THE INFLUENCE OF THE APPLICATION OF PHARMACOKINETICS ON THE EFFECTS OF THEOPHYLLINE UTILISATION UPON MEMBERS OF THE INDIAN POPULATION

by

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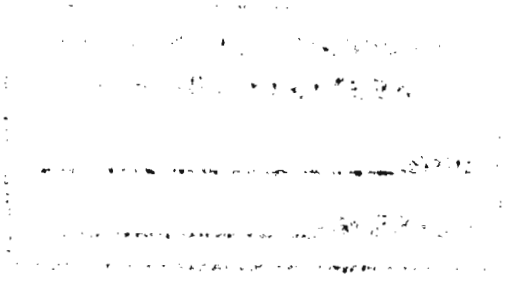
To mom and dad
for more reasons than can be listed here !



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GLOSSARY OF IMPORTANT SYMBOLS AND ABBREVIATIONS

σ	residual intraindividual variance
τ	time interval between doses
Θ	fixed effect population pharmacokinetic parameter
Ω	interindividual variance
ε	random error term for residual intraindividual variability with a mean equal to zero and variance σ^2
$\cap$	random error term for interindividual variability with a mean equal to zero and covariance matrix Ω
Cl	total body clearance
Cp	drug concentration in serum or plasma
Cp_{ss}	Cp at steady state
D	dose
DOBF	difference between the values of 2 objective functions
F	bioavailability factor
f	a pharmacokinetic model e.g. a sum of exponentials
IBW	ideal body weight
K	elimination rate constant
Ka	absorption rate constant
Km	Michaelis Menten constant
NONMEM	Non-Linear Mixed Effects Model - computer programme used for population pharmacokinetic data analysis
P	a pharmacokinetic parameter e.g. Cl
PREDPP	a NONMEM load module used specifically for population pharmacokinetic data analysis
PREP	a user-written NONMEM regression term used to differentiate the Ka values of Alcophyllin^R, Theodur^R and Euphyllin Retard^R
q	a vector valued function as distinct from f above
Ri	rate of infusion
SE	standard error of the fixed effect parameters

SE_{var}	standard error of the variances σ^2 and $\cap$
SM	a user-written NONMEM regression term used to differentiate smokers from non-smokers
t	time of the pharmacokinetic observation
Vd	volume of distribution
Vmax	maximum rate of metabolism
Wt	weight
X	a collection of concomitant patient features e.g. age, smoking habits

CONVERSION FACTOR

Throughout this text, serum theophylline concentration measurements are reported in the locally popular μg/ml units rather than the SI units of mMol/L. The relevant conversion factor for μg/ml to mMol/L is 5.55.

INTRODUCTION

Theophylline is a dimethylated xanthine similar in structure to caffeine which is commonly found in tea, coffee and cola beverages (*Hendeles and Weinberger, 1983; Rall, 1985*). Clinically, its most important pharmacological action is the ability to relax bronchial smooth muscle throughout the bronchial tree (*Persson, 1986*). This effect has found extensive use in the treatment of asthma with the drug being recommended as the first line agent for chronic asthma (*Iafrate et al, 1986*).

The observation that both beneficial effects as well as toxicity correlate with serum concentrations and that the drug displays a narrow therapeutic window (*Finn et al, 1981; Hendeles and Matthay, 1986*) has resulted in the recommendation that theophylline dosing be guided by serum concentration measurements (*Hendeles and Weinberger, 1980; Whiting et al, 1984; Fitzpatrick and Moss-Barclay, 1985; Barlow et al, 1988*). However, this recommendation appears to have been largely ignored locally. In 1986, one of the first local Therapeutic Drug Monitoring Clinics for theophylline was established at R K Khan Provincial Hospital in Chatsworth, Durban. Preliminary results from this clinic confirmed the widespread use of standard theophylline dosing regimens and revealed that 68% (n = 44) of patients given these regimens had serum theophylline concentrations below the generally accepted therapeutic range (*Pillai and Miller, 1988*).

Previous studies have assessed the influence of Therapeutic Drug Monitoring programmes in terms of the attainment of 'therapeutic' serum concentrations (*Whiting et al, 1984; Fitzpatrick and Moss-Barclay, 1985*). This approach has been criticised and it has been recommended that clinical assessment should be the criterion. The purpose of this study was to investigate the influence of serum concentration monitoring on theophylline utilisation at the R K Khan Hospital in terms of clinical control of asthma symptoms.

A secondary purpose of this study was to determine population pharmacokinetic parameters in Indian patients. In order to interpret the serum concentrations and make recommendations on dosage design for individual patients, the Bayesian technique of drug dose optimisation is used (*Sheiner et al, 1972*). This technique has been shown to be accurate, precise and easy to use (*Sheiner and Beal, 1982; Hurley*

and McNeil, 1988) particularly with currently available computer software. It has been emphasised, however, that for satisfactory performance of this technique, good initial estimates of the population parameter distributions are important (*Whiting et al, 1986*). Since this information is not available for the Indian population this study was undertaken. A knowledge of population pharmacokinetics can help one to choose initial dosage, to modify dosage appropriately in response to observed drug levels, to make rational decisions regarding drug regulatory requirements and to investigate and elucidate certain research questions in pharmacokinetics (*Sheiner, 1984*). The NONMEM approach (*Sheiner et al, 1972; 1977*), currently the most satisfactory method of population pharmacokinetic data analysis is utilised in this study.

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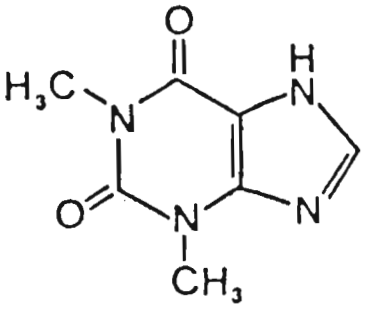
Chapter One

Theophylline - Pharmaceutical Chemistry, Mechanism of Action, Pharmacology, Toxicity and Pharmacokinetics.

1.1 PHARMACEUTICAL CHEMISTRY

1.1.1 Structure



Theophylline

Fig. 1 - Structure of 1,3-dimethylxanthine (theophylline)

Theophylline is a dimethylated xanthine similar in structure to caffeine (1,3,7-trimethylxanthine) and theobromine (3,7-dimethylxanthine). These alkaloids occur in plants widely distributed throughout the world. They are commonly found in coffee, tea, cola beverages and chocolate (*Hendeles and Weinberger, 1983; Rall, 1985*).

1.1.2 Solubility

Theophylline is poorly soluble in water (8 mg/ml at 25°C) and therefore various complexes (so-called 'salts') have been developed, with a view to improving the solubility and absorption of the drug. At physiological pH, theophylline is a weak

base (pKa = 8.8) and only slightly ionised and therefore incapable of existing as a salt. Salts of theophylline with a base e.g. ethylenediamine can only be formed at much higher pH values due to a tautomeric shift in hydrogen. Therefore, at physiological pH these so-called 'salts' are actually mixtures of theophylline and base - the base having no useful pharmacological activity (*Hendeles and Weinberger, 1983*) and may in fact be implicated in adverse effects (*Elias and Levinson, 1981*).

The absorption of the methylxanthines has been shown to relate more to their lipophilic characteristics than to water solubility. The formation of complexes of theophylline with the ultimate aim of increasing absorption is therefore irrational (*Hendeles and Weinberger, 1983*).

In addition, the contribution of the base to the mass of the dosage form complicates the calculation of appropriate doses during therapy. In view of these factors all dosing and labelling of theophylline should be in terms of the content of anhydrous theophylline in the preparation. At present this is not a legal labelling requirement in South Africa. This is unfortunate if one considers the potential for dangerous dosage errors. For example, a change in a patient's prescription of Choledyl^{R} 200 mg to Theodur^{R} 200 mg will result in an increase in theophylline dose of over 56%. This potential for toxicity is not apparent because of the lack of uniformity in labelling requirements. Table I indicates the anhydrous theophylline content of preparations available in South Africa and enables rational dosing with available theophylline preparations. The source of information for construction of the table was a combination of personal communications with the relevant pharmaceutical companies, reference to manufacturer's package inserts and MIMS Medical Specialities (*Botha, 1989*). It was necessary to liase directly with the pharmaceutical manufacturers since the use of theophylline 'salts' with different degrees of hydration also results in differences in the content of anhydrous theophylline. *Miller and Rheeders (1984)* for example, consider the theophylline content of Euphyllin Retard^{R} to be 281.7 mg. However, the manufacturer, Byk Gulden Pharmaceuticals have advised that this actually refers to the monohydrate form of theophylline - the anhydrous theophylline content being 256.1 mg. In cases where no information was

forthcoming from the manufacturer, calculations were based on information extracted from Martindale, The Extra Pharmacopoeia, 29th Edition (*Reynolds, 1989*).

Table I - Theophylline-containing preparations on the South African market

Preparation	Manufacturer	Dosage Form	Labelled content of theophylline (1)	Content of anhydrous theophylline (1)	Notes
Actophlem	Adcock-Ingram	Liquid	Theophylline 3.33 mg/ml Etofylline 0.33 mg/ml	3.33 mg/ml 0.27 mg/ml	3
Alcophyllex	Propan-Lipworth	Liquid	Theophylline 3.33 mg/ml Etofylline 0.33 mg/ml	3.33 mg/ml 0.27 mg/ml	3
Alcophyllin	Propan-Lipworth	Liquid	Theophylline 5.33 mg/ml	5.33 mg/ml	2
Amesec	Eli-Lilly	Capsule	Aminophylline 130 mg	90.72-115.37 mg	2
Aminophylline	Searle	Suppository Tablet	Aminophylline 100;500 mg Aminophylline 100;200 mg	84-87.4;420-437 mg 84-87.4;168-174.8 mg	2
Biotussin	Protea	Liquid	Theophylline 5.63 mg/ml	5.63 mg/ml	2
Choledyl	Warner	Liquid Tablet	Oxtriphylline 10 mg/ml Oxtriphylline 100;200 mg	6.36 mg/ml 63.6;127.2 mg	3
Daral	Noristan	Capsule	Aminophylline 130 mg	104.4-109.2 mg	2
Dilinct	Restan	Liquid	Etofylline 7.03 mg/ml	5.65 mg/ml	2
Diphenamill	Brunel	Liquid	Aminophylline 2.52 mg/ml	2.16 mg/ml	3
D-Tussin	Script Intal	Liquid	Etofylline 6.67 mg/ml	5.36 mg/ml	3

Table I - Theophylline-containing preparations on the South African market
(continued)

Preparation	Manufacturer	Dosage Form	Labelled content of theophylline (1)	Content of anhydrous theophylline (1)	Notes
Efcod	Covan	Liquid	Aminophylline 6 mg/ml	5.14 mg/ml	3
Euphyllin Retard	Byk Gulden	Tablet	Aminophylline 350 mg	256.1 mg	2
Franol/Framol	Sterling	Liquid Tablet	Theophylline 3 mg/ml Theophylline 118.2 mg	3 mg/ml 118.2 mg	2
Lotussin Expect	Searle	Liquid	Aminophylline 6.4 mg/ml	5.38-5.59 mg/ml	2
Medikasma	Vernleigh	Liquid	Aminophylline 130 mg	101.4-109.2 mg	2
Metaxol	Vernleigh	Liquid	Theophylline 3.52 mg/ml	3.52 mg/ml	2
Microphyllin	Script Intal	Capsule	Theophylline 60;125;250 mg	60;125;250 mg	
Nethaprin Syryp and Expect	Mer-National	Liquid	Butaphyllamine 12 mg/ml	8.04 mg/ml	2
Nethaprin Dospan	Mer-National	Tablet	Butaphyllamine 180 mg	120.6 mg	2
Nuelin	Riker	Liquid Tablet	Theophylline 5 mg/ml Theophylline 50;125 mg	5 mg/ml 50;125 mg	

Table I - Theophylline-containing preparations on the South African market (continued)

Preparation	Manufacturer	Dosage Form	Labelled content of theophylline (1)	Content of anhydrous theophylline (1)	Notes
Nuelin SA 250	Riker	Tablet	Theophylline 250 mg	250 mg	
Nutrated	Hoechst	im injection iv injection	Aminophylline 250 mg/ml Aminophylline 25 mg/ml	214.25 mg/ml 21.43 mg/ml	3
Panasma	Propan-Lipworth	Capsule	Aminophylline 130 mg	111.41 mg	3
Peterphyllin	Lennon	Suppository Tablet	Aminophylline 125;500 mg Aminophylline 100;200 mg	100.93;403.75 mg 80.75;161.5 mg	3 2
Peterphyllin Co	Lennon	Tablet	Aminophylline 100 mg	79.05 mg	2
Phyllocontin	Mundipharma	Tablet	Aminophylline 225 mg	192.83 mg	3
Repasma	Lennon	Capsule	Aminophylline 130 mg	102.77 mg	2
Solphyllex	Rio	Liquid	Theophylline 3.33 mg/ml Etofylline 0.33 mg/ml	3.33 mg/ml 0.27 mg/ml	2
Solphyllin	Rio	Liquid	Theophylline 5.33 mg/ml Etofylline 0.67 mg.ml	5.33 mg/ml 0.53 mg/ml	2
Somophyllin CRT	Fisons	Capsule	Theophylline 100;250 mg	100;250 mg	

Table I - Theophylline-containing preparations on the South African market (continued)

Preparation	Manufacturer	Dosage Form	Labelled content of theophylline (1)	Content of anhydrous theophylline (1)	Notes
Sup-phyllin	Vernleigh	Suppository	Aminophylline 500 mg	390-420 mg	2
Tedral	Warner	Liquid Tablet	Theophylline 13 mg/ml Theophylline 130 mg	13 mg/ml 130 mg	
Tedral SA	Warner	Tablet	Theophylline 180 mg	180 mg	
Theodur	Rio	Tablet	Theophylline 200;300 mg	200;300 mg	
Theophen	Lennon	Liquid	Theophylline 5.33 mg/ml Etofylline 0.67 mg/ml	5.33 mg/ml 0.53 mg/ml	2
Theophen Co	Lennon	Liquid	Theophylline 3.33 mg/ml Etofylline 0.33 mg/ml	3.33 mg/ml 0.26 mg/ml	2
Theostat	MPS	Liquid	Etofylline 6.63 mg/ml (equiv to 5.33 mg/ml)	5.33 mg/ml	
Trakasma	Gotra	Liquid	Aminophylline 8.33 mg/ml	7.14 mg/ml	3
Vernaphylline	Vernleigh	Tablet	Aminophylline 200 mg	156-168 mg	2
Vernasma	Vernleigh	Tablet	Theophylline 200 mg	200 mg	2
Vernthol	Vernleigh	Liquid	Theophylline 5.33 mg/ml	5.33 mg/ml	2

Key to notes on Table I

(1) The theophylline content of liquid dosage forms were variously labelled by the manufacturer in terms of a mg per unit dose of liquid e.g. mg per 10 ml or mg per 5ml. In order to facilitate ease of calculations, all liquid dosage forms are reported in Table I as mg per ml.

(2) Source of information - personal communication with the pharmaceutical manufacturer.

(3) The theophylline content was calculated according to the following equation:-

$$\text{Theophylline content} = \frac{\text{Molecular mass of theophylline}}{\text{Molecular mass of theophylline 'salt'}}$$

such that :-

$$\text{Theophylline content of aminophylline} = \frac{2 * 180.2}{420.4}$$

$$= \underline{0.857}$$

$$\text{Theophylline content of etofylline} = \frac{180.2}{224.2}$$

$$= \underline{0.804}$$

$$\text{Theophylline content of oxtriphylline} = \frac{180.2}{283.3}$$

$$= \underline{0.636}$$

All molecular masses were obtained by referring to Martindale, The Extra Pharmacopoeia, 29th Edition (Reynolds, 1989)

1.2 CELLULAR BASIS FOR THE MECHANISM OF ACTION OF THEOPHYLLINE

The mechanism by which theophylline exerts its bronchodilator action has not been conclusively elucidated. However the literature is replete with proposed mechanisms (*Boushey and Holtzman, 1987*).

1.2.1 Phosphodiesterase inhibition

This popular theory for many years suggested that the drug exerted its action by inhibition of the enzyme phosphodiesterase. Phosphodiesterase is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP) to 5' adenosine monophosphate (5'AMP) - an inactive degradation product. Therefore inhibition of this enzyme will result in elevated cAMP levels. In smooth muscle, cAMP acts at different points (see Fig. 2):-

* facilitates the inactivation of myosin light chain kinase.
* inhibits calmodulin-Ca^{2+} complex formation and thus prevents activation of myosin light chain kinase.
* probably facilitates removal of Ca^{2+} via Ca^{2+}-ATPase in the cell membrane.

These effects cause relaxation of smooth muscle (*Katzung and Chatterjee, 1987*).

The phosphodiesterase inhibition theory is not without criticisms.

* The concentration of theophylline required to inhibit phosphodiesterase *in vitro* would be toxic if used *in vivo* (*Bergstrand, 1980*). At therapeutic serum concentrations, the degree of phosphodiesterase inhibition is minimal and not sufficient to explain the bronchodilation observed (*Bukowskyj et al, 1984*).
* Other phosphodiesterase inhibitors e.g. dipyridamole and papaverine are not bronchodilators (*Hendeles et al, 1985*).
* Although theophylline acts synergistically with beta-adrenoceptor agonists in increasing cAMP concentrations in tissues and perfused organs its bronchodilating action *in vivo* is an additive one (*Wolfe et al, 1978*).

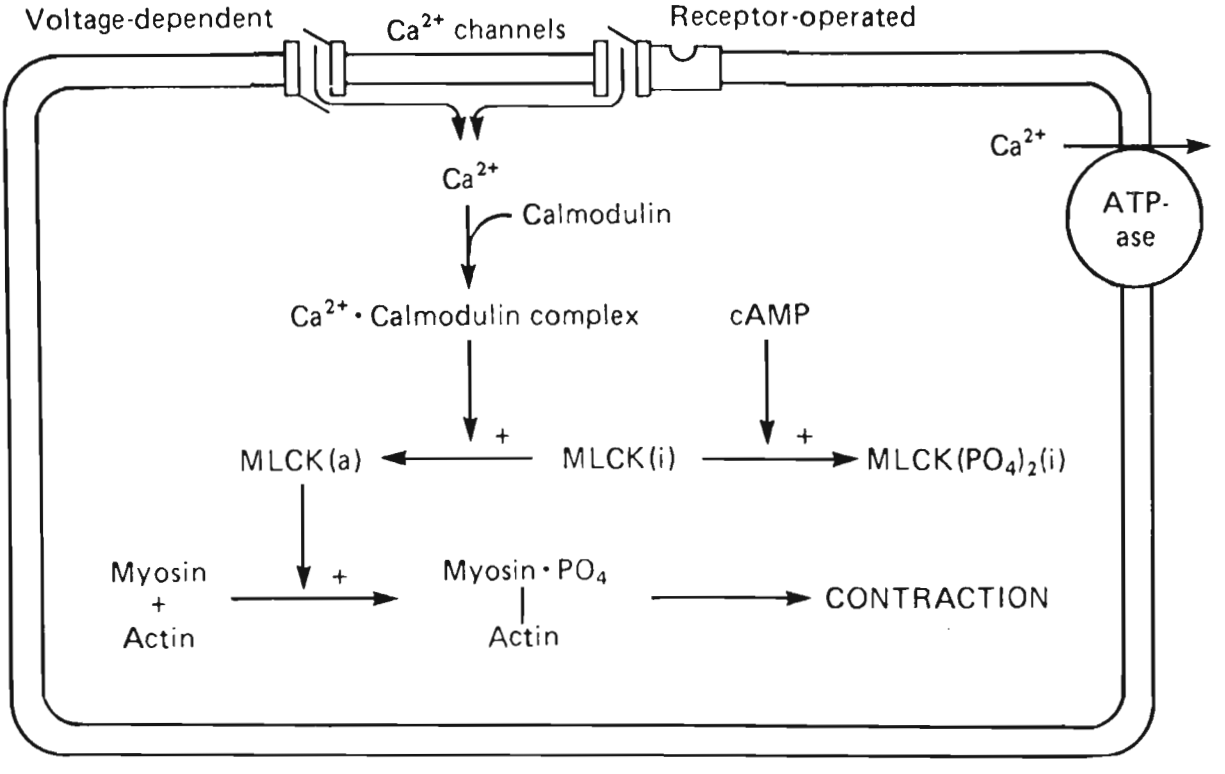


Fig. 2 - Schematic diagram of a smooth muscle cell and some aspects of smooth muscle contraction. Calcium ion enters the cell and forms a complex with a small protein calmodulin. This complex activates an inactive (i) form of the enzyme myosin light chain kinase (MLCK). Activated myosin light chain kinase (MLCK(a)), in turn, is responsible for the interaction with actin to produce smooth muscle contraction (adapted from *Katzung and Chatterjee, 1987*).

1.2.2 Antagonism of adenosine receptors

This theory stems from observations that asthmatics exposed to adenosine experience a rapid spasmatic contraction of smooth muscle, perhaps because of some idiosyncrasy in the cell receptors for adenosine. Adenosine is a breakdown

product of cAMP and is formed when cells have little oxygen available to them. It is released by animals under hypoxic conditions and in humans with asthma (*Murphy, 1985*).

However, enprofylline (3-propylxanthine) - a xanthine derivative, lacks adenosine receptor antagonist properties yet appears to be much more potent than theophylline as a bronchodilator (*Lunell et al, 1982*). Enprofylline does not have a diuretic effect or a stimulant action on the gastrointestinal tract (GIT). In animal studies, it has shown substantially less central nervous system (CNS) and cardiac toxicity than theophylline. This suggests that antagonism of adenosine receptors may relate to the diuretic, cardiac, GIT and CNS effects of theophylline but not necessarily to its bronchodilator activity (*Hendeles et al, 1986; Persson, 1986*).

1.2.3 Translocation of calcium

Calcium plays an essential role in excitation-contraction coupling and it has been proposed that theophylline's beneficial effect stems from alterations in cellular permeability or intracellular binding of calcium (*Stirt and Sullivan, 1981*). As discussed above (Fig. 2), removal of Ca^{2+} from the cell by cAMP results in smooth muscle relaxation, lending evidence for a role for calcium.

The main criticism against this theory is that the threshold for these effects to occur is much greater than the maximal therapeutic concentration of theophylline in serum (*Bukowskyj et al, 1984*).

1.2.4 Stimulation of endogenous catecholamine release

Stimulation of endogenous catecholamine release may partly explain the mechanism of action of theophylline since 50% of the bronchodilator effect can be inhibited by the prior administration of propranolol - a beta-adrenoceptor blocking drug. Furthermore, plasma and urinary catecholamine levels have been found to be increased after the administration of methylxanthines (*Church et al, 1986*). Two

mechanisms for theophylline-induced catecholamine release may be operative here - one dependent and the other independent of extracellular calcium (*Stirt and Sullivan, 1981*).

1.2.5 Other theories

Several other theories have received little attention to date. These include inhibition of the generation of contractile prostaglandins, increased binding of cAMP to cAMP-binding proteins (*Hendeles et al, 1985*), beta agonist activity and inhibition of guanosine monophosphate (GMP) metabolism (*Bukowskyj et al, 1984*).

In summary, there is no one unchallenged theory for theophylline's mechanism of action - in fact each of the above may play contributory or complementary roles to result in the final observed pharmacodynamic effect.

1.3 PHARMACOLOGY OF THEOPHYLLINE

1.3.1 Central nervous system

Theophylline and the other methylxanthines exert potent stimulant effects on the CNS which accounts for both beneficial and adverse effects of these drugs. In low and moderate doses, they cause a mild cortical arousal with increased alertness and deferral of fatigue (*Boushey and Holtzman, 1987*).

The beneficial effects of CNS stimulation relates primarily to theophylline's ability to stimulate medullary respiratory centres. Theophylline appears to increase the sensitivity of medullary centres to the stimulatory actions of CO_2 (*Rall, 1985*) i.e. it increases the hypoxic drive (*Lakshminarayan et al, 1978*). This effect finds use in the restoration of normal respiratory patterns in patients with Cheynes-Stokes respiration; reducing episodes of apnoea in preterm infants and reversing the respiratory depression produced by the opioids.

As the dose is increased, CNS stimulant effects of theophylline produces nervousness, insomnia, tremors and hyperesthesia (*Rall, 1985*). Sleep disorders have been documented as reduced sleep quality, decreased total sleep time, decreased rapid-eye-movement sleep, and increased frequency of arousal (*Bukowskyj et al, 1984*).

At higher doses, focal and generalised convulsions are produced, man being the most sensitive of the several species studied - more sensitive than monkeys, cats, guinea pigs, rats and mice (*Persson, 1986*).

Theophylline has the ability to constrict cerebral blood vessels. This probably accounts for the irreversible brain damage that may be seen as a sequela of theophylline toxicity (*Persson, 1986*).

1.3.2 Cardiovascular system

The actions of theophylline on the cardiovascular system are complex and sometimes antagonistic. The final result on any particular physiological function, if any, depends largely on the conditions prevailing at the time of their administration and the dose used.

Effects on the heart

The methylxanthines have direct positive chronotropic and inotropic effects on the heart (*Boushey and Holtzman, 1987*). At therapeutic concentrations, a modest increase in heart rate is observed. At higher concentrations, a definite tachycardia is seen, while some sensitive individuals experience arrhythmias such as premature ventricular contractions.

The drug also reduces left ventricular ejection time index and isovolumetric contraction time, consistent with an increase in contractile force and a decrease in cardiac preload. In normal individuals inconsistent decreases in cardiac output and stroke volume have been observed probably as a result of reflex regulatory changes. However, in patients with congestive cardiac failure and clinical cardiac disease, where the venous pressure is initially high, an increase in cardiac output has been consistently observed. This probably results from a generalised increase in venous distensibility and an increase in peripheral vascular capacitance with a resultant decrease in cardiac preload (*Ogilvie et al, 1977*).

Blood vessels

Theophylline causes a decrease in peripheral vascular resistance. This effect, together with the increased cardiac output, results in a transient increase in peripheral blood flow. The overall effect on arterial blood pressure, however, is minimal due to possible variable effects on different vascular beds and to compensatory mechanisms (*Ogilvie et al, 1977*).

Contrary to their effect on peripheral vascular resistance, theophylline causes an increase in cerebrovascular resistance leading to a decrease in cerebral blood flow and the oxygen tension in the brain (*Rall, 1985; Persson, 1986*).

Under certain circumstances theophylline increases coronary blood flow. It is uncertain whether this would be of benefit in coronary insufficiency as the drug also increases the work of the heart (*Rall, 1985*).

1.3.3 Urogenital system

Theophylline causes an increase in the production of urine, an effect which appears to be due to a combination of an increase in glomerular filtration rate and a decrease in renal tubular sodium ion reabsorption (*Boushey and Holtzman, 1987*). Tolerance usually develops to this diuretic effect but it may be important in an already dehydrated patient (*Persson, 1986*).
The drug is also reported to inhibit uterine contractions (*Hendeles & Weinberger, 1983*).

