BIOEQUIVALENCE OF SUSTAINED RELEASE THEOPHYLLINE FORMULATIONS

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SUBMITTED FOR THE DEGREE DOCTOR OF PHILOSOPHY

UNIVERSITY OF ASTON

APRIL 1986

SUMMARY

The bioequivalence of sustained release theophylline formulations, marketed in the United Kingdom, has been investigated in relation to the co-administration of food in both single dose and steady state volunteer studies. The effect of food on pharmacokinetic parameters and their clinical relevance was researched. Experimentation using drug induced modification of gastric motility to ascertain the component influences of the rate of gastric emptying on the absorption of theophylline from sustained release formulations was conducted. Prolongation of time to maximum plasma theophylline concentration by food reported in the literature and its clinical importance was investigated in once daily compared with twice daily administration of sustained release theophylline formulations and smoking habit. The correlation between saliva and plasma theophylline concentrations as a means of developing a non-invasive sampling techniques was examined. Data obtained from *in vitro* dissolution studies was compared with *in vivo* results.

This thesis has shown no significant differences occurred in the pharmacokinetic parameters measured between sustained release formulations available in the United Kingdom. The investigations into the influence of food on prolongation of time to maximum plasma theophylline concentration and other measured pharmacokinetic parameters demonstrated no important pharmacokinetic or clinical effects. Smoking adults taking sustained release theophylline formulations had similar drug clearances to those reported in the literature for smokers taking plain uncoated theophylline formulations.

KEY WORDS

Bioequivalence
Theophylline
Sustained Release
Food
Pharmacokinetics

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CONTENTS PAGE

PAGE

CONTENTS

TABLES

CONTENTS

CONTENTS

FIGURES continued PAGE

CONTENTS

FIGURES continued PAGE

INTRODUCTION

SOURCE AND HISTORY OF THEOPHYLLINE

Theophylline, a xanthine alkaloid, occurs naturally as an isomer of theobromine in tea. At least half the world's population drink tea. It is believed that palæolithic man discovered the principal caffeine-containing plants throughout the world including tea (Thea Sinensis), a bush native to southern China and now extensively cultivated in other similar climates. The basis for the popularity of all xanthine containing beverages was that they had stimulant and antisoporific actions that elevated mood, decreased fatigue and increased capacity for work. Legend credits the discovery of tea to a Chinese Mandarin, who, in a severe drought only had water into which tea leaves had fallen to drink. Being forced to drink the contaminated water, he found it to be refreshing and invigorating, hence many thousands of years later tea leaf infusions are still consumed worldwide. The content of theophylline in tea is very small, the major alkaloids being theobromine and caffeine.

One of the largest sources of theophylline in the normal diet is coffee (coffee arabica), which contains up to 10 times the amount of theophylline in tea. Again, coffee is drunk for its stimulant effects. A Prior of an Arabian convent is given credit for introducing coffee into our diet. Shepherds reported to the Prior that sheep that had eaten the berries of the coffee plant frisked about all night long instead of sleeping. The Prior, having difficulty with keeping awake during long nights of prayer that he had to endure, instructed the shepherds to pick the berries so that he might make a beverage from them.

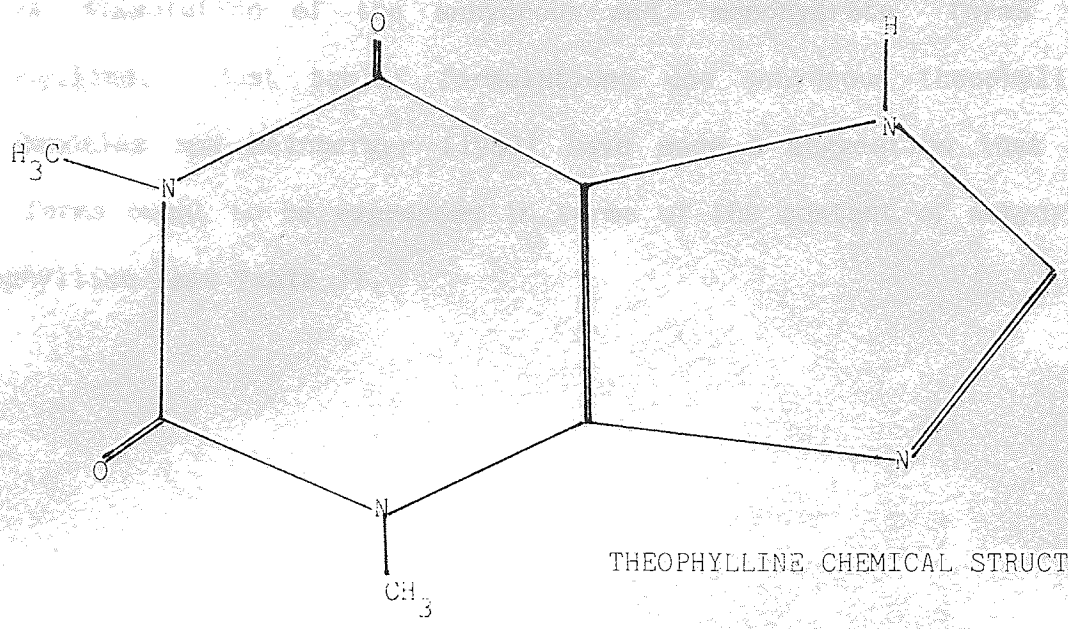
Theophylline was first synthesised at the time of the great Germany chemical industry expansion by Traube in 1900. Initially, its therapeutic role was seen as a diuretic but from 1937 it was used widely for the treatment of asthmatic patients. Theophylline

fell into disrepute as it was associated with a high incidence of unexplained toxicity and inconsistent therapeutic effects. Based on those observations it was thought that the problem was due to variable absorption because of its poor water solubility. Hence aminophylline, the ethylenediamine salt of theophylline, was introduced having been first synthesised in 1908. Other salts and derivatives followed, diprophylline appeared in 1949 followed by acephylline piperazine in 1949, etophylline in 1951, choline theophyllinate in 1954 and proxyphylline in 1956. The improved solubility of micro-crystalline theophylline was being studied as a means of improving theophylline solubility and bioavailability as recently as 1980 (Jones 1980).

In 1978 Weinberger et al showed that theophylline was completely absorbed and that the bioavailability of theophylline was related more to its formulation than solubility. It was the individual variation of theophylline metabolism and clearance that produced the varying therapeutic effects. The era of pharmacokinetics had begun to unravel the mystery of theophylline and with increased knowledge it has been re-established as a useful drug in the treatment of asthma.

CHEMICAL PROPERTIES OF THEOPHYLLINE

Theophylline is 1,3,dimethylxanthine.



THEOPHYLLINE CHEMICAL STRUCTURE

The free proton on the N-7 position makes theophylline a weak acid with a pKa of 8.8 at 23 °C (Merck Index, 9th Edition, 1976).

In most pharmacopoeias both the monohydrate and the anhydrous forms appear.

The water solubility of theophylline is 1 part in 120. In order to increase the solubility in water a number of salts, double salts and N-7 substituted derivatives have been produced. Soluble theophylline salts are characterised by very high pH values in water, higher than the pKa of theophylline. The solubility is strongly pH dependent and decreases rapidly when the pH falls below the pKa of theophylline. At a high pH, salts of theophylline are formed with the base, as a result of a tautomeric shift in hydrogen. At physiological pH, theophylline is a weak base and incapable of existing as a salt. Therefore, these so-called salt complexes are merely mixtures; the bases have no pharmacological activity (Svedmyr 1927). As a result of differences in chemical structure the theophylline salts and N-7 substituted derivatives differ greatly in their physical constants (Table 1) (Zuidema and Merkus 1979, Zuidema 1982, Hendeles and Weinberger 1983).

Shefler and Higuchi (1983) found up to a two fold difference in the dissolution of the anhydrous and monohydrate forms of theophylline. Most tablet formulations use anhydrous theophylline and Hendeles and Weinberger (1983) have made a suggestion that all salt forms ought to be expressed in terms of the content of anhydrous theophylline (see Table 1).

Table 1

CHARACTERISTICS OF THEOPHYLLINE AND RELATED COMPOUNDS

APPROVED NAME	CHEMICAL NAME	SOLUBILITY IN WATER	pH OF SOLUTION IN WATER	SOLUBILITY IN CHLOROFORM	ANHYDROUS THEOPHYLLINE CONTENT
Theophylline	1,3,dimethylxanthine	1 in 120	7	1 in 200	100
Salts					
Aminophylline	Theophylline ethylenediamine	1 in 5	8.5	Slightly Soluble	78 - 86
Choline Theophyllinate	Theophylline cholinate	1 in 1	9.5	Slightly Soluble	65
Double Salts					
Theophylline Sodium Glycinate		1 in 6	8.5 to 9.5	insoluble	50
N-7 Substituted Derivatives					
Acepifylline	Piperazine bis(theophylline -7-ylacetate)	1 in 1.5	7	-	NONE
Diprophylline	7-(2,3,dihydroxypropyl) theophylline	1 in 3	7	Slightly Soluble	NONE
Etofylline	7-(2-hydroxyethyl) theophylline	1 in 18	6.5 - 7	Sparingly Soluble	NONE
Proxyphylline	7-(2-Hydroxypropyl) theophylline	1 in 1.5	7	1 in 6	NONE

PHARMACOLOGY OF THEOPHYLLINE

Theophylline and related alkaloids have several pharmacological actions. They stimulate the central nervous system and respiratory centre (Pouwels 1979), produce diuresis equal to that produced by thiazides (Maren 1961) and stimulate cardiac muscle and bronchial smooth muscle.

Theophylline's main clinical use is in the treatment of bronchial asthma and obstructive airway diseases. Until recently the beneficial effects of theophylline were ascribed to its bronchodilating, cardiovascular and diuretic effects. Since the 1970s the major cellular actions of methylxanthines have been investigated. Methylxanthines have a diverse effect on the immediate type hypersensitivity phenomena (Pouwels 1979). Perper et al (1973) showed that the administration of theophylline in mice suppresses the secondary I_gE antibody response. Methylxanthines inhibit the in vivo and in vitro release of mediators from mast cells (Pouwels 1979). Schmutzler et al (1984) found that at therapeutic concentrations, theophylline inhibits mast cell degranulation with a consequent reduction in histamine release. Its action on the mast cell seems to be as an adenosine antagonist. Although adenosine receptors have been revealed to be different and widely spread in various tissues, theophylline thus far has been proven to be a universal antagonist (Goodman and Gilman 1980). But until the regulatory function of adenosine is established it is unlikely that the exact mechanisms of action for theophylline will be elucidated.

Other mechanisms of action of theophylline have been proposed including inhibition of phosphodiesterase which results in delayed degredation of 3'5' cyclic adenosine monophosphate (Trembath et al 1979), prostaglandin antagonism and translocation of intracellular calcium. These effects have so far only been shown to occur at

concentrations above the therapeutic levels normally obtained in man, so they seem unlikey to be the mechanism whereby theophylline exerts its bronchodilator effects (Bergstrand 1980, Goodman and Gilman 1980). At present most of the experimental evidence would favour the adenosine antagonist theory for the mechanism of action of theophylline.

THEOPHYLLINE THERAPEUTICS

The relationship between pharmacological effect and plasma theophylline concentration was first noted by Turner-Warwick (1957), who observed that symptomatic relief in asthma occurred mostly when the plasma theophylline concentrations were greater than 10 $\mu g\ ml^{-1}$. The paper most often cited as showing a relationship between plasma theophylline concentrations and therapeutic effects, as measured by Forced Expiratory Volume in 1 second (FEV_1), is that of Mitenko and Ogilvie (1973). Upon giving hospitalised asthmatics intravenous aminophylline, found that improvement in FEV_1 was directly proportional to the log plasma theophylline concentration. A therapeutic effect was demonstrated at plasma concentrations of 5 $\mu g\ ml^{-1}$ and improvement continued above concentrations of 20 $\mu g\ ml^{-1}$ but was associated with a higher incidence of side effects. Levy and Koysooko (1975) also demonstrated that if theophylline concentrations were allowed to fall there was a parallel fall in bronchodilator effects.

The relationship between improved pulmonary function tests and theophylline plasma concentrations is now being re-challenged. Rivington (1984), using a sustained release aminophylline product in a heterogeneous group of 21 asthmatic patients showed an improvement in pulmonary function tests with the exception of FEV_1 which was not significantly changed. In asthmatic patients it is difficult to measure a baseline when pulmonary function tests can vary in patients hour by hour (Rees 1983). The choice of a clinically relevant parameter of lung function especially in relation to theophylline plasma concentration is disputed. No improvement in exercise tolerance was seen in patients with chronic obstructive bronchitis treated for a week with placebo, low dose or high dose theophylline, although pulmonary function tests improved (Eaton et al 1982). Evans (1984) showed, in a placebo controlled trial,

that although the dose of theophylline administered correlated well with the plasma concentration, no correlation with improvement in FEV_1 or FVC_1 occurred in twenty patients with chronic bronchitis. Neither effort tolerance nor degree of breathlessness were influenced by the drug.

In the United States where inhaled adrenoceptor stimulants have not been available until recently, theophylline has had to be the first line treatment but in the UK where β_2 receptor stimulants, such as salbutamol, have been available for many years, the use of theophylline has been of concern (Cochrane 1984). Certainly, many clinicians only use theophylline to reduce or prevent daily steroid intake in patients with steroid dependent asthma (Nassif et al 1981) or improve the control of patients difficult to control on inhaled β_2 adrenoceptor stimulants and anticholinergics (Smith et al 1980). When its benefits are equated with its potential toxicity, the use of theophylline in chronic reversible obstructive airway diseases is debatable although most physicians report a greater sense of patient well-being, possibly related to the CNS effects of theophylline.

TOXICITY

Theophylline produces numerous minor and serious toxic effects based on its pharmacological actions. The minor side effects are not necessarily dose related but more serious side effects occur at higher plasma concentrations, above 20 $\mu g\ ml^{-1}$. Minor and frequent side effects include headache, dizziness, nausea, restlessness, palpitations and vomiting. Although using an initial incremental dosage regime to begin theophylline therapy can help to overcome these effects, they are common in the first two weeks and most patients on long term therapy acquire tolerance to them. Toxicity associated with plasma theophylline concentrations > 20 $\mu g\ ml^{-1}$ are tachycardia, insomnia and tremor. Severe toxicity normally at concentrations

over 35 $\mu g\ ml^{-1}$ includes seizures, cardiac arrest, hypotension and death.

The most common cause of severe toxicity is rapid administration of aminophylline injection. Aminophylline should be infused over 20 to 40 minutes to avoid severe toxic symptoms but often in the turmoil of treating a patient with status asthmaticus, the infusion period is more rapid. In patients already taking sustained release theophylline preparations when admitted, additional infusions of aminophylline have proved fatal (Wiggins et al 1984). Among infants and small children severe toxicity including death has occurred as a result of therapeutic misadventure often where multiple administration of suppositories has been involved (Nolke 1956). Individual variation in theophylline clearance between patients makes monitoring of theophylline plasma concentrations mandatory following acute or chronic administration if toxic symptoms are to be avoided (Cochrane 1984).

THEOPHYLLINE PHARMACOKINETICS

ABSORPTION

In 1977 Hendeles, Weinberger and Bighley presented a paper at the American Society of Hospital Pharmaicsts' mid-year clinical meeting in California which showed that theophylline in solution and as a plain, uncoated tablet had 100% bioavailability. They conducted an experiment on 20 adult asthmatics comparing plain, uncoated tablets and theophylline solution with intravenous aminophylline. Both preparations were found to be 100% bioavailable. Earlier, Mitenko and Ogilvie (1973) had conducted bioavailability studies on a sustained release formulation of theophylline, Theograd, and found it to be 77.1 $\pm$ 5.4% bioavailable. The Mitenko and Ogilvie study was conducted on five volunteers whose percentage bioavailability ranged from 59.2% to 91.6%. With such a range of values in five volunteers and no statistical analysis to show any significance, the problem of theophylline absorption was still thought to be more related to the drug than its formulation. It was not until 1978 when Weinberger et al published a study on the bioavailability of theophylline from uncoated, enteric coated and sustained release formulations of theophylline that the relationship between formulation and bioavailability was shown. In all but three formulations, theophylline proved to be 100% bioavailable. Unfortunately, in those three formulations, Aerolate, Theobid and Aminodur only 4, 6 and 5 volunteers respectively were used. This was not a cross-over study and different individuals received different formulations. In the discussion Weinberger et al did suggest that this could only be taken as an indication of incomplete absorption.

Subsequently, Upton et al (1980) found Aminodur to be 100.2 $\pm$ 19.8% bioavailable. Spangler et al (1978) confirmed Weinberger's

et al (1978) data on Theobid, (87.0% and 85.0% bioavailability respectively) but disagreed about the formulation Aerolate finding it to have only 48% bioavailability compared with 81.0% reported by Weinberger et al (1978). Spangler et al again only performed bioavailability studies on 5 volunteers for Theobid and Aerolate, insufficient to make a statistically valid evaluation as especially later, Upton et al (1982), Weinberger et al (1981) and Szefler (1984) were to show the importance of inter and intra subject variation in theophylline pharmacokinetics when conducting standardised studies.

Of those products on the UK market, Theo-Dur has been consistently reported to have good bioavailability but the range varies from 87.7% (Saccar et al 1983) to over 100% (Spangler et al, 1978, Fagerstrom et al 1981, Barrett and Hanigan 1981). As Theo-Dur tends to be used as a standard drug for comparison with other sustained release formulations, numerous bioavailability studies have been performed. The percentage bioavailability of 87.7% reported by Saccar et al (1983) is inconsistent with most other reports (Paulsen et al 1983, 93%, Fagerstrom and Heintz 1983, 94.0%). This trend of a range of bioavailabilities is true of other products on the UK market. Slophyllin has been studied by Weinberger et al (1981), Spangler et al (1978), Upton et al (1980) and Conard et al (1982). A total of 35 subjects in these four studies have produced values for bioavailability ranging from 75.0% (Spangler et al, 1978) to 111.0% (Weinberger et al 1981). Phyllocontin (Levitt and Kann, 1980, Paulsen et al 1983, Fagerstrom and Heintz, 1983), Nuelin SA (Jonkman et al 1981, Conard et al 1982, Harrison et al, 1982) all show similar patterns of reported bioavailabilities. Only Theograd with one known reported bioavailability of 77.1% $\pm$ 5.4 by Mitenko and Ogilvie (1974) and Tedral SA, (59.0% reported by Spangler et al, 1978 and 76 $\pm$ 18.4% reported by Upton et al, 1980)

have not been reported to have 100% bioavailability. The Spangler et al (1978) study did not demonstrate whether ephedrine contained in Tedral SA affected the spectrophotometric assay used (Schack and Waxler 1949). Upton (1980) used a HPLC technique but also did not monitor the effect of ephedrine in Tedral SA on the assay.

Hendeles and Weinberger (1982) published a welcome paper on methods of determining bioavailability of sustained release theophylline products. Until then the studies had been different and difficult to compare. More accurate assays had been developed and authors were beginning to analyse their data using valid statistical methods. In a review paper, Hendeles et al (1984) correlated the data from previous studies and used the technique of estimating the fraction of drug absorbed (Wagner-Nelson 1964) to compare the sustained release theophylline formulations. All of the products tested showed sustained release characteristics and only an American drug, Constant-T was shown to have low bioavailability (70%). Of those products compared which are on the UK market, all showed between 90% and 100% bioavailability.

DISTRIBUTION

Following either intravenous administration or absorption from the gastro-intestinal tract, theophylline distributes rapidly into peripheral tissues other than fat (Hendeles et al 1980). It freely crosses the placenta (Arwood et al 1979), is found in breast milk (Yurchak and Jusko 1976) and crosses the blood brain barrier (Goodman and Gilman 1980). Theophylline saliva concentrations have been shown to be in a fixed ratio with serum concentrations (Galant et al 1977, Goldsworthy et al 1981 and Jonkman et al 1981).

Since only 60% of the drug in serum is bound to proteins, small changes in the degree of binding do not have a significant effect upon the concentration of free theophylline. In premature neonates

and in the presence of acidaemia, protein binding is reduced (Hendeles et al 1980). Theophylline does not concentrate in any one tissue and thus any binding that may occur is readily reversible. The distribution follows a two compartmental model (Mitenko and Ogilvie 1972). The α or early distribution phase is completed within 35 to 45 minutes after an intravenous dose. As a consequence most investigators apply a one compartment open model to their kinetic analysis.

