 1930s Herman, Jacobs, Aynesworth and others established the use of theophylline as a bronchodilator.

A sign that this treatment was gaining acceptance was the drug industries growing interest in developing bronchodilator xanthine derivatives.

(Carl G.A. Persson, 1986)(a).

CHEMISTRY OF THEOPHYLLINE

Pharmaco-dynamics :-

a- Relationship of efficacy and serum concentration :-

The bronchodilator effect of theophylline is proportional to the logarithm of the serum concentration over a range of 10-20 ug/ml. (Levy B. & Koysooko R., 1975). The bronchodilator effect also falls as theophylline disappears from serum.

A relationship between serum theophylline concentration and decrease in nonspecific airway reactivity can similarly be demonstrated by measuring the blocking of exercise induced bronchospasm.

(Weinberger M. & Hendeles L., 1986).

b- Relationship of toxicity to serum concentration :-

The adverse effects of theophylline are associated with serum concentration above 20 ug/ml. and gastro-intestinal tract disturbances are the most common toxic effects.

(Richard et al., 1984).

Other toxic manifestations are headache, irritability, insomnia and at higher serum levels cardiac arrhythmias, seizures and death

Frequently, minor symptoms of theophylline toxicity do

not precede cardiac arrhythmias or seizures and thus cannot be relied upon to give a warning, or use as a dosing end point.

(Hendeles et al., 1977)

Thus serum concentration measurments are the only reliable means of predicting life threatening toxicity from this drug. (Weinberger M. & Hendeles L., 1983). But recently salivary concentration estimation is reliable as in this study.

PHARMACOKINETIC

Pharmacokinetics is concerned with the investigation and mathematical description of drug absorption, distribution, metabolism and excretion. The major reason for elucidating a drug's pharmacokinetics is the general awarness that the pharmacologic effects of that drug are related to and are a function of its concentration at sites of action.

(Gerhard Levy, 1986)

ABSORPTION

Theophylline is rapidly consistently and completely absorbed from all liquid formulation and plain uncoated tablets.

(Hendeles et al., 1977)

Rectal suppositories have been erratically and incompletely absorbed, while absorption from rectal solution is almost as rapid and complete as from oral solution.

(Ridolfo & Kohlstoedt, 1959).

Enteric coated tablets (Waxler & Schack, 1950) and some slow release formulation are erratically and incompletely absorbed.

(Weinberger M. et al., 1978).

However certain newer continuous release formulation have demonstrated excellent drug serum level profile.

DISTRIBUTION :-

Following either intravenous administration or absorption from the gastro-intestinal tract, theophylline distributes rapidly into peripheral tissue other than fat, protein bound average about 40% (Mangion et al., 1978). Theophylline freely cross the placenta (Arwood et al., 1979) and passes into breast milk "Yurchak & Jusko, 1976", Cerebrospinal fluid concentration after distribution are approximately 90% of the serum concentration. (Weinberger M. et al., 1983).

Salivary levels average 48% of serum concentration (Koysooko et al., 1974).

Also "Koysooko et al., 1974" stated that theophylline does not distribute into fatty tissue, but readily crosses the placenta & breast milk.

METABOLISM AND EXCRETION

After a typical single oral or intravenous dose of theophyline, 80% to 90% of the dose may be recovered as theophylline and metabolites in urine collected upto 72 houres after the dose.

The major metabolites as a percentage of dose are:1,3 DMu (Dimethyluric acid) 35% - 40%, 1-Mu (methyluric acid 15% - 20% and 3 Mx (methylxanthine) 10% - 15% which is pharmacologically active metabolite.

Metabolism is mediated by hepatic microsomal enzymes that probably include two separate forms.

It is well known that the metabolic activity of these enzymes in a given person is largely determined by genetic factors and markedly modified by environmental factors such as smoking , diet , diseases and drug interactions .

(Lawrence, 1986).

After a single dose, when serum theophylline concentration is at its highest, the urinary excretion rate of theophylline is elevated as a result of an increase in the urine flow rate.

(Levy G. & Koysooko R., 1976).

EXCRETION :-

The excretion is by the kidney. Less than 15% of the drug is excreted unchanged in the urine. Elimination kinetics vary greatly among individuals. The plasma elimination half life of theophylline average about 7 - 9 hours in adult non-smokers, 4 - 5 hours in adult smokers, 3 - 5 hours in children and 20 - 30 hours in premature neonates. The premature neonates excrete about 50% unchanged theophylline and may accumulate the caffeine metabolites.

Decreased plasma clearance of theophylline occurs in patients with heart failure, liver dysfunction, alcoholism, pulmonary oedema, chronic obstructive pulmonary disease with or without cor pulmonale, respiratory infections and in patients receiving certain other drugs such as troleandomycin erythromycin and cimetidine. High fever for prolonged periods may decrease elimination. Total theophylline clearance appears relatively unaffected by renal failure.

(Erwin K. Kastrop et al., 1985).