1.3.4 Gastrointestinal system

Theophylline significantly increases both acidity and volume of gastric secretion by increasing the secretion of both acid and pepsin (*Rall, 1985; Persson, 1986*). In addition, the drug causes relaxation of the lower oesophageal sphincter, an effect that may contribute to gastroesophageal reflux (*Persson, 1986*).

1.3.5 Respiratory system

The most important pharmacological action of theophylline is its ability to relax bronchial smooth muscle throughout the bronchial tree. The bronchodilator effect is seen irrespective of the stimulus for bronchoconstriction i.e. theophylline is a functional antagonist of bronchoconstrictor mediators (*Persson, 1986*).
Theophylline has recently been shown to have a potent effect on diaphragmatic contractility in normal persons - it improves contractility before and after induction of diaphragmatic fatigue. This apparent ability to reduce diaphragmatic fatigability and to improve contractility may account for the clinical improvement often seen in

patients with non-reversible obstruction after theophylline therapy (*Jenne, 1984; Bukowskyj et al, 1984*). It also assumes importance when respiratory failure threatens.

It has been shown clinically that theophylline increases mucociliary transport immediately and during prolonged treatment. *In vitro* studies have shown that the xanthines are potent stimulants of ciliary beat frequency (*Persson, 1986*).

Preliminary animal studies suggest that xanthines may attenuate microvascular leakage and increase release of alveolar surfactant material (*Persson, 1986*).

1.3.6 Metabolic actions

Theophylline may increase the release of noradrenaline, adrenaline, dopamine, renin, gastrin, insulin, glucagon, glucose, cortisol, parathyroid hormone, growth hormone and free fatty acids. Most of these effects may not occur to any significant degree at therapeutic serum levels (*Persson, 1986*).

1.4 TOXICITY

Side-effects from theophylline may be transient, minor or major. These are usually dose and serum concentration dependent.

1.4.1 Transient - 10 to 20 μg/ml

Within the therapeutic range, side effects are mild, caffeine-like effects to which patients rapidly acquire tolerance. These are often associated with attempts to rapidly achieve therapeutic serum concentrations in ambulatory patients with chronic asthma.
The effects seen are nausea, cramps, insomnia and headache. Small initial doses and slow titration over about 7 - 10 days helps to reduce the incidence of these effects (*Hendeles et al, 1986*).

1.4.2 Minor - 15 to 35 μg/ml especially > 20 μg/ml.

More severe and persistent adverse effects are associated with serum concentrations above 20 μg/ml.
These include persistent nausea, vomiting, insomnia, nervousness, irritability, headache, diarrhoea and sinus tachycardia.
In premature newborns, tachycardia frequently occurs at concentrations above 10 μg/ml while most other patients experience these effects at concentrations greater than 30 μg/ml (*Hendeles et al, 1986*).

1.4.3 Major - > 35 μg/ml especially > 40 μg/ml

The effects seen here include confusion, agitation, hypotension, hyperglycaemia, ventricular arrhythmias, seizures, brain damage and death.

Among infants and small children, severe toxicity has most often been the result of inadvertent administration of multiple adult doses of suppositories. Cocoa butter based suppositories have been associated with delayed and erratic absorption and are therefore currently not recommended (*Hendeles et al, 1986*).

In adults, serious theophylline intoxication frequently has been reported in patients with cardiac decompensation or hepatic dysfunction where clearance of the drug was impaired and excessive serum concentrations accumulated (*Jacobs and Senior, 1974*).

While theophylline-induced ventricular arrhythmias usually respond promptly to lignocaine, theophylline-induced seizures are generally unresponsive to anti-convulsants (*Hendeles et al, 1986*).

An important point to note is that from observations on patients who experienced seizures (*Zwillich et al, 1975*), minor adverse effects do not always precede the more life-threatening side-effects and that these minor effects (nausea and vomiting) cannot be relied upon as a dosing end-point - only serum theophylline concentration measurements can reliably forewarn of impending life-threatening toxicity (*Hendeles et al, 1986*).

1.4.4 Other

Other adverse reactions to theophylline include the rare occurrence of dehydration especially in children - due to a combination of a loss of fluids as a result of vomiting, decreased fluid intake, and the transient diuretic action of the drug (*Hendeles and Weinberger, 1983*).

Patients with ulcer disease may experience an increase in symptoms due to theophylline's ability to increase gastric acid secretion (*Persson, 1986; Hendeles and Weinberger, 1983*).

Allergic reactions (urticaria, exfoliative dermatitis) reported with theophylline use have been associated with the use of aminophylline (theophylline ethylenediamine). It has been suggested that this may be a hypersensitivity reaction to the ethylenediamine component (*Elias and Levinson, 1981*).

1.5 PHARMACOKINETICS OF THEOPHYLLINE

1.5.1 Absorption

Absorption of theophylline from liquids and plain un-coated tablets (i.e. when disintegration and dissolution is not delayed), is rapid, consistent and complete (*Hendeles et al, 1977; Upton et al, 1980*).

The absorption efficiency of aqueous and alcoholic liquid formulations of theophylline is similar (*Koysooko et al, 1975*) and there is therefore no reason to use alcohol as a vehicle since it is more likely to cause side effects than contribute to efficacy.

The use of microcrystalline theophylline in various tablet and capsule formulations does not enhance absorption to any significant degree (*Sansom et al, 1979*).

In the past, enteric coated theophylline preparations were developed with the intention of avoiding the side-effect of nausea and vomiting. Studies have demonstrated that this side-effect is not due solely to a local irritant action and therefore, this rationale is not valid and may in fact be disadvantageous. Enteric coating of theophylline tablets has been shown to decrease dissolution and can result in incomplete or unpredictable delays in absorption (*Upton et al, 1980a*).

The administration of theophylline with food has been found to affect the rate but not the extent of theophylline absorption in rapidly absorbed formulations. This effect is not considered to be clinically important in chronic dosing (*Hendeles et al, 1986*). However, the influence of food on the absorption of theophylline becomes important when dealing with certain slow release products. Formulation dependent interactions between slow release preparations and food composition, temperature, quantity and/or density and time of food intake in relation to concomitant drug intake have been described (*Schulz et al, 1987*). These interactions have resulted either in delays in effect, or in contrast, and more importantly, in toxicities due to dose dumping. It is clear therefore, that in the choice of a sustained release product for routine clinical use, only a preparation whose release is unaffected by food and factors such as pH should be considered.

Concurrent administration of antacids containing aluminium and magnesium hydroxide decreases the rate but not the extent of absorption of theophylline from plain, un-coated tablets. This may be due to a combination of physical adsorption as well as to increased ionisation of theophylline at the higher pH. This effect is probably unimportant when considering chronic theophylline therapy (*Shargel et al, 1981*).

A circadian pattern in theophylline absorption has been reported with slower absorption occurring at night. This results in higher morning trough levels for most of the slowly absorbed products. This may find clinical relevance in timing of blood samples in that this should be standardised within patients (*Taylor et al, 1983; Glynn-Barnhart et al, 1988*) .

The only parenteral route of administration that is currently recommended is the intravenous route. Since the maximum solubility of theophylline in water is ± 8 mg/ml at physiological pH and temperature, intramuscular injection of available parenteral preparations results in precipitation at the injection site, pain, irritation and slow absorption (*Hendeles et al, 1986*).

Rectal suppositories made with a cocoa butter base are not recommended since they have been repeatedly associated with slow and erratic absorption (*Hendeles et al, 1986*).

In children, the use of suppositories have frequently been associated with severe theophylline toxicity, most often due to the administration of multiple adult doses (*Hendeles et al, 1986*) probably because of the delayed and erratic absorption. The rate and extent of absorption from rectal solutions (and experimental polyethylene glycol suppositories) is similar to that of oral solutions and may be used if the patient is unable to take oral medications (*Hendeles et al, 1986*).

1.5.2 Distribution

After theophylline enters the systemic circulation, between 40 - 60% becomes bound to plasma proteins. Evidence seems to favour the lower percentage of 40% since the value of 60% may have been obtained because of the lower temperature and increased pH conditions that occurred during *in-vitro* testing (*Shaw et al, 1982; Hendeles et al, 1986*).

Protein binding is decreased in premature newborns, in adults with hepatic cirrhosis or un-corrected acidemia and in the elderly (*Hendeles et al, 1986*). Preliminary results indicate that plasma protein binding is also markedly reduced in pregnancy, averaging 11.1 ± 4.7% in the second trimester; 13.0 ± 5.9% in the third trimester and 28.1 ± 2.8% in the remote postpartum period (*Frederiksen et al, 1986*). As a result of this decreased protein binding, the apparent volume of distribution (Vd) is slightly larger in these patients (*Hendeles et al, 1986*). In obesity, however, the opposite situation prevails and Vd is found to be decreased (*Bukowskyj et al, 1984*).

Apart from these conditions, Vd remains relatively unchanged even when clearance is altered. It ranges from 0.3 - 0.7 L/kg with an average of about 0.45 L/kg among both adults and children (*Loughnan et al, 1976; Hendeles et al, 1978; Hendeles et al, 1986*).

After intravenous injection, theophylline serum concentrations equilibrate with tissue concentrations within 1 hour. The drug passes readily across the placenta (*Labovitz and Spector, 1982*), blood-brain barrier (*Hendeles et al, 1986*) and into breast milk. A milk to serum ratio of 0.7 has been reported (*Yurchak and Jusko, 1976*).

1.5.3 Metabolism and excretion

Theophylline is eliminated primarily by biotransformation (Fig. 3) in the liver with only about 10% of an administered dose being recovered in the urine unchanged (*Rall, 1985*). Therefore dosage adjustments are not usually necessary in patients with renal function impairment.

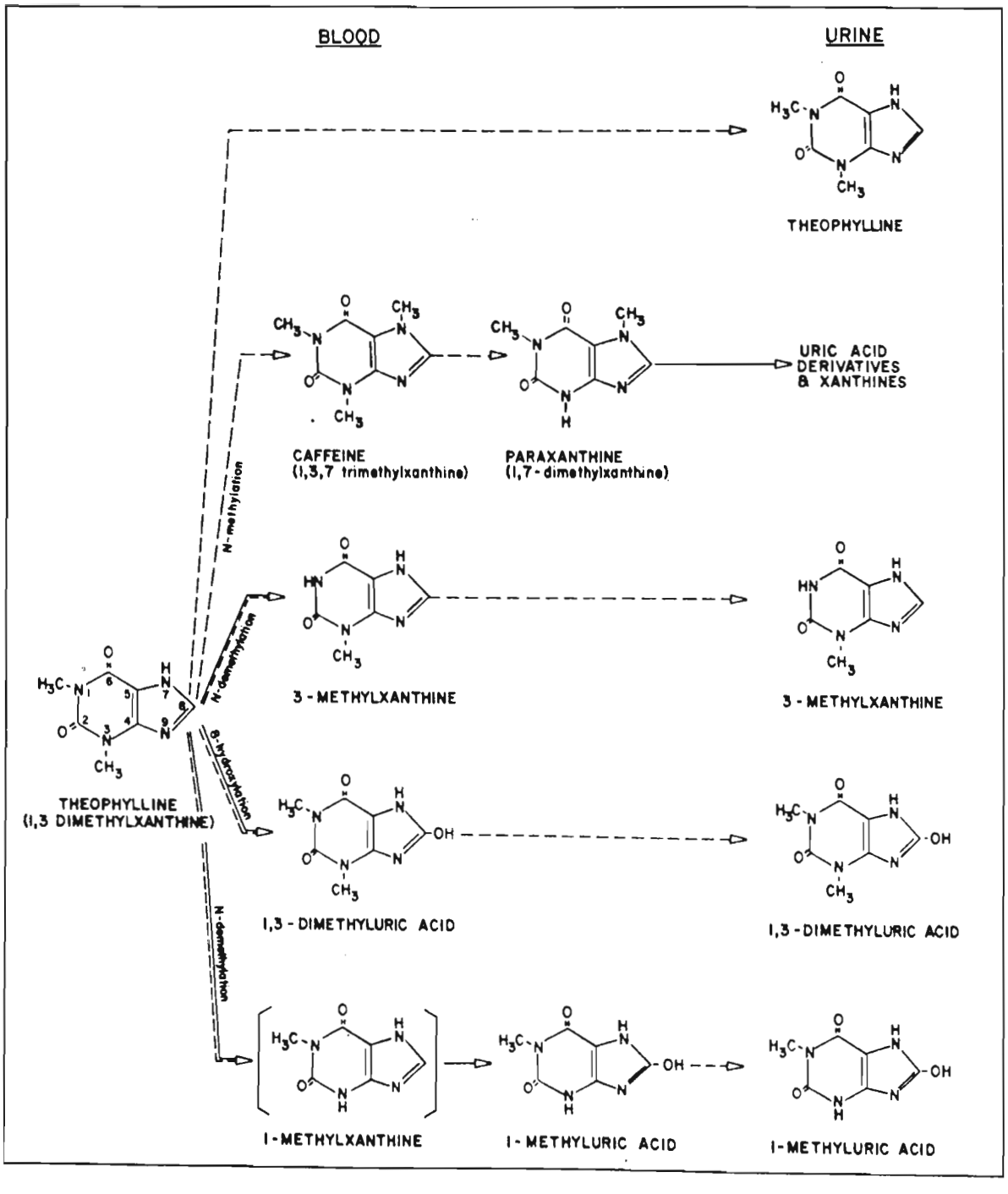


Fig. 3 - Diagram illustrating the hepatic biotransformation of theophylline and urinary excretion of metabolites (*Hendeles et al, 1986*).

Biotransformation is mediated by the liver microsomal mixed - function oxidase system, most likely the cytochrome P-450 system which is responsible for the hydroxylation and N-demethylation of theophylline over multiple parallel pathways by both first order and capacity limited processes (*Hendeles et al, 1986*).

The major metabolite is 1,3-dimethyluric acid accounting for approximately 40 - 50% of excreted metabolites. Lesser metabolites are theophylline, 3-methylxanthine and 1-methyluric acid which each accounts for 10 - 15% and 1-methylxanthine which is excreted in smaller amounts. Xanthine oxidase has been identified as the enzyme responsible for subsequent biotransformation of 1-methylxanthine to 1-methyluric acid. About 6% of a dose of theophylline is N-methylated to caffeine which in turn is converted to paraxanthine (*Bukowskyj et al, 1984; Hendeles et al, 1986*).

In the premature neonate, about 50% of the dose is excreted in the urine unchanged (hence dosage adjustment is necessary in renal failure) and the remainder undergoes N-methylation to caffeine and C-8 hydroxylation to 1,3-dimethyluric acid. Caffeine has a longer half-life in neonates and may result in accumulation. Caffeine may also be responsible for beneficial effects seen when theophylline is administered to neonates with apnoea (*Aranda et al, 1977*).

Theophylline metabolism exhibits a somewhat unique situation in that overall clearance is linear but each metabolic pathway is in fact non-linear. This is the result of different Km and Vmax values for the different metabolites with the major metabolite 1,3-dimethyluric acid having the highest values (*Tang-Liu et al, 1982*).

However linearity in theophylline kinetics depends on the serum theophylline concentration and the overall Km value for the individual patient. An estimated mean pooled Vmax of 1960 mg/day and mean Km of 24.1 mg/l has been reported in the literature (*Wagner, 1985*).

Clinically, this can be important, in that, at the higher dosage range a small increase in dose can result in disproportionately large increases in serum concentration. Such experiences have in fact been reported in both children and adults (*Hendeles et al, 1986*).

1.5.3.1 Factors affecting theophylline clearance

It has been widely reported that there is a large interindividual variation in the rate of theophylline biotransformation (*Jenne et al, 1972; Jusko et al, 1979*). This is due to the fact that theophylline is primarily eliminated via the hepatic route and numerous factors are known to affect the functional capability of the liver. These are discussed below. Table II should be referred to for actual clearance values as reported in the literature.

Table II - Summary of theophylline clearance values for various patient populations

Population characteristics	Age, mean (SD) (years)	Number of patients	Clearance, mean (SD) L/kg/hr
AGE			
Premature neonates with apnoea	7.5 (4.4) days	6	0.020 (0.006)
	41 (12) days	8	0.038 (0.018)
Term infants : under 6 months	18 (2) weeks	3	0.048 (0.006)
: 6 to 11 months	34 (10) weeks	4	0.120 (0.030)
Young children : 1 - 4 years	2.5 (0.9)	10	0.102 (0.036)
Older children : 4 - 12 years	9.4 (3)	17	0.096 (0.024)
: 13 - 15 years	14 (0.8)	6	0.054 (0.012)
: 16 - 17 years	10.7 (2.6)	30	0.084 (0.036)
Adults: otherwise healthy non-smoking asthmatics	31 (10)	16	0.039 (0.011)
Healthy non-smoking volunteers	20 - 32 (25.5)	15	0.040 (0.008)
Elderly - non-smokers with normal cardiac, liver and renal function	67 (5.7)	9	0.035 (0.004)
GENDER	5 - 15	49 females	0.065 (0.025)
		49 males	0.066 (0.017)
CONCURRENT ILLNESS			
Cor pulmonale	64	8	0.029 (0.012)
Cystic fibrosis	13.6 - 27.7 (21.3)	10	0.075 (0.028)
Acute pulmonary oedema	71 (10)	9	0.020 (0.004 - 0.141)
Liver disease - cirrhosis	52 (8.2)	9	0.026 (0.008 - 0.198)
	56 (4)	8	0.019 (0.006 - 0.042)
- acute hepatitis	Not reported	4	0.021 (0.003)
- cholestasis	Not reported	7	0.039 (0.024)
SMOKING HISTORY			
Marijuanha alone	20 - 25	7	0.072 (0.030)
Marijuanha & cigarettes	19 - 27	7	0.090 (0.024)
Cigarettes (heavy smokers)	22 - 31 (27)	7	0.063 (0.019)
Ex-cigarette smokers - for at least 2 years	22 - 39 (28)	6	0.051 (0.012)
Elderly smokers	67 - 79 (75)	6	0.043 (0.012)
PREGNANCY*			
24 - 26 weeks pregnant			
36 - 38 weeks pregnant			
6 - 8 weeks postpartum	28.6 (3.4)	5	
more than 6 months postpartum			

adapted from *Hendeles et al, 1986*

* *Frederiksen et al, 1986*

1.5.3.1.1 Age

Theophylline clearance is reduced in infants and elderly patients. Children up to adolescence have rapid theophylline clearance while non-smoking adults have values between these two extremes. In infants the decreased clearance rate is related to oxidative pathways that have not yet been established. Hence the urinary excretion consists largely of unchanged theophylline or caffeine. At age approximately 1 year, clearance increases and is approximately 40% greater than that of adults. This increased value is maintained throughout childhood and into adolescence. Thereafter the clearance progressively decreases with age. This may be related to either relative loss of functional ability or to the amount of enzymes available (*Bukowskyj et al, 1984*). The increased incidence of congestive heart failure and liver function impairment in the elderly may also be a contributory factor (*Jusko et al, 1979*).

1.5.3.1.2 Gender

Available evidence suggests that there is no clinically significant difference between males and females in their rates of theophylline clearance (*Jusko et al, 1979; Hendeles et al, 1981*).

1.5.3.1.3 Concurrent illness

Fever

Clearance of theophylline is reduced during febrile viral respiratory tract infections. It is not clear whether this is due to the fever or the viral infection since chemically induced fever caused a decrease in clearance while afebrile volunteers who had been administered influenza vaccine also showed a decrease in clearance (*Hendeles et al, 1983*). Whatever the cause, the magnitude of the decrease in clearance is such that a decrease in dose may be necessary in order to avoid toxicity (*Hendeles et al, 1985*) especially if maintenance serum theophylline concentrations lie at the upper end of the therapeutic range.

Heart disease

Several authors describe a decrease in theophylline clearance in patients with congestive heart failure , either left or right sided (*Bukowskyj et al, 1984; Hendeles et al, 1986*). A large number of the reported cases of serious theophylline toxicity have occurred in patients with congestive heart failure who have been prescribed standard doses.

Possible mechanisms for the decrease in clearance are :

* passive congestion of the liver which results in hepatocellular damage. This may alter the capacity of the liver to extract and metabolise theophylline.
* decreased liver blood flow . However the low extraction ratio tends to make this explanation less likely.
* liver hypoxia secondary to inadequate perfusion.

Patients with congestive heart failure may frequently need theophylline therapy (due to the drug's positive inotropic action, diuretic action and for symptomatic treatment of the wheezing symptoms). Therefore, in order to avoid toxicity, dosage should be very carefully titrated using serum theophylline concentration measurements.

Resolution of the congestive heart failure has resulted in marked improvement (increase) in theophylline clearance (*Bukowskyj et al, 1984*).

Liver disease

Liver disease results in a decrease in theophylline clearance due to liver cell injury. This decrease may be large and is of major clinical importance. Some authors have found a change in the pattern of urinary excretion of theophylline metabolites. The degree of decrease in theophylline clearance depends on the type of liver dysfunction, the most marked decrease occurring in decompensated cirrhosis, while patients with cholestasis had clearance values similar to that of normals (*Bukowskyj et al, 1984*).

Cystic fibrosis

Adolescents with cystic fibrosis have been found to have a more rapid than average rate of clearance (*Isles et al, 1983*).

Hyperthyroidism

Hyperthyroidism causes an increase in theophylline clearance possibly due to increased activity of hepatic enzymes and increased hepatic blood flow. The observation that there is a correlation between thyroxine and theophylline clearance suggests that interindividual differences in thyroid function may contribute to variability in theophylline clearance (*Hendeles et al, 1985*).

1.5.3.1.4 Diet

A high protein, low carbohydrate diet increases the rate of theophylline clearance, while a low protein, high carbohydrate diet decreases theophylline clearance compared to a normal diet. Ingestion of charcoal broiled beef can also increase theophylline clearance due to the influence of enzyme inducing hydrocarbons from the charcoal.

However, these effects are unlikely to be of any real clinical significance unless permanent drastic changes in diet are made (*Hendeles et al, 1986*).

1.5.3.1.5 Smoking

Cigarette and marijuanha smokers have rapid clearance and these patients usually require much higher doses on average in order to achieve serum theophylline concentrations within the therapeutic range. The reason for this effect is the presence of enzyme inducing substances in cigarette smoke e.g. polycyclic hydrocarbons (*Hunt et al, 1976*). The effect of cigarette smoking in causing an increase in clearance may modify the effect of other factors that tend to decrease theophylline clearance e.g. old age. These patients therefore tend to have slightly higher clearance than their non-smoking counterparts.

Upon cessation of smoking theophylline clearance will return to normal very slowly (*Hunt et al, 1976*) with some reports indicating a timespan of up to 2 years.

1.5.3.1.6 Pregnancy

Patients in their second and third trimesters of pregnancy appear to have a decreased hepatic clearance of theophylline. *Frederiksen et al (1986)* have shown that plasma protein binding is decreased during pregnancy hence increasing free theophylline concentrations. This tends to expose the mother and the foetus to increased theophylline concentrations and potential toxicity. *Carter et al (1986)* reports 2 patients who experienced signs of theophylline toxicity and who required dose reductions during pregnancy. The question of the influence of the state of pregnancy on theophylline clearance appears important and warrants further investigations.

1.5.3.1.7 Drug interactions

Erythromycin

Erythromycin has been reported to cause a decrease in theophylline clearance. The mechanism of the interaction involves inhibition of the cytochrome P-450 mixed function oxidase system. The effect was found to be dependent on dose and duration of therapy. Theophylline may also cause a decrease in erythromycin levels so that the physician is faced with a dual problem - potential theophylline toxicity and inadequate erythromycin concentrations. Similar results have been observed with other macrolide antibiotics e.g. troleandomycin (*Prince et al, 1981; LaForce et al, 1981*).

Other antibiotics

Other antibiotics such as amoxycillin, ampicillin, cefaclor, metronidazole and tetracycline have no effect on theophylline clearance (*Bukowskyj et al, 1984; Hendeles et al, 1986*). Although initial animal studies showed no interaction between

rifampicin and theophylline (*Bukowskyj et al, 1984*), increases in clearance of up to 79% after 14 days of concurrent administration, probably due to induction of the cytochrome P-450 system, have been reported in humans. The resultant decrease in serum theophylline concentrations may imply loss of asthma control. It is recommended, therefore, that serum theophylline concentrations be measured 5 days after commencement of rifampicin therapy with a view to dose adjustment if necessary (*Hauser et al, 1983*).

Enoxacin, a relatively new antibiotic, has been associated with higher than expected serum theophylline concentrations and symptoms of toxicity in 8 of 10 patients (*Wijnands et al, 1984*). In one patient the steady state serum theophylline concentration doubled following concurrent administration of intravenous aminophylline and oral enoxacin for 3 days.

Cimetidine and ranitidine

Cimetidine, a histamine H_2 receptor antagonist has been reported to cause a decrease in theophylline clearance. This effect occurs rapidly with changes seen within 24 hours of the first dose. The mechanism appears to be competitive inhibition of the hepatic microsomal mixed-function oxidase system. This interaction is considered to be life-threatening with at least 1 report of a fatality. It has not been noted with the structurally dissimilar H_2 receptor antagonist ranitidine (*Bukowskyj et al, 1984; Hendeles et al, 1986*), although more recent reports suggest the contrary (*Muir et al, 1989; Roy, 1989*).

Antiepileptic drugs

The antiepileptic drugs phenobarbitone, carbamazepine and phenytoin have been reported to cause increases in theophylline clearance, the degree of increased clearance ranging from a mean of 25% for phenobarbitone, 59% for carbamazepine and 75% for phenytoin (*Hendeles et al, 1986*). In the case of phenytoin a mutual decrease in theophylline and phenytoin levels may occur. In order to avoid loss of asthma or seizure control, these patient's therapy should be adjusted on the basis of serum concentration monitoring if it is considered essential that they be treated with both agents.

Allopurinol

A decrease of 21% in theophylline clearance occurred in patients given high doses (600 mg/daily) of allopurinol (*Hendeles et al, 1986*). At lower doses of 300 mg/daily, *Vozeh et al, 1980* did not notice any alteration in the theophylline clearance.

The mechanism of the interaction is unlikely to be due to inhibition of xanthine oxidase, since this enzyme is not involved in hydroxylation or demethylation of theophylline. It appears as though allopurinol is a non-specific inhibitor of hepatic microsomal enzyme activity (*Hendeles et al, 1986*).

Oral contraceptives

A decrease in theophylline clearance of approximately 34% was observed when compared to a group of age-matched controls in 8 non-smoking women who had been taking oral contraceptives for 6 months or longer (*Bukowskyj et al, 1984*). The mechanism is presumably one of competitive inhibition of hepatic microsomal enzyme activity.

Theophylline toxicity may be avoided in these patients if doses are adjusted on the basis of serum concentration measurements (*Hendeles et al, 1986*).

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Chapter Two

The principles of applied pharmacokinetics with particular emphasis on theophylline

2.1 INTRODUCTION

Therapeutic drug monitoring is an expanding new scientific discipline that can make important contributions to treatment in coronary care, intensive care , general medicine and surgery, and general practice. It involves the use of drug concentrations, pharmacokinetic principles and pharmacodynamic criteria to optimise drug therapy in individual patients.
With some drugs optimisation is accomplished primarily by minimising the probability of toxicity, while with other drugs benefits are achieved by increasing the probability of the desired therapeutic effects. With the drugs for which therapeutic drug monitoring is indicated, a balance between these two end-points is sought.