The apparent volume of distribution at steady state averages 0.5 l Kg^{-1} body weight (Piafsky et al 1977 and Jenne et al 1972), and is not affected by sex (Powell et al 1977), age from 1 to 87 years, although it tends to be larger in neonates (Aranda et al 1976), cigarette smoking (Hunt et al 1976, Powell et al 1977) and obesity (Rohrbaugh et al 1982). A slight decrease in volume of distribution in obese subjects was reported by Gal et al (1978). A slightly larger distribution volume in patients with hepatic cirrhosis was reported by Piafsky et al (1977).

THEOPHYLLINE METABOLISM AND ELIMINATION

Theophylline undergoes extensive metabolism. In 1957 Cornish and Christman reported the recovery of 3-methylxanthine (3-MX), 1-methyluric acid (1-MU), 1,3-demethyluric acid (13-MU) and intact theophylline in urine. Up to 80% of the total dose is metabolised with only 13% of theophylline appearing unchanged in the urine. A metabolic pathway was proposed by Tang-Liu et al (1981).

The metabolic pathway for theophylline in rats and mice involves hepatic microsomal enzymes and xanthine oxidase (Levy and Koysooko 1976). The enzyme system responsible in man is not yet known but it is thought that the haem proteins cytochrome P-450 and P-448 are involved. Cytochrome P-448 can be induced by cigarette smoke (Jusko et al 1979) to decrease theophylline elimination half life. Grygiel et al (1980) has suggested that different cytochrome P-450s are involved in the N-demethylation of theophylline to 3-methylxanthine and 1-methylation than those involved in the 8-hydroxy-lation of theophylline to 1,3-dimethyluric acid. In premature neonates, only unchanged theophylline and caffeine are found in urine, indicating the absence of oxidative pathways for theophylline metabolism. (Grygiel et al, 1980). As it is known that enzyme systems catalysed by cytochrome P-450 are not developed in neonates, this provides evidence for the existence of such a system in adults. Urinary theophylline metabolic patterns are similar in older children and adults, indicating that the increased clearance in children is not associated with induction of a specific pathway (Grygiel et al 1980).

Grygiel et al (1979) showed that subjects receiving allopurinol 300 mg a day increased 1-methylxanthine renal excretion and decreased 1-methyluric acid excretion indicating that 1-methylxanthine is an intermediate metabolite of theophylline (Tang-Liu et al 1981).

The premise that the elimination of theophylline follows a first order process (Brown et al 1983) has, in recent years, been re-examined. Sarrazin et al (1980) and Weinberger and Ginchansky (1977) have demonstrated dose dependent kinetics in children. Massey et al (1984) and Butcher et al (1982) have also found clinical evidence of dose dependent kinetics in adults. The mechanism for dose dependent kinetics has been proposed by Tang-Liu et al (1981). Formulations of 3-MX, 1-MU and 13-MU were shown to obey Michaelis-Menten kinetics with a V_{max} of 5, 13 and 34 mg h^{-1} respectively. The evidence for a saturated enzyme system is further provided by the work of Caldwell et al (1977) who found that after the first 12 h after an intravenous dose of ^{14}C labelled theophylline, 3-methylxanthine was excreted by Michaelis-Menten kinetics. In the same experiment Caldwell restricted the dietary intake of methylxanthine for seven days and then repeated the intravenous dose of ^{14}C labelled theophylline. The elimination half life decreased from 10.1 h on a normal diet to 6.9 h after a xanthine free diet. Variability in xanthine uptake is a likely cause of inter and intra-patient variability in theophylline elimination. This demonstrates that the saturable enzyme system could be the N-demethylation to the major metabolite 3-methylxanthine. 3-methylxanthine is pharmacologically active with an intrinsic activity 5 times less than theophylline (Persson and Anderson 1977).

Wagner (1985) reviewed the literature on saturation kinetics for theophylline and using data available from combining literature reports he calculated the mean V_{max} for theophylline as 1960 mg day^{-1} and the mean K_m as 24.1 mg l^{-1}. Wagner put forward the suggestion that because most pharmacokinetic studies on theophylline have been single dose studies, the Michaelis-Menten kinetics would not be seen, only becoming apparent at steady state. Wagner demonstrated using these values of V_{max} and K_m that increasing the dose of theophylline

from 300 mg to 1500 mg would increase the apparent elimination half life by 17%.

The renal clearance of theophylline has ranged from 3 to 9 ml/min per square metre body surface area (Ogilvie 1978). During the diruesis associated with theophylline administration, the renal clearance of theophylline was higher than during periods of lower urinary flow rates. The renal clearance of theophylline is flow dependent (Wagner 1985) and is not related to plasma drug concentration. An average haemodialysis clearance of 0.24 $l\,kg^{-1}\,h^{-1}$ is about 1/3 to 1/2 the body clearance in healthy adults (Levy et al 1976).

FACTORS AFFECTING THEOPHYLLINE CLEARANCE

Under normal circumstances, clearance, serum concentrations and dosage requirements in most patients generally remain acceptably stable over time with little intra-patient variability. But many other factors such as disease state, diet, concomitant drug therapy, and age interact to produce great inter-patient variability.

AGE

Premature neonates treated with theophylline for apnoea have extremely low plasma theophylline clearance values. It is thought that this is due to the absence of hepatic cytochrome activity (Aranda et al 1976). Nassif et al (1981) showed a linear relationship between age in weeks and the dose required to achieve a steady state serum theophylline concentration between 10 - 20 $\mu g\ ml^{-1}$ among 50 infants 6 - 48 weeks old. They suggested that the increasing dose required was related to the development of a hepatic mixed function oxidative enzyme system increasing theophylline clearance. From the age of 1 to 16 years the mean theophylline clearance is around 0.9 $l\ Kg^{-1}h^{-1}$. and this slowly decreases to the adult norm of 0.4 $l\ Kg^{-1}h^{-1}$. Most studies with children have mixed age groups so it is hard to band the total body clearance to age bands (Simmons and Simmons 1978). Jusko et al (1979) reviewed the clinical data on 200 volunteers and patients and showed a pronounced variability of total body clearance of theophylline over all age groups. Applying regression analysis to the data, Jusko showed that theophylline clearance is age dependent, decreasing throughout life, in spite of the great variability in the clearance values. Piafsky et al (1977) and Powell et al (1978), to counterpoint Jusko, claimed that old age did not alter theophylline clearance. Antal et al (1981), however, cites reduced serum protein binding in old age as the reason for reduced

theophylline clearance. The clinical significance of this reduced clearance with age has not been demonstrated apart from the recommendation that care should be taken in the dosing of older people (Jusko et al 1978).

SEX

No difference has been found between the clearance of theophylline in men and women (Powell et al 1977, Hendeles et al 1981). Most American studies, though, tend to be carried out on men due to FDA investigational requirements.

OBESITY

Rohrbaugh et al (1982) found that obesity had no effect on theophylline's volume of distribution in a small study on eight lean and eight obese subjects. This data confirms that theophylline is not extensively distributed into adipose tissue. Gal et al (1978) showed that the clearance and volume of distribution is best calculated on ideal body weight rather than on total body weight in obese patients. When the clearance of theophylline in obese patients was corrected for IBW there was no significant difference between obese and normal subjects.

SMOKING HABITS

Both tobacco and cannabis smoking increases the clearance of theophylline (Jusko et al 1979). It is thought that the polycyclic aromatic hydrocarbons in the tobacco smoke induce liver enzymes, notably cytochrome p-450 and P-488 mediated pathways. The increase in clearance has been shown to correspond to the amount smoked (Hunt et al 1976) and when smoking is stopped the rate of clearance remains unchanged for up to 3 months. Smoking habit is one of the most dramatic and possibly clinically important influences which alters theophylline clearance (see chapter 7).

DIET

The composition of food can affect the clearance of theophylline. Caldwell et al (1977), as previously discussed, showed that a diet containing other methylxanthines can reduce theophylline clearance. Kappas et al (1977) demonstrated that when the diets of volunteers was changed from a low carbohydrate, high protein diet to a high carbohydrate, low protein diet, the mean theophylline half life increased from 5.2 h to 7.6 h. Kappas demonstrated that these changes in half lives were accompanied by changes in metabolic clearance rates. Charcoal broiled food with a high polycyclic carbon content can variably increase the rate of theophylline biotransformation in man (Kappas et al 1978).

CONCOMITANT DRUG THERAPY

Allopurinol has been shown to have no effect on theophylline clearance by Vozeh et al (1980) but using much higher doses of 600 mg a day for over 14 days, Monfredi and Vessel (1981) have shown a decrease in theophylline clearance. It is not known if this is an effect of the xanthine oxidase inhibition or a reduction in microsomal enzyme activity brought about by allopurinol.

Antacids have only been shown to have an effect on one formulation, Nuelin SA (Myhre and Walstad 1983), and not to have any effect on Theo-Dur or Slo-Phyllin (Shargel et al 1981). This is possibly due to the known pH dependent dissolution of Nuelin SA (Jonkman et al 1981).

Cimetidine decreases the metabolism of a number of drugs which use the P-448 or P-450 pathway eg, warfarin, and it has been shown to have a similar effect on theophylline by Jackson et al (1981). Theophylline clearance has been shown to be decreased by around 40% (39 $\pm$ 1% Jackson and Plachetka 1981) (30 $\pm$ 17% Reitberg et al 1981), (45% Vestal et al 1982). Ruff 1982 and Powell et al 1982 have shown that ranitidine dose not have the same effect as cimetidine.

Phenytoin has been reported to increase the clearance of theophylline (Sklar and Wagner 1985, Miller et al 1983, Marquis et al 1982). The increase reported by both Sklar and Wagner and Marquis is approximately two fold. Sklar and Wagner demonstrated with case studies that the effect of phenytoin on individual patient's theophylline clearance can be variable in onset and magnitude.

Jusko et al (1979) showed a tendency towards increased theophylline clearance in barbituate users and Landay et al (1978) found that a 28 day course of phenobarbitone increased theophylline clearance by about a third (33 $\pm$ 21%). This is of particular importance as many older pharmaceutical formulations, such as Franol, contain theophylline and phenobarbitone in the same formulation.

Two reports, Rosenberry et al (1983) and Reed and Schwartz (1983), have indicated a decrease in theophylline half life when co-administered with carbamazepine.

Conrad and Nyman (1980) have reported a decreased theophylline clearance due to propranolol, the effect being greater in smokers than non-smokers. Metoprolol also decreased theophylline clearance but not to such an extent. The clinical importance of this is not great due to the reluctance to give β-blockers to patients with bronchial obstruction.

Oral contraceptives may have an effect on theophylline clearance. Jusko et al (1979) showed no correlation between oral contraceptives and theophylline clearance but Roberts et al (1983) reported a 29% reduction in theophylline clearance in women using "the pill".

A recent report by Burnakis et al (1983) has cited two case presentations in which theophylline clearance has been reduced by the calcium antagonist, verapamil. A preliminary report by Hauser et al (1983) described an increase in theophylline clearance by rifampicin.

Erythromycin decreases theophylline elimination, the confusing reports in the literature are due to the length of time erythromycin and theophylline have to be concomitantly administered to obtain an effect. Zarowitz et al (1981) found that short term administration (48 h) had no effect on the pharmacokinetics of theophylline. After a 10 day course of erythromycin a decrease of 9 $\pm$ 13% in theophylline clearance was demonstrated. Those studies where no difference in clearance was demonstrated when erythromycin was given with theophylline (Pfeifer et al 1978, Kelly et al 1981) used a short course of therapy. The effect of theophylline and erythromycin on theophylline clearance has been reported to be between 49 $\pm$ 6% (Cummins et al 1977) and 9 $\pm$ 13% (Jarowitz et al 1981). The majority of studies and the conclusion from Hendeles and Weinberger (1983) review would indicate that about a 40% reduction in theophylline clearance could be expected from a long term course of erythromycin of over 6 days duration.

INFLUENZA VACCINE

Chang et al (1978) reported an increase in theophylline half life in six children with a viral infection. Renton et al (1980) reported an increase of between 85 and 219% in serum theophylline concentrations in three asthma patients within 12 to 24 hours after vaccination. But the evidence for influenza vaccination decreasing theophylline clearance has not been substantiated. Goldstein et al (1982) reported unchanged serum theophylline concentrations 24 h after injection in sixteen patients. Fischer et al (1982) also found no change in theophylline concentrations 12 h, 3 days, 7 days and 14 days after vaccination in 12 patients.

DISEASES ALTERING THEOPHYLLINE ELIMINATION

Cardiac diseases

Increased toxicity has been reported in patients with congestive heart failure (Hendeles et al 1977, Jenna et al 1977, Jusko et al 1977). The mechanism responsible for altered theophylline elimination in CHF is unknown but a combination of hypoxaemia and reduced hepatic blood flow is likely.

Pulmonary Disease

There is no good evidence that uncomplicated asthma or chronic bronchitis per se alters theophylline clearance. The development of complications such as chronic obstructive lung disease or pneumonia has been associated with reduced theophylline elimination (Ogilvie 1978).

Hepatic Disease

Mangione et al (1978) investigated the disposition of oral theophylline in eight cirrhotic patients, 57 young healthy adults and 25 age matched controls. The cirrhotics had markedly decreased clearances (18.8 ml $kg^{-1}h^{-1}$) when compared with the age matched controls (53.7 ml $kg^{-1}h^{-1}$). Jusko et al (1979) and Piafsky et al (1977) also confirmed reduced elimination of theophylline in patients with hepatic cirrhosis.

INTER-AND INTRA-SUBJECT VARIABILITY IN THEOPHYLLINE PHARMACOKINETICS

A number of factors previously discussed alter the elimination of theophylline in patients but evidence is accumulating to show that not only is there an inter-subject variability but also an important intra-subject variability in theophylline pharmacokinetics. Upton et al (1982) demonstrated that 39 out of 60 individuals varied in their terminal disposition rate constant on the different occasions each was required to take the dose during the course of a cross-over bioavailability study. In one study Upton identified 9 out of 12 individuals who showed statistically identifiable variation in terminal disposition rate constants (β) between two dosing occasions when each individual serum theophylline concentration was measured. Fluctuations in β of 60% were reported. Upton could not relate these changes in β to either sex, smoking or body weight. He concluded that no chronological pattern has as yet been recognised in the individual variation in the terminal disposition rate constant, but suggested that the urinary excretion of theophylline could be important. Urinary excretion of theophylline averages at 10 - 13% but as Tary et al (1982) has shown, the renal clearance of theophylline varies directly with urine flow and serum concentration as diuresis is a pharmacological effect of the drug. When serum concentrations of the drug are high, diuresis is greater and the renal clearance of the drug is larger. As the serum concentration falls, diuresis is less, urinary excretion is reduced and metabolic clearance may be affected by salt and water intake amongst other variables (Upton 1982).

Bell et al (1980) reported significant differences in the pharmacokinetics of oxtriphylline (a choline salt of theophylline) between two groups of patients in a multicentre trial. A number of suggestions were made for the differences, including body weight, diet and dosedependent kinetics.

Pollack et al (1984), Dederich et al (1981) and Szefler (1984) reported significant differences in the rate of absorption on different sampling days in volunteers. Pollack found sustained release tablet formulations to have greater fluctuations in rate of absorption than a multipellet capsule formulation. As the rate of absorption varied between dosing intervals, Pollack found that in the tablet formulation carry over of the drug occurred when the absorption was prolonged causing greater fluctuations in measured serum theophylline concentrations than when absorption was faster. Pollack et al (1984) suggest that changes in gastro-intestinal physiology were the cause of intra-volunteer changes in rate of absorption. Pedersen (1984) reported a very wide inter-individual variation in absorption in a study on 10 asthmatic children taking a multipellet capsule formulation with food.

The only study so far which has tried to estimate intra and inter-subject variation is that of Halkin et al (1982). Halkin found the degree of inter-individual variation in serum theophylline results in 15 asthmatic patients to be in the range of 20 - 44%. The intra individual co-efficient of variation was 22 - 24%. Halkin cites a computer programme for predicting theophylline serum concentrations being based on a 70% value for inter-individual variation and a 10% intra individual variation. After taking into account assay variables, Halkin estimates an 11 - 18% random unexplained variability in day to day serum concentrations of theophylline should be expected.

CHANGES IN THEOPHYLLINE DISPOSITION WITH CIRCADIAN RHYTHM

Diurnal changes in the pharmacokinetics of theophylline have been suggested for explaining intra-subject variation. Certainly a number of workers, (Lemmer 1982, Birkett et al 1982, Birkett et al 1984, Lesko et al 1980 and Taylor et al 1983) have reported diurnal variations in morning and trough concentrations. Theophylline clearance is said to remain unaltered (Scott et al 1984, Birkett et al 1984, Taylor et al 1983) but this has been contested by MacLeod et al (1982) who not only showed decreased absorption at night but also increased theophylline clearance. This is the only report known to show theophylline clearance changes at night. Taylor et al (1983) found no difference in theophylline clearance, half life or volume of distribution over a 24 h period.

A number of reports state that theophylline absorption does show diurnal variation. Scott et al (1984) found in children that the rate and extent of theophylline absorption from sustained release formulations was less at night than during the day. Time to peak concentration has been reported to be shorter after a morning administration than afternoon or evening administration (Lemmer 1984, Taylor et al 1983). Birkett et al (1984) showed that the absorption from Nuelin SA 250 mg was so prolonged at night that morning pre-dose concentrations were peak concentrations in some patients. However, Nolte and Newmann (1982) showed no difference in plasma time profiles of Uniphyllin administered once daily in the morning or early evening.

These findings tend to support, in general, a trend that circadian rhythm probably reflects differences in absorption more than alterations in metabolism or excretion. Diurnal variation in theophylline absorption could offer some explanation for intra-subject variation.

INFLUENCE OF FOOD ON SUSTAINED RELEASE THEOPHYLLINE

The presence of food, its composition and water content have all been shown to influence the absorption of theophylline from sustained release formulations. Food intake exerts a complex influence on the bioavailability of drugs. It may interfere not only with tablet disintegration, drug dissolution and drug transit time but also affect the metabolic transformation of drugs in the gastro-intestinal wall and in the liver. Different food components can have different effects and food may interact in opposite ways, even with drugs that are chemically related. As judged mainly from single meal single dose studies food intake enhances the bioavailability of several different drugs such as propranolol, metoprolol, hydralazine, hydrochlorothiazide, spironolactone, nitrofurantoin, erythromycin stearate, dicoumarol, phenytoin and carbamazepine but reduces that of drugs such as isoniazid, rifampicin, tetracycline, penicillin and ampicillin, while having a inconsistent effect on the bioavailability of metronidazole, oxazepam, propylthiouracil and sulphonylureas. For some drugs such as digoxin and paracetamol, the rate but not the extent of absorption is reduced (Melander 1978).

Food may enhance bioavailability by reducing gastric emptying. This is apparently the case with hydrochlorthiazide and nitrofurantoin. The food induced enhancement of bioavailability of propranolol, metoprolol and hydralazine is probably due to reduced first pass metabolism of these drugs, while food induced improvement of drug dissolution may explain the enhanced bioavailability of carbamazepine, spironolactone, dicoumarol and phenytoin. An increased gastro-intestinal pH may be the cause of the food induced reduction of the bioavailability of drugs such as isoniazid and tetracycline (Melander 1978). The difference between many of these drugs and

theophylline is that theophylline is mainly taken orally as sustained release formulations. Hence there is not only a reaction of food with the drug but with its formulations. With the range of formulations used to prolong the release of theophylline, each individual preparation will react differently to the effect of food.

Studies conducted on plain theophylline tablets and theophylline liquid have demonstrated that theophylline elimination half life can be affected by the composition of food (Feldman et al 1982, Feldman et al 1980, Kappas et al 1976). In asthmatic children Feldman et al showed that a high protein diet shortened the elimination half life and a high carbohydrate diet significantly increased it relative to a normal diet. Heimann et al (1982) showed that in premature infants feeding significantly decreased theophylline absorption rate when administered as an aqueous solution. Therefore, it would appear in children, at least, that theophylline in its simplest form can be affected by the composition of food and the presence of food.

The first experiments on sustained release formulated theophylline were unfortunate in their choice of formulation. Welling et al (1975) conducted an experiment on a combination product, Tedral, containing 130 mg of theophylline, 8 mg of phenobarbitone and 24 mg of ephedrine, a combination of drugs known to affect theophylline disposition. Even so, Welling demonstrated that the volume of fluid taken with Tedral affects its rate of release, (the larger the volume of water taken the faster the release) and that the absorption of theophylline was faster when the drug was given with a high protein meal than a high fat meal.

In 1981 Pedersen published a letter showing a dramatic reduction in the rate of absorption of theophylline from Nuelin SA when taken with food. Again, this was an unfortunate choice of formulation.