2.1.1 Which drugs should be monitored ?

Drugs which have a wide therapeutic ratio i.e. they do not produce toxicity at doses required for clinical effect, will not usually require monitoring. For such drugs e.g. penicillin, it is common to use dosages that are high enough to ensure "therapeutic concentrations" in essentially all patients, since toxicity is of little concern. An exception to this practice might arise when non-compliance or malabsorption is suspected, or when the cost of the drug is so great that therapy with the minimum effective dose is advantageous (*Evans, 1986*) .

2.1.2 Why monitor theophylline levels ?

In many discussions on the value of therapeutic drug monitoring in clinical medicine, the successes achieved with measurement of serum theophylline concentrations have been used as the descriptive model. The pre-eminence of theophylline in this context is based upon the following:

* The relationship between dose and response is erratic and unpredictable. This is secondary to a poor dose-serum concentration relationship.
* Serum theophylline concentrations are a determinant of both efficacy and toxicity.
* Theophylline has a low toxic to therapeutic ratio.
* There is a large interindividual variability in rate of theophylline elimination.
* Serum concentrations may be affected by many factors that affect liver microsomal enzyme function and alter elimination kinetics.
* Theophylline is administered to the chronic asthmatic as a prophylactic agent.

(*Finn et al, 1981; Hendeles and Matthay, 1986*)

2.2 ANALYTICAL METHODS

During the past 25 years enormous advances have been made in the development of sensitive and specific methods for the determination of drug and drug metabolite concentrations in biologic fluids. The improved methodologies have resulted in an almost explosive proliferation of commercial drug assay kits and instrumentation. This is particularly true in the case of theophylline. The different methods available differ in important aspects including sensitivity, specificity, sample size needed, technical difficulty, amount of technician time required and initial equipment costs (*Hendeles and Weinberger, 1981*). The following discussion traces the evolution of the available theophylline assay techniques from initial tedious, technically difficult assays to modern day automated immunoassays with extremely rapid turnaround time.

2.2.1 UV spectrophotometric assay

In this method theophylline is extracted from serum with organic solvent and the absorbance of ultraviolet light is measured in a spectrophotometer.
Since most laboratories have a spectrophotometer, the method does not require an investment in new equipment. However, it does require a relatively large sample size. In addition, a variety of commonly used drugs (e.g. furosemide and aspirin) interfere with this assay, producing false results. Other disadvantages include the need for more technician time and the poor reproducibility of the results compared to other available methods. For these reasons, the UV spectrophotometric assay method should not be relied upon to guide dosage adjustment in the clinical setting (*Hendeles and Weinberger, 1981*).

2.2.2 Gas-liquid chromatography

The poor specificity and relatively large sample size required for the UV spectrophotometric method lead investigators to develop gas-liquid chromatography (GLC) methods for measuring theophylline (*Hendeles and Weinberger, 1981*).
The first step in a GLC assay involves an extraction step to dissolve the drug into an organic solvent. The sample plus an internal standard with chemical properties similar to the drug being assayed, is then injected into the gas chromatograph. This is carried into a high temperature column by an inert gas (e.g. helium) which constitutes the mobile phase. Column temperatures of 100°C to 350°C volatilise the sample, which then comes into contact with an inert stationary phase, usually coated with a nonvolatile liquid. As the mobile phase passes through the column, the analyte is separated from other sample constituents based on affinity for the stationary phase. The mobile phase then passes from the column to a detecting device that draws curves whose peaks correspond to the concentrations of the unknown substances. The internal standard produces a reference peak. Detecting devices include electron capture, mass spectrometry, or more commonly, flame ionisation (*Bottorff and Stewart, 1986*).

Advantages of GLC include flexibility in drug assays (by altering column length and temperature), simultaneous assay of parent drug and metabolites and the ability to use small sample volumes. The disadvantages are the time consuming procedure, high equipment cost, column deterioration and the need for a skilled analyst. Few laboratories currently use this technique (*Hendeles and Weinberger, 1981; Bottorff and Stewart, 1986*).

2.2.3 High pressure liquid chromatography (HPLC)

Liquid chromatography (LC) is similar to GLC except that the mobile phase is a liquid, usually a mixture of acetonitrile or methanol with water. Compared to GLC, the need for high temperatures is eliminated and columns packed with stationary phase are kept at ambient temperature. Substances are separated in LC according to their solubility in aqueous or organic solvents. Highly polar compounds will be more soluble in highly polar solvents like water, whereas, less polar drugs will dissolve better in organic solvents such as chloroform. As the mobile liquid phase and the stationary phase come in contact in a column, separation occurs in a fashion similar to other chromatographic methods.

The addition of 200 to 1000 pounds of pressure per square inch to the separation column converts liquid chromatography to high pressure liquid chromatography (HPLC), producing rapid separation and determination of drug concentrations.

Reverse phase liquid chromatography uses a non-polar column packing and polar mobile phase. This technique allows for the direct determination of theophylline concentrations within 10 - 20 minutes without the need for an organic solvent extraction step (*Bottorff and Stewart, 1986*).

Advantages of this method include the low cost, once the method has been established; the ability to operate without the need for commercially available reagent kits and the ability to simultaneously measure caffeine which is a clinically important metabolite in neonates.

The disadvantages are the high initial cost of the equipment; the high degree of technician skill required and the difficulty in performing stat or small batch testing due to the equipment preparation time required. Large doses of some drugs e.g.

ampicillin, cephalothin, acetazolamide and trisulfapyrimidine cause falsely elevated results under some operating conditions and represents another disadvantage of this technique (*Hendeles and Weinberger, 1981; Bottorff and Stewart, 1986*).

2.2.4 Enzyme immunoassay

In the enzyme multiplied immunoassay technique (EMIT^{R}), a known quantity of analyte labelled with an enzyme (glucose-6-phosphate dehydrogenase) competes with the drug from the patient sample for antibody binding sites. At equilibrium, the amount of unbound enzyme-labelled analyte will be directly proportional to the concentration of drug. Substrate (nicotinamide adenine dinucleotide - NAD) added to the sample catalyses an enzymatic indicator reaction (NAD to NADH) that can be detected spectrophotometrically. Since the antibody-bound enzyme is inactivated or reacts more slowly with substrate, the unbound or free portion is responsible for the detection reaction. Therefore, the fractions need not be separated prior to substrate addition and the assay is termed homogeneous.
The advantages of this method include the rapid turnaround time and high precision. The disadvantages are the need to frequently recalibrate the instrument and the technician time required to perform dilution steps to analyse abnormally high serum concentrations (*Bottorff and Stewart, 1986*).
This technique is one of the more popular methods currently available.

2.2.5 Radioimmunoassay

The labelling molecule for radioimmunoassay (RIA) can be either ^{57}Co, ^{3}H or more commonly, ^{125}I. At equilibrium, the amount of radioactive labelled analyte bound to antibody is inversely related to the amount of analyte from the patient sample. Before measuring drug concentration, the sample must first be separated into its free and bound phases to prevent radiation interference. Radioimmunoassay procedures are therefore regarded as being heterogeneous. Once separated, drug levels are determined by gamma counting equipment (*Bottorff and Stewart, 1986*).

The advantages are high sensitivity, ability to detect concentrations in the picogram range and small sample size requirements. The disadvantages are the long turnaround times; the many interfering substances; radiation hazards; inconvenience of recording and disposing radioactive waste; short shelf life of RIA reagents and the need for daily calibration of the instrument. This method is now less popular because of these many disadvantages (*Hendeles and Weinberger, 1981; Bottorff and Stewart, 1986*).

2.2.6 Fluorescence polarisation immunoassay

This is a variation of the enzyme immunoassay technique in which the antigen label is fluorescein. Fluorescein-tagged drug and unlabelled drug are incubated with antibody and then excited with light passed through a polarising lens. With high drug concentrations, there is an increase in unbound fluorescent-labelled molecules that tumble free in solution causing the light to be depolarised upon emission. At low drug concentrations, the labelled antigen-antibody complex rotates more slowly and polarisation of the emitted light is maintained (*Bottorff and Stewart, 1986*).
The advantages are the high degree of automation; rapid turnaround times, good sensitivity (lower limit of detection is 0.5 μg/ml at the 95% confidence interval), good stability of reagents; good stability of calibration curves and the ability to analyse small or large batches of samples. A disadvantage is the presence of background interference inherent in some serum samples. In order to minimise this, blank readings are taken and background interferences are subtracted. (*Bottorff and Stewart, 1986; Hendeles et al 1986*)

2.2.7 Newer techniques

2.2.7.1 Ames Diagnostics have recently introduced a new immunoassay technique that utilises a dry reagent contained on a plastic strip - see Chapter Four for an evaluation of this technique.

2.2.7.2 Syntex Medical Diagnostics recently developed a method to analyse theophylline concentration without the need for a processing instrument. This system combines the technology of immunoassay with thin layer chromatography. The specificity of the assay should be comparable to that of other immunoassays since the principle involved viz. use of monoclonal antibodies is the same. It requires only 12 µl of whole blood from finger stick and turnaround time is about 15 minutes (*Hendeles et al, 1986*). The ability to use whole blood rather than serum or plasma means that the time-consuming centrifugation step is eliminated. This is a real advantage, since in many assay techniques currently available, centrifugation of the sample is the rate limiting step.

2.3 SALIVA THEOPHYLLINE CONCENTRATIONS

In order to avoid the trauma of venipuncture in children, it has been suggested that theophylline concentrations in saliva be used to estimate indirectly the serum concentration. However, numerous studies have demonstrated that the saliva to serum concentration ratio often does not remain stable in the same patient. In view of the danger involved in possible dosage adjustment errors and the ability of newer techniques to measure levels using as little as 50 µl of serum (i.e. sufficient from a finger or a heel stick), saliva measurements are not recommended at this time (*Hendeles et al, 1986*).

2.4 WHEN TO DRAW SAMPLES

Since drug administration is a dynamic process, the timing of sample collection is critical to its proper interpretation. It is important that samples for serum theophylline concentration monitoring be drawn at steady state since levels measured before steady state may be erroneously low. Steady state conditions usually occurs after approximately 48 hours of stable dosage. However if computer facilities are available to perform the relevant complex calculations, then samples may be drawn prior to steady state. Blood samples should not be drawn during the absorption phase in view of the many factors that affect absorption of theophylline; neither should levels be drawn during the distribution phase since therapeutic effect correlates with levels obtained after completion of the distribution phase (*Robinson and Taylor, 1986*).
The following recommendations serve as a guide to the determination of appropriate sample collection times.

Intravenous therapy (*Taylor and Finn, 1981*)
Loading dose - Thirty minutes after administration.
Infusions - Prior to commencing the infusion (if the patient has a history of theophylline use in the previous 24 hours) and 4 - 8 hours later. Thereafter, samples are drawn as needed to ensure that the desired concentration is maintained.

Oral therapy (*Taylor and Finn, 1981*)
Peak level - Solution or solid dosage form with rapid release characteristics : 2 hours after the dose.
Slow release formulations : 4 hours after the dose.
Trough levels - immediately before the next oral dose.

The above recommendations serve as a guide and should not be viewed as absolute. Factors such as reason for assaying the sample e.g. the assessment of possible drug toxicity necessitates that sample collection times be individualised.

2.5 STABILITY OF SERUM THEOPHYLLINE CONCENTRATIONS

Whole blood samples containing theophylline may be stored for up to 3 days either at room temperature (25°C) or under refrigeration (4°C). Serum samples containing theophylline may be stored for up to 3 days at 25°C; 7 days at 4°C and 48 weeks when frozen at -20°C (*Johnson et al, 1984*).

2.6 THEOPHYLLINE DOSING METHODS AND INTERPRETATION OF SERUM CONCENTRATIONS

The interpretation of serum theophylline concentrations requires an understanding of the basic concepts of pharmacokinetics and a background in pathophysiology and pharmacotherapeutics (*Beane, 1979*). Numerous dosing methods have been developed in an attempt to improve the relationship between dose, serum theophylline concentration and response. These may be considered under the following headings:

* Standard doses.
* Predictive algorithms
* Pharmacokinetic models
* Bayesian feedback

2.6.1 Standard doses

In 1973, *Mitenko and Ogilvie* recommended an aminophylline loading dose of 5.6 mg/kg and a continuous infusion rate of 0,9 mg/kg/hr to achieve target serum concentrations of 10 - 20 µg/ml.

While these recommendations appeared to be appropriate at the time, numerous investigators (*Weinberger et al, 1976; Kordash et al, 1977; Hendeles et al, 1977*) subsequently evaluated these guidelines and found that administration of this standard dose frequently gave rise to serum theophylline concentrations greater than 20 µg/ml.

This led to the suggestion that "*it is not possible to achieve optimal therapeutic aminophylline dosage without monitoring serum theophylline concentrations.*" (*Weinberger et al, 1976*) and the conclusion that for most patients fixed dosage recommendations are inadequate (*Burton et al, 1985*).

2.6.2 Predictive algorithms

Based on studies illustrating the danger of using standard doses of theophylline and other studies demonstrating the large number of factors that affect theophylline clearance, dosing nomograms were developed (*Koup et al, 1976; Jusko et al, 1977*). These nomograms predicted the dose needed to achieve a particular target serum concentration using information known about the patient such as presence of concurrent diseases (e.g. congestive heart failure or hepatic disease) and known pharmacokinetic characteristics of the drug. In 1980, the United States Food and Drug Administration published a nomogram with guidelines for aminophylline therapy. Due to its official status, these guidelines were largely accepted as the standard for a number of years. This is unfortunate since individualisation of therapy should have been the standard (*Burton et al, 1985*).

In general, predictive algorithms are useful as starting points but their inaccuracy limits their utility. This is because of the considerable variability in the population and the fact that most of these algorithms have been developed using small populations of patients, usually homogeneous groups (*Burton et al, 1985*). They are usually most successful if used in the same population for which they were developed.

Dosage algorithms that are currently popular are those of *Hendeles et al (1980)* for the determination of optimal intravenous theophylline doses for acute asthma and *Hendeles et al (1978)* for the determination of optimal theophylline dose for chronic asthma. A useful feature in both these nomograms is the guidelines on dose adjustment following serum theophylline concentration determination.

2.6.3 Pharmacokinetic models

Pharmacokinetic models were originally developed for use in formal pharmacokinetic studies to describe the behaviour of drugs in man. However, they can also be used in clinical pharmacokinetics to predict the serum drug concentrations that will result from a dosing regimen.

A number of pharmacokinetic methods have been used to individualise theophylline therapy. With all methods at least one serum theophylline concentration is measured and used to estimate an individual patient's pharmacokinetic parameters. Future dosing decisions are then based on these parameter estimates.

A simple pharmacokinetic based method is the steady state clearance method of *Slotfeldt et al (1979)*. In this method, the serum concentrations measured at the end of a continuous intravenous infusion of approximately 48 hours duration is assumed to be the steady state concentration. Clearance is then estimated using equation (1).

$$Cl = \frac{Ri}{Cp_{ss}} \qquad (1)$$

where Cl is the clearance in L/hr

Ri is the rate of infusion in mg/hr

Cp_{ss} is the steady state concentration in µg/ml

This method is simple to use and produces mean clearance values similar to those obtained using other available pharmacokinetic methods (*Hurley and McNeil, 1988*). However the obvious disadvantage is that this method can only be used in patients who have been administered intravenous therapy.

A popular method is that of *Chiou et al (1978)* in which clearance is estimated from

equation (2) using data obtained during a constant intravenous infusion of theophylline.

$$Cl = \frac{2 * Ri}{Cp_1 + Cp_2} + \frac{IBW * (Cp_1 - Cp_2)}{(Cp_1 + Cp_2) * (t_2 - t_1)} \qquad (2)$$

where IBW = ideal body weight (kg)

Cp_1 = post loading dose serum concentration (μg/ml)

Cp_2 = second serum theophylline concentration measurement obtained 4-6 hours after the loading dose in children and smokers or after 8 hours in non-smokers (μg/ml).

t_1 and t_2 = times at which Cp_1 and Cp_2 samples were drawn respectively (hr).

The Chiou method accurately predicts theophylline dosage provided certain stringent requirements are fulfilled e.g. the infusion rate must be regulated by an infusion pump; the patient's elimination half-life is shorter than the time interval between the 2 measured samples (*Hendeles and Weinberger, 1983*) and laboratory precision must be excellent. *Hurley and McNeil (1988)* found that the Chiou method gives accurate results only when the 2 serum concentrations were taken 11 - 17 hours apart.

Least squares estimation or fitting of a pharmacokinetic model to the data is the method most often used to obtain pharmacokinetic parameter estimates from a formal pharmacokinetic study. Using appropriately drawn samples, the method can be used to interpret routine clinical data. The least squares method is based on the well-known method of statistical estimation known as maximum-likelihood.

An iterative computer method that uses the least squares estimation technique to individualise theophylline therapy has been described and evaluated (*Mungall et al, 1982*). *Mungall et al* set a target serum theophylline concentration of 15 μg/ml, and the iterative computer method achieved 95% confidence intervals of 10.6 - 18.2

μg/ml with all patients achieving therapeutic concentrations. On the other hand, application of an empirical predictive algorithm achieved 95% confidence intervals of 3.3 - 28.5 μg/ml with only 7 of 15 patients achieving concentrations in the therapeutic range.

An inherent problem with the least squares method and indeed with all the pharmacokinetic methods described above is their total reliance on serum level data. This means that no provision is made for comparison of the results with any prior expectations based on previous experience and known patient characteristics. This can potentially magnify the errors associated with inaccurate serum drug level determinations, resulting in large errors in parameter estimates. In order to provide accurate and precise estimates, multiple samples are necessary - at least equal to the number of parameters but preferably more. However, clinical realities preclude drawing multiple samples at kinetically optimal times.

2.6.4 Bayesian approach

The Bayesian approach (*Sheiner et al, 1972*) is a type of pharmacokinetic approach that is based on Bayes' theorem. It combines statistical probability and a weighting for each factor that may affect theophylline disposition, including the error involved in assaying the drug.

The Bayesian method assumes that the chances of a pharmacokinetic parameter being different in an individual are the same as the variability observed in the population. Consequently, if the volume of distribution in the population is relatively constant with a small coefficient of variation, and clearance is more variable with a large coefficient of variation, the Bayesian re-estimation of the individual pharmacokinetic parameters will modify clearance more than volume of distribution. In addition, this method allows weighting for variability in the assay, in sampling and dosing time, in compliance to out-patient therapy, and in giving the most recent serum drug concentrations the most weight (*Peck et al, 1980*).

If the accuracy of the data obtained is questionable or limited, a Bayesian method will analyse the data and identify a dosage somewhere between that which the population average and the serum levels would have predicted separately. If no serum theophylline levels are available then the population pharmacokinetic parameters serve as the starting point. In view of this, the Bayesian approach for initial drug dosage design may not be different clinically from any other well developed nomogram method . If, however, the population pharmacokinetic parameters are well defined, then this approach becomes a much more powerful clinical tool. Similarly as more of an individual patient's levels are obtained, their weighting increases and the population parameters become less significant (*Frakes et al, 1986*).

In this manner, Bayesian approaches attempt to combine many of the advantages of some previously discussed methods. Given adequate blood level data, the Bayesian approach will produce results as accurate as any other method currently in clinical use.

Sheiner and Beal (1982) compared the Bayesian method with other pharmacokinetic based methods and found it to be significantly better than the others when assessing both accuracy and precision. *Hurley and McNeil (1988)* recently compared the accuracy of a least squares regression, a Bayesian, Chiou's and the steady state clearance method of *Slotfeldt et al (1979)* in individualisation of theophylline dosage (intravenous and oral) in 48 patients. They found the Bayesian method to be the easiest of the computer based methods to use. Since its accuracy was comparable with the other methods evaluated, they recommend it for clinical use. They note however, that "*none of the methods evaluated were accurate in absolute terms*" and suggest that clinicians regard pharmacokinetic parameters obtained with these methods to be estimates only.

2.6.5 CONCLUSION

This report on theophylline dosing methods and interpretation of serum theophylline concentrations has traced the developments over the years with the culmination of the now widely accepted Bayesian approach. It has been noted that there is no ideal approach or perfect method. None of the methods guarantee clinical efficacy especially in the case of a changing clinical environment. All dosage changes made with any of the techniques outlined above should be made cautiously and the resulting serum theophylline concentrations checked. In view of its demonstrated accuracy, precision and ease of use, the Bayesian technique of drug dose optimisation is currently the preferred option.

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Chapter Three

Estimation of population pharmacokinetic parameters

3.1 INTRODUCTION

The axiom "*Drugs don't have doses - people have doses!*" (*Cipolle, 1986*) is central to the motivation for population pharmacokinetic studies. Population pharmacokinetics describes the typical relationships between physiology, pathology and pharmacokinetics, the interindividual variability in these relationships, and their residual intraindividual variability.

A knowledge of population pharmacokinetics can help one to choose initial drug dosage, to modify dosage appropriately in response to observed drug levels, to make rational decisions regarding certain drug regulatory requirements, and to investigate and elucidate research questions in pharmacokinetics (*Sheiner, 1984*). Its most important role thus far has been shown to be in therapeutic drug monitoring programmes that utilise the Bayesian forecasting technique. A prerequisite for satisfactory performance of this technique of drug dose optimisation is good estimates of the population parameter distributions. If these estimates are good, then the performance of the Bayesian system is improved (*Whiting et al, 1986*).

3.2 POPULATION PHARMACOKINETIC PARAMETERS

There are 3 distinct types of population pharmacokinetic parameters that are of interest to clinicians and researchers in pharmacokinetics :-

3.2.1 *Fixed effects parameters*

These measure central tendency in the values of the essential pharmacokinetic parameters (Cl, Vd, Ka, F). The fixed effects parameters usually represent the mean values of the parameters and/or a number of parameters which describe these mean values as functions of various patient characteristics or pathophysiology e.g. age, smoking habits, body weight or liver function status.

3.2.2 *Interindividual random-effects parameters*

In a population of individuals with a particular mean value for a fixed effect parameter, there exists a probability distribution about this mean value. The difference between any individual's parameter and the mean is referred to as the interindividual variability. A knowledge of the magnitude of this variability is useful in order to know to what extent the serum concentration will vary if an individual in the population is given some empirical dose of the drug in question.

3.2.3 *Intraindividual random-effects parameters*

Also referred to as residual variability. It explains all sources of variability that cannot be accounted for on the basis of the fixed effects and the interindividual variability. Thus the patient's day to day variability according to his biorhythms, assay error, model misspecification error, or any other variability are considered here. A knowledge of intraindividual variability is desirable in order to set reasonable thresholds for responding to changes in measured drug levels.

3.3 TECHNIQUES FOR THE ESTIMATION OF POPULATION PHARMACOKINETIC PARAMETERS

3.3.1 Traditional approach

The subjects used as the source of data in the traditional approach to the determination of population pharmacokinetic parameters are a group of 10 - 30 individuals selected so as to represent a spectrum of severity of a particular condition (*Sheiner, 1984*). For ethical reasons they are usually normal healthy volunteers or patients with lesser degrees of illness. The dosage schedule for the subjects is of simple design and the sampling times and number of samples (often more than 20 per subject) are the same for each individual. The design of these studies results in the provision of maximum information about individual kinetics .

However, various problems are apparent in this traditional approach (*Sheiner, 1984; Miller, 1985*).

* The use of volunteers or patients with lesser degrees of illness and the small sample number means that the results obtained may not be representative of the patient population in whom the drug is eventually used therapeutically.
* The study is costly since, in addition to the expense involved in assaying a large number of samples, one has to consider the cost of temporary hospitalisation and compensation of volunteers.
* The rigid experimental protocol in which all study conditions are strictly controlled can actually prevent the discovery of unexpected but important influences on kinetics.

The data generated by these studies are analysed using either the 'naive pooled data approach' or the 'two stage method' (*Sheiner and Beal, 1980*). In the naive pooled data approach, all the individuals' data are fitted together as though there were no individual kinetic differences. This method lacks popularity since it does not distinguish interindividual from intraindividual variability. Further in simulation studies, the parameter estimates have been found to be biased and less precise than those obtained by other means. In the more popular two stage method, the first stage involves analysing data from each subject to obtain estimates of the individual pharmacokinetic parameters. In the second stage, average parameter values are calculated and attempts may be made to quantitate the relationship between physiological and pathological factors and kinetic parameters. This method is also not ideal primarily because of the study design but also because parameter estimates tend to have an upward bias (*Sheiner, 1984*).

Whiting et al (1986) in a review article on population pharmacokinetics state that the traditional methods of data analysis "*have been thoroughly studied and are not, in general, satisfactory*".

3.3.2 NONMEM approach

Sheiner et al (1972; 1977) recognised the above-mentioned handicaps of traditional pharmacokinetic studies and data analysis techniques. The novel approach of using data gathered directly from patients receiving the drugs of interest i.e. routine clinical data, was therefore introduced. In order to analyse such data, the concept of non-linear mixed effects modelling was developed and implemented in the form of the computer programme NONMEM.

The NONMEM approach uses a statistical model in which individual patients' pharmacokinetic parameters are assumed to arise from a distribution which has a population mean and a particular quantifiable deviation from this mean. It can be seen therefore that the emphasis is shifted away from the individual patient to a system in which the population is treated as the unit of analysis.

NONMEM describes the available data in terms of a number of fixed effect parameters denoted theta (Θ) and the two random effect parameters viz. the interindividual covariance matrix (Ω) and the variance, σ^2, of intraindividual and measurement error. The programme simultaneously derives fixed effects and random effects - hence the name mixed effects modelling.

3.3.2.1 Statistical model

The statistical model used by NONMEM to describe pharmacokinetic observations i.e. drug concentrations from N individuals, each with n_i, i = 1, N observations, in terms of Θ, Ω and σ^2 is described by equation (3).

$$y_{ij} = f(P_i, D_i, \tau_i, t_{ij}, \varepsilon_{ij}) \qquad (3)$$

where y_{ij} is the jth observation in the ith individual; f is a pharmacokinetic model (often involving a sum of exponentials); P_i is the vector of parameters of the model for the ith individual; D_i is the dose administered and τ_i is the interval between doses - together they describe the entire dosing history of the individual from a point

in the suitably remote past up to and including time t_{ij}, the time of response; and the ε_{ij} are independent identically distributed univariate random errors with mean zero and variance σ^2.
The P_i are further modelled in terms of population parameters according to equation (4).

$$P_i = q(\Theta, X_i, \eta_i) \qquad (4)$$

where q is a vector-valued function, X_i is the collection of all concomitant patient features (e.g. age, weight and smoking habits) relevant to predicting P_i, and the η_i are independent identically distributed multivariate random vectors with mean vector zero and covariance matrix Ω.
To estimate Θ, Ω and σ^2, equation (4) is essentially substituted into equation (3), and the method of extended least squares (*Beal, 1984*) is applied. This method's objective function involves estimates of the expected value and variance of y_{ij}. The former can be expressed in terms of Θ only; the latter, in terms of Θ, Ω and σ^2. The parameter values yielding the minimum of the objective function are the extended least squares estimates (*Sheiner and Grasela, 1984*).

3.3.2.2 Validation

NONMEM relies on a precise statistical background; its theoretical basis has been investigated, and the statistical properties of the extended least squares estimate are well established (*Steimer et al, 1984*). However, a true measure of its success is the numerous publications reporting on analysis of a number of commonly used drugs e.g. digoxin (*Sheiner et al, 1977*), phenytoin (*Sheiner and Beal, 1980; Grasela et al, 1983; Rheeders, 1985*), gentamicin (*Kelman et al, 1984*), procainamide (*Grasela and Sheiner, 1984*), mexiletine (*Vozeh et al, 1982, 1984*) lignocaine (*Vozeh et al, 1984, 1984a*), warfarin (*Mungall et al, 1985*), alfentanil (*Maitre et al, 1987*) and metoclopramide (*Grevel et al, 1988*). In these reports, dosing guidelines for specific patient sub-populations are determined and the influence of disease states on

pharmacokinetics are identified. Most reports comment on increased efficiency in dosage adjustment usually based on some form of subsequent feedback procedure - most commonly one based on Bayes' theorem.

3.4 CONCLUSION

In the study of population pharmacokinetics, attempts are made to describe kinetic variability observed within groups of individuals by finding relationships between physiology, pathology and pharmacokinetics. Its most important role thus far has been in therapeutic drug monitoring programmes, particularly those that utilise the Bayesian system. Examination of available methods of analysing population pharmacokinetic data reveals that the NONMEM approach is currently the most satisfactory.

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Chapter Four

Evaluation of a new dry phase, strip immunoassay technique for analysis of serum theophylline concentrations

4.1 INTRODUCTION

The wide interpatient variability in elimination rates for theophylline, its narrow therapeutic index and the well documented relationship between serum concentration, clinical effect and toxicity are some of the important reasons for monitoring serum levels of this drug.

Available assay methods for theophylline have been discussed in Chapter Two, Section 2.2. Recently, Ames Division, Miles Laboratories, Indiana have introduced the Seralyser^{R} in South Africa. This is a new analytical technique that combines an immunoassay with a dry chemistry procedure. The method utilizes a dry reagent contained on a plastic strip with a colorimetric indicator that is measured by a reflectance photometer. The Ames Seralyser^{R} theophylline assay has been recommended as being suitable for small-volume work in places such as the physician's office and the emergency room (*Cheung and Soldin, 1986*). This would facilitate rational dosage adjustment based on serum concentrations while the patient waits in the doctor's consulting rooms. Other currently available methodologies have problems such as accuracy, prolonged time to process samples, size of sample required, complicated technology and high cost of system hardware and reagents, which limit their utility for this application (*Lotner et al, 1985*).

This study evaluates the analytical performance of the Ames Seralyser^{R} against Abbott's TDx^{R}.

4.2 MATERIALS AND METHODS

4.2.1 Sample collection

Over a 2 month period 52 samples were collected from 34 patients attending the Asthma Clinic at R K Khan Provincial Hospital. Venous blood was collected into plain glass tubes, allowed to clot and then centrifuged. Serum was separated and then an aliquot was analysed using the Ames Seralyser^{R} housed in the Hospital's Pharmacy Department. The remainder of the serum was analysed using the Abbott's TDx^{R} system at the University of Durban-Westville. Samples that could not be analysed immediately were stored at -20^{o}C until analysis. Frozen samples were allowed to thaw at room temperature and were analysed within 7 days of collection. The concentration values obtained with the 2 instruments are recorded in Appendix A, Table A1.

4.2.2 Sample analysis

Ames Seralyser^{R}

All components for the Ames Seralyser^{R} system together with serum based standards (2.5 µg/ml and 25 µg/ml) and control (15 µg/ml) were supplied by Ames Division, Miles Laboratories, Indiana.

Thirty microlitres of either standard, control or sample were diluted with 800 µl of distilled water using fixed volume pipettes supplied by Ames. After thorough mixing, a 30 µl aliquot was dispensed onto the reagent area of the test strip according to manufacturer's instructions.

The rate of formation of a blue colour was measured at 740 nm by the Seralyser^{R}'s reflectance photometer after 80 seconds. This rate of colour formation is proportional to the theophylline concentration. A calibration curve was constructed for each new batch of reagent strips or if the control results were greater or less than 10% of their stated values. Calibration curves were stored in a removable Test

Module that formed part of the instrument and were used to calculate the theophylline concentration of samples and controls. The Seralyser^{R}'s lower limit of assay detection is 3 µg/ml.

Abbott's TDx^{R}

All components for the Abbott's TDx^{R} system for theophylline together with reagent packs, serum based standards and controls were obtained from Abbott Laboratories, Diagnostics Division, Irving, Texas.

A minimum of 50 µl of standard, controls or samples were pipetted or poured into sample cartridges. These were then placed into a carousel which has the capacity to accommodate 20 such sample cartridges. The carousel together with a theophylline reagent pack were placed into the TDx^{R} Analyser and the batch assay process started as per manufacturer's instructions. All dilutions and subsequent sampling were performed automatically by the instrument.

On each occasion, prior to analysis, the concentration of 3 known theophylline controls were measured. A new calibration curve was constructed whenever any of the 3 control results were greater or less than 10% of their stated values. The lower limit of detection at the 95% confidence limit is 0.51 µg/ml.

4.2.3 Data analysis

The concentration measurements obtained using the 2 methods were analysed by linear regression analysis using the STATGRAPHICS^{R} computer programme by Statistical Graphics Corporation available from the Computer Services Division, University of Durban-Westville. Graphs were generated using HARVARD GRAPHICS^{R} (Version 2.10, 1987), by Software Publishing Corp..

4.3 RESULTS

Theophylline concentrations ranged from 0.75 to 34.5 μg/ml. Eight samples were excluded from the comparative analysis because concentrations less than 3 μg/ml are not measurable by the Seralyser^{R} technique.
The linear regression equation for the best fit line with the Seralyser^{R} (y) and TDx^{R} (x) was y = 1.057x + 0.078; R-squared = 95.68% (Fig. 4).

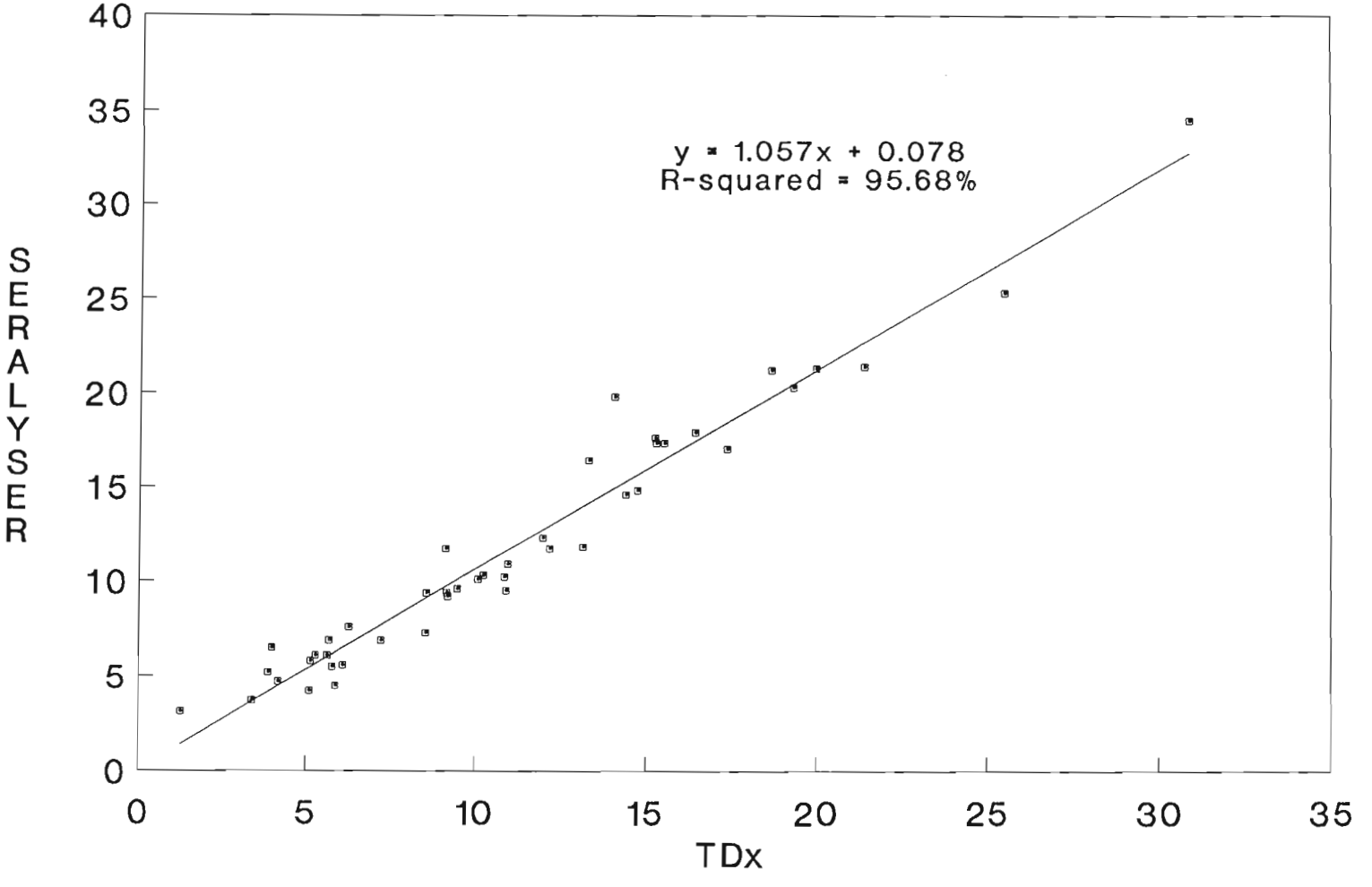

Fig.4 Linear regression of serum theophylline conc. measured using the Seralyser vs TDx

During the 2 month evaluation period the TDx^{R} was calibrated once only, while the Seralyser^{R} needed to be recalibrated a total of 7 times (Table III). The total cost involved inclusive of calibrators and controls was as follows:-

Ames Seralyser^{R} R804-28 (equivalent to R15-47 per sample)
Abbott TDx^{R} R706-68 (equivalent to R13-59 per sample)

Table III - Comparison of Seralyser^{R} with TDx^{R}

	Seralyser^{R}	TDx^{R}
Number of batches of samples	11	11
Number of calibration runs	7	1
Number of calibrators used	14	12
Cost per calibrator[1]	R2-78	R0-46
Number of controls used	18	36
Cost per control[1]	R1-72	R0-31
Number of samples analysed	52	52
Total number of assays performed	14 + 18 + 53[2] = 85	12 + 36 + 52 = 100
Cost per assay[1]	R8-64	R6-90
Total cost to measure the 52 samples	R804-28	R706-68
Average cost	R15-47	R13-59

[1]Prices valid as at June 1989.
[2]One sample had to be diluted and re-assayed on the Seralyser^{R} because of a concentration > 30 ug/ml.

4.4 DISCUSSION

In this study, the performance of the Seralyser^R compared favourably and without bias with the more established TDx^R. The regression equation with its slope of 1.057 and intercept 0.078 was similar to values of slope = 1.083, intercept = -0.287, r = 0.98 (*Cheung and Soldin, 1986*) and slope = 1.05, intercept = 2.79 , r = 0.99 (*Vocich et al, 1985*) previously reported. These results closely approach the slope of 1.00 and intercept of 0.00 required for perfect correlation of the two assay methods. Examination of Fig. 4 shows nearly equal scatter of data points on either side of the line of identity, indicating comparable results with either assay.

Over the 2 month period, the Seralyser^R required recalibration more frequently than the TDx^R. The Seralyser^R uses a 2 point calibration curve while the TDx^R uses a 6 point curve in duplicate. The average cost of the assays was found to be higher for the Seralyser^R (Table III). However, this may be partially offset by the fact that the capital outlay for the instrument itself is considerably lower. Other authors have found the cost per assay for the Seralyser^R to be comparable to that of the TDx^R and Syva Corporation's EMIT^R (*Cheung and Soldin, 1986*).

The minimum sample volumes required with both techniques is very similar viz. 30 µl for the Seralyser^R and 50 µl for the TDx^R. The lower sample volume required with the Seralyser^R is unlikely to be of any additional clinical advantage.

While *Vaughan et al (1986)* found that the Seralyser^R underestimates and produces variable results at concentrations less than 7.5 µg/ml, these findings were not corroborated by this study. The inability of the Seralyser^R to detect theophylline levels less than 3 µg/ml precludes its use in pharmacokinetic studies where it is important to be able to accurately and precisely measure concentrations at this level. However, these drawbacks are unlikely to be of clinical relevance in the applications for which this instrument is intended viz. for dosage adjustment in the emergency room or general practitioner's office.

4.5 CONCLUSIONS

The performance of the Ames Seralyser^{R}, a new dry phase strip immunoassay technique compares favourably and without bias with the established fluorescence polarisation immunoassay technique of Abbott's TDx^{R}. The higher average cost of the assays with the Ames Seralyser^{R} is probably offset by the considerably lower initial cost of the associated equipment. Its inability to detect serum levels < 3 μg/ml precludes its use in pharmacokinetic studies. However, the method has sufficient sensitivity and speed to enable it to find a useful place in therapeutic drug monitoring in the emergency room or physician's office to handle low volume work.

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Chapter Five

The influence of the application of therapeutic drug monitoring on theophylline utilisation at R K Khan Hospital

5.1 INTRODUCTION

Prior to 1973, there was a paucity of information on appropriate theophylline dosage regimens or the therapeutic range in serum concentration for optimal therapy (*Burton et al, 1985*). This situation changed when *Mitenko and Ogilvie (1973)* published their controversial recommendation of a standard intravenous infusion rate of 0.9 mg/kg/hr for all patients. This dosage regimen was later shown to result in clinical toxicity as well as serum drug concentrations greater than 20 μg/ml in a large number of patients (*Weinberger et al, 1976 ; Kordash et al, 1977 ; Hendeles et al, 1977*), since it did not take into account the wide inter-patient variability in theophylline clearance.

Subsequent reports of serious serum concentration related side-effects and toxicity (*Hendeles and Weinberger, 1983; Fitzpatrick and Moss-Barclay, 1985*) as well as inadequate serum concentrations and therapeutic failure (*Jacobs et al, 1976*) with the use of standard doses of theophylline have been published.

In an evaluation of *Mitenko and Ogilvie's* standard dose of aminophylline, *Weinberger et al, 1976* commented that "*it is not possible to achieve optimal aminophylline dosage without monitoring serum theophylline concentrations*".

While serum concentration monitoring of the anti-epileptic drugs now appears to be well established in South Africa (*Miller et al, 1982 ; Klein et al, 1986*), the use of serum concentration monitoring to individualise theophylline dosage remains very limited despite widespread documentation of the potential improvement in patient care (*Hendeles and Weinberger, 1980; Whiting et al, 1984; Fitzpatrick and Moss-Barclay, 1985; Barlow et al, 1988*).

In 1986, one of the first local therapeutic drug monitoring programmes for theophylline was initiated at R K Khan Provincial Hospital, Chatsworth, Durban. This report evaluates the influence of this programme on theophylline utilisation at the hospital. It also considers the outcome of standard doses of theophylline administered to this population.

5.2 MATERIALS AND METHODS

5.2.1 Institutions

The clinical study was conducted at the R K Khan Provincial Hospital in Chatsworth, Durban. This 680 bed hospital is under the control of the Department of Hospital Services of the Natal Provincial Administration. It caters primarily for members of the Indian population who provide an out-patient workload of approximately 1500 patients per working day.
Serum theophylline concentration measurements and analysis of data were performed at the University of Durban-Westville, Durban.

5.2.2 Patients/subjects

Over a 2 year period, serum theophylline concentration measurements were performed on 181 patients. Ninety four patients were excluded from the study for a variety of reasons (see Table IV). The remaining 87 patients consisted of 49 females and 38 males, with an average age of 40.3 years and an average mass of 56.4 kg (Table V). All relevant data pertaining to patients included in the study are presented in Appendix B, Tables B1 to B5. These patients were categorised into groups (Table VI) on the basis of criteria detailed in this section.

Table IV - Patients excluded from the study.

New patients i.e. seen within 1 month of this analysis.	14
Records not available	10
Transferred to another hospital	2
Died soon after initial consultation (1 * pancreatitis, 1 * acute exacerbation of asthma and 1 * motor vehicle accident)	3
Less than 2 interviews with the researcher	65

Table V - Demographic details of the study population

Sample number		87
Age (yrs)	average (SD)	40.3 (15.3)
	range	4.5 - 74
Mass (kg)	average (SD)	56.4 (12.9)
	range	16 - 92
Sex	males	49
	females	38

Table VI - Classification of the study population

Group 1 - Clinically controlled on initial dose	21
Group 2 - NOT clinically controlled on initial dose 2.1 Serum theophylline concentration > or = 15 ug/ml 2.2 Serum theophylline concentration < 15 ug/ml	 5 35
Group 3 - Clinically toxic or potentially toxic	27
Group 4 - Compliance problems	24

NB: All groups are not mutually exclusive.

GROUP 1 - Patients clinically controlled on their initial dose of theophylline.

These are patients who were diagnosed by a pulmonologist to be stable or clinically well controlled and whose episodic exacerbations of asthma were rapidly relieved by inhaled beta-stimulants. In the majority of patients, the initial dose consisted of the manufacturer's recommendation of 1 sustained release tablet twice daily - either Euphyllin Retard^{R} (256.1 mg) or Theodur^{R} (200 mg or 300 mg). These doses had been prescribed prior to the initial consultation with the researcher.

GROUP 2 - Patients NOT clinically controlled on the initial dose of theophylline

These patients, who received similar doses of theophylline as patients in GROUP 1, experienced frequent exacerbations of asthma symptoms that required emergency room treatment or hospitalisation. This group was further sub-divided into:-

GROUP 2.1 - Serum theophylline concentration ≥ 15 μg/ml

In this group of patients measurement of serum theophylline concentration at initial consultation recorded levels of approximately 15 μg/ml or more and further dose increases were considered potentially dangerous.

GROUP 2.2 - Serum theophylline concentration < 15 μg/ml

This group of clinically uncontrolled patients, formed the basis of a study to determine the influence of active intervention based on pharmacokinetic principles. The procedure followed in the pharmacokinetic assessment of patients on theophylline is outlined in a flow diagram (Fig. 5). All evaluations and dosage adjustments were performed in consultation with a pulmonologist. During consultation with the patient a questionnaire (Fig. 6) was completed by the researcher. At the initial consultation, compliance was assessed by means of careful questioning and represented the interviewer's impression there-of.

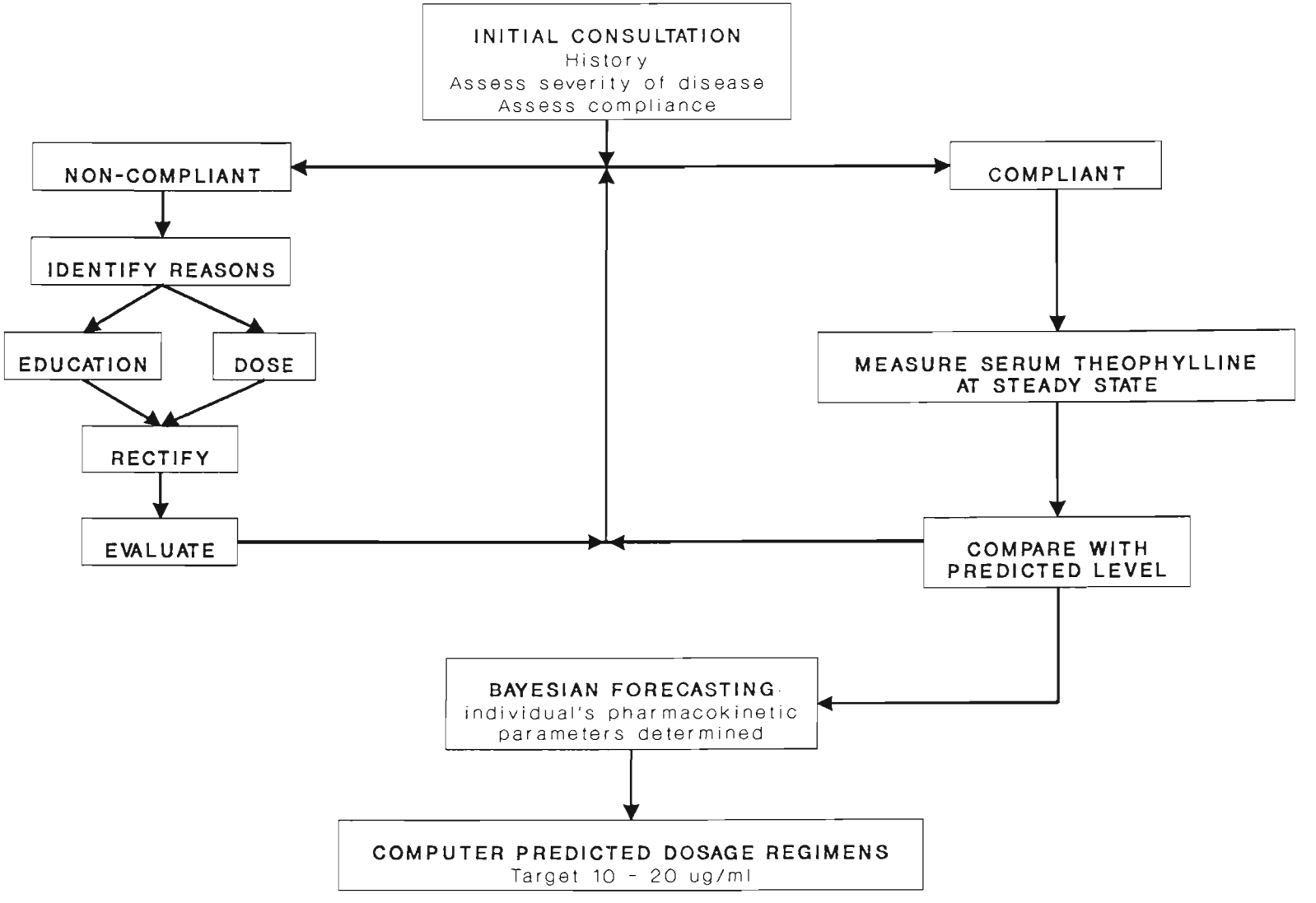

Fig. 5 - Flow diagram to show the procedure followed at R K Khan Hospital when assessing a patient's theophylline requirements

DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF DURBAN-WESTVILLE
PRIVATE BAG X54001
DURBAN
4000

PHONE : 8202249

ASTHMA CLINIC
R K KHAN HOSPITAL
PRIVATE BAG X004
CHATSWORTH
4030

PHONE : 433223 X320

THEOPHYLLINE SERUM CONCENTRATION ANALYSIS

NAME :

PATIENT NO. :

ADDRESS :

SEX :

PHONE :

AGE :

DIAGNOSIS :

RENAL FUNCTION :

LIVER FUNCTION :

CARDIAC FAILURE : 1. ABSENT 2. MILD/MODERATE 3. SEVERE

HEIGHT : cm inches

WEIGHT : kg lb

FRAME :

OBESITY :

CAFFEINE INTAKE : Cups of tea/coffee per day

ALCOHOL INTAKE : 1. NONE 2. SOCIAL DRINKER
3. HEAVY DRINKER

SMOKING STATUS

CIGARETTES : 1. NONE
2. 20/DAY
3. 20/DAY

DAGGA : _____ JOINTS/DAY

NO. OF HOSPITAL ADMISSIONS IN PREVIOUS MONTH :
NO. OF VISITS TO EMERGENCY ROOM/G.P. IN PREVIOUS MONTH :

CURRENT DRUG THERAPY

DRUG	DOSE PRESCRIBED	DOSE TAKEN

TECHNIQUE WHEN USING INHALER POOR SATISFACTORY GOOD

TOXICITY AND SIDE EFFECTS

1. NONE 2. NAUSEA 3. TACHYCARDIA 4. CONVULSIONS
5. SLEEP DISTURBANCE 6. OTHER (SPECIFY)

INTRAVENOUS THERAPY

PREPARATION :
THEOPHYLLINE CONTENT :

START		STOP		DOSE	DURATION
DATE (M/D/Y)	TIME	DATE (M/D/Y)	TIME		

ORAL THERAPY

PREPARATION		PREPARATION		PREPARATION	
DATE (M/D/Y)	TIME	DATE (M/D/Y)	TIME	DATE (M/D/Y)	TIME

INTERVIEWER'S IMPRESSION OF PATIENT COMPLIANCE

GOOD MINOR LAPSES POOR UNCERTAINTY

HOW DO YOU FEEL NOW COMPARED TO PREVIOUS MONTH : BETTER
WORSE
SAME

HAS THERE RECENTLY BEEN ANY CHANGE IN HOME OR WORK ENVIRONMENT:

YES NO

DRUG ASSAY DATA

SAMPLE DATE (M/D/Y), TIME _____
TIME SINCE LAST DOSE _____
MEASURED CONC. _____
ANALYSIS DATE, TIME _____

Fig. 6 - Questionnaire used during consultations with patients at the Asthma Clinic at R K Khan Hospital.

Compliance was later assessed objectively by comparing measured theophylline concentrations with that predicted using average population pharmacokinetic parameters. Thereafter, dose individualisation was performed with the aid of a drug dose optimisation computer package, OPT^{R} Version 4b, available from Clydesoft^{R} Statistical and Scientific Software. This programme utilises the Bayesian feedback techniques previously described (see Section 2.6.4).
These patients were followed for a period sufficient to determine therapeutic success or failure. To make an objective assessment, the patient's hospital records were evaluated retrospectively for a similar period and the following information was obtained :

* Frequency of emergency room visits and hospital admissions for acute exacerbations of asthma. The average number of visits per month over a 3 - 6 month period prior to and after dosage review was recorded and evaluated using the sign test.
* Clinical evaluation of asthma symptoms at each clinic visit.

Clinical evaluations were performed by the same pulmonologist throughout the period under review.

GROUP 3 - Patients clinically toxic or serum theophylline concentration $\geq$ *20 μg/ml.*

Patients were diagnosed as clinically toxic if they experienced any of the generally accepted symptoms of theophylline toxicity such as nausea, vomiting, tachycardia, irritability, tremor or convulsions. They were considered to be potentially at risk of toxicity if their serum theophylline concentration was greater than 20 μg/ml.

GROUP 4 -Patients with compliance problems.

Patients were judged to be noncompliant if :-

* they admitted to this during the interview, or

* evaluation of their serum theophylline concentration revealed a difference of more than 2 standard deviations from the expected concentration calculated using average population pharmacokinetic parameters. This was confirmed if subsequent serum concentration determinations recorded values consistent with prescribed doses.

It was not possible to categorise patients into exclusive groups and therefore some patients appear in more than one category in Table VI e.g. 2 patients who improved clinically after they became compliant appear in Groups 2.2 and 4. However Groups 1 and 2.1 are mutually exclusive.