Nuelin SA is now known to be a pH dependent formulation with slower release characteristics in acid pH compared with neutral or alkaline pH (Jonkman 1981). The retention of a tablet in the stomach caused by reduced gastric motility due to the presence of food is more likely to show a reduction in the rate of absorption of theophylline from the Nuelin SA than any other formulation. The graph displayed in Pedersen's letter and its implied conclusion has now been repeated in review and text books justifying the statement that food affects the absorption of theophylline from sustained release formulations. The letter by Pedersen was followed in 1982 by a full article by Pedersen and Moeller-Petersen (1982). Using Nuelin SA, again Pedersen was only able to show that food influenced the rate of absorption in six children, not on the six adults participating in the study. In the six children the delay produced a time to peak concentration of a staggering 16.6 h. Such a delay has not been able to be reproduced by any other workers in either children or adults.

Osman et al (1983) showed that administration of food did not affect Theo-bid 260 mg and Theo-Dur 200 mg formulations. Sips et al (1984) failed to find any significant differences when Theo-Dur 300 mg was taken with food and Leeds et al 1982 found a variable response to food for Theo-Dur 100 mg and 300 mg formulations. Leeds demonstrated that food reduced the theophylline concentration obtained from Theo-Dur 100 mg formulation at 1 to 4 h but only at the 4 h interval for the 300 mg formulation. Lagas and Jonkman (1983) reported a significantly slowed absorption when Theograd 250 mg was taken with food, resulting in an enhanced bioavailability compared with fasting subjects. Unlike Pedersen, Lagas and Jonkman obtained higher maximum concentrations with food resulting in an increase in the amount absorbed by 40%. From the Lagas and Jonkman (1983) study it is hard to determine why the bioavailability for Theo-grad in fasting

subjects was only 64 ± 22%. Both Mitenko and Ogilvie (1974) and Sharma et al (1981) have shown the bioavailability from Theo-grad to be much higher at around 80%. Using Somophyllin-CRT, both Birkett et al (1984) and Pedersen (1984) have shown no effect of food on this sustained release product.

Again, a variety of effects of food have been reported for the multipellet designed formulation. Green et al (1981) and Lotner et al (1983) have shown that Slophyllin, when administered with apple sauce in both opened and un-opened capsules, is not affected by the presence of apple sauce. Pedersen (1984), however, using Theo-Dur sprinkle showed that by administering the formulation with 300 g of apple sauce, the time to maximum concentration was slower than fasting and faster than when taken with a dry meal. Again, in the Pedersen study using children, the differences in mean data showed a delay of 9 h between fasting and taking the formulation with apple sauce. A delay of this magnitude has not been reported by any other worker. Hendeles et al (1985) showed that a very large meal resulted in dose dumping from Theo-24, half the dose of 6 mg kg^{-1} was released in 4 h when the formulation was taken with food.

It can be seen from this review of the available literature that the effects of food on sustained release theophylline is formulation specific. Reports in the literature relating to one formulation cannot be extrapolated to another. Coupled with the pronounced intra-subject variations that occur with theophylline, any authoritative study comparing the effects of food on sustained release theophylline formulations would be difficult and expensive to organise and conduct. It would appear, at present, that the effect of food on sustained release formulations of theophylline can only be described as variable.

SUSTAINED RELEASE FORMULATIONS OF THEOPHYLLINE

A wide variety of techniques have been used to develop sustained release oral dosage forms. These techniques include the development of drug salts to decrease solubility and variation of particle size, ion exchange resins to bind drug substances, porous, non-disintegrating, inert carriers as matrices for the drug and slowly eroding coatings or matrices and coatings that serve as a membrane for drug diffusion. Theophylline is marketed as a multipellet capsule formulation or as a matrix. The plastic matrix is a system where the drug is mixed with inert, insoluble powdered matrix material consisting of plastic resins and other ingredients and compressed. In the gastro-intestinal tract, drug particles from the surface of the matrix system dissolve and leave pores through which the drug from within the tablet leaches out. The matrix retains its shape during the leaching process.

The multipellet design is a mixture of sustained release beads in a hard gelatin capsule. The capsule may contain several kinds of beads. The first is an uncoated bead to provide an initial burst of drug. The second has a coating that resists disintegration for 3 hours, the next has a 6 h coating and further coatings of 9, 12 or more hours may be added. In some cases the beads are compressed to form a tablet rather than a capsule. An example of this is Theo-Dur.

THE "CONTINUS" MECHANISM

The continus is the trade mark for sustained release mechanisms manufactured by Napp Laboratories. It is a system which relies upon the processes of diffusion and dissolution. Theophylline is first coated with a hydrophilic cellulose which has been selectively hydrated with water or an alternative suitable polar solvent. The primary controlled release granular system is then dried and subsequently incorporated within the melt of a hydrophobic higher

aliphatic alcohol which acts as a potentiator to the primary system. By varying either the amount of cellulose, the degree of cellulosic hydration, the amount of higher aliphatic alcohol or the ratio of water soluble to water insoluble cellulose it is possible to vary the rate of drug diffusion through the matrix and subsequent rate of dissolution (Leslie 1980).

STAGE I Drug + Cellulose = Hydration

STAGE II Drug + Cellulose + Aliphatic Alcohol = The Continus Mechanism

It is claimed that this mechanism can be controlled to obtain release characteristics from 1 h to 12 h and in the case of Uniphyllin it is claimed to be 24 h. Phyllocontin is controlled to give release of aminophylline over a period of six hours, a process claimed by Leslie to be pH independent.

THEO-DUR

Theo-Dur relies on a process of osmosis, diffusion and dissolution. The Theo-Dur tablet has two sustained release principles, coating and embedding. The basically two phase dividing system comprises, a granulated theophylline matrix and numerous tiny cores. Each core consists of a sucrose seed to which multiple layers of cellulose acetate phthalate and theophylline are applied and the whole is encapsulated in a coat of cellulose acetate phthalate and wax. The wax is insoluble but permeable in GI fluids. Cellulose acetate phthalate is permeable in gastric fluid and soluble in intestinal fluid.

The cores of Theo-Dur are evenly distributed throughout a matrix of granulated theophylline in each Theo-Dur tablet. The granulation allows Theo-Dur to provide an initial dose, fulfilling the requirement of sustained release. The mix betwen the cores and the theophylline

granules is compressed to form the tablet. Precise compression is required for the Theo-Dur core and the granulation phases to complement each other's dissolution patterns. Too much compression could crack the cores; insufficient compression would allow faster absorption and lessen duration of action.

GI fluids penetrate the granulation matrix and dissolve the granules on the tablet surface. The gastric fluids pass through the core coat and the theophylline layers and dissolve the sugar seed by osmosis. While being drawn through the theophylline layers within the core, the fluid becomes saturated with theophylline. Because the sugar seed absorbs fluid, the cellulose acetate phthalate and wax layers will eventually burst as a result of increased "inner fluid pressure". The theophylline saturated fluid is released from the core in the intestine, the cellulose acetate phthalate layers then dissolve, the diffusion from the cores increases and the release starts to decline from the granules which are largely already dissolved in the stomach. It is claimed that the dissolution takes place over a 12 h period (manufacturer's literature).

SLO-PHYLLIN

The manufacturers of Slo-Phyllin, "Lipha", were unable to provide a large amount of detail on their formulation. But the process relies on a starch lactulose granule initially in a similar way to Theo-Dur. In order to achieve the sustained release characteristics a retarding agent, almost certainly wax or a cellulose derivative, and theophylline are sprayed alternatively and at intervals in a precise procedure on to an inert matrix or granule of starch/cellulose. As the starch lactulose coated granule dissolves, theophylline is released. This occurs in both the stomach and the intestine. The retarding agent is not absorbed and may be visible in the stools of patients (manufacturer's literature).

GRADUMET (Abbot)

This consists of a plastic matrix, honeycombed by narrow passages which contain the active drug together with a water soluble channelling agent. As the tablet passes down the gastro-intestinal tract, the theophylline is leached out; this action is claimed to be independant of pH, viscosity, ion concentration, surface tension and gut motility. The spent matrix is excreted in the stools.

PRO-VENT

Pro-Vent is a multipellet capsule formulation. The manufacturers claim that the mechanism of action involves a dialysing membrane. Water passes into the pellet under an osmotic gradient, most probably caused by the sugar seed principle. The theophylline within the pellet dissolves to form a saturated solution and then diffuses out through the dialysing membrane. As the hydrated membrane expands, the pores through which theophylline diffusion takes place also become enlarged and the permeability of the system increases. This effect offsets the diminished concentration gradient which results as the theophylline content in the pellet falls. Each pellet is an individual sub-unit delivering its own amount of theophylline at its own controlled rate (manufacturer's literature).

METHODS OF THEOPHYLLINE ASSAY

Six methods are used for the analysis of theophylline in biological fluids. They differ in sensitivity, specificity, sample size, technical difficulty and turn around time.

U V SPECTORPHOTOMETRIC ASSAY

The method of Schack and Waxler (1949) has been used extensively and was the first method for determining theophylline in biological fluids. It has, however, several disadvantages. Blood sample volumes needed are relatively large and the plasma blanks are variable because the method also measures uric acid, xanthine and hypoxanthine (Ogilvie 1978). False high or low theophylline concentrations may occur in the presence of caffeine, theobromine, theophylline metabolites, paracetamol, frusemide, thiamin salicylates and warfarin (Banner et al 1977, Matheson et al 1977). Modification has been made to reduce interference but even the modified Schack and Waxler method has been reported to have a co-efficient of variation of 27% and a standard deviation of $\pm$ 4.2 (Hendeles et al 1980) when a spiked sample of 15 $\mu g\ ml^{-1}$ is used as an unknown sample.

The only paper of any significance to use the Schack and Waxler assay method was that of Welling et al (1975). This paper is often quoted in reviews establishing the effect of food on Tedral and the results are frequently extrapolated to other sustained release theophyllines.

GAS LIQUID CHROMATOGRAPHY

Several gas liquid chromatographic assays have been developed (Ogilvie 1978). They involve technically demanding extraction and derivitisation procedures. While most GLC methods are very specific and require samll sample size, the lengthy procedure and a high

potential for errors (CV 24.6%, Hendeles 1980), unless the analyst is very skilled, has meant that very few laboratories now use this method.

RADIO IMMUNOASSAY

This is a very specific accurate method of analysis requiring a small sample size but is expensive and slower than other immunoassay methods such as enzyme immunoassay. Due to more rapid assay methods now being available, it is not the assay method of choice for reporting laboratories (Hendeles et al 1980).

HIGH PRESSURE LIQUID CHROMATOGRAPHY

A large number of laboratories use various HPLC assays. Many different HPLC methods have been proposed (Ogilvie 1978, Hendeles et al 1978). Reverse phase is the most commonly used method. In most methods sample preparation is easy, and the method is accurate although there are reports of drugs taken in large doses showing interference (Hendeles 1980). An average assay is longer to perform than the enzyme immunoassay technique, but cheaper.

FLUORESCENT IMMUNOASSAY (AMES)

This variation of the antibody inhibition method uses a fluorescent marker instead of a radio marker. It is comparable with enzyme immunoassay for speed, reliability and accuracy and it is claimed to be considerably cheaper, but it has already been shown that caffeine interferes (Hendeles et al 1980).

HOMOGENOUS ENZYME IMMUNOASSAY

The homogenous enzyme immunoassay technique marketed by Syva (EMIT) was the first commercially available method using an antibody inhibition technique to quantify the concentration of theophylline in serum or plasma. The principal is that a drug is labelled with an enzyme, and when the enzyme labelled drug becomes bound to an

antibody to the drug, the activity of the enzyme is decreased. The drug in a sample competes with the enzyme labelled drug for the antibody, thereby decreasing the antibody induced inhibition of the enzyme. Enzyme activity correlates with the drug concentration in a sample and is measured by an absorbance change related to the enzyme's catalytic action on a substrate.

The method is rapid, specific, requires small sample size and can be easily automated. On a spiked 15 $\mu g\ ml^{-1}$ sample 97 reporting laboratories had a standard deviation of $\pm$ 1.8 and a co-efficient of variation of 11.3% (Hendeles et al 1980).

This is the assay method used for all the experiments in this thesis. In this author's hands the batch to batch co-efficient of variation ranged between 4.2% to 9.4% with a mean of 6.1% $\pm$ 1.96%. Although the manufacturers do not recommend measurement below 2 $\mu g\ ml^{-1}$ experiments in this thesis were accurately reproducible down to 1.0 $\mu g\ ml^{-1}$.

Of the various methods available, the EMIT method has advantages of speed, ease of operation, specificity and automation for dealing with large numbers of samples. In many of the study days reported in this thesis, up to one thousand assays were carried out in 24 h using an automated technique.

PROBLEMS ASSOCIATED WITH VOLUNTEER AND PATIENT STUDIES ON THEOPHYLLINE

Theophylline is a drug which demonstrates great inter and intra-subject variation. It presents difficulties in obtaining a suitable experimental population to conduct controlled studies. The literature reflects this ambiguity. In answer to the question; "can saliva be used as a reliable means to measure theophylline concentrations?", Galant et al (1977), Goldsworthy et al (1981), Jonkman et al (1981) and Koysooko et al (1974) have indicated that saliva is a good medium, whereas Boobis et al (1979), Munch et al (1981) and Sharma et al (1981) have all found saliva to be unreliable. Similarly conflicting evidence can be found with other aspects of theophylline therapy such as the effect of erythromycin on theophylline clearance etc. A large part of this variability in results between workers can, in many cases, be the result of too few subjects to provide adequate power to detect relevant differences and the over-reliance on significance testing. To detect small differences, larger subject studies need to be performed. With theophyline it would be valid to select a certain population such as fast metabolisers or smokers. In this thesis the effect of food on sustained release theophylline products has been investigated. The evidence that food does delay the rate of absorption has mainly been carried out by one worker, Pedersen, in a total of 16 children (Pedersen 1981 and Pedersen and Moeller-Petersen 1982) with one formulation, Nuelin SA. Yet these findings have been reproduced in standard text (Gibaldi 1982) and reviews (Hendeles and Weinberger 1983) to manufacture fact, that food (all food) delays the absorption of sustained release theophyllines (all formulations) in patients (children and adults).

The problem of obtaining sufficient number of either patients or volunteers is not inconsiderable. In this thesis, to obtain a total of 20 volunteers even with financial inducements in an academic environment, required a lot of persuasive power. The selection of a healthy population which is taking no-concurrent medication including the contraceptive pill, within narrow limits for age and weight, smoker or non-smoker and restricting diet before and during the study makes obtaining a reliable large experimental population difficult. Jusko et al (1979), Weinberger and Hendeles (1983) and Upton et al (1982) have, in part, overcome this by combining analysis to overcome the differences.

Statistical analysis itself can cause misinterpretation and increase the risk of false positive claims. A probability of 0.05 is dominant in many minds as a barrier beyond which a relationship becomes fact and not as it should be interpreted as a significant difference which is not coincidental. $P = 0.05$ means that a relationship between measurements has a probability of occurring by chance in 1 in 20 cases. When measuring a drug with such inter and intra-subject variability a probability of 1 in 20 certainly does not allow for factual conclusions. The other much quoted study on the effect of food on sustained release formulations of theophylline, Leeds et al (1982), found a significance of $P = 0.05$ for one formulation of Theo-Dur (Theo-Dur 100 mg) in six healthy non-obese male students for the effect of food on the rate of absorption at 2, 3 and 4 hours after administration of the drug. This does not establish the fact that food universally affects the rate of absorption from sustained release formulations but it is often quoted as an established fact. Statistical analysis of uncontrolled or poor quality data is not an adequate substitute for carefully designed studies in which the confounding variables of theophylline pharmacokinetics are controlled.

Diet is one factor that must be controlled. Caldwell et al (1977), Kappas et al (1976) and Thompson et al (1981) have demonstrated that the composition of food can affect the absorption and metabolism of theophylline. Many bioavailability studies on theophylline which have produced conflicting data have not taken the effect of food or it's composition into account. Some americans can apparently consume up to a gramme of caffeine a day by coffee consumption alone. Although fasting over night is stated (Mitenko and Ogilvie 1974) it is only in later studies that xanthine containing foods and beverages are mentioned as being excluded (Upton et al 1980). A lot of the early studies are still quoted as evidence for poor bioavailability of theophylline sustained release formulation, but the knowledge of theophylline pharmacokinetics was not developed to allow the investigators to design studies with sufficient accuracy.

Studies often fall into four categories regarding age, studies on children, Domson et al (1979), Ginchansky and Weinberger (1977), Pollock et al (1977) and much of Hendeles' work, studies on healthy volunteers, normally 18 - 40 years, Barrett et al (1981), Upton et al (1980) and thirdly studies on patients which can have a large range of ages 24 - 53 years (Dasta et al 1979), 26 - 70 years (Thompson et al 1983), 24 - 76 years (Butcher et al 1982) and some studies where no age range is given (Mitenko and Ogilvie 1974). If, in a study, one volunteer is elderly or young compared with the majority, it could skew the results. As Jusko et al (1979) demonstrated, theophylline clearance decreases with age. To obtain as similar a population as possible, narrow age ranges would be preferable.

If a standard dose of drug is being given, such as on 300 mg tablet, the weight of subjects can become important as the dose for a 50 kg woman is higher per kilogramme than a 95 kg man (58 - 112 kg, Fagerstrom and Heintz 1983; 48 - 93 kg, Jones et al 1980;

48 - 125 kg, Langaker et al 1984). The subsequent theophylline concentrations, C_{max} and AUC will be affected. It becomes difficult to interpret data when the dose per kg for one subject can be as much as three times greater than another subject with the same study.

How the drug is administered orally is often not cited. Welling et al (1975) and Pedersen (1984) have demonstrated that the volume of fluid taken with sustained release theophylline formulations can affects its absorption. Upton et al (1980) used 200 ml of water, Talseth (1981) and Spangler et al (1978) appear not to have given any fluid with the drug and Sharma et al (1981) gave an unspecified amount of water 2 hours after administration. Such are the problems of theophylline that even the posture of the subject can affect the plasma theophylline concentrations obtained. Warren (1983) has reported that higher concentrations of theophylline were obtained in upright subjects than those who were supine.

The differences between many of the earlier reports (Welling et al 1975, Mitenko and Ogilvie 1974, Jenne et al 1975, Kappas et al 1974) and the later investigations on theophylline are the assay methods available. All the afore mentioned key studies used the method of Schack and Waxler (1949). This assay has subsequently been shown to suffer interference from other drug including caffeine, theobromine and aspirin to give falsely high measurements of theophylline concentrations (Hendeles et al 1978). The results have to be reviewed in the light that some of the measurements may not, with more accurate methods of analysis now available, be comparable with results from 1977 onwards.

EXPERIMENTAL OBJECTIVES

Initially this thesis was concerned with the comparison of sustained release theophylline formulations related to the co-administration with food. Patients are more likely to cue dose administration to meal times than the fasting conditions so frequently used for experimental methods. Several workers, Pedersen (1981) and Leeds et al (1982) had conducted inconclusive experiments on the effects of food on the absorption of theophylline from sustained release formulations. To conduct comparative studies on the pharmacokinetic profiles of theophylline formulations with food to mimic a more realistic environment is important. In other comparative studies either food was not given with the formulation or was given at some period after the administration of the drug whilst the absorption of the drug was taking place, 2 hours (Domson et al 1979), 4 hours (Conard et al 1982) and 6 hours after administration (Barrett et al 1981).

Jonkman (1981) had shown that the in vitro release of theophylline from Nuelin SA was pH dependent and from Theo-Dur was pH independent. As Nuelin SA was the drug indicated by Pedersen (1981) and Pedersen and Moeller-Petersen (1982) to be affected by the co-administration of food, this may have been related to change in pH in vivo. Food delays gastric emptying and might expose a sustained release formulation designed for duodenal release to a more prolonged acid exposure. The question arose as to whether simple in vitro tests could be used to predict which formulation would be affected by longer exposure to acidic conditions in vivo as Jonkman (1981) and Crombeen and De Blaey (1983) had suggested. Therefore, in this thesis in vitro experiments have been designed to study the behaviour of several formulations to acidic and alkaline conditions and in vivo comparative volunteer studies have been performed, coadministering slow release preparations with food.

As single dose study results may not accurately reflect the effects of food at steady state. An experiment on Nuelin SA and Theo-Dur was conducted at steady state under fasting and non-fasting conditions. The data from single dose studies for these two drugs was projected by a method of superposition to steady state and compared with experimental results.

If the release of theophylline was not related to pH but just reduced gastric motility caused by the consumption of food, this might explain the reported variable effect of food and fluid on sustained release theophylline formulations (Welling et al 1975, Leeds et al 1982). Modification of gastric motility using metoclopramide and propantheline has already been demonstrated to affect the absorption of paracetamol (Nimmo et al 1973). Such modifications might affect the absorption of sustained release formulations and indicate the role of gastric motility in the release of drugs from such products. A study has therefore been designed in this thesis to elicit the effect of modification of gastric motility using metoclopramide and propantheline on sustained release theophylline formulations.

Studies were to be performed to observe whether co-administration of sustained release theophylline products with food might produce a flatter blood concentration time profile by delaying absorption. This would potentially allow such drugs to be given once daily. Uniphyllin has been marketed by Napp Laboratories for this purpose and it was of interest to study this once daily dosage form and compare it with a twice daily administered sustained release formulation also administered with food. Investigations to see if coadministration with food produced favourable effects were conducted. Similarly, it was desirable to study the effects of a slower rate of absorption in smokers, who demonstrate rapid clearance of theophylline. Reduction in the fluctuation of blood concentrations of theophylline might

result in better patient response by obtaining a more constant concentration time profile.

With the inconclusive nature of the reports of the effects of food on sustained release theophyllines this thesis would contribute to the evidence for assessing the significance to the patient of cueing the administration of sustained release formulations of theophylline with meal times.

METHODS

SELECTION OF SUBJECTS

All the experiments in this thesis were conducted with subject populations as similar as possible. All volunteers were healthy adults with a narrow age range taking no medication for any known disease, chronic or acute. No formal medical examination took place and no laboratory tests other than plasma or serum theophylline concentrations were measured. All volunteers were asked to fast overnight prior to commencing a study day and refrain from xanthine containing beverages. No check was carried out to see if this request was complied with, and it would be difficult to do so unless the volunteers were under supervision prior to the start of the experimental period. Starting the study days between 6.30 and 7.30 am by necessity often guaranteed compliance by default.

The period of overnight sleep is variable from one subject to another and in some cases short periods of sleep may have affected diurnal variation. On the whole, though, the pharmacokinetic characteristics of volunteers did not change dramatically from one study day to another, fast metabolisers remained fast and slow remained slow. In some of the larger experiments where up to 20 volunteers were required, recruitment was difficult especially when venepuncture was involved. In some experiments volunteers were excluded from the study due to overweight, drug therapy or disease state. Once recruited, the volunteers were co-operative and compliant, many were students of biology or pharmacy with an insight into compliance and adherence to experimental protocol.

BLOOD SAMPLING

All blood samples were taken via a 2 way or 3 way tap attached to a Venflon cannula inserted by a qualified medical practitioner.

Samples were immediately transferred to an appropriate container, centrifuged, plasma separated and normally assayed immediately. Timing and a constant supply of materials required for taking blood was vital. The blocking of cannulae on occasions resulted in missed samples but in only a few incidents did it necessitate withdrawal from the study. Medical advice was available throughout the study periods but again was very seldom required. Those occasions were when re-siting of cannula was needed or a volunteer felt unwell.

ADMINISTRATION OF THEOPHYLLINE FORMULATION

All drugs were taken either fasting or with food depending upon the study day with a measured amount of water according to a strict timing interval, to allow for the time to take blood samples. In all experiments diet during the study day was controlled, the same standard breakfast was used in all experiments and lunch was not eaten until 5 or 6 hours after dose administration. This was normally a light salad but varied in some experiments to a normal but standard hospital canteen meal, depending on the experiment being conducted. Evening meals and breakfast on the following days after dose administration were again from the hospital canteen but no control was sought over these meals apart from requesting abstinence from xanthine containing beverages.

ASSAY OF SAMPLES

All serum or plasma samples were assayed by enzyme immunoassay (EMIT). Normally the samples were separated or assayed immediately. If there was a delay in assaying the sample, the plasma was refrigerated over night and, in the case of saliva, frozen to allow for ease of pipetting. A standard was included at the beginning and end of each run of 60 samples and every batch of reagent had a new calibration graph, tested against standard concentration of theophylline.

The co-efficient of variation ranged from 4.2 to 9.4%. If any sample result was for any reason doubtful it was repeated until duplicate assays gave similar readings to $\pm$ 0.5 $\mu g\ ml^{-1}$.

MEASUREMENT OF PHARMACOKINETIC PARAMETERS

All pharmacokinetic calculations are based on a simple open one-compartment model. The rate of decay and elimination both assumed first order elimination and were calculated from the terminal part of the plasma concentration time curve where the absorption of theophylline from the sustained release formulation is assumed to be complete.

The mean of two duplicate assays was used for the determination of all results. The measurement of C_{max}, t_{max}, C_{min}, t_{min} were the maximum and minimum concentrations actually recorded and the sampling time respectively. The measurement of other pharmacokinetic parameters is explained in Appendices 1 to 3 and in the experimental test.

STATISTICAL ANALYSIS

Analysis of variance was the most frequently applied statistical analysis. This was carried out using the computer programmes at both Aston and Sheffield Universities. In some studies additional statistical interpretation was required.

C H A P T E R 1

THE COMPARATIVE PHARMACOKINETICS OF SUSTAINED RELEASE ORAL THEOPHYLLINE PREPARATIONS

INTRODUCTION

Much work has been done to develop sustained release formulations which give rise to minimal fluctuations in plasma concentration in the steady state. The ultimate goal should be to produce a solid dosage form from which constant (zero order) absorption of theophylline could be achieved over a 12 hour or 24 hour period to mimic an intravenous infusion situation.

When this study was conducted, six sustained release theophylline formulations were on the UK market recommended for 12 hourly administration. No direct comparison between the pharmacokinetic parameters of all six products had been made in the past. Spangler et al (1978) compared five sustained release products available on the American market of which two were also available in the UK. Hendeles et al (1984) in a review article, presented compiled data for twelve sustained release theophylline formualtions of which a number were on the UK market or have been marketed since 1982. Fagerstrom and Heintz (1983) compared three sustained release products on the Swedish market and a number of other authors compared formulations, one with another, normally using Theo-Dur as a standard comparison. [Conard et al (1982), Walker et al (1982), Upton et al (1980) amongst others].

None of these studies had been conducted with co-administration of the drug with food. Pedersen (1981) had demonstrated in children that co-administration of a theophylline sustained release tablet (Nuelin SA) and a light breakfast had prolonged t_{max}, reduced C_{max} and produced prolonged flatter plasma time profiles, a beneficial effect if sustained release products were ideally going to mimic an intravenous infusion. It was therefore decided to conduct a

study on the then current sustained release theophylline formulations available on the UK market to compare their pharmacokinetic parameters. At the same time as administration of the drug it was planned that a light breakfast would be eaten to determine the effect on C_{max} and t_{max}.

METHODS

Subjects were seven healthy, non-smoking male volunteers, aged between 23 and 37 years and weighing 68 to 76.5 kg. Informed consent was obtained and the study protocol was approved by the Central Birmingham Health District Research Committee. All subjects refrained from xanthine containing foods and drinks for 24 h before and 30 h following drug administration. Single oral doses of Theo-Dur (500 mg), Theograd (350 mg), Phyllocontin (650 mg aminophylline = 520 mg theophylline), Nuelin SA (500 mg), Rona-Slophyllin (500 mg) and Theocontin (400 mg) were given at least seven days apart in random order. Products were supplied from a single batch as whole tablets or capsules.

The dose was swallowed with 180 ml of water immediately following a standard breakfast (cereal, toast, marmalade and milk; 17 g protein, 27 g fat and 76 g carbohydrate). At four hours post-dose, the subjects ate a standard salad lunch (17 g protein, 19 g fat and 51 g carbohydrate).

Blood samples were taken either via an indwelling cannula or by venepuncture, immediately before dosing and at 2, 3, 4, 5, 6, 8, 11, 24 and 30 h. Plasma was assayed for theophylline by enzyme immunoassay (EMIT, Syva, UK). The between batch co-efficient of variation was 9.4% and the lower limit of measurement was 1 $\mu g\ ml^{-1}$. The pharmacokinetic parameters, C_{max}, t_{max}, elimination half life $t_{\frac{1}{2}}$ and decay constant k_d were calculated graphically. The area under the plasma concentration time curve (AUC_{0-30}) was calculated by the trapezoidal rule and $AUC_{30-\infty}$ was determined by dividing the final concentration by the decay rate constant. The rates of absorption k_A (first order) and k_o (zero order) were calculated using the method of Wagner and Nelson (1964). Statistical analysis was performed by one way analysis of variance.

RESULTS

The results are summarised in table 2 and figure 1. There were no statistically significant differences between the products in any of the parameter measured. Using a linear fit (correlation co-efficient) of the plasma concentration data, absorption equally fitted both first and zero order models. The zero order absorption rate constants and the first order absorption rate constants are presented in tables 3, 4 and 5.

C_{max} and AUC values for Theocontin and Theograd at the dose administered were lower than the corresponding values for the other four products. However, when the AUC was adjusted to a standard 500 mg dose, the values for all preparations were similar. The highest C_{max} associated with the least t_{max} for Rona-Slophpyllin and Phyllocontin. The mean t_{max} ranged from 7.3 to 10 h, the highest value being found for Theo-Dur. The decay half life of Nuelin SA was longer than that of the other products and it also had the highest standard error of the mean. All products produced a plasma concentration at 11 h which was greater than 80% of C_{max}.

Volunteer 2 produced erratic plasma concentrations but these were found throughout the six products tested and therefore were included in the results. Volunteer 5 withdrew from the study and the data was not included therefore, all data was based on the results of the remaining six volunteers.

Figure 2 shows the superposition projection (Gibaldi 1982) of the mean plama theophylline concentrations following a single dose (500 mg) of Nuelin SA and Theo-Dur to steady state in the six volunteers.

Table 2

COMPARISON OF MEAN ($\pm$ SEM) DATA FOR SIX SUSTAINED RELEASE PREPARATIONS OF THEOPHYLLINE

Preparation	C_{max} ($\mu g ml^{-1}$)	t_{max} (h)	AUC_{0-30} ($\mu g ml^{-1} h$)	$AUC_{0-\infty}$ ($\mu g ml^{-1} h$)	$AUC_{0-\infty}$ (Adjusted to 500 mg dose)	kd* (h^{-1})	$t_{\frac{1}{2}}$ (h)	% of C_{max} at 11 h
Nuelin SA	7.71 ($\pm$ 0.52)	8.8	134.4 ($\pm$ 10.8)	173.4 ($\pm$ 10.0)	173.4	0.06	12.3 ($\pm$ 2.1)	91.4
Theo-Dur	8.53 ($\pm$ 0.48)	10.0	144.8 ($\pm$ 12.9)	175.4 ($\pm$ 19.5)	175.4	0.08	8.9 ($\pm$ 0.8)	95.9
Rona-Slophyllin	9.20 ($\pm$ 0.37	7.3	143.3 ($\pm$ 7.7)	152.2 ($\pm$ 10.6)	152.2	0.13	6.0 ($\pm$ 0.9)	80.2
Phyllocontin	9.10 ($\pm$ 0.71)	8.0	148.0 ($\pm$ 16.7)	160.3 ($\pm$ 21.9)	153.9	0.13	6.3 ($\pm$ 0.9)	80.2
Theocontin	6.49 ($\pm$ 0.49)	9.0	103.5 ($\pm$ 5.1)	119.0 ($\pm$ 6.3)	148.8	0.11	8.5 ($\pm$ 2.2)	88.1
Theograd	6.63 ($\pm$ 1.07)	8.7	105.6 ($\pm$ 21.2)	112.5 ($\pm$ 24.9)	160.7	0.12	6.5 ($\pm$ 0.8)	81.2

* kd is the decay constant and is preferred to the term 'elimination rate constant' as drug absorption from slow-release preparations may be incomplete during the elimination phase.

Table 3

LINEAR FIT (CORRELATION COEFFICIENT) OF PLASMA LEVEL DATA TO ZERO AND FIRST ORDER ABSORPTION MODELS

Subject	Correlation Coefficient											
	NUELIN SA		THEO-DUR		THEOGRAD		THEOCONTIN		RONA-SLOPHYLLIN		PHYLLOCONTIN	
	Zero Order	First Order	Zero Order	First Order	Zero Order	First Order	Zero Order	First Order	Zero Order	First Order	Zero Order	First Order
1	0.9927	0.9502	0.9782	0.9541	0.9806	0.9725	0.9961	0.9774	0.9839	0.9912	0.9955	0.9799
2	0.9848	0.9903	0.9647	0.9697	0.9799	0.9955	0.9656	0.9519	0.9786	0.9754	0.9903	0.9686
3	0.9783	0.9810	0.9736	0.9876	0.9679	0.9886	0.9803	0.9523	0.9954	0.9615	0.9748	0.9905
4	-	-	0.9853	0.9532	0.9420	0.9982	0.9871	0.9763	0.9896	0.9855	0.9782	0.9480
6	0.9768	0.9612	0.9909	0.9663	0.9889	0.9955	0.9972	0.9854	0.9883	0.9936	0.9972	0.9893
7	0.9748	0.9811	0.9940	0.9641	0.9753	0.9974	0.9752	0.9429	0.9900	0.9814	0.9866	0.9544

Table 4

ZERO ORDER ABSORPTION RATE CONSTANTS (ko, h^{-1})

Subject	NUELIN SR	THEO-DUR	THEOGRAD	THEOCONTIN	RONA-SLOPHYLLIN	PHYLLOCONTIN
1	8.48	9.61	12.1	16.4	10.6	17.6
2	9.20	9.31	10.6	7.31	9.61	14.0
3	14.60	8.71	10.3	8.88	9.31	10.5
4	-	11.9	7.64	8.80	11.3	8.96
6	14.5	9.52	12.2	10.1	10.1	11.9
7	8.0	9.94	10.0	9.57	10.6	14.1

Table 5

FIRST ORDER ABSORPTION RATE CONSTANTS (ka, h^{-1})

Subject	NUELIN SA	THEO-DUR	THEOGRAD	THEOCONTIN	RONA-SLOPHYLLIN	PHYLLOCONTIN
1	0.248	0.327	0.213	0.256	0.360	0.228
2	0.206	0.352	0.228	0.106	0.387	0.170
3	0.266	0.209	0.294	0.280	0.209	0.189
4	no data	0.278	0.188	0.133	0.124	0.196
6	0.270	0.139	0.204	0.164	0.192	0.157
7	0.112	0.146	0.119	0.137	0.222	0.256

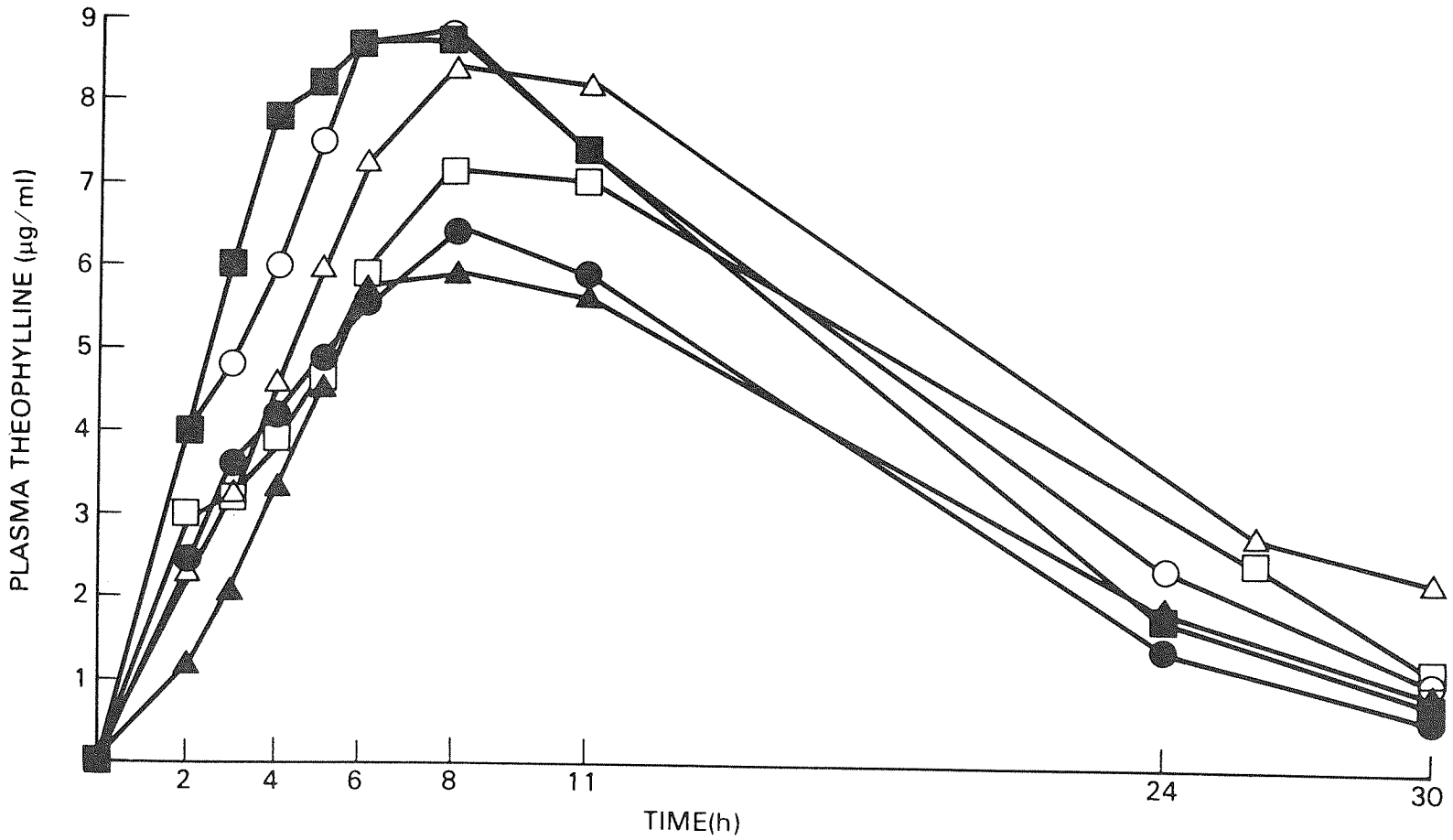


Fig. 1. Mean plasma theophylline concentrations in six healthy volunteers after a single oral dose of Nuelin-SA, 500 mg (□); Theodur, 500 mg (△); Rona-Slophyllin, 500 mg (■); Phyllocontin, 520 mg (○); Theocontin, 400 mg (▲) and Theograd, 350 mg (●).

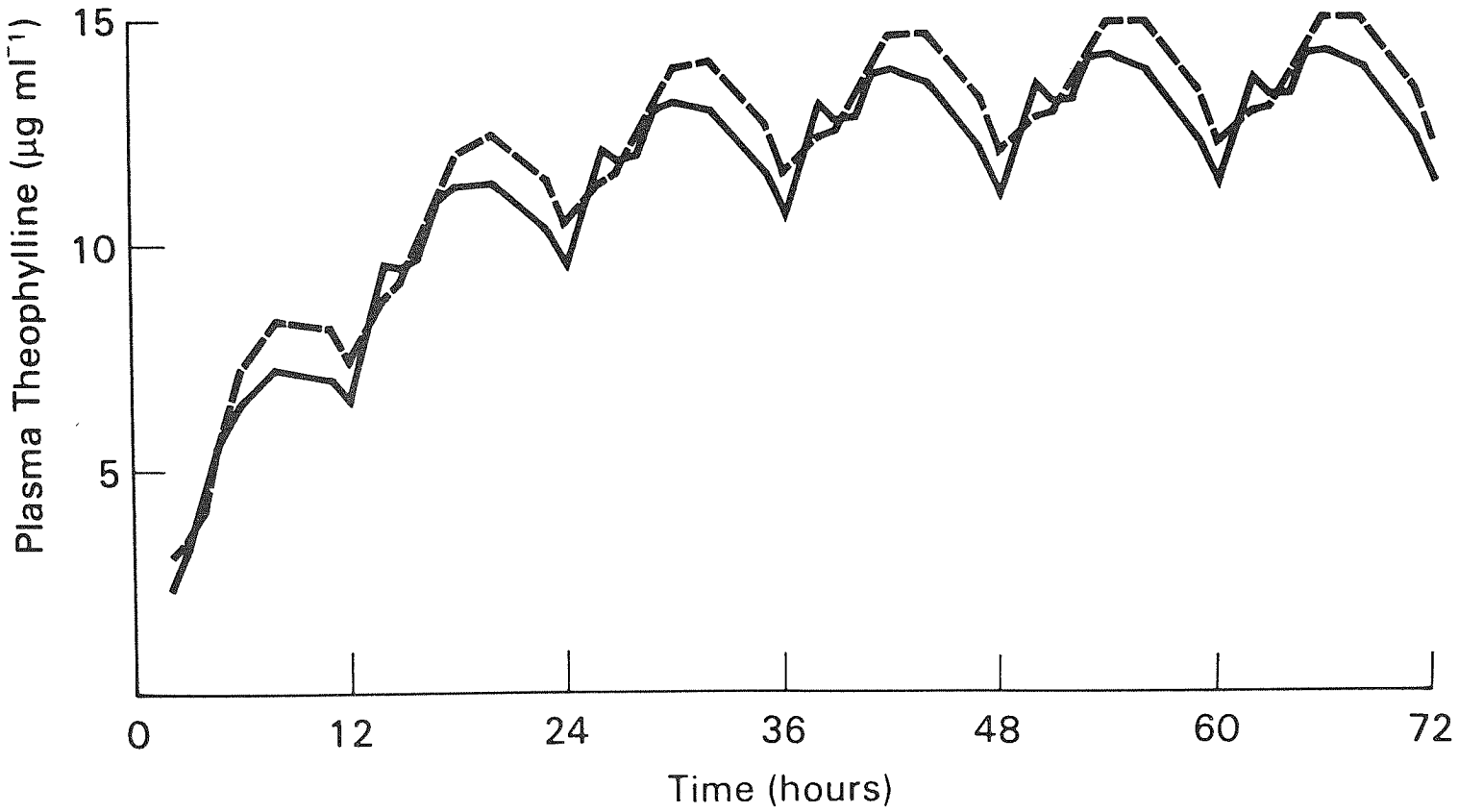


Figure 2. Superposition projection of mean plasma theophylline concentrations following single doses (500 mg) of Nuelin SA (continuous line) and Theo—Dur (broken line) to steady state in 6 healthy volunteers.