5.2.3 Statistical analyses

The sign test used to evaluate the change in frequency of emergency room visits and hospital admissions was performed using the STATIS2^{R} Statistics Package (Version 2.1, June 1987) available from Clydesoft^{R} Statistical and Scientific Software. For statistical comparison the $p < 0.01$ level was regarded as significant. All other statistical analyses were performed using the STATGRAPHICS^{R} computer programme by Statistical Graphics Corporation. Graphical illustrations of data were performed using the HARVARD GRAPHICS^{R} package (Version 2.10, 1987) by Software Publishing Corp..
The OPT^{R}, HARVARD GRAPHICS^{R} and STATIS2^{R} programmes are licenced to the Department of Pharmacology while the University's Computer Services Division is the licencee for the STATGRAPHICS^{R} programme. All software were used on IBM^{R} compatible personal computers.

5.3 RESULTS

The classification of patients into the relevant groups is presented below. Where applicable, results quoted are the average for the group with the standard deviation shown in parenthesis. A linear regression of dose on serum theophylline concentration is presented in Fig. 7. The regression analysis does not include patients who were non-compliant (Group 4). The equation for the line of best fit was $y = 0.51x + 8.33$ (R-squared = 6.46%).

GROUP 1 - Patients clinically controlled on their initial dose of theophylline

Twenty one patients (7 males and 14 females), i.e. 24% were clinically stable or well controlled on their initial dose of theophylline. These patients received an average dose of 9.6 (±2.5) mg/kg/day (range 4 - 15 mg/kg/day) theophylline. This dose resulted in an average serum theophylline concentration of 10.7 (±3.7) μg/ml (range 2.68 - 19.1 μg/ml). Six patients demonstrated serum theophylline concentrations less than 10μg/ml while 15 had levels between 10 - 20 μg/ml.

GROUP 2.1 - Clinically uncontrolled - serum theophylline concentration ≥ 15 μg/ml

Five patients, 1 male and 4 females, average mass 62.7 (±20.3) kg who were clinically not controlled on their initial dose of theophylline were classified as being potentially at risk of theophylline toxicity, in the event of an increase in theophylline dose. The average dose of theophylline in this group was 9.96 (±3.73) mg/kg/day (range 5.8 - 16 mg/kg/day). Average serum theophylline concentrations of 16.3 (±1.7) μg/ml (range 15 - 18.6 μg/ml) were recorded.

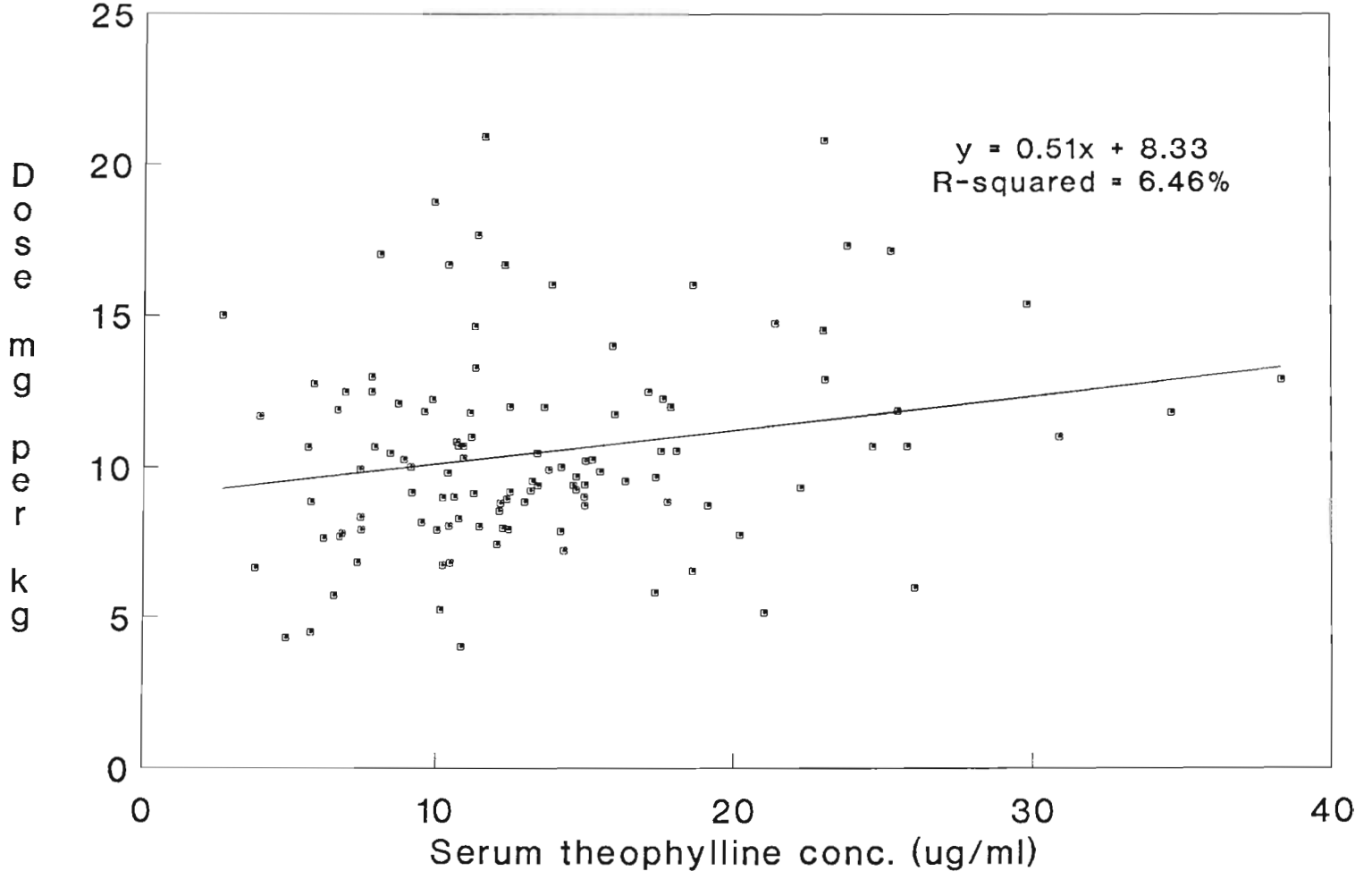

Fig. 7 - Linear regression of dose on serum theophylline concentration

GROUP 2.2 - Clinically uncontrolled - serum theophylline concentration < 15 μg/ml

Thirty five patients (18 males, 17 females) had serum theophylline concentrations less than 15 μg/ml and poor control of their asthma. Six months after dose individualisation as described, 24 (68.6%) patients were judged to have improved clinically. This was shown to be statistically significant for the group (sign test $p < 0.00001$). In 5 patients, this decision was based solely on the clinical evaluation conducted by the pulmonologist and researcher during the patient's monthly visit to the Asthma Clinic. In the remaining 19 patients, clinical improvement was associated with a decrease in the frequency of emergency room visits (sign test $p < 0.00001$; see Fig. 8). In 11 of these 19 patients, a decrease in the number of hospital admissions was also noted (sign test $p < 0.001$; see Fig. 9).

Five of the 24 patients required regular oral prednisolone in addition to the individualised theophylline dose. Exclusion of these 5 patients from analysis still revealed a statistically significant decrease in emergency room visits (sign test $p < 0.0001$) and hospital admissions (sign test $p < 0.002$).

In 2 patients previously on steroids, theophylline dose individualisation resulted in a decrease in steroid requirement. In the one patient steroid requirement was decreased by 67% while in the other, steroids were stopped completely. A further two patients improved clinically after they became compliant and required no theophylline dose adjustment.

The 11 patients (31.4%) not controlled after individualisation of theophylline dose were found to be severe steroid dependent asthmatics. Three patients showed poor reversibility of their bronchospasm as evidenced by a poor response to a short course of high dose steroids. In one patient her environment aggravated her symptoms while another two experienced serious social problems that contributed to their frequent exacerbations of asthma.

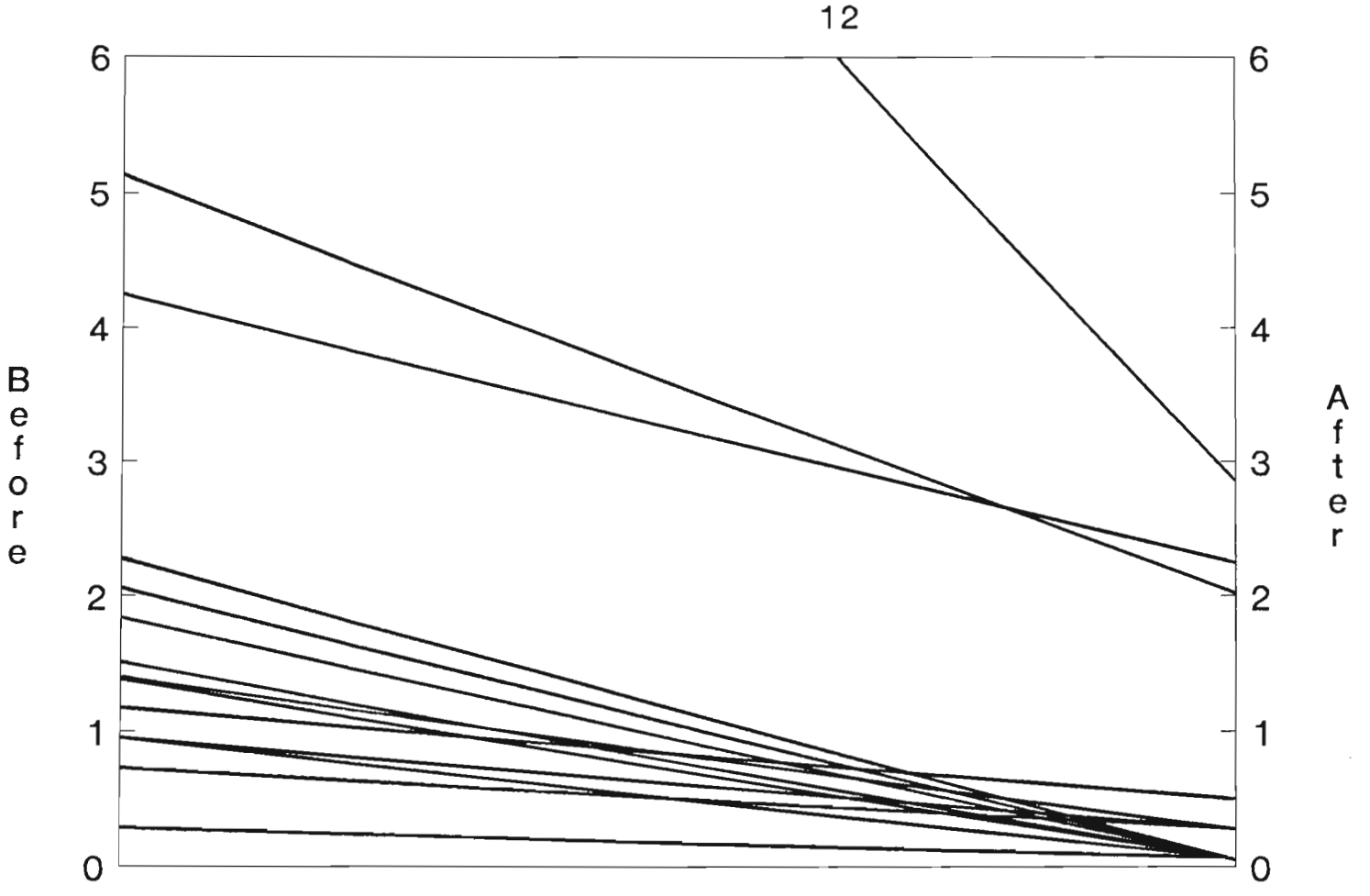

Fig. 8 - Graph showing change in frequency of emergency room visits after dose individualization

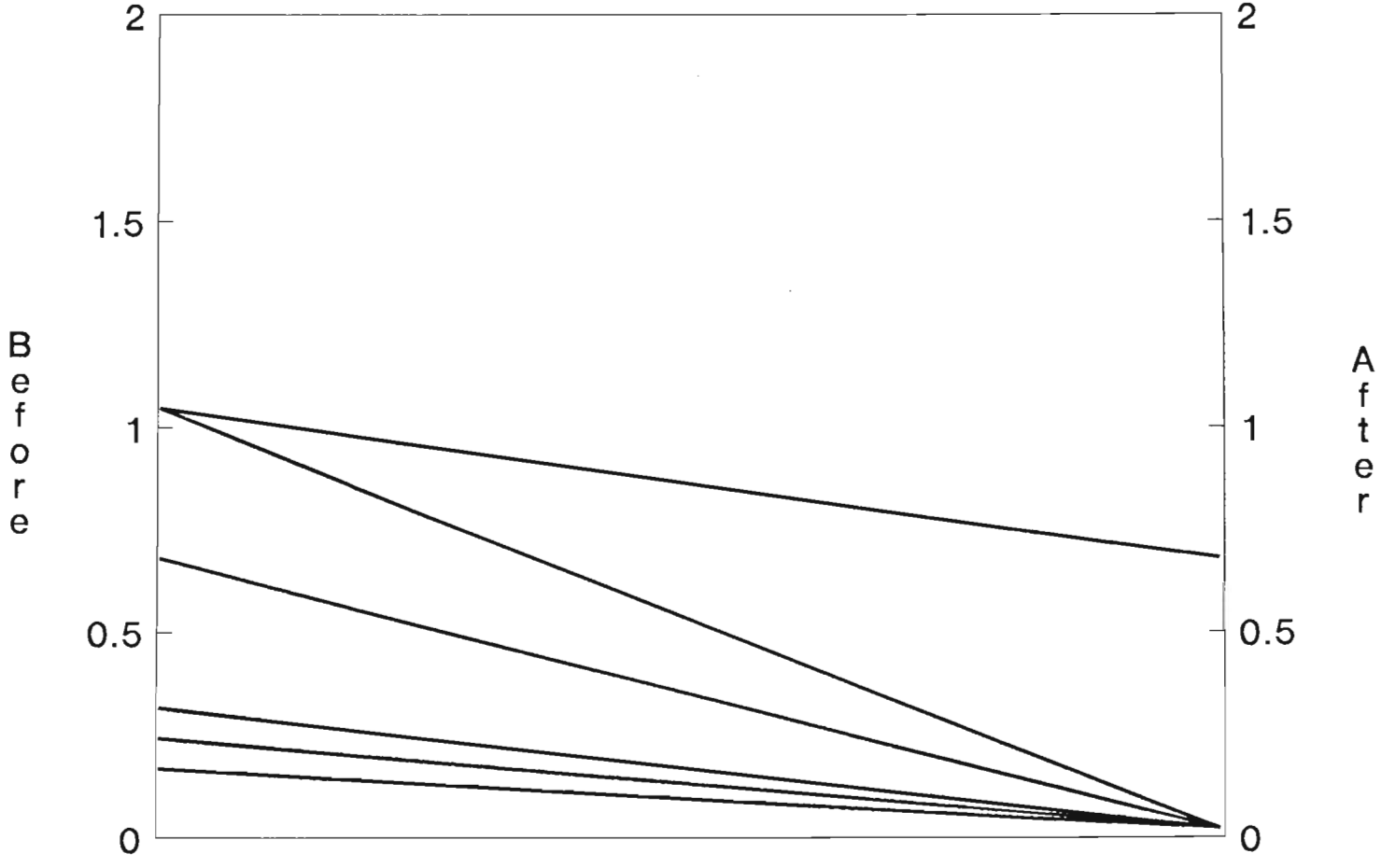

Fig. 9 - Graph showing change in frequency of hospital admissions after dose individualization.

GROUP 3 - Patients clinically toxic or serum theophylline concentration > 20 μg/ml
Details of the 27 patients (13 males, 14 females) exhibiting theophylline toxicity or potential toxicity are listed in Table VII.

Table VII - Possible reasons for theophylline toxicity

Sample number	27
Drug - disease interaction	
CHF	10
Liver function impairment (inferred from alcohol abuse)	2
Drug - drug interaction	
erythromycin	2
cimetidine	1
Age related decrease in clearance	10
Concurrent intravenous and oral therapy	5
No apparent / obvious reason	2

NB: Classification is not mutually exclusive

These patients, average mass 55.8 (±15.2) kg received an average dose of 10.22 (±5.4) mg/kg/day. Serum theophylline concentrations averaged 25.4 (±6.3) μg/ml (range 17.36 - 42 μg/ml). Eighteen patients displayed signs of theophylline toxicity which varied from mild symptoms of nausea, vomiting and tremor to severe life threatening seizures (3 patients).

In one patient a serum theophylline concentration of 16.5 μg/ml was measured 24 hours after the patient had experienced a seizure while being infused with aminophylline at the emergency room. Using available dosing information it was possible to estimate her serum theophylline concentration at the time of the seizure by means of Bayesian statistics as approximately 30 μg/ml. This value was used in subsequent statistical analyses of the group as it reflects the approximate serum theophylline concentration at the time of the toxic manifestation. All other values used were those actually measured. A drug-disease interaction was the possible reason for toxicity in 12 patients, while in 3 cases, a drug-drug interaction was identified. In 10 occurrences of toxicity (age > 60 years), the decrease in theophylline clearance that occurs with age possibly accounted for the toxicity.
Five patients experienced toxicity subsequent to concurrent intravenous and oral therapy, of which 2 were due to inadvertent continuation of oral therapy after institution of intravenous aminophylline. In the other 3 (1 seizure), toxicity occurred during treatment at the emergency room with standard doses of aminophylline.
In 2 cases, no obvious reason for theophylline toxicity could be identified.

GROUP 4 - Patients with compliance problems

Non-compliance was detected in 24 patients (28%, 14 males and 10 females). This consisted of 19 cases of under-dosing, 4 cases of over-dosing and in one patient both on different occasions. Eleven patients admitted to being non-compliant on interview while in the remaining 13 patients, non-compliance was ascertained only after the measurement of serum theophylline concentrations that were inconsistent with predicted concentrations using average population pharmacokinetic parameters. In all these patients this conclusion was confirmed when repeat analysis produced serum concentrations that were consistent with the prescribed dose.

5.4 DISCUSSION

In any clinical situation that requires titration of drug dose to a desired therapeutic endpoint, the ideal is to have a close correlation of dose to effect (*Burton et al, 1985*). Unfortunately this ideal is not realised in the case of theophylline. Three pharmacokinetic/pharmacodynamic relationships are apparent with theophylline therapy:-

* dose-clinical effect relationship
* dose-serum concentration relationship
* serum concentration-clinical effect relationship

The average dose of 9.6 mg/kg/day administered to the patients who achieved *clinical control* on their initial dose (Group 1), does not differ markedly from the 10.22 mg/kg/day dose administered to the patients who experienced *theophylline toxicity* (Group 3), or the dose of 10.03 mg/kg/day in the patients who were *not controlled* on their initial dose (Group 2). This implies a poor relationship between dose and clinical effect.

The linear regression of dose on serum theophylline concentration (Fig. 7), shows a large scatter of data points and a coefficient of determination (r^2) of 6.46%. This indicates that a very small percentage of the variation in the data can be explained by the regression line. This implies a poor relationship between dose and serum theophylline concentration. *Hendeles et al (1977)* found a similar large variability in serum drug concentrations relative to dose in 48 subjects given high doses of aminophylline by constant infusion.

On the other hand, a relationship between serum theophylline concentration and efficacy is now well established (*Mitenko and Ogilvie, 1973; Levy and Koysooko, 1975*). However, this may sometimes have the effect of shifting the emphasis away from achieving clinical control to a situation in which a serum theophylline concentration within the therapeutic range is sought. Indeed, most studies in the past have measured the utility of therapeutic drug monitoring in terms of the achievement of a 'therapeutic' serum theophylline concentration (*Whiting et al, 1984; Fitzpatrick and Moss-Barclay, 1985*).

The present study has highlighted the advantages of measuring clinical response directly, if at all possible. Of the 49 patients in Groups 1 and 2 with serum theophylline concentrations within the generally accepted therapeutic range (10 - 20 μg/ml), only 33 (67%) were well controlled. It is clear therefore, that clinical improvement is a better measure of satisfactory treatment with theophylline, although the achievement of therapeutic serum theophylline concentration provides a useful guide to therapy.

Examination of the serum theophylline concentrations achieved in the 21 patients who were clinically stable on the initial dose (Group 1) reveals that while the majority of patients (71%) had serum theophylline concentrations within the therapeutic range, 6 patients were controlled at serum levels below 10 μg/ml. This then serves to emphasize the need to view the therapeutic range as a statistical concept with respect to group means, within which individuals differ both in efficacy and side-effects (*Jenne, 1984*).

The advantage of therapeutic drug monitoring in this context is that it eliminates the uncertainty in the relationship between the dose and the serum theophylline concentration in an individual. Further, it allows one to predict the likelihood of producing therapeutic effects or potential toxicity with any dose change.

Classification of patients into Group 2.1 attempts to identify possible theophylline treatment failures. The criterion not to increase theophylline dosage if the level is greater than 15 μg/ml is unique to this clinic and was considered in the best interests of the patient. The need to be conservative relates to a practical problem observed with respect to theophylline dosing patterns in the emergency room. Here patients who present with acute asthma are given a standard loading dose of 250 mg of aminophylline irrespective of whether there is a history of prior therapy with theophylline in the previous 24 hours. If one assumes an average Vd of 0.5 L/kg then each mg/kg dose of theophylline will result in a 2 μg/ml increase in serum theophylline concentration. Since the average mass of this population is 56.4 kg then a standard loading dose of 250 mg aminophylline (3.79 mg/kg theophylline) should give an average increase in the serum concentration of approximately 7 μg/ml. A patient with an average serum theophylline concentration of 15 μg/ml therefore can be expected to have an increase in this level to ±22 μg/ml hence being potentially at

risk of toxicity. These mathematical projections are validated by the observation that 3 of the patients in Group 3 became toxic after administration of the standard loading dose in the emergency room. In view of this problem, the emergency room dosing regimen was the subject of a prospective evaluation in 31 asthmatics (see Chapter Six).

A major difficulty in evaluating the clinical efficacy of any therapeutic regimen in asthma results from the variable and unpredictable nature of the disease itself and because it is precipitated by many factors. The decision to use frequency of emergency room visits and hospital admissions as the main criterion in assessing control is based on the recommendation of *Bredon et al (1985)*. A major drawback is that this tends to place more emphasis on the severe attacks of asthma while not detecting a chronic level of bronchospasm that the patient may have. This chronic level of bronchospasm may severely restrict the quality of life of the patient. In order to overcome this drawback the patient's subjective symptoms were also assessed, both by the pulmonologist as well as the researcher in the monthly evaluation of the patient. Although observer bias could not be excluded completely in this assessment, this was kept in mind during the retrospective analysis and a patient was only judged to have improved if both the researcher's and the pulmonologist's assessments concurred and if there was a definite indication by the patient of an improvement in the quality of life.

The results in Group 2.2 have clearly shown that in asthmatics who do not achieve satisfactory clinical control with a standard dose of theophylline, it is possible to increase and individualise the dose with significant additional clinical benefit. Such increases in dose should be guided by serum concentration measurements in order to ensure concentrations in the safe therapeutic range. This observation echoes that of numerous other authors (*Hendeles and Weinberger, 1980; Whiting et al, 1984; Fitzpatrick and Moss-Barclay, 1985; Barlow et al, 1988*). However, the results of this study are particularly encouraging in view of the fact that patients attending the Asthma Clinic at R K Khan Hospital may be considered to be a 'survivor population' of asthmatics attending the hospital. These patients are only admitted to the Asthma Clinic after experiencing an acute exacerbation of asthma that was

severe enough to warrant hospital admission. In general, when seen at the Clinic for their initial consultation they have already been prescribed all available anti-asthma medications.

In the 11 patients in Group 2.2 who did not improve after theophylline dose individualisation, attempts were made to find the reason for their poor response. While information about poor reversibility of the airways are easily obtained, reasons such as psychosocial problems are much more difficult to assess. These physical manifestations of the many stresses and conflicts that the patient is experiencing would probably benefit more from a trial of 'warmth and understanding' (*Peck and King, 1985*) than an individualised dose of theophylline.

The clinical symptoms of theophylline toxicity are well documented, as is the correlation of serum concentrations with toxicity (*Zwillich et al, 1975; Hendeles et al, 1977*). The decision to classify patients with serum theophylline concentrations greater than 20 μg/ml into Group 3 despite the absence of clinical symptoms of toxicity was based on an observation by *Hendeles and Weinberger (1983)*. Commenting on the *Zwillich* study, they noted that minor symptoms of toxicity such as nausea and vomiting do not always precede severe life-threatening toxicity and that only serum theophylline concentration measurements can reliably forewarn the physician of such an eventuality.

Examination of the possible reasons for toxicity in the 27 patients in Group 3 (Table VII) reveals that in many cases, this toxicity could have been avoided if pharmacokinetic considerations had guided the choice of initial dose. Ten patients with congestive heart failure received the same standard dose as the otherwise healthy, 'normal' patients. Several reports have described a decrease in theophylline clearance in patients on theophylline therapy who develop congestive heart failure e.g. *Hendeles et al (1986)* warn that " *the decrease in theophylline clearance can be quite large and of major clinical significance*". While the mechanism for altered theophylline metabolism is unknown, at least 3 possible explanations have been proposed. These have been alluded to in Chapter One, Section 1.5.3.1.3.

In 2 patients, toxicity was due to the concurrent administration of erythromycin, an enzyme inhibitor. While this interaction has been widely reported (*Prince et al, 1981; LaForce et al, 1981*), it is this researcher's observation from this study that prescribers consider it to be clinically insignificant. This probably relates to the fact that theophylline is often prescribed in doses that result in sub-therapeutic serum concentrations in a large percentage of the population. Administration of erythromycin in these patients merely results in the serum theophylline concentration being increased to within the therapeutic range. However, toxicity may occur if the patient's serum theophylline concentration is in the upper level of the therapeutic range.

In another patient, potential toxicity was due to the concurrent administration of another enzyme inhibitor, cimetidine. This drug interaction which may result in rapid decreases in theophylline clearance (within 24 hours) is reported to have been the cause of at least one fatality (*Hendeles et al, 1986*). The interaction is clinically important since the two drugs are often prescribed concurrently to patients in intensive care units who have gastrointestinal bleeding and who are intubated and being maximally bronchodilated. In this patient, the alternate H_2 receptor antagonist, ranitidine was substituted and the serum theophylline concentrations subsequently decreased.

In 2 patients, toxicity occurred following overcompliance with oral theophylline. These patients experienced poor control of their asthma and in an attempt to obtain relief from their bronchospasm, unwittingly increased the dose and frequency. Their overcompliance is consistent with observations that patients with poor control of symptomatic conditions (e.g. arthritis) frequently tend to self-medicate leading to overdosage (*Kubacka and Juhl, 1985*).

Non-compliance with medical regimens is a major obstacle to the provision of adequate medical care. It is a particular problem in therapy with long term prophylactic regimens. A review by *Sackett and Snow (1979)* suggests that 20 - 30% of patients fail to follow short term medication regimens when the regimen is curative, and 30 - 40% of patients when the regimen is preventative. In long term regimens, non-compliance rates average about 50% and increase with time.

The results of this study (28% non-compliance) are in general agreement with the above-mentioned observations. Theophylline is a prophylactic in the management of asthma. Therefore, one can expect occasional under-compliance in a patient who either experiences good control with this agent or who has episodic exacerbations of asthma. Another problem that has been identified by this study is that of over-compliance (4 patients - 2 of whom became toxic), particularly in those patients who experience poor control. It is envisaged that the role of therapeutic drug monitoring would be to identify these patients, who would then be counselled and/or prescribed additional anti-asthma medications.

5.5 CONCLUSIONS

From the results of this study, it may be concluded that :-

1. A poor correlation exists between theophylline dose and clinical effect.
2. A poor relationship exists between theophylline dose and serum concentration.
3. While a good correlation exists between therapeutic serum theophylline concentration and clinical efficacy, this is not absolute - some patients are well controlled at so-called sub-therapeutic concentrations.
4. In patients who do not achieve satisfactory clinical control with the manufacturer's recommended initial doses of theophylline, and who have serum concentrations considered to be sub-therapeutic, it is possible to increase and individualise the dose with significant clinical improvement. Such dosage adjustments should be guided by serum concentration measurements.
5. Theophylline related toxicity could probably be reduced if dosage is guided by consideration of the many factors that influence theophylline clearance.
6. Serum theophylline concentration measurements are a useful guide to the objective assessment of patient compliance.

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Chapter Six

Evaluation of the use of a standard fixed dose of theophylline in the emergency room management of acute asthma

6.1 INTRODUCTION

It is common practice at R K Khan Hospital to administer a standard intravenous dose of 250 mg aminophylline (equivalent to 214 mg theophylline) to patients with acute asthma irrespective of body mass or history of prior intake of theophylline. It has been recommended, however, that theophylline loading dose should be calculated taking these factors into consideration (*Hendeles and Weinberger, 1981*). *Hendeles et al (1980)*, suggest that a dose of 5 mg/kg is an appropriate loading dose in a patient who has not received any theophylline-containing medications in the previous 24 hours, while in a patient who has taken some theophylline, a dose of 2.5 mg/kg is considered to be relatively safe, provided the patient does not already have symptoms of theophylline toxicity (HWJ dose).

The motivation for this study was the finding that patients given the fixed dose of 250 mg aminophylline experienced severe life-threatening seizures (1 patient) or serum theophylline concentrations greater than 20 μg/ml (2 patients) - see Chap[ter Five.

In this study no attempt is made to correlate clinical control with serum theophylline concentrations. The primary purpose of this study was to determine how often therapeutic or toxic concentrations were obtained with the standard dosing regimen prescribed at R K Khan Hospital and to compare this with concentrations expected if the dose as recommended by *Hendeles et al, 1980* had been used.

6.2 MATERIALS AND METHODS

Over a 6 month period, 35 patients presenting to the emergency room between 16h30 and 21h00 with an acute exacerbation of asthma were included into the study depending on the availability of the researcher.
After clinical assessment by the casualty medical officer, patients were transferred to the emergency treatment room where nursing staff administered the following standard treatment protocol as authorised by the casualty medical officer :-

Salbutamol nebulisations
Hydrocortisone 200 mg intravenous injection
Aminophylline 250 mg in 200 ml normal saline infused over approximately 2 hours (the RKK dose).

After completion of treatment a blood sample was drawn at a time not less than thirty minutes after cessation of the theophylline infusion. Samples were drawn by venipuncture on the arm opposite to that in which the infusion was administered . These were then centrifuged and the serum stored at -20°C until ready for analysis with either the EMIT^{R} or TDx^{R} methods.
When the acute phase of the attack was over, the patient was interviewed by the researcher and a questionnaire was completed (Fig. 6, Chapter Five). If at this stage, potentially high serum theophylline concentrations were suspected based on available information and average population pharmacokinetic parameters, then it was recommended to the casualty medical officer that theophylline therapy be terminated.
The estimated serum theophylline concentration that would have been achieved with the *Hendeles et al, 1980* recommended dose of 2.5 or 5 mg/kg depending on history of theophylline use in the previous 24 hours was calculated proportionately from the measured serum concentration and mg/kg dose in the individual patient using equation (5).

$$Cp_{HWJ} = \frac{Cp_{meas} * Dose_{HWJ}}{Dose_{admin}} \qquad (5)$$

where Cp_{HWJ} is the estimated serum theophylline concentration if the HWJ dose had been used.

Cp_{meas} is the measured serum theophylline concentration in μg/ml.

$Dose_{HWJ}$ is the mg/kg HWJ dose previously described .

$Dose_{admin}$ is the mg/kg RKK dose administered.

All relevant data pertaining to the patients included in this study are recorded in Tables C1 to C3, Appendix C.

6.3 RESULTS

The 35 patients (22 males, 13 females) included in the study had an average age of 36.8 (±11.4) years (range 16 - 65 years) and average mass of 58.6 (±9.4) kg (range 43 - 89 kg) - see Table VIII.

Four patients (all males) did not respond to an initial course of treatment. These patients were reviewed by the casualty medical officer who prescribed an additional dose of aminophylline (250 mg) and further nebulisations with salbutamol. Measurement of serum theophylline concentrations 30 minutes after completion of this second infusion revealed that 3 patients had levels within the therapeutic range and 1 patient a level greater than 20 μg/ml.

Of the remaining 31 patients, 14 patients (45%) achieved serum theophylline concentrations less than 10 μg/ml, 12 patients (39%) had concentrations between 10 - 20 μg/ml and concentrations greater than 20 μg/ml were recorded in the remaining 5 patients.

Table VIII - Demographic details of the study population

Sample number		35
Age (yrs)	average	36.8 (11.4)
	range	16 - 65
Mass (kg)	average	58.6 (9.4)
	range	43 - 89
Sex	males	22
	females	13

All values quoted are average (SD)

In two patients, the infusion was stopped before completion - 1 due to side-effects (severe nausea and vomiting - serum theophylline concentration 8.05 μg/ml) and another because of suspected high serum levels. The latter patient admitted to over-compliance with oral theophylline prior to admission to the emergency room. Using average population pharmacokinetic parameters his serum theophylline concentration was estimated to be approximately 25 μg/ml. Subsequent measurement after cessation of intravenous therapy recorded a level of 22 μg/ml. Since complete emergency room dosing information was not available for these 2 patients, the expected serum theophylline concentration with the HWJ dose was not calculated.

In the 33 patients in whom the calculation was performed, the results indicate that 11 patients (33%) would have had levels below the range, 20 (61%) patients within the range and 2 patients (6%) would have had serum theophylline concentration greater than 20 μg/ml (Table IX).

Table IX - Comparison of serum theophylline concentrations obtained using the RKK loading dose with that expected using the HWJ dose.

	<10 ug/ml	10-20 ug/ml	>20 ug/ml
RKK DOSE n = 35			
Patients given 1 dose of aminophylline	14	12	5
Patients given 2 doses of aminophylline	0	3	1
Total	14 (40%)	15 (43%)	6 (17%)
HWJ DOSE n = 33*			
2.5 mg/kg theophylline	8	13	2
5.0 mg/kg theophylline	3	7	0
Total	11 (33%)	20 (61%)	2 (6%)

* Calculation not done in 2 patients due to incomplete dosing information

6.4 DISCUSSION

The average RKK dose of 3.65 mg/kg theophylline administered to this population (average mass 58.6 kg) can be expected to increase the serum theophylline concentration by approximately 7 μg/ml if one assumes an average volume of distribution of 0.5 L/kg. The HWJ recommended dose of 2.5 or 5 mg/kg is expected to increase the concentration by 5 or 10 μg/ml respectively.

While the RKK dose has been shown to be typically conservative (40% with levels below the range and 43% within the range), it is noteworthy that 6 patients (17%) had serum theophylline concentrations greater than 20 μg/ml after administration of the first dose of aminophylline.

Under ideal circumstances, serum theophylline concentration measurements should be performed prior to the administration of a loading dose if there is a history of theophylline use in the previous 24 hours (*Hendeles and Weinberger, 1981*). This was not possible in the present study since the necessary equipment was not available at the hospital - all serum theophylline concentration determinations being done at the University of Durban-Westville, 25 km away. If dosage had been guided by serum theophylline concentration determinations in these patients, then it is envisaged that more patients (if not all) would have achieved serum theophylline concentrations in the therapeutic range. In addition, the patient who had been over-compliant with his out-patient prescription of oral theophylline would have been identified earlier and not subjected to the potential risks of high serum theophylline concentrations and toxicity.

Despite the absence of facilities to measure stat theophylline levels, the results of this study indicate that the use of a mg/kg loading dose of theophylline individualised on the basis of the history of prior theophylline use will produce satisfactory concentrations in 61% of patients. This is not entirely surprising since the calculation of loading doses requires a knowledge of the volume of distribution, which in the case of theophylline does not exhibit as much inter-individual variability as does clearance (*Hendeles et al, 1986*). One can therefore administer the same mg/kg loading dose of theophylline to a heterogeneous group of patients with a minimum of variation in the serum theophylline concentrations.

A possible explanation for the nausea and vomiting experienced by the patient with a relatively low serum theophylline concentration of 8.05 μg/ml may have been an unintended faster than normal infusion rate. Excessively rapid intravenous administration results in transiently high serum concentration, because of the finite time required for distribution from the central compartment into the whole-body theophylline distribution space (*Hendeles et al, 1986*).

6.5 CONCLUSIONS

A standard fixed dose of theophylline administered to patients irrespective of body mass or history of prior intake of theophylline has resulted in serum theophylline concentrations ranging from sub-therapeutic to potentially toxic.

Dosing according to body mass and history of theophylline use results in calculated serum theophylline concentrations that are much more acceptable in terms of the therapeutic range.

The recommended doses of 2.5 mg/kg for a patient who has ingested theophylline in the previous 24 hours and 5 mg/kg for the patient who has not, appears to be satisfactory in the majority of patients.

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Chapter Seven

Population pharmacokinetics of theophylline

7.1 INTRODUCTION

Good therapeutic practice should always be based on an understanding of pharmacokinetic variability. This ensures that dosage adjustments can be made to accommodate differences in pharmacokinetics due to genetic, environmental, physiological or pathological factors (*Whiting et al, 1986*).

The introduction of the NONMEM computer programme has facilitated the identification of circumstances in which the above factors are important and has enabled a quantification of pharmacokinetic variability using routine clinical data (*Sheiner et al, 1972*). The purpose of this study was to apply the NONMEM approach to determine the pharmacokinetics of theophylline in an Indian population. This information is currently not available. In addition to ascertaining any differences in pharmacokinetic parameters compared to other populations previously studied, the estimates obtained from this analysis may be used in Bayesian forecasting computer programmes to increase the accuracy of dosage predictions for this population.

To this end, theophylline pharmacokinetic parameters and the degree of inter- and intra-individual variability were determined in a smoking and a non-smoking population. Two separate sets of data were used in this study. In Study 1, data from a traditional pharmacokinetic investigation was used i.e. a rigid protocol, small number of volunteers and many samples per subject; while Study 2 can be regarded as consisting of typical routine clinical data. In view of the difference in the study protocols, they were analysed separately in the NONMEM programme.

7.2 MATERIALS AND METHODS

7.2.1 Subjects and patients

7.2.1.1 *Study 1 - Traditional Pharmacokinetic Study*

This data was derived from a multi-centre comparative bioavailability study done on smokers and non-smokers. The preparations investigated were Euphyllin Retard^{R} tablets, Theodur^{R} 300 mg tablets and Alcophyllin^{R} elixir.

The smokers were a group of 12 otherwise healthy volunteers, 9 men and 3 women with an average mass of 73.40 (±13.99) kg, range 48 to 97.5 kg and average age 36.4 (±11.3) years, range 22 to 60 years. All of the subjects smoked more than 15 cigarettes per day. This part of the study was conducted by Miller and associates at the Department of Pharmacology, Potchefstroom University for CHE, Potchefstroom, Transvaal in 1984 and is hereafter referred to as the PUCHE data (*Miller and Rheeders, 1984*).

The non-smokers were a group of 11 otherwise healthy male volunteers with an average mass of 78.2 (±10.1) kg, range 69.5 to 105 kg and average age of 20 years. This part of the study was conducted by Straughn and associates at the Department of Pharmacology, University of Cape Town, Cape and is hereafter referred to as the UCT data.

All relevant data pertaining to the subjects included in this study are recorded in Tables D1 to D12, Appendix D.

7.2.1.2 *Study 2 - Routine Clinical Data*

The data for this study (referred to as the RKK data) was collected between 1986 and 1988 at the R K Khan Provincial Hospital in Chatsworth, Durban during routine clinical consultations at the Asthma Clinic.

The following patients were excluded from the NONMEM analysis:-

* Patients with concomitant illnesses known to affect theophylline clearance e.g. congestive heart failure, liver disease or febrile illnesses.
* Patients who had recently been treated with any drug known to alter theophylline clearance e.g. cimetidine, erythromycin or phenobarbitone.
* Patients less than 20 or greater than 40 years of age.
* Patients with a known compliance problem in whom the dosing history was considered to be unreliable.

The RKK data set consisted of 30 patients (12 males, 18 females), age 30 (±5) years, range 21 - 39 years; mass 58 (±11) kg, range 36.9 - 80.5 kg. The group consisted of 10 smokers (all males) and 20 non-smokers. All relevant data pertaining to these patients are recorded in Tables D13 to D15, Appendix D.

7.2.2 Dosing regimen and sampling times

7.2.2.1 *Study 1 - Traditional Pharmacokinetic Study*

Subjects received Theodur^{R} (Rio Ethicals), Euphyllin Retard^{R} (Byk Gulden) and Alcophyllin^{R} elixir (Propan Lipworth) in a randomised fashion during 3 consecutive weeks. Alcophyllin^{R} 30 ml (anhydrous theophylline 160 mg) was given three times daily at 08h00, 14h00 and 20h00, while Theodur^{R} (anhydrous theophylline 300 mg) and Euphyllin Retard^{R} (anhydrous theophylline 256.1 mg) were given twice daily at 08h00 and 20h00. All 3 products were administered for 4 days, with blood samples being drawn prior to dosage on day 1. On day 4, blood samples were drawn at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 27 and 33 hours after administering tablets and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 14, 27, and 33 hours after administering elixir.
Exclusion of some data points: Examination of the theophylline plasma concentration - time data revealed the presence of a significant lag time in absorption of the tablets. This was particularly prominent for Theodur^{R}. At present NONMEM'S PREDPP package does not have an appropriate means of

determining lag time (*Beal, 1985*) and therefore, various time points during the absorption phase corresponding to a possible lag time were omitted. The absorption rate constant (Ka), determined using this data, is therefore an average from the time of administration.

7.2.2.2 *Study 2 - Routine Clinical Data*

In the routine clinical study, subjects received either Theodur^R or Euphyllin Retard^R on an out-patient basis. The average dose of Theodur^R was 10.17 (±2.28) mg/kg/day (range 5.23 to 16.67 mg/kg/day) and Euphyllin Retard 10.41 (±3.80) mg/kg/day (range 6.61 to 20.81 mg/kg/day). With the exception of 1 patient who received doses 8 hourly, all other doses were administered on an approximate 12 hour schedule. Blood samples were drawn at steady state and not less than 4.0 hours after the last oral dose. The 30 individuals included in the study had a total of 58 dose-concentration pairs, 6 patients had 3 pairs each, 10 had 2 and in 12 patients, there was only one dose-concentration pair each.

7.2.3 Theophylline serum concentration analysis

In Study 1, serum theophylline concentrations were measured using the EMIT^R technique , while in Study 2, samples were measured using either the EMIT^R or the TDx^R systems.

7.2.4 NONMEM Analysis

The population pharmacokinetic analysis was performed on a mainframe computer (ICL2988) at the University of Durban-Westville using Double Precision NONMEM 77 - version II level 1.4 together with the PREDPP package (ADVAN 2, TRANS 2 AND SS2) (*Beal and Sheiner, 1980 - 1986*).
A one compartment linear pharmacokinetic model with first order absorption was implemented by choosing the ADVAN 2 subroutine provided in the NONMEM-PREDPP load module. The use of the subroutine TRANS 2 makes it

possible to estimate the pharmacokinetic parameters, clearance (Cl) and volume of distribution (Vd) while the model in PREDPP operates with the parameters, elimination rate constant (K) and absorption rate constant (Ka),

where $$K = \frac{Cl}{Vd} \qquad (6)$$

7.2.4.1 Statistical model

A log-normal distribution was assumed to describe the variability of the pharmacokinetic parameters.
The error models for interindividual variability in the jth individual were :-

$$\ln Cl_j = \ln \text{true } Cl_j + {}^{\cap}Clj$$

or $$Cl_j = \text{true } Cl_j * \exp(\cap^{Clj}) \qquad (7)$$

and similarly,

$$Vd_j = \text{true } Vd_j * \exp(\cap^{Vdj}) \qquad (8)$$

$$Ka^j = \text{true } Ka_j * \exp(\cap^{Kaj}) \qquad (9)$$

where $\cap$ has a mean value equal to zero and a covariance matrix Ω.

Residual variability in the ith concentration of the jth individual was modelled as follows:-

$$\text{Measured } C_{ij} = \text{Predicted } C_{ij} * \exp(\varepsilon_{ij}) \qquad (10)$$

where ε has a mean value equal to zero and variance of σ^2.

The standard error (SE) of the parameters, Cl, Vd and Ka and the variances (SE_{var}), σ^2 and Ω are estimated by NONMEM. The standard error of the inter- and intra-individual variability was approximated using equation (11),

$$SE = (\cap \text{ or } \varepsilon + SE_{var})^{0.5} - (\cap \text{ or } \varepsilon)^{0.5} \qquad (11)$$

and expressed as a percentage (*Vozeh et al, 1982*).

The RKK data consisted of samples collected during the post-absorptive phase, as required for purposes of therapeutic drug monitoring. During the analysis of this data therefore, the values of Ka for Theodur^R and Euphyllin Retard^R were fixed at 0.18 hr^{-1} and 0.462 hr^{-1} respectively as estimated from the prior analysis of the data from Study 1.

7.2.4.2 NONMEM regression model

Absorption rate constants (Ka) for all 3 preparations under study were obtained by use of the following regression model which was coded into the user-written subroutine PK of the PREDPP package using standard FORTRAN^R.

$$Ka = (\Theta_3 + \Theta_5 + \Theta_6) * PREP \qquad (12)$$

where PREP = 1, 2, or 3 depending on whether the patient had received Alcophyllin^R elixir, Theodur^R tablets or Euphyllin Retard^R tablets respectively. In this way , the values of Θ_3, Θ_5 and Θ_6 in the PK subroutine could be constrained to equal zero where applicable in order to differentiate the Ka values for all three preparations.
A second regression model was implemented in order to test the null hypothesis that smoking does not exert a significant influence on theophylline clearance.

$$CL = (\Theta_1 + (SM * \Theta_4)) * Wt \qquad (13)$$

where Wt is the body mass in kg and the value of SM was either 1 or 0 depending on whether the patient was a smoker or non-smoker respectively.

7.2.5 Criteria for hypothesis testing (*Grevel et al, 1988*)

The criteria used in determining whether the hypothesis could be rejected were as follows:-

7.2.5.1 Each NONMEM run provides in its output the value of its objective function, which is 2 times the negative logarithm of the likelihood function. The difference in the value of the objective function (DOBF) obtained for the general and the constrained model is approximately chi square distributed with degrees of freedom equal to the number of fixed parameters. A DOBF of more than 8 indicates a significant improvement ($p < 0.005$) in the fit of the data and suggests that the constrained model should be accepted.

7.2.5.2 A minimum of correlation between parameters by inspection of the correlation matrix of the estimate provided in the NONMEM output. A value close to 1.0 is regarded as perfect correlation.

7.2.5.3 Small standard errors of the estimates.

7.2.5.4 Weighted residuals which are randomly scattered around zero when plotted against the predicted concentration.

7.2.5.5 Decrease in the estimate of inter-individual variances.

7.3 RESULTS

7.3.1 Hypothesis testing - see Table X

Table X - HYPOTHESIS TESTING:

The influence of smoking on theophylline clearance

Null Hypothesis	Clearance (l/kg/hr)	Interindividual variability (%)	Objective function	Intraindividual variability (%)	Correlation Matrix
STUDY 1					
Cl not influenced by smoking (general model)	0.0571 (0.0197)	42 (22)	712.642	20 (5)	Cl vs Vd = 0.928
Cl corrected for smoking (constrained model)	0.0441 (0.0039)	32 (9)	766.135	20 (4)	CL vs Vd = 0.834
STUDY 2					
Cl not influenced by smoking (general model)	0.0505 (0.0168)	50 (3)	209.606	34 (12)	Cl vs Vd = 0.896
Cl corrected for smoking (constrained model)	0.0375 (0.004)	25 (4)	187.260	25 (3.9)	Cl vs Vd = 0.802

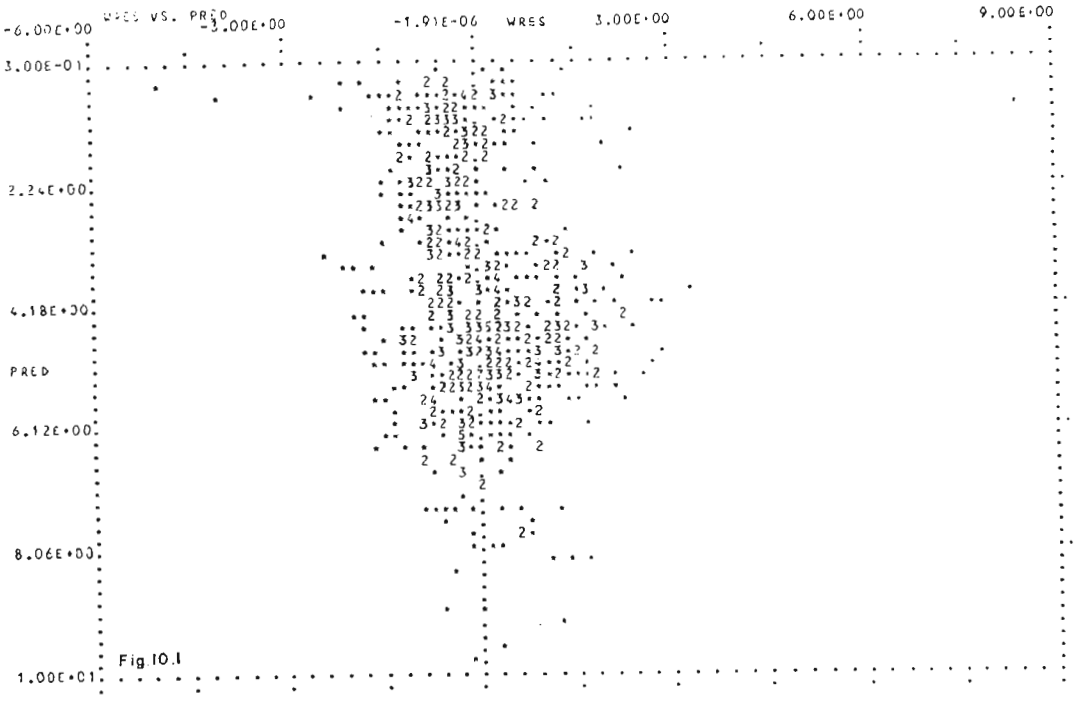
standard error is shown in parenthesis

Study 1

The objective function showed an increase from 712.642 (general model) to 766.13 (constrained model) i.e. the DOBF of greater than 8 required for rejection of the null hypothesis at the $p < 0.005$ confidence interval was not observed.
The correlation between the parameters, Cl and Vd decreased from 0.928 for the general model to 0.834 for the constrained model.
The standard errors of both the fixed and the random effect parameters for the constrained model are smaller than that obtained with the general model.
The graphs of weighted residuals against predicted concentrations are shown in Fig. 10. The graph for the constrained model (Fig. 10.2) shows a more random scatter of data points around zero when compared with that of the general model (Fig. 10.1).
The interindividual variability in Cl decreased from 42% to 32%.

Study 2

The value of the objective function decreased from 209.606 (general model) to 187.260 (constrained model). This corresponds to a DOBF of 22.
The value of the correlation matrix decreased from 0.896 for the general model to 0.802 for the constrained model.
The standard errors for the Cl parameter and the intraindividual variability displayed a decrease while the standard error for the interindividual variability showed a small increase (from 3% to 4%).
The graphs of weighted residuals against predicted concentrations are shown in Fig. 11. The graph for the constrained model (Fig. 11.2) shows a more random scatter of data points around zero when compared with the graph for the general model (Fig. 11.1).
The estimate of the interindividual variability in Cl decreased from 50% to 25%.



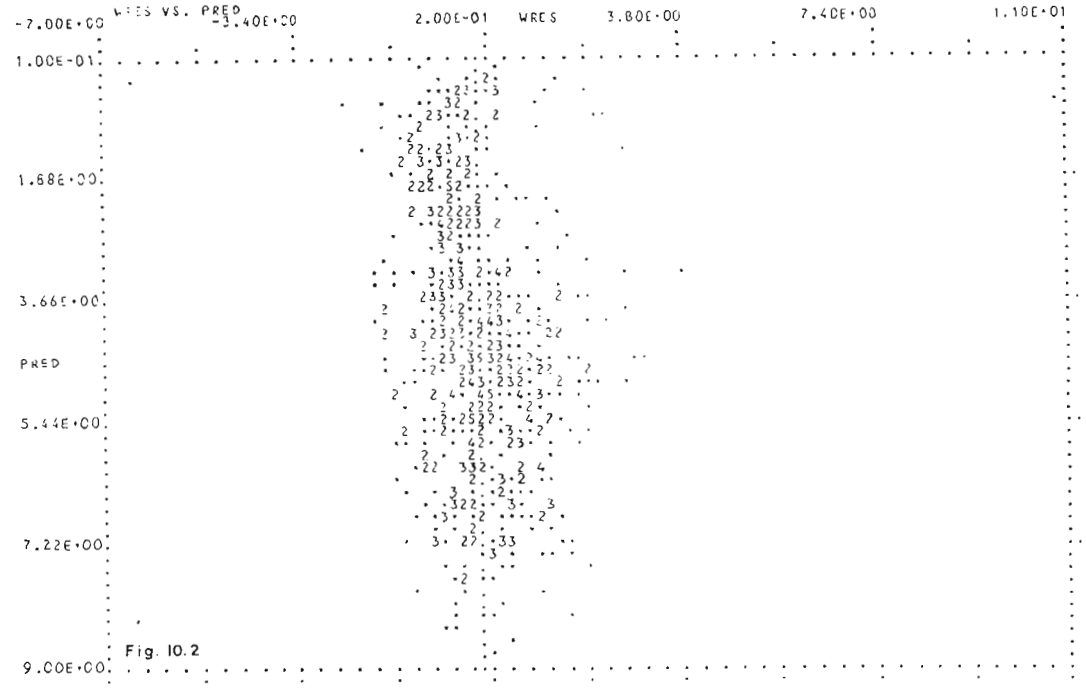
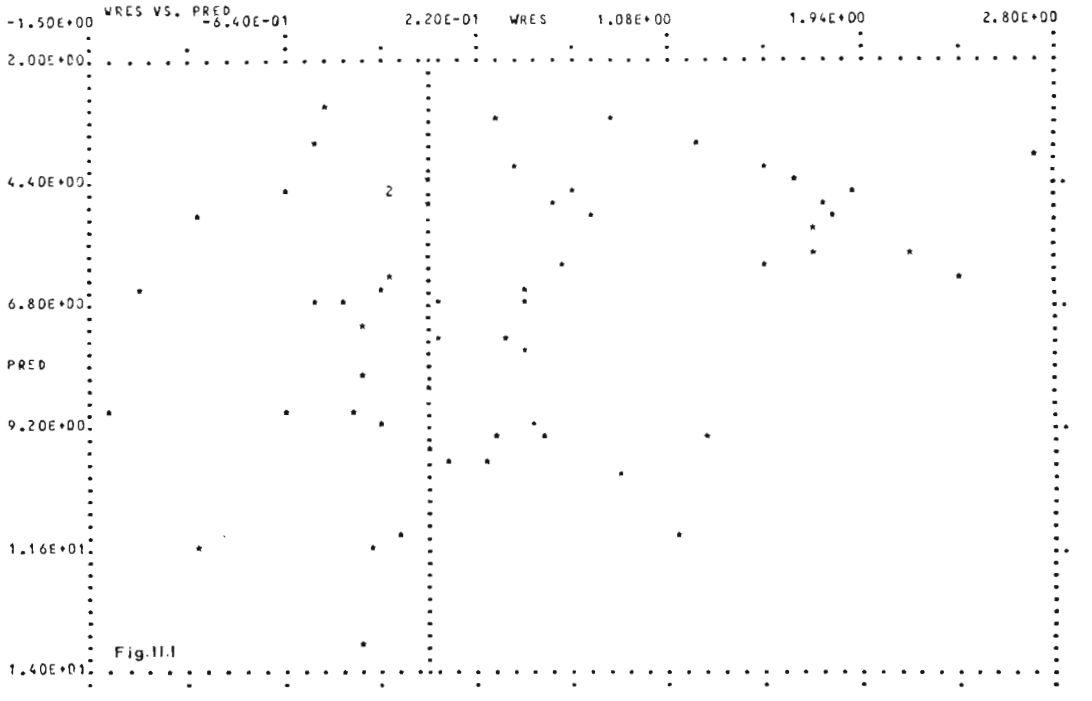


Fig. 10 - Hypothesis testing - Criterion No. 7.2.5.4 - Study 1
Graph of weighted residual (WRES) vs predicted serum theophylline concentration (PRED) for the general (10.1) and the constrained (10.2) regression models. Note the data points randomly scattered around zero in graph for the constrained model.