DISCUSSION

No statistical differences in any of the parameters measured were seen between the sustained release theophylline formulations examined. These findings are similar to those of Sharma et al (1981), who carried out a single dose comparative study with Theograd, Theo-Dur, Theolair SR (Nuelin SA) and Rona-Slophyllin and concluded that "there is little to choose between the preparations in maintaining plasma levels over 12 hours".

In this study the sustained release preparations did partition into two distinct groups, Nuelin SA and Theo-Dur in one group and Rona-Slophyllin, Phyllocontin, Theocontin and Theograd in the other. Both Nuelin and Theo-Dur had longer rates of decay, k_d, larger $AUC_{0-\infty}$, higher half lives and increased t_{max} when compared with other sustained release products. In most studies comparing Theo-Dur with other sustained release preparations, it has been shown that absorption of this formulation was either close to zero order [Spangler et al (1978), Fagerstrom and Heintz (1983), Sharma et al (1981), Walker et al (1982)] or was no different from the other formulations with which it was compared [Domson et al (1979), Langaker et al (1981)]. Although not statistically significant in the present study, Theo-Dur correlated to zero order (table 4) closer than any other preparation. In common with other studies, Theo-Dur was shown to have the longest t_{max}. However, in chronic dosing a difference of this degree between the other products does not appear to be clinically important. This can be illustrated using figure 2, which is a twice daily multiple dose computer simulation using the manually generated absorption and elimination rate constants derived in this study. At steady state, the t_{max} for Theo-Dur still remains longer than for Nuelin SA but is of no clinical importance. The peak to trough variation is less than 3.0 $\mu g\ ml^{-1}$ for both products.

Walker et al (1982) compared Theo-Dur with Phyllocontin in fasting volunteers. Using a single dose, they demonstrated a significant difference in t_{max} between the two formulations and computer simulation of single dose data to steady state showed no difference in peak to trough variation or C_{max} between the products at projected steady state levels. Certainly, single dose studies are useful for obtaining basic pharmacokinetic parameters but for comparisons between products with clinical implications, experimentation at steady state must also be conducted. At steady state the differences seen in single dose studies become less dramatic. Hendeles (1984) is in favour of single dose studies using computer predictions to predict steady state serum concentrations as a practical and inexpensive way of comparing large numbers of sustained release products. The problem with this approach is that the pharmacokinetic parameters used are assumed to be independent of population and as already shown by Dederich et al (1981) and Bell et al (1980) amongst others, the pharmacokinetic parameters can vary widely amongst the general population as opposed to a selected population of healthy volunteers. Even in controlled studies on theophylline the range of reported data is large. The bioavailability for Slophyllin has been reported between 75.0% (Spangler et al 1978) and 111.0% (Weinberger et al 1978) using single dose studies. At steady state other factors such as diurnal variation, gastric motility and diet tend to become less influential.

The half life of Nuelin SA in this study was longer than any of the other products tested, 12.3 h. In theory, with a 12 h dosing interval the peak to trough variation should be less with Nuelin SA than with the other formulations. When projected by computer simulation to steady state, however, this is not apparent (figure 2). Only Conard et al (1982) has reported a half life for Nuelin SA of

this magnitude, 10.7 h in fasting adults. In Conard's (1982) study this half life was twice as great as that reported for Slo-phyllin, and concurs with the present study. Very few studies have measured half lives of Nuelin. Sips et al (1984) measured a half life of 6 h for a new 300 mg Nuelin preparation.

Apart from Nuelin SA most of the reported half lives in the literature are longer for the sustained release products than in this study. Sharma et al (1981) reported a value for Theograd of 12 h, Theo-Dur 10.6 h, Nuelin SA 250 mg, 10.6 h and Rona-Slophyllin, 7.1 h. Jones (1979) gave Phyllocontin a half life of 9.16 h in asthmatic patients and similarly McDevitt et al (1979) reported 10.3 h for Phyllocontin. In the study by Sharma et al (1981) the half life was calculated using the apparent elimination rate constant from plasma concentration up to 24 h. It is possible that this simple method for calculating elimination rate constants in sustained release products is liable to error as in the earlier part of the elimination phase of the plasma concentration time plot drug could still be absorbed. In this study the last plasma concentration measurement was taken somewhat later, at 30 h, and only the later plasma concentration taken to calculate the rate of decay to avoid this problem.

The t_{max}s reported by Sharma et al (1981) are less than those found in this study and this may be explained by a delay caused by food (Pedersen 1981). No food or water was taken with the drugs in the Sharma study until 2 h after dosing and the amounts were not controlled. Similarly reported values for Phyllocontin of a t_{max} of 4.4 h (Jones 1979) and 3.9 h (McDevitt et al 1979) did not take food into consideration. A number of investigators have reported the t_{max} of Nuelin SA without food to be between 3.6 and 4.7 h (Langaker et al 1981, Domson et al 1979). Similarly for Theo-Dur a t_{max} of 3.6 h (Langaker et al 1981) and 10 h (Domson et al 1979) have been reported.

Only Leeds et al (1982) found a prolongation of t_{max} for Theo-Dur by 2 h in six adult volunteers. If the values of t_{max} reported in the literature are used, the co-administration of food appears to have increased t_{max} in this study for Nuelin SA and Theo-Dur.

When corrected for a 500 mg dose, all of the products have similar C_{max} and, as Sharma et al (1981) concluded, given at 12 h intervals all would be capable of producing adequate theophylline concentrations. The design of the formulation does not appear to matter, whether it is a multipellet preparation (Rona-Sl.phyllin), a matrix (Theo-Dur, Nuelin and Theograd) or a "continus" (Phyllocontin and Theocontin). The effect of food to reduce C_{max} can only be extrapolated from other data. If this is valid, for equivalent doses of Nuelin SA and Rona-Slophyllin the C_{max} from the Sharma et al (1981) study would have been 9.8 $\mu g\ ml^{-1}$ and 10.0 $\mu g\ ml^{-1}$ respectively. The data for Theograd at the same dosage, 350 mg does differ, Sharma et al (1981) obtaining a very low C_{max} of 3.9 $\mu g\ ml^{-1}$ compared with 6.6 $\mu g\ ml^{-1}$ in this study. The C_{max} of Theo-Dur seems to be consistent with those reported by a number of workers, Talseth et al (1981), 8.6 $\mu g\ ml^{-1}$, Leeds et al (1982) 7.8 $\mu g\ ml^{-1}$ with food. Similarly, values for Nuelin SA are compatible with the reports of Mitchell et al (1980), C_{max} 8.0 $\mu g\ ml^{-1}$ with food and with the work reported by Pedersen 1981, 10.2 $\mu g\ ml^{-1}$ and the later work by Pedersen and Moeller-Petersen (1982) of 8.7 and 9.8 $\mu g\ ml^{-1}$ in children with food. The reported C_{max} for Phyllocontin for a 450 mg dose is 10.05 $\mu g\ ml^{-1}$ in fasting patients (Jones 1979). If it is valid to extrapolate reported data to this study it would appear that the co-administration of food may have caused a small reduction in C_{max} but this is unlikely to be either statistically or clinically significant.

The bioavailability of the six products compared as measured by the $AUC_{0-\infty}$ was not statistically significant between products.

In comparison with other studies where food was not co-administered, no product seems to be affected by food (Sharma et al 1981). No one product was affected to any extent although the release of theophylline from Nuelin SA has been demonstrated to be pH dependent *in vitro* by Jonkman et al (1982) and could be expected to be affected by co-administration of food. Concurrent *in vivo* work by Jonkman et al (1982) showed the 250 mg Nuelin formulation to have a biphasic absorption concentration time profile but this was not seen in this experiment.

CONCLUSION

This study has shown that for the sustained release theophylline preparations on the UK market, no significant differences occur in the pharmacokinetic parameters measured. All products, given in adequate doses with food, would result in clinically effective plasma concentrations of theophylline for a substantial part of the dosing interval, although preparations with a shorter half life such as Phyllocontin would produce greater peak to trough variation.

CHAPTER 2

DISSOLUTION TESTING OF SUSTAINED RELEASE THEOPHYLLINE FORMULATIONS ON THE UK MARKET

INTRODUCTION

The British Pharmacopoeia applies the dissolution test to those drugs which have demonstrated formulation problems in the past. These problems can affect the solution of the drug, eg, digoxin, warfarin, oxytetracycline. No such standard has, however, been applied to sustained release products in any official pharmacopoeia, yet it has been demonstrated by a number of authors (Mitenko and Ogilvie 1974, Spangler et al 1978 and Weinberger et al 1978) that enteric coated and sustained release formulations of theophylline have different absorption profiles. Depending upon the formulation characteristics, the release of theophylline from various dosage forms can differ substantially. Weinberger et al 1981 demonstrated that formulation and dosing interval were important considerations if fluctuations of serum theophylline concentrations in children with chronic asthma were to be avoided. Thus in vitro dissolution testing of sustained release theophylline preparations may provide useful information before proceeding to studies in volunteers, in vivo.

Jonkman et al 1981, using a modified disintegration test apparatus performed a dissolution experiment on Theolair Retard (Nuelin SA) and Theo-Dur. By altering the pH of the dissolution media from 0·1 M Hydrochloric acid pH 1 to phosphate buffer pH 6.8 he demonstrated that the release of theophylline from Nuelin SA was far more rapid at pH 6.8 than at pH 1.0. The same author repeated the dissolution experiment in 1982 (Jonkman et al 1982) using the USP dissolution model apparatus 2 (paddle) and apparatus 3 (oscillating tube) on the same theophylline formulations and correlated this in vitro data with in vivo data. He found the best correlation to be between the apparatus 2 (paddle) method of dissolution and the in vivo data. Later Simons et al 1983 used the USP rotating-basket

dissolution apparatus, which had now become the pharmacopoeia recommended apparatus, to compare the dissolution profiles of eight sustained release theophylline formulations available on the american market (Aerolate 65 mg and 130 mg capsules, Slo-phyllin 125 mg and 250 mg gyrocaps, Theo-Dur 100 mg, 200 mg and 300 mg tablets and Theo-lair (Nuelin SA) 250 mg and 300 mg tablets). He used the United States pharmacopoeia simulated gastric and intestinal fluid at pH 1.2 and 7.48 respectively. Simons found that all products tested displayed sustained release characteristics and that different strengths of the same formulation displayed different dissolution rates. A substantial inter-product variability in dissolution rate was demonstrated. Once again Simons commented that theophylline sustained release formulations cannot be considered as a single entity and can provide very different release characteristics.

It was therefore decided to conduct an experiment similar to the Simons 1983 study on the sustained-release theophylline preparations available on the UK market to see if analogous problems occur with these formulations as with the american products and to see if there was any correlation between the dissolution rate profiles for these products and the absorption phase of the plasma concentration-time profiles obtained in the previous experiment (Chapter 1).

METHOD

Single batches of Nuelin SA 250 mg, Phyllocontin 225 mg, Rona-Slophyllin 250 mg, Theocontin 250 mg, Theograd 350 mg, Theo-Dur 300 mg and Theo-Dur 200 mg were evaluated using the dissolution test for tablets and capsules. Five replicate tests were carried out on each dosage form in simulated gastric fluid and simulated intestinal fluid. The simulated gastric fluid was prepared by dissolving 2 g of NaCl and 3.2 g pepsin in 7 ml of concentrated HCl with sufficient water to make 1000 ml. The pH of the solution was 1.2. Simulated intestinal fluid was prepared by dissolving 6.8 g of KH_2PO_4 in 250 ml of water then adding 190 ml of 0.2 M NaOH and 400 ml of water. The solution was mixed, 10 g pancreatin was added and the pH adjusted to pH 7.48 with 0.2 M NaOH and made up to 1000 ml with distilled water.

Each tablet was placed into the apparatus when the temperature of the dissolution medium had reached 37 °C. 5 ml samples were withdrawn from the midpoint of the rotating basket between 33 - 39 mm from the bottom of the flat bottomed glass flask holding the dissolution medium at 0, 1, 2, 3, 4, 5, 6, 8, 12, 16, 20 and 24 hours after addition of the dosage form. Samples were filtered immediately through a 0.45 micron millipore filter and the volume replaced by pre-heated fresh dissolution medium. The quantitative determination of theophylline was determined spectrophotometrically by the method of Yound and Shelver (1976).

$$\text{Calculation of theophylline concentration } (\mu g\ ml^{-1}) = \frac{(A - B)}{C}$$

Where A = Absorbance of sample at 275 mm minus absorbance of sample at 310 mm

B = Absorbance of sample at 275 mm minus absorbance, of blank, 310 mm

C = Slope of standard calibration curve

The standard curve was prepared from stock solutions made by dissolving 50 mg of anhydrous theophylline in 500 ml buffer solutions of pH 7 and 9. The stock solution was then diluted with each buffer to obtain concentrations of 10, 20, 40, 50 and 60 $\mu g\ ml^{-1}$.

The basket was rotated at a constant 100 rpm throughout the study periods.

RESULTS

Both calibration curves of theophylline in simulated gastic and intestinal fluid were linear over the concentrations measured, 0 - 30 mg l^{-1}. The percentage drug dissolved against time is summarised in table 6 and graphically in figures 3 to 6.

SIMULATED GASTRIC FLUID

All products tested released between 10 and 25% theophylline in the first hour. The release of theophylline from Theograd was the most rapid, 50% being dissolved in 2.5 h and 100% in 7.5 h. Nuelin SA and Phyllocontin had similar profiles (see figure 3), both producing the lowest percentage dissolved at 24 h, 78.2% for Nuelin and 69.3% for Phyllocontin. Theocontin and Phyllocontin both having the same continus release mechanism, produced almost identical dissolution profiles, up to 8 h. After that time, the rate of dissolution for Theocontin increased, with 88% being dissolved after 24 h compared with 69% for Phyllocontin. Similarly, 61.3% and 63.7% of the 2 dosage forms of Theo-Dur were dissolved (300 mg and 200 mg formulations respectively) at 6 h but then the 300 mg formulation had a slightly increased rate until 16 h when 96.4% and 97.9% of theophylline was dissolved for the 300 mg and 200 mg formulations respectively. Rona-Slophyllin released 95% theophylline over 16 h then remained constant at 95% up to 24 h.

SIMULATED INTESTINAL FLUID

Nuelin SA and Rona-Slophyllin had rapid dissolution in simulated intestinal fluid. After 2 h 57% and 80% of theophylline had been released from each formulation respectively. In intestinal fluid the formulation from the same manufacturers of Theo-Dur 200 mg and 300 mg tablets, Theocontin and Phyllocontin had different dissolution profiles. At 2 h Theo-Dur 200 mg and 300 mg tablets were almost identical at 27.3% and 26.9% respectively, but thereafter

the release of theophylline from the 200 mg formulation was much faster, 95% of theophylline being dissolved after nearly 6 h compared with 12 h for the 300 mg formulation. Theocontin's release of theophylline was more prolonged than Phyllocontin. After 6 h twice as much theophylline had been dissolved from Phyllocontin, 69% compared with Theocontin's 33.2%. Theograd had, again, a rapid dissolution profile, 63.7% of theophylline being dissolved in 6 h.

All products tested showed sustained release characteristics in both simulated gastric and intestinal fluid.

Table 6

COMPARISON OF DISSOLUTION DATA FROM SIMULATED GASTRIC AND INTESTINAL FLUID

PERCENTAGE OF THEOPHYLLINE DISSOLVED

TIME	NUELIN SA 250 mg		PHYLLOCONTIN 225 mg (Aminophylline)		RONA-SLOPHYLLIN 250 mg		THEOCONTIN 200 mg		THEOGRAD 350 mg		THEO-DUR 300 mg		THEO-DUR 200 mg	
HOURS	GF	IF	GF	IF	GF	IF	GF	IF	GF	IF	GF	IF	GF	IF
0	3.1	1.2	0.0	2.0	0.0	0.3	0.0	1.1	2.3	0.4	0.9	1.5	0.1	0.9
1	14.8	24.4	13.0	29.5	21.7	46.2	11.4	7.6	20.8	3.7	17.3	14.0	13.2	6.7
2	26.3	57.0	22.5	42.3	34.4	80.0	21.5	15.3	41.2	17.0	27.5	27.3	21.2	26.9
3	33.8	82.0	28.1	52.0	43.6	93.2	26.9	21.4	62.6	37.6	32.2	34.9	32.1	48.3
4	38.6	92.5	33.8	58.4	49.7	94.0	32.9	26.5	74.9	57.0	40.1	45.5	44.0	64.2
5	42.8	99.5	39.0	64.8	54.8	94.4	38.3	30.1	85.4	82.5	52.7	52.1	54.2	82.0
6	50.4	103.3	43.5	69.0	61.8	94.4	43.0	33.2	94.3	93.7	61.3	56.7	63.7	97.5
8	52.2	102.7	49.3	76.0	66.5	95.7	50.5	39.6	101.1	107.3	72.3	75.3	86.4	103.0
12	59.2	103.1	56.4	79.0	84.8	97.0	61.5	47.5	106.6	110.1	85.4	94.7	96.5	100.6
16	68.8	-	60.9	89.2	94.8	100.8	81.0	61.0	108.0	106.2	96.4	99.0	97.9	101.5
20	70.4	-	68.0	89.2	94.0	100.1	87.7	68.9	108.0	-	99.1	101.8	101.4	-
24	78.2	-	69.3	-	94.6	-	88.0	74.5	108.0	-	105.9	103.0	103.8	-

GF = Simulated gastric fluid

IF = Simulated intestinal fluid

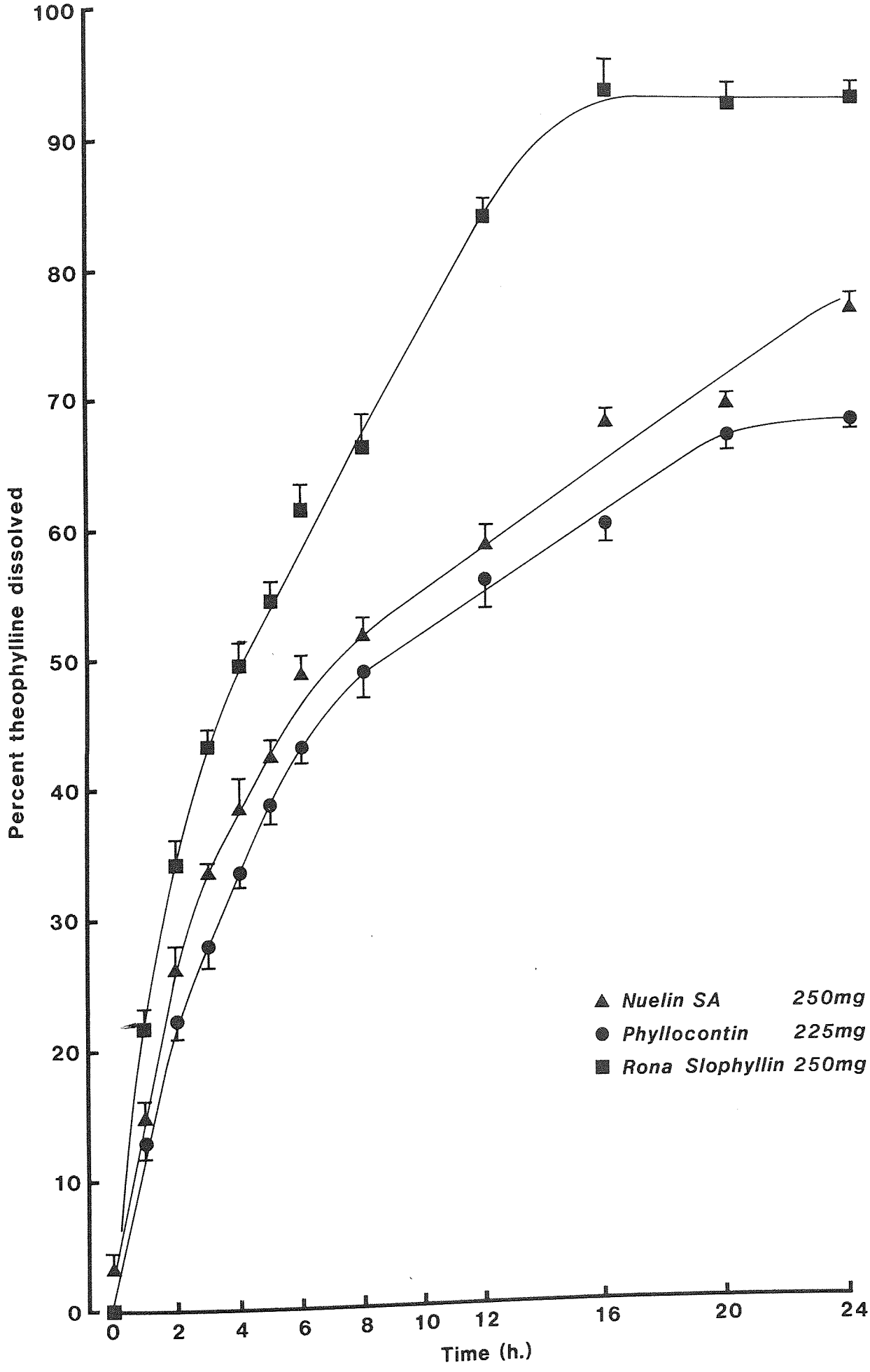


Figure 3. PERCENT THEOPHYLLINE DISSOLVED IN SIMULATED GASTRIC FLUID VERSUS TIME. Results are mean ± S.D.