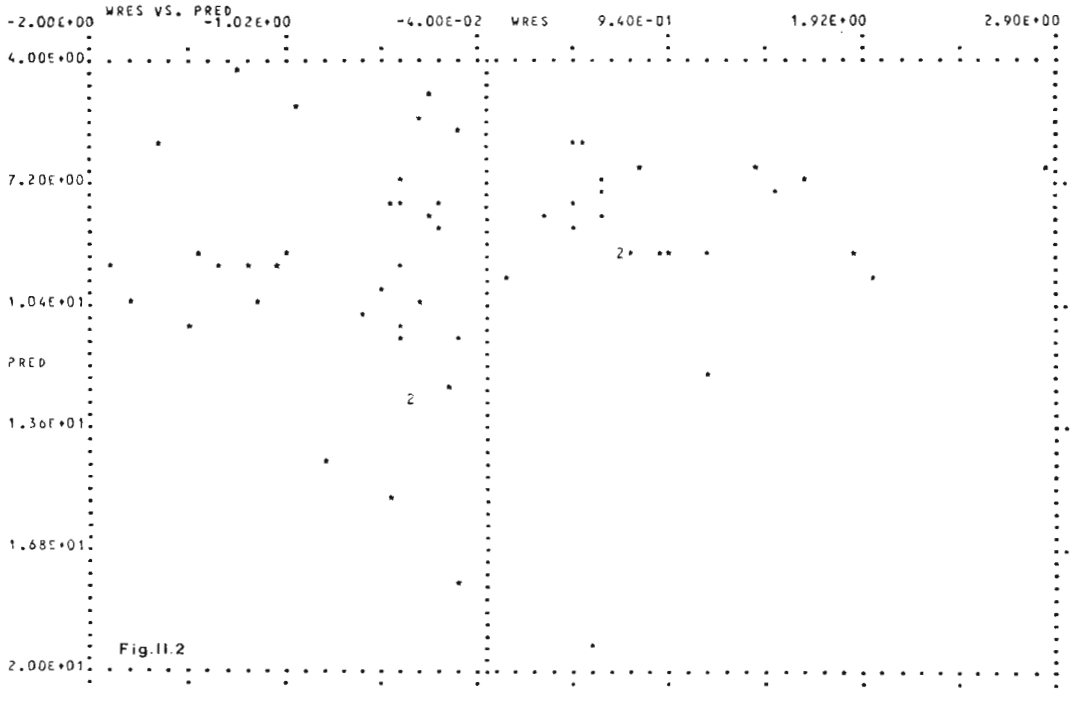


Fig. 11 - Hypothesis testing - Criterion No. 7.2.5.4 - Study 2
Graph of weighted residual (WRES) vs predicted serum theophylline concentration (PRED) for the general (11.1) and the constrained (11.2) regression models. Note the data points randomly scattered around zero in graph for the constrained model.

7.3.2 *Population pharmacokinetic parameters*

The fixed and random effects parameters for both studies are shown in Tables XI and XII.

Table XI - FIXED EFFECTS PARAMETERS

PARAMETER	STUDY 1	STUDY 2
$Cl_{non\text{-}smoker}$ (l/kg/hr)	0.0441 (0.0039)	0.0375 (0.004)
Cl_{smoker} (l/kg/hr)	0.0641 (0.0176)	0.0505 (0.009)
Vd (l/kg)	0.8 (0.164)	0.8 (0.42)
Ka_{flex} (hr^{-1})	4.61 (1.17)	not applicable
$Ka_{Euphylin}$ (hr^{-1})	0.28 (0.054)	constrained
Ka_{theoph} (hr^{-1})	0.18 (0.04)	constrained

All values quoted are the population mean with the standard error reported in parenthesis.

Table XII - RANDOM EFFECTS PARAMETERS

PARAMETER	STUDY 1	STUDY 2
Interindividual variability in Cl (%)	32 (9)	25 (4)
Interindividual variability in Vd (%)	61 (20)	negligible
Interindividual variability in Ka (%)	107 (41)	-
Intraindividual variability (%)	20 (4)	25 (3.9)

All values reported are the population mean with the standard error in parenthesis.

7.4 DISCUSSION

The study of population pharmacokinetics has its most important role in therapeutic drug monitoring programmes that utilise the Bayesian forecasting technique (*Whiting et al, 1986*). Although the Bayesian feedback technique has been shown to be superior to all other currently available techniques for theophylline dosage design (*Hurley and McNeil, 1988*), a prerequisite for obtaining accurate results with this method is good initial estimates of both the pharmacokinetic parameters as well as their variances. The greater the confidence in these prior distributions, the better will be the performance of the associated Bayesian system.

The distinction of the NONMEM method of population pharmacokinetic data analysis, is the ability to exploit routine clinical data. In this study, however, available data from a traditional pharmacokinetic study was also analysed. In addition to providing estimates of the average pharmacokinetic parameters of this population, this data facilitated the estimation of Ka values for Theodur^{R} and Euphyllin Retard^{R} which were subsequently used in the analysis of the RKK data. Since Ka values are formulation dependent parameters, it appears reasonable to assume that the values obtained in Study 1 would be relevant for the Study 2 population. The purpose for which samples were collected in the RKK patients viz. theophylline dose individualisation, precluded the collection of samples during the absorptive phase. For purposes of dose individualisation samples collected during the absorptive phase are avoided due to the many factors affecting drug absorption (see Section 1.5.1).

A review of the literature on theophylline's pharmacokinetics reveals that after oral administration, the drug distributes rapidly into tissues with the early distribution phase being complete within 30 - 45 minutes. It is for this reason that a one compartment model was chosen to analyse the data. Other authors have also found that pharmacokinetic analysis applied using this model gives satisfactory results (*Loughnan et al, 1976*).

NONMEM allows for different error structures to be used in the determination of inter- and intra-individual variability. In this study, the exponential error model was chosen i.e. the variability in the pharmacokinetic parameters was assumed to be

log-normal. It has been previously shown (*Vozeh et al, 1982; Maitre et al, 1987 and Grevel et al 1988*) that a log-normal rather than a normal distribution describes the interindividual variability in pharmacokinetic parameters appropriately since the distributions of individual parameters in a patient population are generally skewed.
When testing for the influence of smoking on theophylline clearance in Study 1, four of the five criteria for rejection of the null hypothesis were satisfied while in Study 2, all 5 criteria were fulfilled. The null hypothesis that smoking does not influence theophylline clearance was therefore rejected. In Study 1, the criterion not satisfied viz. DOBF (which displayed an increase instead of the required decrease of greater than 8) was until recently considered to be the most important one. If this had been regarded as the sole criterion in the present study then it would have been incorrectly concluded that smoking does not influence theophylline clearance. Indeed two recent reports (*Mungall et al, 1985; Maitre et al, 1987*), a workshop on NONMEM data analysis (*Beal et al, 1986*), as well as numerous reports on NONMEM claim that DOBF is sufficient criterion to select the most appropriate model to describe the data.
The observation in the present study that DOBF cannot be used as the sole criterion in accepting or rejecting a model is supported by similar observations by *Grevel et al, 1988.* In their investigation of the population pharmacokinetics of metoclopramide using the NONMEM approach, they noted that particular demographic factors did not consistently cause changes in DOBF for all models.

The populations used in the data analysis were a group of volunteers (Study 1) and a group of asthmatics (Study 2). In the ensuing discussion regarding the pharmacokinetic parameters estimated by NONMEM, comparisons are made with similar populations of volunteers or asthmatics (as indicated) whose pharmacokinetic parameters have been reported in the literature (Table II, Chapter 1).
The value of 0.0441 ± 0.0039 L/kg/hr for clearance in the group of non-smoking volunteers (UCT data) is very similar to a value of 0.0402 ± 0.0078 reported by *Powell et al (1977)* in a study of 15 healthy non-smoking volunteers aged 20 - 32 years. The clearance of 0.0375 ± 0.004 L/kg/hr reported in Study 2 (RKK data -

non-smoking asthmatics) is similar to a value of 0.039 ± 0.011 L/kg/hr reported by *Hendeles et al (1978)* in a similar population of otherwise healthy non-smoking asthmatics.

The clearance for the smokers in Study 1 (PUCHE data) of 0.0641 ± 0.0176 L/kg/hr matches the value of 0.063 ± 0.019 L/kg/hr obtained by *Powell et al (1977)* in a group of 7 heavy smokers aged 22 - 31 years. The value of 0.0505 ± 0.009 L/kg/hr obtained in Study 2 (RKK data) is lower than this value by approximately 20%. The RKK study did not differentiate between light and heavy smokers and this may partly explain the difference. The clinical relevance of this difference is that this population may require more conservative initial doses of theophylline.

It is noteworthy that the relatively sparse data used in Study 2 has produced results that are comparable with those obtained from traditional pharmacokinetic studies. This is a reflection on the usefulness of the NONMEM approach to pharmacokinetic data analysis.

The interindividual variation in clearance of 32% obtained in Study 1 is high. This may be accounted for on the basis of a difference in theophylline clearance due to age. Age was not included in another regression model in view of the small sample numbers.

The value of 0.8 L/kg for Vd in both Study 1 and 2 is somewhat higher than that obtained by other workers - 0.5 L/kg, range 0.3 - 0.7 (see Section 1.5.2). These different results are most likely due to the fact that this data set consisted entirely of information collected during steady state conditions. Such data contains little information about the volume parameter (*Mungall et al, 1985; Whiting et al, 1986; Grevel et al, 1988*). The data also consisted entirely of information obtained after oral administration. A possible decreased bioavailability may therefore also contribute to the large value for the Vd. It must be noted that the Vd reported by NONMEM is in fact Vd/F. 'F' is a bioavailability factor and is usually assumed to have a value of one. However, any value of F less than unity will increase the corresponding value of Vd.

The interindividual variability in Vd obtained in Study 1 is also very large (61%). This large variability indicates that there is not much confidence in the value of the parameter. In the Study 2 population, on the other hand, due to difficulty in estimating a value for interindividual variability in Vd, a very low value was obtained with a large standard error of the estimate (0.42). This indicates that the parameter has not been precisely estimated and the 95% confidence interval is an unrealistic 0 - 1.64 L/kg.

The Ka values estimated by NONMEM for Euphyllin Retard^{R} (0.462 hr^{-1}) and Theodur^{R} (0.18 hr^{-1}) correspond to values used in currently available Bayesian forecasting computer programmes (*Kelman et al, 1982; Lenert et al, 1982*). A very large interindividual variability in Ka (107 ± 41%) was estimated by NONMEM. Similarly, other studies have reported large interindividual variability in absorption rates (*Pollack et al, 1984; Rogers et al, 1985*) particularly with sustained release preparations. This has been related to host factors such as gastrointestinal transit time, posture, and presence of food which may affect the rate of theophylline absorption (*Glynn-Barnhart, 1988*).

However, the large variability seen in this study is still surprising if one considers that in Study 1, factors known to affect the absorption rate would have been carefully controlled. A possible reason here may be the influence of a time lag for absorption. In a study to determine the population pharmacokinetics of mexiletine (*Vozeh et al, 1982*), implementation of an absorption time lag parameter significantly reduced the interindividual variability in the Ka. In the *Vozeh* study a different version of NONMEM was used. The version of NONMEM used in the present study does not have an appropriate means of determining lag time.

This study has revealed that the pharmacokinetics of theophylline in members of the Indian population group shows close similarity with that reported on other population groups. An important outcome is the good agreement between the results of previous, more traditional forms of data analysis and those provided by this new methodology. This study has also facilitated quantification of the interindividual variability in theophylline pharmacokinetics. A knowledge of the fixed effect parameters are sufficient to guide initial dosage but in a particular patient the concentration actually achieved may differ considerably from the

expected average value. A knowledge of the inter-individual variability may enable one to place a level of confidence on the predicted concentration. This is achieved by calculating the 68% (i.e. mean ± 1 SD) or the 95% (i.e. mean ± 2 SD) confidence intervals. Such calculations may be done by means of currently available Bayesian forecasting computer programs such as OPT^R .

7.5 CONCLUSIONS

1. NONMEM analysis of data from a population of smokers and non-smokers has confirmed that smoking has a significant influence on theophylline clearance.
2. Analysis of routine clinical data on theophylline derived from non-smoking asthmatics, has yielded pharmacokinetic parameters for the Indian population that are in general agreement with published values in other population groups.
3. However, theophylline clearance in asthmatic Indian smokers is 20% lower than that reported in smokers from other population groups. This suggests that a more conservative initial dose be used in these patients.
4. The volume of distribution of 0.8 L/kg is higher than that reported by other workers. In view of the reservations expressed regarding this value, it is recommended that a study designed to provide maximum information about this parameter be undertaken.
5. Interindividual variability in theophylline clearance for the Indian population has been quantified. This enables greater confidence to be given to theophylline dosage design in this population group.

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SUMMARY

Chapter One

Theophylline, a dimethylated xanthine, is a popular bronchodilator drug and has been in use for many years, yet its mechanism of action is still elusive. The drug's beneficial effects relates primarily to actions on the respiratory system. These effects, as well as toxicity, correlate well with serum theophylline concentrations. Studies of theophylline pharmacokinetics reveals a wide interindividual variation in clearance, primarily because hepatic biotransformation is the major route of elimination. Numerous factors that affect theophylline clearance have been identified and are discussed in this chapter.

Chapter Two

Therapeutic drug monitoring is an expanding new discipline that uses drug concentrations in body fluids to optimise drug therapy. Recent interest in the field is in large part due to the availability of sensitive, specific and easy-to-use methods of drug and metabolite analysis. Theophylline concentration analysis is performed on blood, serum or plasma - saliva concentrations having been found to be unreliable. For accurate dosage predictions, appropriate timing of blood samples and interpretation of the drug concentrations are important considerations. The Bayesian technique of serum drug concentration interpretation is currently the most efficient and popular method available.

Chapter Three

Population pharmacokinetics attempts to find typical relationships between physiology, pathology and pharmacokinetics. An important application of population pharmacokinetics has been in therapeutic drug monitoring programmes

in order to improve dosage predictions. The NONMEM approach to population pharmacokinetic data analysis involves the use of data gathered directly from patients receiving the drugs of interest. Such an approach has definite advantages over more traditional methods that utilise volunteers or patients with lesser degrees of illness.

Chapter Four

The Seralyser^{R}, an instrument for theophylline concentration analysis, has recently been introduced locally. Its performance was evaluated against the TDx^{R} method using 52 serum samples collected from 34 asthmatics attending the Asthma Clinic at R K Khan Hospital. The linear regression equation for the line of best fit for Seralyser^{R} (y) and TDx^{R} (x) was $y = 1.057x + 0.078$ ($r^2 = 95.68\%$). The average cost per sample during the evaluation period was R15-47 for the Seralyser^{R} and R13-59 for the TDx^{R}. It is concluded that the Seralyser^{R}'s performance compares favourably and without bias with the more established TDx^{R} method.

Chapter Five

The influence of a therapeutic drug monitoring (TDM) programme on theophylline utilisation was evaluated over a 2 year period at R K Khan Hospital. Eighty seven asthmatics presenting to the Asthma Clinic were categorised as being controlled, toxic, non-compliant or uncontrolled based on serum theophylline concentration (STC) determinations and clinical assessments. A linear regression of dose on STC confirms the absence of any correlation between these parameters ($r^2 = 6.46\%$). Twenty one patients (24%) were found to be clinically controlled on their initial dose of theophylline. Twenty seven patients (31%) were categorised as being clinically toxic or to have STC's > 20 μg/ml while 24 patients (28%) were found to be non-compliant. Forty patients (46%) were considered to be clinically uncontrolled but 5 of these were excluded from further dosage adjustments because of fears of toxicity (STC's > 15 μg/ml). In the remaining 35 patients, dosage adjustment based on pharmacokinetic principles resulted in clinical improvement in

24 (68.6%) patients. This was statistically significant for the group (sign test $p < 0.00001$). These results illustrate the value of TDM in theophylline dosage design.

Chapter Six

Thirty five acute asthmatics were randomly included in a study to determine the consequences of administering a standard fixed dose of 250 mg intravenous aminophylline to all patients i.e. irrespective of body mass or history of prior intake of theophylline-containing preparations. Serum theophylline concentrations were determined 30 minutes after completion of a 2 hour infusion of the aminophylline dose. The results obtained indicate 40% of patients with levels < 10 μg/ml, 43% within the therapeutic range and 17% with levels > 20 μg/ml. Implementation of an alternate recommended dosage regimen based on body mass and history of prior intake of theophylline (5 mg/kg if no theophylline taken - otherwise 2.5 mg/kg) would have produced more acceptable results viz. 33% with levels < 10 μg/ml, 61% within the range and 6% with levels > 20 μg/ml.

Chapter Seven

The pharmacokinetics of theophylline were determined in smokers and non-smokers using the NONMEM computer programme. Data from a traditional pharmacokinetic study (23 subjects - approximately 15 samples per subject for each of 3 preparations under investigation) was used in order to determine absorption rate constants (Ka) for Theodur^{R} and Euphyllin Retard^{R}. These Ka values were subsequently used in the determination of theophylline's pharmacokinetics in the Indian asthmatic population attending R K Khan Hospital from whom routine clinical data was available (approximately two samples per patient in each of 30 patients). The results obtained confirms that smoking has a significant influence on theophylline clearance. The pharmacokinetic parameters obtained for the non-smoking Indian asthmatic population from R K Khan Hospital are in general

agreement with published values of other population groups. However, theophylline clearance in Indian asthmatics who smoke was found to be approximately 20% lower than that reported in smokers from other population groups. This suggests that a more conservative initial dose should be used in these patients.

APPENDIX A

Table A1

Serum theophylline concentrations (μg/ml) measured using the Seralyser^{R} and TDx^{R}

see Chapter Four

Seralyser^{R}	TDx^{R}	Seralyser^{R}	TDx^{R}
4.7	4.17	6.9	5.67
19.8	14.05	5.2	3.85
6.1	5.27	21.2	18.65
12.3	11.98	10.9	10.94
6.1	5.62	17.9	16.43
17.6	15.24	4.2	5.08
20.3	19.3	4.5	5.88
9.5	10.89	9.4	8.58
17.3	15.27	17.3	15.52
5.8	5.13	34.5	30.89
14.8	14.73	10.3	10.23
11.7	9.12	17	17.36
16.4	13.31	9.2	9.2
3.1	1.25	10.2	10.84
7.6	6.28	21.3	19.97
9.4	9.16	11.7	12.17
6.5	3.97	11.8	13.15
21.4	21.4	9.6	9.47
14.6	14.38	<3	1.5
3.7	3.37	<3	0.5
25.3	25.49	<3	0.24
5.5	5.77	<3	1.6
10.1	10.07	<3	4.63
7.3	8.56	<3	1.48
5.6	6.11	<3	0.78
6.9	7.25	<3	0.75

APPENDIX B

Table B1

Group 1 - Patients stable on initial dose

see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Cp (ug/ml)	Cp_{ss} (ug/ml)
103	30	M	66.0	9.10	11.26	11.80
112	39	M	58.0	10.30	10.90	9.50
128	41	F	52.0	9.90	13.80	17.90
134	35	F	75.0	6.80	7.32	10.10
155	38	F	45.0	13.30	11.32	16.00
167	60	F	81.0	7.40	12.05	15.50
175	24	F	50.7	7.90	12.45	13.40
178	25	F	57.5	8.90	12.39	17.40
179	39	F	43.6	11.70	3.95	8.80
184	51	M	61.0	9.80	10.38	13.20
207	47	F	45.0	4.44	10.85	13.30
219	36	F	54.5	11.00	11.18	14.10

Table B1 (continued)
Group 1 - Patients stable on initial dose
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Cp (ug/ml)	Cp_{ss} (ug/ml)
222	57	F	61.7	8.30	7.42	9.10
233	34	M	46.0	13.04	7.80	11.10
242	46	F	64.0	9.40	15.00	12.10
250	54	M	50.0	10.24	15.01	18.40
258	37	F	69.0	8.70	19.10	19.00
261	52	F	60.0	6.67	10.20	12.10
268	45	F	48.0	10.67	10.90	12.70
281	28	M	60.0	10.00	9.13	10.00
282	5	M	16.0	15.00	2.68	5.30

Table B2
Group 2.1 - Patients NOT controlled on initial dose - Cp > or = 15 ug/ml
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Cp (ug/ml)	Cp_{ss} (ug/ml)
104	37	F	61.0	9.84	15.50	14.68
108	61	F	69.0	8.70	15.00	18.60
117	23	F	88.3	5.80	17.35	19.80
141	74	F	32.0	16.00	18.60	15.60
192	52	M	63.0	9.52	16.34	18.50

Table B3
Group 2.2 - Patients NOT controlled on initial dose - Cp < 15 ug/ml
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Emergency room visits Before/After	Hospital Admissions Before/After	Dose (mg/kg/day) Before/After	Cp (ug/ml) Before/After	Comments
106	25	F	49.0	0.33/0	0.17/0	10.45/10.45	0/13.4	
113	44	F	67.0	1.5/0.2	0/0	7.65/8.96	6.7/10.2	
130	37	F	64.0	0.83/0.33	0.33/0	8.0/9.38	10.42/14.60	now on steroids
143	42	F	66.0	2/0	0.33/0	7.76/12.12	6.80/8.70	
144	23	M	48.0	0.5/0.75	0/0	12.5/16.67	7.79/10.40	not improved
145	21	F	63.0	8/9	1/1	8.13/9.52	9.50/13.25	not improved
150	27	M	48.0	12/3	1/0.67	10.67/18.75	5.60/9.90	
151	32	F	60.5	1/0	0/0	6.61/9.92	3.80/7.40	now on steroids
152	43	M	68.0	Frequent	Frequent	8.82/11.76	13/16	not improved
158	31	M	56.0	1.75/0	0/0	9.15/12.50	12.51/17.10	now on steroids
160	31	F	76.5	0/0	0/0	5.23/7.84	10.14/14.20	
164	31	F	67.5	Frequent	Frequent	7.58/11.85	6.14/9.59	not improved

Emergency room visits and hospital admissions are average over 3 to 6 months.

Table B3 (continued)
Group 2.2 - Patients NOT controlled on initial dose - Cp < 15 ug/ml
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Emergency room visits Before/After	Hospital Admissions Before/After	Dose (mg/kg/day) Before/After	Cp (ug/ml) Before/After	Comments
165	51	M	56.0	Frequent	Frequent	9.14/10.71	9.16/10.73	not improved
171	37	F	65.0	0/0	0/0	7.88/11.82	7.43/11.14	
177	48	F	60.0	0/0	0/0	8.50/10.0	12.13/14.22	
182	32	F	65.0	1.5/0	0/0	7.88/9.23	10.01/14.70	
187	27	F	62.0	3/4	0/1	8.26/9.68	10.75/14.7	not improved
193	24	F	55.6	1/0	0/0	6.47/7.19	0/14.28	
199	55	M	57.0	0.67/1.67	0/0	8.98/10.53	14.97/17.54	not improved
205	36	M	65.1	4.25/2.38	0.67/0	9.20/12.27	13.2/17.6	
210	47	M	64.1	1/0.33	1/0	7.99/9.36	11.46/13.42	
234	47	M	50.0	5.17/2	0/0	10.24/12.0	15.24/17.86	now on steroids
235	55	F	70.0	0/0	0/0	4.29/5.71	4.86/6.49	
247	15	M	41.0	Frequent	Frequent	12.5/14.63	6.9/11.3	not improved

Emergency room visits and hospital admissions are average over 3 to 6 months.