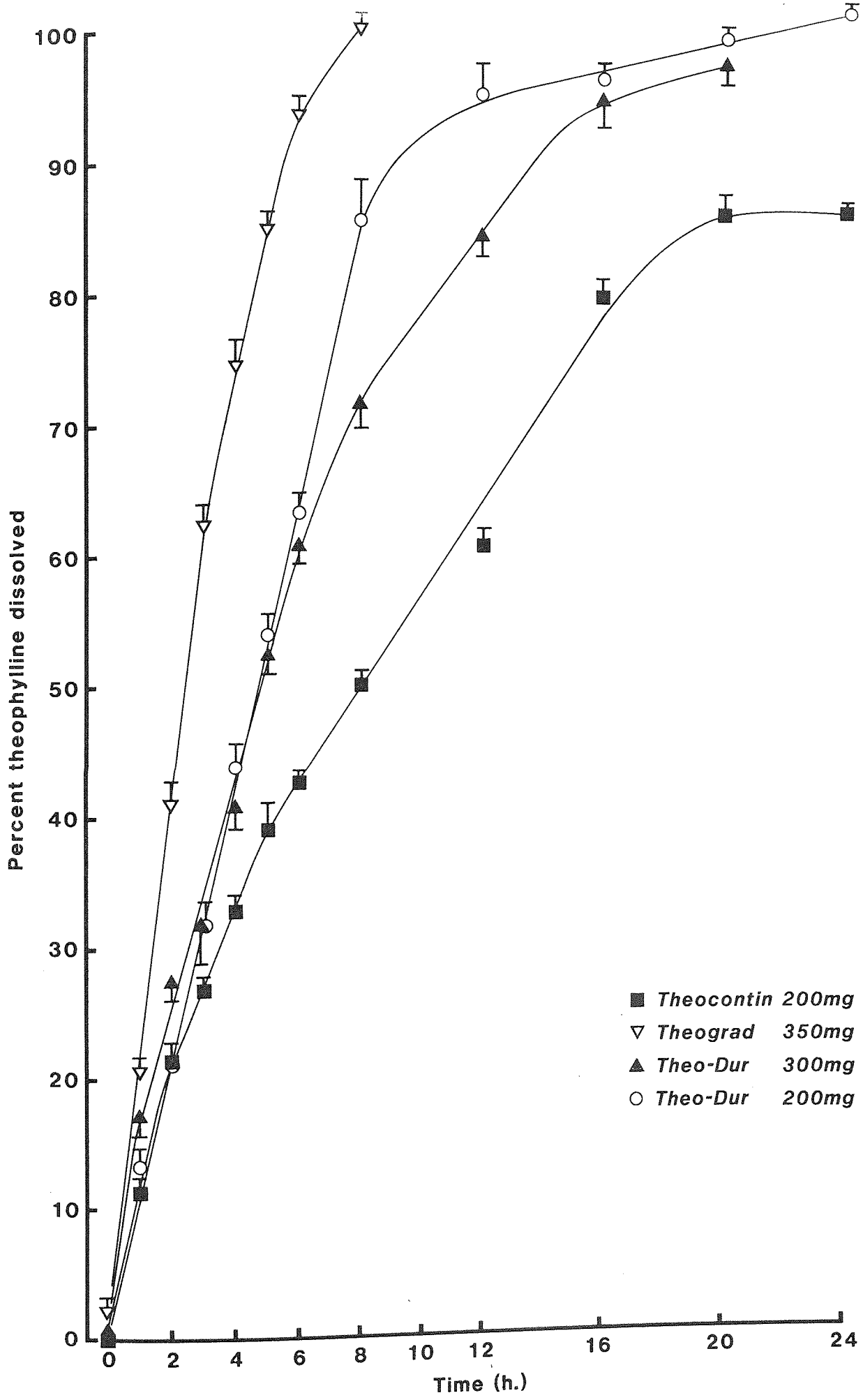


Figure 4. PERCENT THEOPHYLLINE DISSOLVED IN SIMULATED GASTRIC FLUID VERSUS TIME. Results are mean ± S.D.

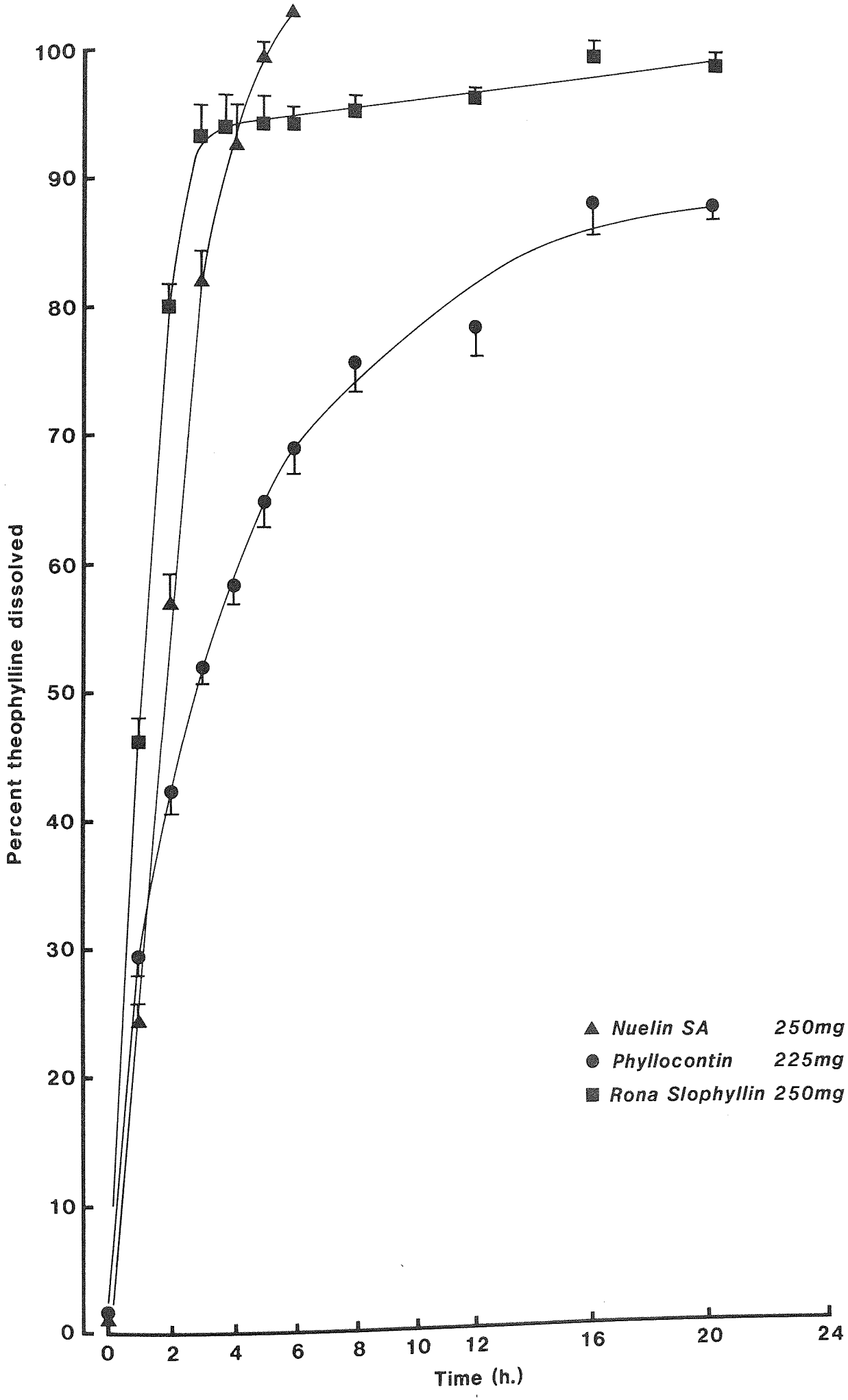


Figure 5. PERCENT THEOPHYLLINE DISSOLVED IN SIMULATED INTESTINAL FLUID VERSUS TIME. Results are mean ± S.D.

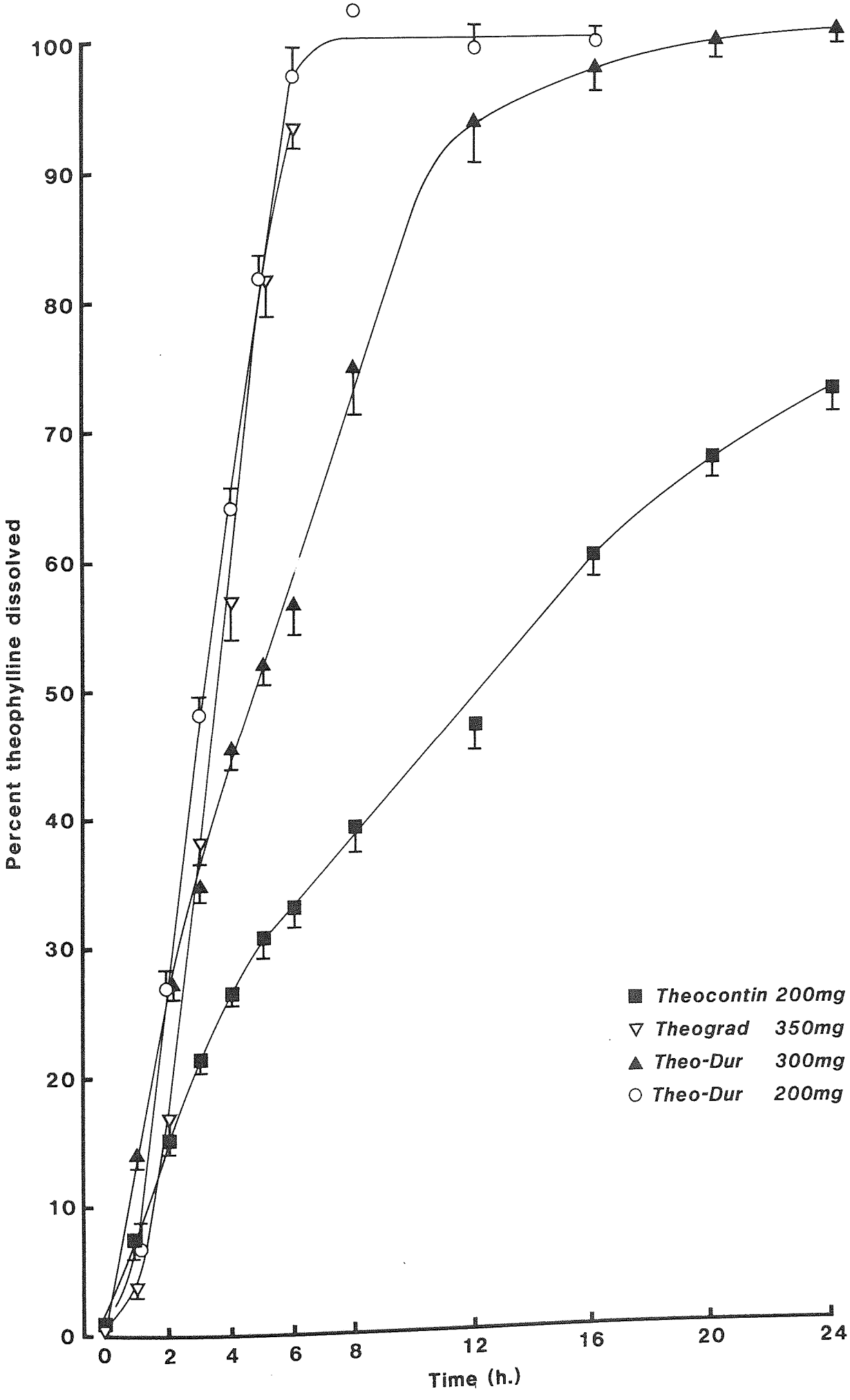


Figure 6. PERCENT THEOPHYLLINE DISSOLVED IN SIMULATED INTESTINAL FLUID VERSUS TIME. Results are mean ± S.D.

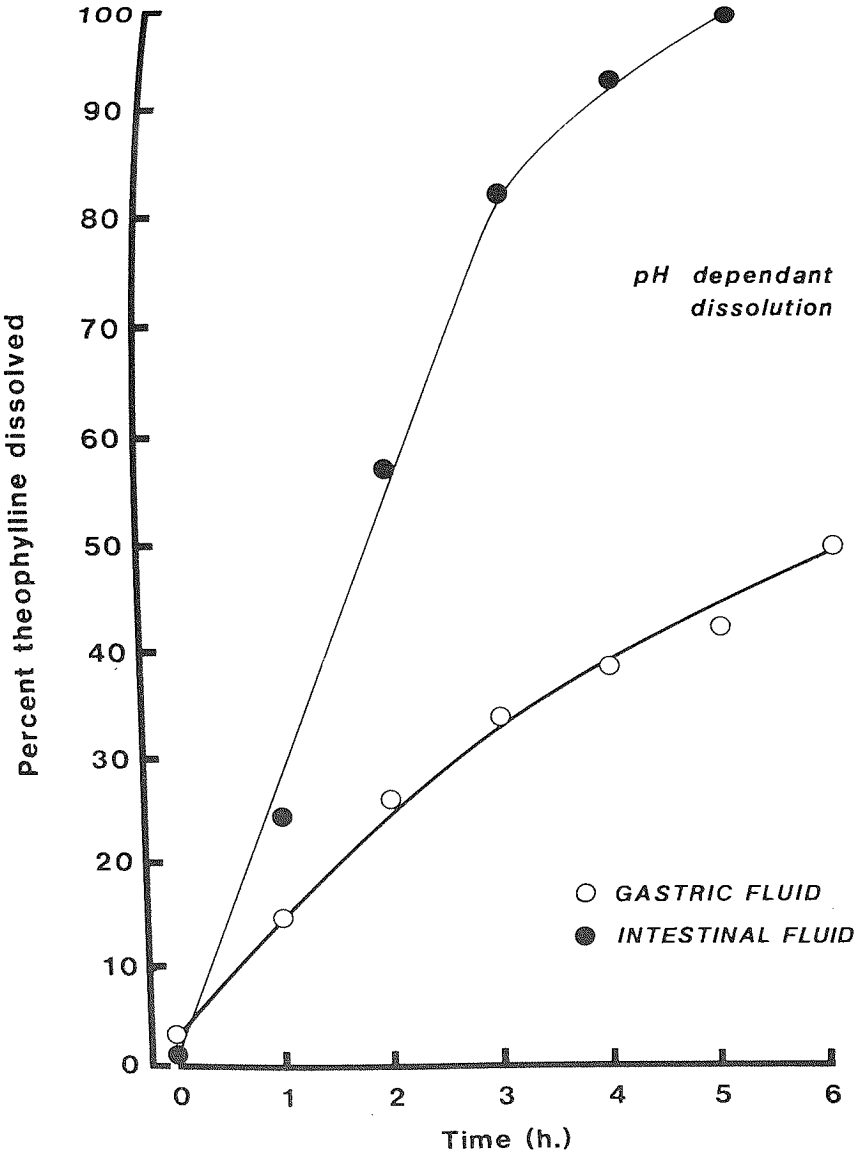


Figure 7. COMPARISON OF NUELIN SA DISSOLUTION IN SIMULATED GASTRIC AND INTESTINAL FLUIDS

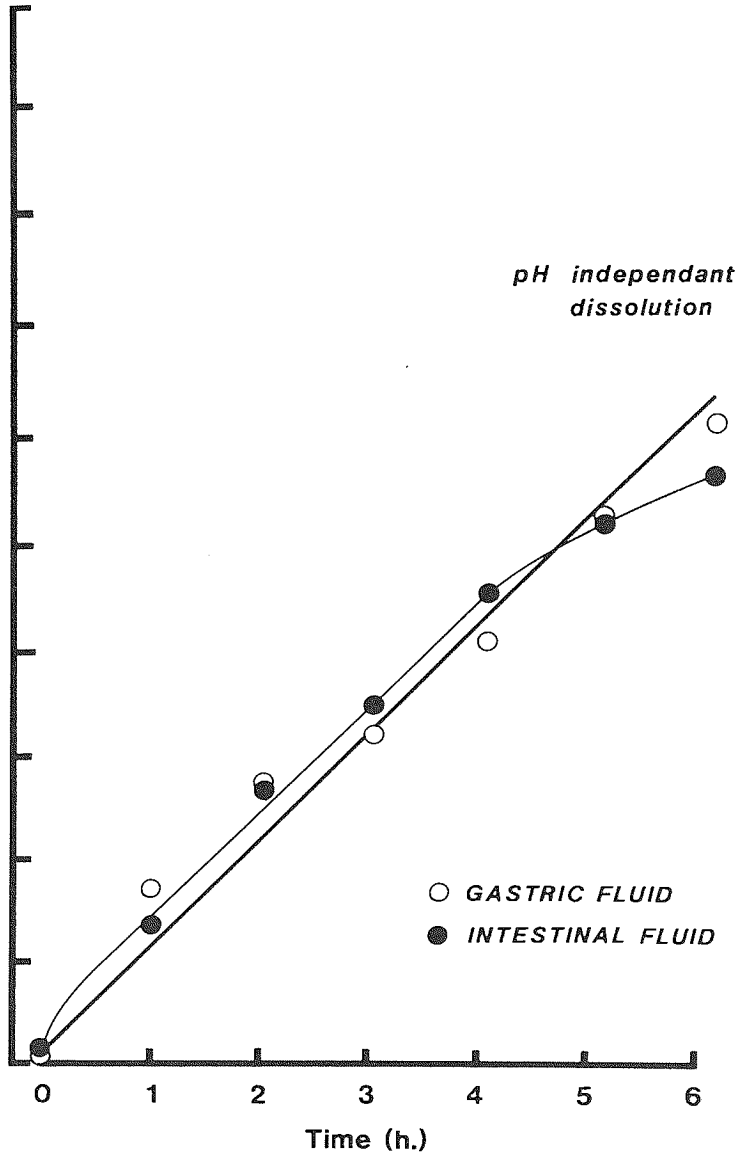


Figure 8. COMPARISON OF THEO-DUR DISSOLUTION IN SIMULATED GASTRIC AND INTESTINAL FLUID

DISCUSSION

The ideal sustained release theophylline formulation should have a constant release mechanism over the 12 h dosing interval in both gastric and intestinal fluids. Its release should not differ with regard to pH or digestive enzyme systems. Dissolution experiments where changes in pH and dissolution media can be affected economically could be used to test formulations prior to *in vivo* experimentation if such *in vitro* methods could be designed to reflect the release of the drug in patients. The mean gastric residence time has been reported to be 3.61 $\pm$ 1.47 h (Wagner 1969) therefore the formulation has to be subjected to an acidic gastric environment for about 2 to 5 h and then during the remaining dosage or release interval to alkaline intestinal fluids. To meet the ideal, the formulation should be pH independent and release approximately a third to a quarter of the total theophylline dose in the first 3 h interval in gastric fluid. In this experiment five out of seven formulations tested released between a quarter and a third of the total theophylline in the first 3 h in gastric fluid as follows:

Formulation	% Theophylline Released
Theograd	62.6%
Rona-Slophyllin	43.6%
Nuelin SA	33.8%
Theo-Dur 300 mg	32.2%
Theo-Dur 200 mg	32.1%
Phyllocontin	28.1%
Theocontin	26.9%

Using the same dissolution media and rotating basket method of dissolution, Simons et al (1984) also obtained results which when analysed showed five out of nine formulations from four different manufacturers to release between a third and a quarter of theophylline by 3 h in simulated gastric fluid. Unfortunately Simons labelled the formulations from A to J so the brand of sustained release cannot easily be identified. It is of interest to note that in the Simons study all the tablet formulations did achieve the third to a quarter of theophylline released in 3 h but none of the capsule formulations achieved this ideal. Two capsule formulations from one manufacturer obtained a slow release of 13.9 and 8.6% of theophylline after 3 h and a further two formulations from another single manufacturer released 61.9 and 72.3% over 3 h. In our study, one capsule formulation was tested, Rona-Slophyllin, and again this formulation released a high percentage of theophylline during 3 h in gastric fluid (43.6%). This dissolution test may be a disadvantage to a capsule formulated product due to the agitation causing the gelatin capsule to rapidly swell and burst its contents. The multipellet formulation being designed for rapid dispersion into the alkaline duodenum may be erratically affected by a constant acidic environment. Recently, Hendeles et al 1985 reported dose-dumping by a multipellet capsule formulation, Theo-24, when given with a large meal. When given to fasting patients it has sustained release characteristics but when it is delayed in the stomach by the presence of food, rapid release of theophylline may occur. Dissolution experiments may be able to predict such flaws in formulations. It would be interesting to carry-out a dissolution test on the american product, Theo-24, and its sister formulation, Provent, which is available on the UK market to see if rapid dissolution in gastric fluid does take place. (This study was,

unfortunately, unable to be done due to the initial experimentation being conducted some years before Provent was marketed and insufficient time to repeat the experiment.)