Table B3 (continued)
Group 2.2 - Patients NOT controlled on initial dose - Cp < 15ug/ml
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Emergency room visits Before/After	Hospital Admissions Before/After	Dose (mg/kg/day) Before/After	Cp (ug/ml) Before/After	Comments
249	45	M	43.0	Frequent	Frequent	11.91/20.93	6.61/11.63	not improved
253	48	F	50.0	5/5	1/2	10.84/12.00	10.67/12.50	not improved
254	29	M	50.0	1.33/0.25	0.33/0	10.24/16.00	8.89/13.89	
255	13	M	34.0	1.00/0.33	0.33/0	8.82/17.65	5.70/11.40	
257	42	M	57.0	2.30/0	0.33/0	8.99/8.77	0/12.18	
265	50	F	75.6	1.50/0	0.25/0	6.78/7.94	10.46/12.25	
266	44	M	50.0	9/9	0/0	12/14	13.64/15.91	not improved
286	34	M	47.0	1.2/0.4	0/0	12.77/17.02	5.80/8.06	now on steroids
287	29	M	49.0	1/0	0/0	10.45/12.25	8.42/9.87	
292	34	M	48.0	0/0	0/0	10.67/16.67	7.89/12.32	
299	13	F	44.5	1.33/0	0.67/0	4.49/8.98	5.70/10.60	

Emergency room visits and hospital admissions are average over 3 to 6 months

Table B4
Group 3 - Patients clinically toxic
or Cp > 20 ug/ml
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Cp (ug/ml)	Route	Symptoms	Comments
102	68	M	58	17.30	23.80	ivl	nausea,tremor,irritable	-
107	68	M	55.0	9.30	22.25	p.o.	tachycardia	CHF,Alcohol abuse
125	68	F	78.0	5.13	21.05	p.o.	none	-
125	68	F	78.0	7.7	20.20	p.o.	seizure	6 months after above
129	61	F	92.0	6.52	18.60	p.o.	nausea,tachycardia	CHF average Cp=23.8 ug/ml
131	65	F	67.0	5.97	26.05	p.o.	nausea,vomitting,tremor	CHF
136	66	M	62.2	9.65	17.36	p.o.	none	CHF average Cp=27.1 ug/ml
138	48	M	75.8	11.87	25.49	p.o.	nausea,seizure	over compliance
140	12	M	27.5	14.50	23.00	p.o.	nausea,irritable,headache	erythromycin
152	43	M	68.0	8.82	17.75	p.o.	insomnia	cimetidine average Cp=27.6 ug/ml
159	36	F	69.5	14.73	21.40	p.o.	tremor	over compliance
159	36	F	69.5	?	34.50	ivi + p.o.	Irritable,tremor	ivi + p.o.
191	47	M	56.2	10.68	25.80	p.o.	none	CHF

Table B4 (continued)
Group 3 - Patients clinically toxic
or Cp > 20 ug/ml
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Cp (ug/ml)	Route	Symptoms	Comments
191	47	M	56.2	10.68	24.65	po	none	
194	70	F	35.0	17.14	25.25	po	tachycardia, tremor	CHF
199	55	M	57.0	10.53	18.05	po	nausea	erythromycin average Cp = 20.6 ug/ml
219	36	F	54.0	11.01	30.89	po	none	
246	71	F	46.5	12.9	38.30	po	vomitting, nausea	CHF
246	71	F	46.5	12.9	23.05	po	vomitting, nausea	38 hours later dose stopped CHF
247	15	M	41.0	?	42.00	ivi + po	irritable	-
247	15	M	41.0	?	21.90	ivi + po	tachycardia	-
250	54	M	50.0	15.36	29.80	po	none	-
251	32	F	43.0	?	22.45	po	none	Euphyllin + Franol
262	46	F	45.0	?	16.50	ivi + po	seizure	estimated Cp at time of seizure is 30 ug/ml
267	48	M	46.5	?	24.35	ivi + po	tremor	alcohol abuse
284	53	F	50.8	11.81	34.65	po	none	-
285	29	F	36.9	20.8	23.03	po	none	-

Table B5
Group 4 - Patients with compliance problems
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Nature of non compliance	Detected at interview	Corrected	Comments
106	25	F	49.0	10.45	UNDERDOSING	NO	YES	-
127	28	F	41.0	12.49	BOTH	YES	NO	POOR CONTROL
138	48	M	75.8	7.92	OVERDOSING	YES	YES	IGNORANCE
145	21	F	63.0	8.13	OVERDOSING	YES	NO	POOR CONTROL
146	21	F	53.5	11.22	UNDERDOSING	NO	YES	SOCIAL PROBLEMS
150	27	M	48	18.75	UNDERDOSING	YES	NO	POOR CONTROL
151	32	F	60.5	9.92	UNDERDOSING	NO	YES	SOCIAL PROBLEMS
159	36	F	69.5	7.37	OVERDOSING	YES	YES	POOR CONTROL
180	28	M	58.0	13.79	OVERDOSING	YES	NO	POOR CONTROL
185	54	M	57.0	8.98	UNDERDOSING	NO	YES	IGNORANCE
209	15	M	43.0	11.63	UNDERDOSING	NO	YES	-
214	17	M	60.0	11.67	UNDERDOSING	NO	YES	-

Table B5 (continued)
Group 4 - Patients with compliance problems
see Chapter Five

Id	Age (yrs)	Sex	Mass (kg)	Dose (mg/kg/day)	Nature of non compliance	Detected at interview	Corrected	Comments
230	45	F	56.0	9.14	UNDERDOSING	NO	NO	-
247	15	M	41.0	14.63	UNDERDOSING	NO	NO	SOCIAL PROBLEMS
249	45	M	43.0	11.91	UNDERDOSING	YES	YES	-
255	13	M	34.0	8.82	UNDERDOSING	NO	YES	-
257	42	M	57.0	8.98	UNDERDOSING	NO	YES	SIDE EFFECTS
260	44	M	55.0	10.91	UNDERDOSING	YES	YES	POOR CONTROL
265	50	F	75.6	7.94	UNDERDOSING	NO	YES	-
266	44	M	50.0	14.00	UNDERDOSING	YES	NO	LABILE
267	48	M	46.5	11.01	UNDERDOSING	YES	YES	SIDE EFFECTS
269	56	F	66.4	9.04	UNDERDOSING	NO	YES	SIDE EFFECTS
287	29	M	49.0	12.25	UNDERDOSING	NO	YES	-
299	13	F	44.5	8.99	UNDERDOSING	YES	YES	-

APPENDIX C

Table C1

Patients treated with aminophylline at the emergency room

Serum theophylline concentrations < 10 ug/ml

see Chapter Six

Id	Sex	Age (yrs)	Mass (kg)	Dose (mg/kg)	STC (ug/ml)	Use in prior 12 - 24 hours	Expected STC with HWJ dose (ug/ml)
116	M	64	44	4.86	8.75	Y	4.81
119	M	16	44	4.86	9.15	Y	5.03
139	M	30	57	3.75	5.85	N	8.33
164	F	31	73	2.93	6.93	N	11.79
169	F	48	63	3.40	7.6	N	11.99
187	F	27	62	3.45	9.2	Y	7.12
205	M	36	65.2	3.28	6.9	Y	5.62
208	F	43	65	3.29	9.45	N	15.34
217	F	44	55	3.89	9	N	12.36
221	M	31	53	4.04	8.5	Y	5.64
221	M	31	53	4.04	6.5	N	8.62
254	M	29	50	4.28	8.1	Y	5.06
267	M	48	46.5	4.60	9.16	N	10.65
321	M	36	56	3.82	8.05	N	incomplete information

Table C2

Patients treated with aminophylline at the emergency room
Serum theophylline concentrations between 10 - 20 ug/ml
see Chapter Six

Id	Sex	Age (yrs)	Mass (kg)	Dose (mg/kg)	STC (ug/ml)	Use in prior 12 -24 hours	Expected STC with HWJ dose (ug/ml)
118	M	30	62	6.90	15.45	N	11.99
145	F	21	63	3.40	18.7	Y	17.34
157	M	65	69	3.10	13.3	Y	12.52
158	M	31	56	3.82	14.6	Y	12.46
164	F	31	68	3.15	17.6	Y	16.68
164	F	31	73	2.93	12.6	Y	11.72
170	M	31	43	4.98	10.5	Y	6.2
180	M	28	56	3.82	11.3	Y	9.16
180	M	28	56	3.82	13.9	Y	11.76
187	F	27	62	3.45	14.9	Y	13.44
195	F	50	89	2.40	19.2	Y	19.7
253	F	48	53	4.04	16.4	Y	13.86
254	M	29	50	4.28	17.2	Y	14.2
329	M	28	58	7.38	16	N	11.59
333	M	47	61	7.02	10.7	N	8.16

Table C3

Patients with aminophylline at the emergency room

Serum theophylline concentrations > 20 ug/ml

see Chapter Six

Id	Sex	Age (yrs)	Mass (kg)	Dose (mg/kg)	STC (ug/ml)	Use in prior 12 - 24 hours	Expected STC with HWJ dose (ug/ml)
148	M	39	61	3.51	20.3	Y	18.74
187	F	27	62	3.45	21.2	Y	19.74
199	M	55	57	7.51	26.75	Y	19.05
267	M	48	46.5	4.60	24.35	Y	20.75
288	F	40	62.5	3.42	31.6	Y	30.20
320	M	38.5	58	3.69	22	Y	incomplete information

APPENDIX D

Table D1
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 1
Male, 88kg, 60yr,
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	1.7	0	4.5	0	6.8
0.25	3.1	0.5	5.1	0.5	7.2
0.48	4.2	1.02	6.1	1	6.9
0.75	4.1	2	7.2	2	7.3
1	4.6	2.98	6.9	3.07	8.6
1.48	4.2	4	6.7	4	6.3
1.97	4.3	6.12	6.1	5.93	6.7
2.47	5.2	8	6.2	8	6.1
3	3.9	12.05	3.7	11.93	4.3
4.02	3.6	24.1	0.7	23.7	1.3
5.98	2.5	27.07	0.5	26.38	0.8
7.92	1.6	33	0.2	32.43	0.42
11.88	0.75				
23.9	0.1				
26.95	0.07				

Subject No. 2
Male, 70.5kg, 45yr
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	2.3	0	4.9	0	4.2
0.22	5.9	0.53	4.6	0.47	3.5
0.48	7.1	1	6.2	0.98	3.4
0.73	5.9	1.98	6	2.02	3.4
1	5.9	2.98	4.4	3.03	3.2
1.5	5.2	3.98	3.3	4.03	3.1
2	5.4	6.03	0.5	6.03	3.5
2.63	4.8	8.02	0.9	7.95	4
3.17	4.9	11.87	1.0	11.02	4.1
4.13	4.2	23.37	0.5	11.75	2.7
6.17	3.1	26.38	0.28	26.78	0.75
8.17	2.3	32.37	0.08	32.78	0.33
12	1.2				
23.82	0.32				
26.85	0.42				

Table D2
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 3
Female, 48kg,
41yr, Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	5.5	0	8.5	0	10.3
0.25	13.9	0.48	8.3	0.48	11.8
0.50	14.7	1.12	8.1	1	13.9
0.75	15.7	2.08	7.9	1.98	13.3
1.03	14.8	3.08	8.6	2.98	13.3
1.70	12.9	4.12	7.7	3.98	12.4
2.00	12.8	6.07	7.8	6.07	12.8
2.55	10.1	8.1	7.4	7.8	13.9
3.08	10.7	12.02	6.2	12.02	10.6
4.08	10.3	23.62	1.6	23.78	3.2
6.05	9.1	26.88	1.2	26.97	2
8.00	5.0	32.8	0.58	32.73	0.97
11.92	5.1				
23.53	1.00				
26.5	0.76				

Subject No. 5
Male, 72.3kg, 28yr
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	2.4	0	6.1	0	5.7
0.25	9	0.5	6.8	0.5	5.3
0.48	6.4	1	7	1	5.9
0.75	6.3	2	6.8	2.05	6.4
1	5.7	2.93	6.2	2.98	6.6
1.48	5.7	3.92	6	4.13	6.7
2	4.9	5.92	5.6	5.92	7.3
2.48	4.9	7.92	4.6	8.05	7.7
2.98	4.5	11.93	4.6	11.83	5.4
4.02	4.3	23.62	1.5	23.65	1.1
5.98	3.2	26.82	1.2	26.75	0.8
8	2.3	32.92	0.9	32.82	0.4
12.02	1.2				
24.07	0.2				
27.15	0.2				
32.77	0.19				

Table D3
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 6
Male, 85.2kg,
30yr, Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	2.1	0	2.7	0	3.7
0.22	6.4	0.5	3.1	0.63	6.5
0.48	6.2	1	3.3	1	6.9
0.73	5.4	2.05	5.2	2.02	8.6
0.98	5.0	2.98	6.6	3	9.5
1.48	4.1	4	8.2	4	10.2
1.97	3.7	6.08	6.1	6	10.1
2.52	3.4	7.95	4.3	7.93	7.8
2.98	2.9	11.95	3.3	11.8	6.1
3.97	2.6	23.92	1.6	23.7	1.1
5.92	2.1	27	3.4	26.65	0.5
7.92	1.4	32.78	0.4	32.75	0.4
11.87	0.8				
23.9	0.13				
26.98	0.1				

Subject No. 7
Male, 71.5kg, 45yr
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	0.2	0	2.1	0	1.9
0.25	4.9	0.5	3	0.48	2.8
0.50	3.8	1.02	2.8	0.98	2.8
0.73	4	2	4.1	2.03	2.9
1	3.3	2.77	3.2	3	3
1.52	3.8	4.18	2.8	4.08	2.3
2.1	2.4	6.05	2.6	6.03	1.9
2.43	2.3	8.07	2.3	8.03	2.8
2.85	2.2	11.9	1.4	11.97	2.4
3.93	1.8	23.98	0.4	23.72	0.3
6.02	1.0	27	0.2		
8.07	0.7	33.05	0.01		
11.93	0.3				

Table D4
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 8
Male, 82.2kg,
33yr, Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	3.4	0	2.7	0	8.2
0.25	4.9	0.5	2.9	0.48	8
0.5	6.1	0.98	4.4	1	8.9
0.75	6.6	1.95	5.3	2	8.7
1	6.4	2.9	4	3	9.2
1.52	6.4	3.92	4.8	3.98	9.8
2	6.7	5.98	4	6.02	10.3
2.5	5.8	7.92	3.9	7.92	9.7
3	5.1	12.08	3.8	12	7.2
4	5.9	23.97	1.1	23.98	1.6
6	4.7	26.98	0.7	26.95	1.2
7.9	3.7	32.93	0.4	32.82	0.7
11.8	2.4				
23.38	0.5				
32.8	0.18				

Subject No. 9
Female, 58kg, 44yr
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	0.6	0	3.1	0	5.7
0.23	2.9	0.5	3.2	0.5	6.7
0.48	4.7	1.02	3.4	1	6.8
0.73	5.2	2.03	3.6	1.95	7.1
0.98	4.4	3.2	3.3	2.97	7
1.5	4.3	4.12	2.8	4.03	7.3
2.02	4.3	6.12	2.6	6	6.3
2.53	3.7	7.95	1.4	8	5.1
3.03	3.7	11.95	0.4	11.95	2.5
4.13	1.5	23.92	0.1	23.7	0.6
6.12	1.1	26.83	0.2	26.93	0.4
8.10	0.9			32.67	0.1
12.13	0.4				

Table D5
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 10
Female,58.5kg,
40yr, Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (ug/ml)	Time (hr)	Cp (ug/ml)	Time (hr)	Cp (ug/ml)
0	2	0	6.4	0	6.1
0.25	3.5	0.5	7.3	0.48	7
0.48	4.5	1	8.8	0.98	7.1
0.77	5.6	2.02	8.3	2.02	7.8
1.02	4.8	3	8.9	3	7
1.5	6.3	4	9.1	4.1	5
2	6.1	6	7.3	6.07	7.3
2.50	6.3	8	6.6	8.1	6.3
3	5.9	12.35	3.8	12.13	6.6
4.02	5.4	23.75	3.8	23.72	1.2
6.02	3.7	27	2.7	26.92	0.7
7.93	2.6	32.77	1.3	32.77	0.3
12.1	1.4				
24.08	0.2				
28.17	0.08				

Subject No. 11
Male, 71.2kg, 24yr
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (ug/ml)	Time (hr)	Cp (ug/ml)	Time (hr)	Cp (ug/ml)
0	1	0	2.4	0	6.4
0.25	2.3	0.48	2.4	0.52	6.4
0.5	4.1	1	3.2	1	6
0.73	4.2	2	4.4	2	6
1	3.1	2.98	6.1	3.02	6.4
1.3	3.5	3.93	5.7	4	5.7
2.02	3.3	5.79	5.7	5.92	5.7
2.52	3.5	7.69	5.3	8.17	4.7
3	3.1	12.03	1.7	12.1	4.8
3.92	3.2	23.9	0.7	24.12	1.7
5.88	2	27.02	0.6	26.2	1.4
7.83	1.6	33.02	0.3	29.12	1.1
11.92	0.8				
24.38	0.1				
25.98	0.08				

Table D6
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 12
Male, 78kg, 22yr,
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	2.6	0	4.8	0	5.8
0.27	3.6	0.47	5.2	0.5	6.3
0.5	6.2	0.98	5.3	1.5	6.7
0.75	5.3	2.02	4.9	2.5	5.4
1.02	5.9	2.97	4.4	3.5	5.7
1.48	5.7	3.98	4.2	4.5	5.8
1.98	5.6	5.95	3.6	6.48	4.1
2.48	5	7.93	3.1	8.48	4.1
3	5	12	2.5	12	4.3
4	4.9	23.8	2	23.43	1.9
5.98	3.6	26.9	2.6	26.43	1.7
7.92	2.8	32.8	1.9	32.43	0.8
12	2.1				
24	0.6				
27.17	0.4				

Subject No. 13
Male, 97.5kg, 25yr
Smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	1	0	1.3	0	3.9
0.23	1.3	0.5	1.5	0.52	4.1
0.48	3.6	1	1.8	0.98	4.3
0.73	4	2	1.9	2	4.4
0.98	3.8	2.98	2.4	3.03	4.4
1.45	3.5	4	1.7	4	4.3
2	3.4	6	1.6	5.88	3.5
2.48	3.2	8	1.2	8.23	3.7
2.97	3.1	12.1	1.0	12.13	3.1
4	2.4	24.53	1.4	24.15	0.6
5.18	2	26.15	1.1	26.68	0.5
8.03	1.6	29.22	0.8	29.15	0.2
12.06	1				
23.98	0.2				
27.02	0.1				

Table D7
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 14
Male, 73kg, 20yr,
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	4.3	0	4	0	7
1	6.1	1	5.1	1	7.1
2	7.8	2	4.7	2	6.2
3	8	3	4.6	3	6.1
4	7.1	4	4.2	4	5.9
6	5.6	6	6	6	7
8	5.3	8	6.5	8	10.4
12	2.9	12	5.5	12	8.2
24	1.6	24	1.9	24	2.4
		27	1.2	27	1.9
		33	0.6	33	1.1

Subject No. 15
Male, 105kg, 20yr
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	3	0	3.0	0	6.4
1	5.5	1	3.3	1	6.6
2	6.1	2	3.3	2	7.2
3	5.5	3	8.6	3	6.7
4	5.4	4	6.2	4	6.7
6	4.2	6	6.1	6	9.2
8	3.9	8	5.0	8	8.6
12	2.6	12	3.6	12	6.4
24	0.6	24	0.8	24	2.1
		33	0.2	27	1.7
				33	0.7

Table D8
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 16
Male, 81kg, 20yr,
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	2.6	0	4	0	7
1	4.6	1	3.8	1	7.5
2	5.7	2	4.1	2	7.5
3	5.6	3	3.5	3	7.5
4	5.9	4	3.8	4	7.1
6	4.9	6	2.2	6	8.6
8	3.7	8	2.4	8	7.9
12	2.4	12	1.9	12	5.9
24	0.9	24	0.8	24	1.7
		33	0.1	27	1.6
				33	0.8

Subject No. 17
Male, 70kg, 20yr
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	3.1	0	7.3	0	7.5
1	5.1	1	5.2	1	6.9
2	5.8	2	7.3	2	6.3
3	6.0	3	6.5	3	5.5
4	5.0	4	6.1	4	5.9
6	4.3	6	9.5	6	7.6
8	3.5	8	10.2	8	8.7
12	3.0	12	8.6	12	7.6
24	0.9	24	3.4	24	2.8
		27	3.0	27	2.5
		33	1.7	33	1.3

Table D9
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 18
Male, 69.6kg,
20yr, Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	2.9	0	3.0	0	5.5
1	5	1	3.3	1	4.7
2	5.8	2	3.3	2	5.1
3	6	3	3.8	3	4.8
4	5.3	4	6.1	4	4.3
6	4.1	6	6.4	6	5.7
8	3.6	8	5.7	8	5.5
12	2.3	12	4.1	12	4.4
24	0.7	24	1.4	24	0.9
		27	1.0	27	0.6
		33	0.4	33	0.1

Subject No. 19
Male, 76kg, 20yr
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	1.3	0	4.2	0	5.7
1	3.5	1	3.8	1	4.7
2	3.9	2	3.7	2	5.1
3	3.5	3	3.3	3	4.6
4	3.3	4	3.3	4	4.1
6	2.6	6	3	6	4.0
8	1.9	8	2.8	8	4.1
12	1.1	12	3.5	12	6.7
24	0.5	24	2.3	24	1.7
		27	1.8	27	1.3
		33	0.3	33	0.4

Table D10
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 20
Male, 76.9kg,
20yr, Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	4.2	0	5.9	0	8.2
1	7.1	1	5.9	1	7.7
2	8.3	2	5.4	2	7.7
3	7.9	3	5.4	3	8.3
4	7.6	4	5.7	4	7.2
6	6.3	6	7.7	6	9.2
8	5.8	8	7.1	8	10.4
12	3.8	12	6.9	12	9.0
24	1.7	24	3.0	24	3.5
		27	2.6	27	3.5
		33	1.6	33	2.2

Subject No. 21
Male, 75.5kg, 20yr
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time Cp (hr)	(µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	4.9	0	2.8	0	9.2
1	8.3	1	2.4	1	10.0
2	10.0	2	3.2	2	9.0
3	9.7	3	4.3	3	8.7
4	10.0	4	4.2	4	6.5
6	8.3	6	6.9	6	7.9
8	6.1	8	6.3	8	7.3
12	4.7	12	5.6	12	8.3
24	1.7	24	2.1	24	4.1
		27	2.0	27	4.1
		33	1.2	33	2.3

Table D11
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 22
Male, 69.5kg,
20yr, Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	4.7	0	6.8	0	9.0
1	6.2	1	9.7	1	8.7
2	7.3	2	9.1	2	7.6
3	7.4	3	8.4	3	7.0
4	6.9	4	8.3	4	7.2
6	5.1	6	8.5	6	8.2
8	4.4	8	6.4	8	9.6
12	2.8	12	6.5	12	10.6
24	1.0	24	1.8	24	3.2
		27	1.8	27	2.7
		33	0.5	33	1.2

Subject No. 23
Male, 82.5kg, 20yr
Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	3.3	0	5.2	0	6.7
1	5.2	1	4.5	1	7.3
2	6.3	2	4.6	2	7.0
3	5.3	3	4.7	3	7.8
4	5.5	4	5.2	4	6.6
6	3.9	6	9.6	6	6.8
8	3.1	8	8.5	8	6.2
12	1.8	12	6.5	12	4.8
24	0.4	24	1.7	24	1.2
		27	1.0	27	0.9
		33	0.3	33	0.3

Table D12
NONMEM Data Set - Study 1
see Chapter Seven

Subject No. 24
Male, 81.6kg,
20yr, Non-smoker

Alcophyllin Elixir		Euphyllin Retard		Theodur	
Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)	Time (hr)	Cp (µg/ml)
0	6.1	0	3.1	0	9.6
1	8.1	1	3.5	1	11.0
2	10.1	2	4.0	2	10.9
3	8.6	3	4.6	3	10.5
4	8.5	4	5.0	4	9.8
6	7.1	6	6.5	8	11.0
8	5.7	8	6.0	12	9.7
12	5.4	12	5.6	24	4.6
24	2.8	24	3.7	27	4.4
		27	2.9	33	3.3
		33	1.9		

Table D13
NONMEM Data Set - Study 2
Patients 106 to 150
see Chapter Seven

Id	Mass (kg)	Age (yr)	Sex	Preparation	Dose (mg/kg/day)	Time (hr)	Cp (ug/ml)	Smoker
106	50.5 49.0	25	F	Euphyllin	10.14 10.45	12.75	4.87 9.80	No
111	80.5	35	F	Theodur	7.45	14.5	9.02	No
112	58.4 59.0	39	M	Theodur	10.27 10.17	4.75 14.5	10.90 5.46	Yes
115	75.5	27	F	Euphyllin	6.78	13.0	5.6	No
130	64.5 64.5 63.7	37	F	Theodur	9.30 9.30 9.42	13.10 15.00 16.25	15.62 11.80 11.00	No
134	75	35	F	Euphyllin	6.83	12	7.32	No
142	47.6 45.3 47.6	32	M	Theodur	12.61 8.80 12.61	4.50 15.00 4.80	4.63 2.16 7.57	Yes
144	48.0	23	M	Theodur	12.50	5.00	10.50	No
145	64.0	21	F	Theodur	9.38	13.25	12.94	No
146	57.0 60.3 58.5	21	F	Theodur	10.53 9.95 10.26	12.00 12.50 12.75	8.36 5.40 7.50	No
150	48.0	27	M	Theodur	8.33	8.75	5.20	Yes

Table D14
NONMEM Data Set - Study 2
Patients 151 to 204
see Chapter Seven

Id	Mass (kg)	Age (yr)	Sex	Preparation	Dose (mg/kg/day)	Time (hr)	Cp (ug/ml)	Smoker
151	64.9	32	F	Theodur	9.25	11.50	5.70	No
158	58.3 61.5 58.3	31	M	Theodur	10.29 11.38 10.29	11.25 10.25 12.50	9.05 16.50 10.24	Yes
160	76.5	31	F	Theodur	7.84 5.23	15.25 13.67	5.67 4.17	No
178	55.0 57.5 56.0 56.0	25	F	Euphyllin	9.31 8.91 9.15 9.15	4.83 13.75 13.25 14.50	12.67 17.73 9.36 12.39	No
179	43.6	39	F	Euphyllin	11.75	15.17	3.95	No
180	58.0 55.5	28	M	Euphyllin Theodur	8.83 14.40	5.75 4.75	6.35 10.90	Yes
182	65	32	F	Theodur	9.23	12.50	12.40	No
187	59.5 62.2	27	F	Theodur	10.08 9.65	12.50 15.00	9.02 11.60	No
193	55.6	24	F	Theodur	7.19 7.19	11.75 13	12.63 11.77	No
204	77.5	30	F	Euphyllin	6.61	11.5	2.25	No

Table D15
NONMEM Data Set - Study 2
Patients 205 to 292
see Chapter Seven

Id	Mass (kg)	Age (yr)	Sex	Preparation	Dose (mg/kg/day)	Time (hr)	Cp (ug/ml)	Smoker
205	65.2	36	M	Theodur Euphyllin Euphyllin Theodur	9.2 7.86 7.86 12.27	11.75 7.5 6.17 10.5	11.65 8.41 10.0 5.05	Yes
219	54.5	36	F	Theodur Theodur	11.01 11.01	5.5 5.67	11.0 11.55	No
233	45.6	34	M	Theodur	13.16	14.17	7.8	Yes
251	46 43	32	F	Euphyllin Euphyllin	11.14 11.91	14.75 14.75	10.31 6.3	No
254	50.3	29	M	Euphyllin Euphyllin Theodur	10.18 10.18 11.93	13 11.25 12.5	7.3 7.6 9.0	Yes
281	60	28	M	Theodur	10.0	10.17	9.13	Yes
285	36.9	29	F	Euphyllin Euphyllin	20.8 20.8	15.5 13.5	18.1 23.03	No
287	49.2	29	M	Euphyllin Theodur	10.41 12.2	19.0 9.5	2.4 8.9	Yes
292	48	34	M	Euphyllin Theodur Euphyllin	10.67 16.67 10.67	10.5 11.75 10.33	2.7 9.4 5.85	No