Simons et al, 1984, was concerned about the variation in dissolution rates of the same formulation containing different strengths of theophylline. This was not seen in the present study where almost identical values for percentage theophylline dissolved were recorded for the Theo-Dur 200 mg and 300 mg formulations both at 3 h and 6 h dissolution in gastric fluid (see table 6) and similarly with Phyllocontin and Theocontin. The behaviour of the formulation pairs was not so similar in intestinal fluid, the variation in the Theo-Dur formulations becoming apparent after two hours dissolution and although Theocontin and Phyllocontin had the longest dissolution rates in intestinal fluid, they were substantially different. In Simons's work the only formulation used (also in our study) was Theo-Dur 200 mg and 300 mg and, although unable to identify the brand of formulations, only two products produced a percentage dissolution rate over 46% at 6 h in gastric fluid and both were capsule formulations. Therefore, by deduction the rates of release from Theo-Dur in the Simons study were far less than measured in this study. Indeed, only the slow dissolution of Theocontin and Phyllocontin had similar values at 6 h in the present study compared with the majority of products tested by Simons. The dissolution media, temperature and the speed of basket rotation were identical in both experiments, but the UK products would appear to be dissolved faster than the USA counterparts.

Jonkman et al, 1982, had conducted experiments to see which of three dissolution apparatuses compared most favourably with the in vivo solution but the rotating basket dissolution apparatus was not used. It is therefore difficult to compare the results of Jonkman to this study and that of Simons. As Jonkman identified

in his 1982 work, the apparatus used affects the dissolution results obtained. Jonkman (1982) also tried to mimic the gastric emptying time by changing the dissolution media from 0.1 M Hydrochloric acid to a phosphate buffer solution pH 6.8 after two hours, whereas no change of media whilst dissolution was taking place was attempted in either Simons's or this study. Possibly because the dissolution media used by Jonkman was different from our own and Simons's study, Jonkman reported problems in tablet wetting affecting the rate of dissolution. Jonkman added polysorbate 30 to the dissolution media to speed up dissolution rates to try to obtain a similar dissolution profile to serum concentration time profiles in patients. In a number of patients some correlation was achieved between in vitro and in vivo data although the mean dissolution rate data was at variance with the mean percentage absorbed as calculated by the Wagner-Nelson analysis (Wagner and Nelson 1964). In our experiment the percentage of theophylline absorbed over time was not measured (chapter 1) but the rate of absorption of the formulations, as measured by the zero order constants, when placed in rank according to rate of absorption is different from either the rank of products based on the rate of dissolution in gastric or intestinal fluid. The dissolution data both in Jonkman's study and our own does not appear to reflect the in vivo situation. The factors affecting absorption from sustained release products in vivo are complex and many, but a simplistic in vitro could serve to detect major formulation faults eg, Theo-24.

It was Jonkman et al in 1982 who highlighted the problem of pH dependant release in dissolution studies of Theolair (Nuelin SA). He showed that 25 % of theophylline was released from Theolair up to 2 h in acidic media. When changed to phosphate buffer pH 6.8 after a further 2 h, 90% of the drug was in solution, ie, in a

total of 4 h, the majority of the drug had been released from Nuelin SA/Theolair. In this study, Nuelin SA 250 mg behaved as predicted by Jonkman. Over the first 4 h in gastric fluid it behaved the same as the other sustained release products tested. In simulated intestinal fluid, Nuelin's dissolution was rapid (see figure 7). Only Theo-Dur 300 mg had similar release characteristics in both gastric and intestinal fluid (see figure 8). Jonkman's study was a comparison between Nuelin and Theo-Dur and hence Nuelin was labelled pH dependent, and Theo-Dur non-pH dependent. All other formulations, with the exception of Theo-Dur, in my study showed similar pH dependency to Nuelin. The effect of such dependency as in vivo is difficult to predict. Certainly no difference in pharmacokinetic parameters between Theo-Dur and the other formulations tested were seen in the in vivo studies in chapter 1. Jonkman offers no indication of the clinical significance of the pH dependent release of Nuelin SA. It may be assumed that providing the release of Nuelin SA and other pH dependent formulations are still slow enough, dose-dumping would not occur. If rapid release occurs in intestinal fluid, the delay of theophylline absorption in pH dependent products by food would be important. It is interesting to note that the only substantial report of food prolonging the absorption of theophylline has been that of Pedersen 1982 using Nuelin SA. Efforts of other workers to reproduce such delays in theophylline absorption, reported by Pedersen, have been frustrated (Leeds et al 1982). It is possible that this is because the pH independent formulation, Theo-Dur, has been used. If the difference in dissolution rate between gastric and intestinal fluid is taken, the order of pH dependence is Nuelin SA > Rona-Slophpyllin > Phyllocontin and Theo-Dur 200 mg > Theocontin > Theograd and Theo-Dur 300 mg. If this theory is correct, food would be expected to decrease the absorption of these

products in the same rank order. In the Leeds 1982 study, the 100 mg formulation of Theo-Dur (not available in the UK) was shown to be more affected by food at 1, 2, 3 and 4 hours compared with the 300 mg formulation. In my experiment the 200 mg formulation was more pH dependent than the 300 mg. It could be that this is also true of the 100 mg formulation and hence it would be more affected by food. Theograd rapidly dissolves in both gastric and intestinal fluid and because the difference is not great, although rapidly dissolving in intestinal fluid, it would be expected to be uninfluenced by food.

CHAPTER 3

REPRODUCIBILITY OF SALIVA AND PLASMA THEOPHYLLINE CONCENTRATIONS FOLLOWING SINGLE DOSE ADMINISTRATION OF TWO SUSTAINED RELEASE PREPARATIONS

INTRODUCTION

The advantage of monitoring a patient's drug therapy by non-invasive techniques has encouraged investigations into the correlation of drug concentrations in other body fluids, notably urine and saliva, with serum drug concentrations. Saliva is a readily accessible fluid and has attracted great interest as to its suitability for measurement and prediction of therapeutic levels. Correlation between saliva and serum concentrations of phenytoin (Bochner et al 1974, Friedmann et al 1981) and carbamazepine (Troupin and Friel 1975, Rylance and Moreland 1981) have been proved useful. But the usefulness of theophylline saliva concentrations still remains to be determined. Some studies (Galant et al 1977, Goldsworthy et al 1981, Jonkman et al 1981 and Koysooko et al 1974) have demonstrated a good correlation between saliva and serum concentrations of theophylline, whilst others have suggested that saliva levels are of little use in predicting serum concentrations (Boobis et al 1979, Munch et al 1981, Sharma et al 1981). The problems associated with the use of saliva concentrations are those of variation of theophylline pharmacokinetics, the uniformity of collection of saliva samples, saliva pH, the diffusion of theophylline from plasma into saliva, the effects of the rate of saliva flow and the composition of saliva.

Theophylline is well absorbed from oral solution, plain and uncoated tablets (Hendeles et al 1978) and sustained release formulations (Weinberger et al 1978) but the greatest inter-individual variations in human subjects are related to its clearance. Theophylline clearance varies with smoking (Jenne et al 1975), age (Nassif et al 1981), disease state (Piafsky et al 1977), con-current drug therapy (Kozak et al 1977, Weinberger et al 1981) and diet (Feldman et al 1980) therefore any assumption that a fixed serum

to saliva ration will remain stable even for the same patient over a period of time is tenuous.

Methods in the literature for the collection of saliva are varied. Some investigators have used whole saliva collected by various means or individual glandular secretions. Saliva flow can be stimulated by the use of citric acid, lemon juice, glass beads, teflon, paraffin film or arabica gum (Mucklow 1982). Parotid saliva can be collected by cannulation of Stenson's duct, and submandibula saliva has also been used (Truelove et al 1967). As the methods of collection of saliva vary, the composition also varies and hence correlation between one study and another may be limited in value.

With the exception of the gums and the anterior part of the hard palate, minor mucus glands exist in most areas of the oral mucosa. Fluid from these glands, as well as from the paired parotid, submandibular and sublingual glands mix in the confluence of oral secretions known as whole saliva. The relative contributioin made by different glands varies with total flow rate. Under resting conditions the submandibular glands account for about 65%, the parotid 23% and the minor mucosa glands 8% and the remaining 4% drains from the sublingual glands. When saliva is stimulated with citric acid or lemon juice, 50% of whole saliva is from the parotid glands (Mucklow 1982).

The main constituents of human saliva are proteins, sodium, potassium, calcium, magnesium, chloride, bicarbonate and inorganic phosphate. Also found in human saliva are intact and disintegrating leucocytes, epithelial cells, bacteria, dental plaque and food debris. The proportion of saliva from each gland, its rate of production and its composition varies throughout a 24 h cycle in individuals (Dawes 1972).

Under resting conditions, parotid saliva pH lies in the range of 5.5 to 6.0 and the submandibular pH 6 to 7. Within an individual resting saliva pH is fairly constant, but following stimulation it can rise by as much as two pH units and the extent of the increase is dependent upon the increase in flow rate (Dawes and Jenkins 1964).

With these variables in mind it was decided to conduct an experiment to investigate the inter-subject variations of saliva concentrations of theophylline and their correlation to serum concentrations.

METHODS

Six healthy, non-smoking, male volunteers aged between 24 and 37 years with weights ranging from 65 to 78 Kg participated in this study. All received Nuelin SA (500 mg of theophylline) or Phyllocontin Continus (650 mg aminophylline ≡ 520 mg of theophylline) as a single dose, administered at least 1 week apart. Tablets were swallowed whole. The subjects refrained from xanthine-containing foods and drinks for 24 h before and during each test. A standard breakfast and lunch were given on each day of the study and the tablets were swallowed immediately after breakfast. The mouths were then rinsed with 50 ml of water. In addition, three of the subjects were administered Nuelin SA on a second occasion under identical conditions, 6 weeks later.

Blood was drawn via an indwelling cannula or by venepuncture at 2, 3, 4, 5, 6, 8, 11 and 24 h following ingestion of tablets. Saliva samples stimulated by tongue movements, were collected at the same time. Saliva was centrifuged to separate mucoid and serous fractions. All samples were stored at -20 °C until analysis by enzyme imunoassay (EMIT Syva Corporation). The between batch co-efficient of variation was 9.4% and the lower limit of measurement was 1 $\mu g\ ml^{-1}$. Statistical analysis was by linear regression analysis using the method of least squares. Approval for the study was given by the Central Birmingham Health District Ethical Committee.

RESULTS

A clear relationship between saliva and plasma values was obtained using all measurements recorded for both preparations (102 paired samples available for analysis, figure 10).

However, there was a poor predictive value for plasma concentrations using individual saliva values. For example, a saliva concentration of 2.5 $\mu g\ ml^{-1}$ gave corresponding plasma values ranging from 2.8 to 0.6 $\mu g\ ml^{-1}$. Considerable improvement in the correlation coefficient could be produced when the mean saliva and mean plasma values, for the six subjects, for each time point in the study, were plotted. Using mean values, the correlation coefficient for Nuelin SA was 0.98 ($n = 62$; $P < 0.001$) and for Phyllocontin was 0.96 ($n = 40$; $P < 0.001$).

The results for the three volunteers, who were studied on a total of three occasions, are shown in figure 9. Volunteer A showed a good, consistent correlation between saliva and plasma theophylline concentrations on each occasion studied. For volunteer B there was a reasonable correlation on the first occasion ($r = 0.9$) following Nuelin SA but a much poorer correlation when this was repeated. Volunteer C showed good correlation coefficients on two out of three occasions but the ratio between saliva and plasma concentrations varied.

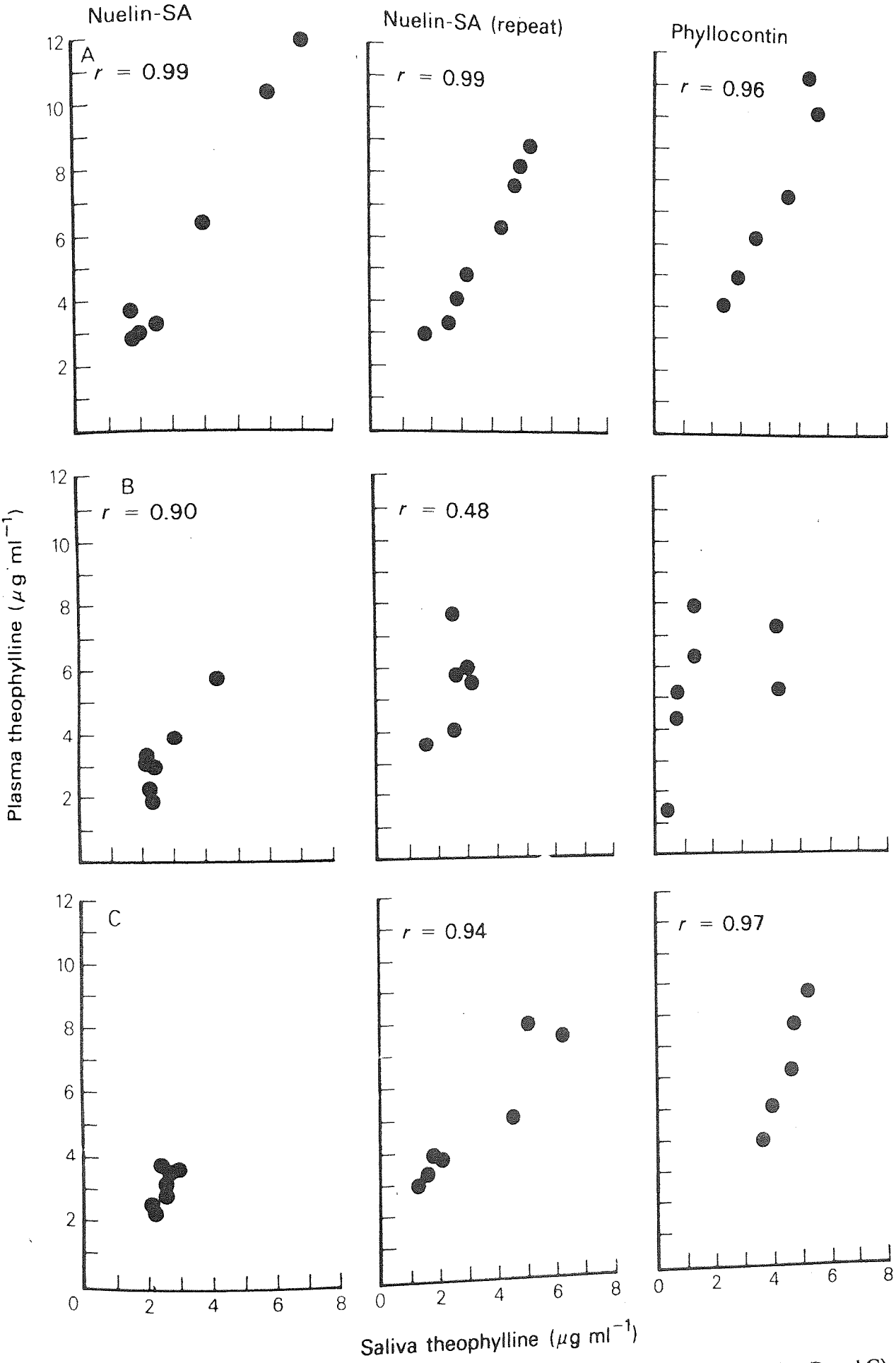


Figure 9 The relationship between plasma and saliva theophylline levels for three subjects (A, B and C) each studied on three occasions. Correlation coefficients have been calculated where the relationship appeared linear. The preparation taken is indicated.

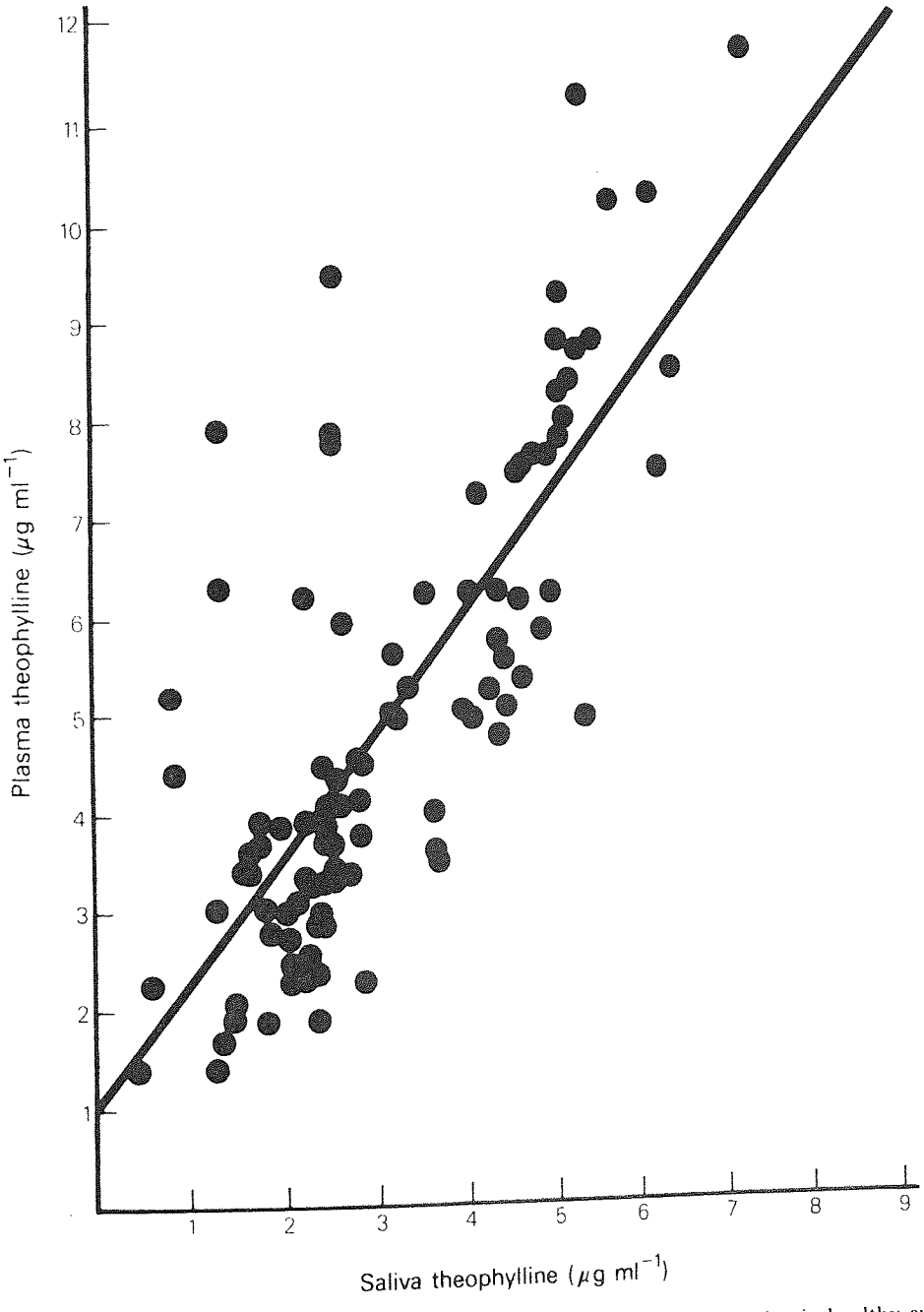


Figure 10 Correlation between plasma and saliva concentrations of theophylline in six healthy subjects for all samples collected (n = 102). The regression line is represented by the equation. y = 1.28x + 1.04 (r = 0.768, $P <$ 0.001) where y = plasma concentration and x = saliva concentration.

DISCUSSION

This study confirms the work of others (Boobis et al 1979, Munch et al 1981, Sharma et al 1981) that saliva estimations are unreliable predictors of plasma values of theophylline following single dose administration in adults. The reasons for this are uncertain but may be due to inter-individual variation in the factors which affect transfer of drug from blood to saliva, such as saliva pH and flow rate. The collection of mixed saliva samples may also introduce greater variation than collection from an individual gland (Stephen & Speirs 1976). Individual variation in elimination rates of theophylline is well recognised (Ogilvie, 1978) and variability in the plasma profiles of theophylline following repeated single dose administration has been noted by Dederich et al (1981) and was noted in some of our subjects. In agreement with Culig et al (1982), we found an improvement with time in the correlation coefficient between saliva and plasma levels ($r = 0.31$ at 3 h and $r = 0.89$ at 8 h for Nuelin SA). This improved correlation at later times after dosing may reflect the delayed absorption and longer distribution phase with this type of sustained release preparation (Mucklow 1982). Variable binding of drug to albumin in the saliva is unlikely and would not have been detected in our study, but some drugs have been shown to bind to the mucoid sediment of saliva which contains mucoproteins and cell debris and this may represent a source of variation when centrifuging and sampling (Paxton et al 1977, Anaveker et al 1978).

CONCLUSION

The data from this study supports the view that saliva concentrations of theophylline in adults are not useful predictors of concomitant plasma concentrations, though for some subjects, the relationship may be consistent.

CHAPTER 4

PLASMA THEOPHYLLINE CONCENTRATIONS IN HEALTHY

VOLUNTEERS AFTER MULTIPLE DOSING OF THEO-DUR

AND NUELIN SA

INTRODUCTION

Many sustained release theophylline formulations are available using a variety of mechanisms to achieve slow/sustained release (Weinberger et al 1978). Administered once or twice daily theophylline SR is effective in the treatment of airways obstruction (Ogilvie 1978, Hendeles and Weinberger 1982) and provides the possibility of better patient compliance than rapidly absorbed preparations (Tinkleman et al 1980). The opportunity for less frequent dosing may be particularly important in the treatment of children and smoking adults whose rapid metabolism may require treatment schedules with unrealistically short intervals with serious loss of compliance (Jenne et al 1975, Hendeles and Weinberger 1978).

However, even 12 hourly dosing schedules involve taking medication in association with meals, particularly the taking of the morning doses with, before or after breakfast. The evening tablet is less likely to be taken with an evening meal, which for most people is necessarily more varied in timing than breakfast. Food has been reported to delay the rate of absorption of some of these preparations and this has been markedly demonstrated in single dose studies (Pedersen 1981, Leeds et al, 1982). Food constituents themselves have been reported to affect the metabolism of theophylline. A protein-rich diet increases metabolism whilst the half-life of theophylline is longer after carbohydrate-rich meals (Welling et al 1975, Kappas et al 1976). Taking sustained release theophylline with different volumes of water or without any water has also been shown to affect the release of theophylline (Welling et al 1975, Pedersen 1984). A previous single dose study (Chapter 1) showed no significant differences between the sustained release products available in the UK following single doses taken immediately after breakfast.

Since sustained-release theophylline preparations are exposed for a longer time to gastro-intestinal influences than conventional preparations, the effect on both single and multiple dosing of sustained release theophylline needs to be evaluated (Pedersen, 1981). Multiple dosing schedules are more realistic representations of normal prescribing in therapeutic valuation than single dose studies, although both are needed to fully elucidate the kinetic characteristics of any preparation.

Comparison of two leading theophylline formulations, Theo-Dur and Nuelin SA, have been made by others, (Domson et al 1979, Langaker et al 1981 and Talseth et al 1981). Domson et al (1979) carried out a single dose study in children under fasting conditions. Langaker et al (1981) and Talseth et al (1981) both reported steady state studies but neither was conducted with co-administration of food. Jackson and Wright, 1983, conducted a study on Theo-Dur alone with what was described as, "actual clinical conditions." Fourteen patients taking theophylline were allowed to eat, drink and otherwise live normal lives during the study. The eating habits were left to the discretion of each individual.

No steady state study comparing two leading theophylline formulations in a standardised experiment to elucidate the effect of food has been made in the past. It was therefore decided to conduct an experiment to:

1) Observe whether co-administration of Theo-Dur and Nuelin SA with food affected the pharmacokinetic parameters of the formulations compared with reported literature values.
2) Observe any differences in pharmacokinetic parameters between Theo-Dur and Nuelin SA under these standardised conditions.

METHODS

Eleven healthy male volunteers participated in this study. Their ages ranged from 20 to 34 years and their weights between 62.6 and 81.6 kg. All were non-smokers. Informed consent was obtained and the study protocol was approved by both the Central Birmingham Health District Ethical Committee and the University of Aston, Human Sciences Ethical Committee.

Nuelin SA and Theo-Dur tablets were given in a randomised, cross-over design for 5 days at a dose of 250 mg and 300 mg respectively every 12 h with a wash-out period of 48 h between treatments. The tablets were taken whole, immediately following the evening meal and breakfast. On day 6 the dose was swallowed with 200 ml of water immediately following a standardised breakfast consisting of cereal, toast, marmalade and milk (17 g protein, 27 g fat and 76 g carbohydrate). No xanthine containing foods or drinks were allowed for 24 h before and during the period of blood sampling.

Blood samples were taken on day 5 by venepuncture before the morning and evening doses to check that steady state conditions had been attained. Serial blood samples were taken on day 6 using an indwelling cannula immediately before dosing and then 1, 2, 4, 6, 8, 10 and 12 h after the morning tablet. Plasma was assayed in duplicate for theophylline by enzyme immunoassay (EMIT, Syva, UK).

C_{max} and t_{max} were estimated graphically. The area under the plasma concentration time curve (AUC_{0-12}) was calculated by the trapezoidal rule.

The plasma concentration data was subjected to a 2 way analysis of variance and the pharmacokinetic parameters in the two treatment groups were compared using a two tailed Student's t-test.

RESULTS

The mean plasma serum theophylline concentrations measured at steady state on day 6 are shown in table 7. comparison of the two pre-dose plasma theophylline concentrations on days 5 and 6 confirmed steady state conditions. The plasma profiles are represented graphically in figure 11 in which the concentrations obtained during Theo-Dur treatment have been corrected to a 500 mg dose for comparison with Nuelin SA.

There were no statistical differences in any of the pharmacoinetic parameters measured (table 8). Theo-Dur had a smaller mean peak to trough variation (2.4 $\mu g\ ml^{-1}$) compared with Nuelin SA (2.8 $\mu g\ ml^{-1}$) but the difference was not significant. Both formulations were similar with respect to t_{max}, AUC_{0-12} and corrected C_{max}. There was a signficant effect of the the order of administration ($P < 0.001$). Although the volunteers were assigned products to be taken in a randomised, coded way, the mean plasma concentrations after Nuelin SA were lower in volunteers taking the preparation first rather than second, (6.1 $\mu g\ ml^{-1}$ and 8.3 $\mu g\ ml^{-1}$ respectively) whereas Theo-Dur was reversed (7.9 $\mu g\ ml^{-1}$ and 6.6 $\mu g\ ml^{-1}$). However, adjusting for order of administration there was no difference overall between the mean serum concentrations for both products.

Table 7

MEAN (± SEM) PLASMA THEOPHYLLINE CONCENTRATIONS DURING A 12 HOUR DOSING INTERVAL AT STEADY-STATE

Time (h)	0	1	2	4	6	8	10	12
Nuelin SA 500 mg	7.0 (± 1.0)	7.1 (± 0.9)	7.5 (± 0.9)	7.7 (± 1.0)	8.1 (± 1.0)	7.2 (± 1.0)	6.7 (± 0.9)	5.6 (± 0.8)
Theo-Dur 500 mg (Corrected for dose)	7.0 (± 0.9)	7.2 (± 0.8)	7.5 (± 0.9)	7.4 (± 1.0)	8.0 (± 1.1)	7.5 (± 0.9)	6.9 (± 0.75)	6.3 (± 0.75)
Theo-Dur 600 mg (Observed values)	8.4 (± 1.1	8.6 (± 1.0)	9.0 (± 1.1)	8.9 (± 1.2)	9.6 (± 1.3)	9.0 (± 1.1)	8.3 (± 0.9)	7.6 (± 0.9)

Table 8

MEAN ($\pm$ SEM) DATA AT STEADY-STATE

	C_{max} $\mu g\ ml^{-1}$	T_{max} hours	AUC 0 - 12 hr (adjusted to 500 mg) $\mu g\ ml^{-1}\ h$	Peak-trough Variation* $\mu g\ ml^{-1}$
Nuelin SA	8.4 ($\pm$ 0.9)	4.5 ($\pm$ 0.5)	86.8 ($\pm$ 10.7)	2.8 ($\pm$ 0.2)
Theo-Dur	10.2 ($\pm$ 1.1)	4.5 ($\pm$ 0.7)	86.8 ($\pm$ 10.2)	2.4 ($\pm$ 0.4)

* Peak-trough variation calculated as C_{max} minus C_{min} on Day 6

Table 9: COMPARISON OF STUDIES ON THE PHARMACOKINETICS OF NUELIN SA AND THEO-DUR

Author	Formulation	Subjects	C_{max} ($\mu g\ ml^{-1}$)	t_{max} (h)	Coadministration of food
Leeds et al 1982	Theo-Dur 300 mg	6 Volunteers	8.0	6	X
Leeds et al 1982	Theo-Dur 300 mg	6 Volunteers	7.8	8	✓
Pedersen 1981	Nuelin SA 250 mg	10 Children	16.5	3.6	X
Pedersen 1981	Nuelin SA 250 mg	10 Children	10.2	9.2	✓
Pedersen & Moeller-Petersen 1982	Nuelin SA 11-12.9 mg/Kg	6 Children	12.9	4.7(±1.0)	X
		6 Children	8.7	21.3(±2.1)	✓
		6 Adults	11.6	4.7(±1.0)	X
		6 Adults	9.8	15.3(±5.9)	✓
Jackson S H D & Wright J M 1983	Theo-Dur 464±134 mg	15 Adults	15.5	6	Normal Food Intake
Domson J F et al 1979	Theo-Dur 10 mg/Kg	8 Children	10.1	6 - 10	X
	Nuelin SA 10 mg/Kg	8 Children	9.1	4	X
Mitchell E A et al 1980	Nuelin SA 10 mg/Kg	21 Children	8.0	4	✓
Talseth et al 1981	Theo-Dur 250 mg (half tablets)	14 Volunteers	8.6	4.8(±1.25)	X
	Nuelin SA 250 mg	14 Volunteers	9.0	4.0(±1.3)	X
Langaker K E et al 1981	Theo-Dur	20 Adult Patients	12.7	3.6(±1.12)	X
	Nuelin SA	20 Adult Patients	12.6	4.3(±1.03)	X
Langaker K E	Nuelin SA	10 Adult Volunteers 10 Adult Patients	15.5	4.0	X
Sips et al 1984	Nuelin SA 300 mg	10 Adult Patients	4.6	7.5	X
	Nuelin SA 300 mg	10 Adult Patients	4.7	6.9	✓

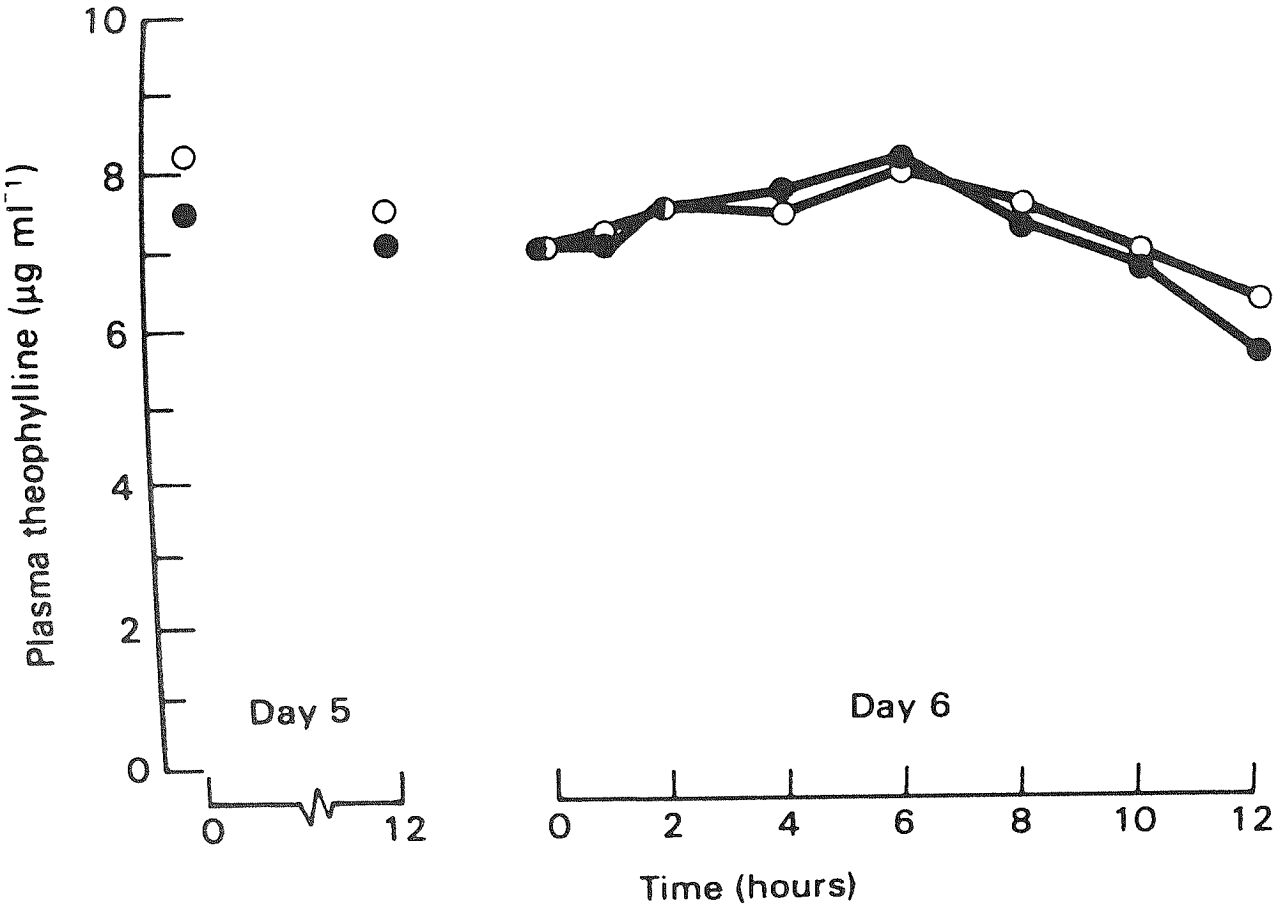


Figure 11. Mean plasma theophylline concentrations in healthy volunteers during a 12-h dosing interval at steady state following administration of Neulin SA (250 mg, 12-hourly after food) and Theo-Dur (300 mg, 12-hourly after food). The results for Neulin SA (●——●) have been plotted as measured and for Theo-Dur (○——○) have been corrected to a dose of 250 mg 12-hourly

DISCUSSION

Only three publications have shown Nuelin SA or Theo-Dur to be affected by co-administration of food, two of these by the same author, Pedersen. Leeds et al (1982) showed in six volunteers that Theo-Dur 300 mg when taken with food, (2 poached eggs, toast, margarine and 4 ounces of skimmed milk) had a delayed t_{max} of 2 h compared to fasting. Leeds et al (1982) found that when the fraction absorbed with time was calculated "those subjects who tended to absorb Theo-Dur at faster or slower rates did so consistently regardless of food or fasting treatments". For 300 mg tablets the only significant difference in serum concentrations was found at the 4 h sample, not at 1, 2, or 3 h after administration or at subsequent sampling intervals over the 24 h. Leeds (1982) applied analysis of variance to the fraction of drug absorbed but not to the t_{max} or C_{max} parameters. These were displayed graphically and there is no indication in the paper whether this 2 h delay in t_{max} in six volunteers is significant or not.

In a letter in the British Journal of Clinical Pharmacology in 1981, Pedersen published a report in which 10 children received Nuelin SA with breakfast. The breakfast given consisted of a weighed quantity of cornflakes, rye bread, butter, salami and skimmed milk, composed of 68 - 70% carbohydrate, 19 - 20% fat and 12 - 13% protein. No statistical analysis was applied to the results obtained in the study by Welling et al (1975) using Tedral tablets. A similar diet of 80% carbohydrate, 11% fat and 9% protein did not cause delay in theophylline absorption. When the proportion of fat or protein was altered to an artificially high proportion, (over 50%) delay in absorption took place. In a study by Fieldman et al (1980), changes in theophylline metabolism were demonstrated when the proportions of protein and fat were abnormally altered.

Pedersen and Moeller-Petersen (1978) gave the same breakfast as was given in Pedersen's first paper (1981). The delay in t_{max} with a corresponding reduction in C_{max} when Nuelin Retard (= Nuelin SA) was given with food was dramatic. Pedersen and Moeller-Petersen increased the t_{max} in 6 children from 4.7 h on fasting to 21.3 h after food and in 6 adults from 4.7 h to 15.3 h. Pedersen explained the difference between the children and adult data by the fact that the adults ate less than the children! This large prolongation of t_{max} has not been reproduced by other workers. Indeed Sips et al (1984) conducted a similar study on Nuelin Retard using a standard breakfast of 2 slices of brown bread, 1 egg, 1 glass of orange juice and 1 glass of skimmed milk (17% protein, 17% fat, 58% carbohydrate) and found the t_{max} was reduced when food was co-administered with Nuelin Retard by a non-significant amount in 10 adult asthmatic patients from 7.5 to 6.9 h. The findings of Mitchell et al (1980) also differed from the Pedersen and Moeller-Petersen (1982) work. Mitchell gave 21 children an undefined light breakfast with Nuelin SA. The t_{max} was 4 h after administration in both single dose and steady state studies.

In those studies where food has not been given at the time, the t_{max} for Theo-Dur is reported to be between 3.6 - 7.5 h for Nuelin SA (see table 9). These results agree with this experiment. In other comparisons between Theo-Dur and Nuelin SA where food has not been co-administered (Talseth et al 1981, Langaker et al 1981), the reported t_{max} for Theo-Dur has been 4.8 and 4.3 h, likewise for Nuelin SA, 4.0 and 4.3 h respectively. In the present study a value of 4.5 h was found.

In the light of evidence from these studies the effect of food in normal dietary proportions on the release of Theo-Dur and Nuelin SA must be in doubt. It is possible that when large amounts

of food are consumed or the proportions of fat and protein are abnormally high the rate of gastric emptying is affected enough to prolong the absorption of theophylline from a sustained release formulation. With a normal dietary intake, the present study, supported by the work of Sips et al (1984) and Mitchell et al (1980), has shown that food did not delay the t_{max} for Theo-Dur and Nuelin SA.

The evidence for a reduction in C_{max} when sustained release products are given with food is even less. Only Pedersen (1981) and Pedersen and Moeller-Petersen (1982) have shown a significant reduction in C_{max} when Nuelin SA is given with food. Both of these studies were in paediatric patients. Pedersen and Moeller-Petersen (1982) were unable to show a significant reduction in C_{max} in adults. Indeed no-one has shown a fall in C_{max} when sustained release theophyllines are taken with food in adults. As Pedersen (1982) commented, the children in his study ate more than the adults. Physiologically, the stomach is smaller and the effect of even similar quantities of food in children and adults could result in alterations in gastric motility sufficient to cause reductions in the C_{max} which Pedersen achieved in children. Children are known to metabolise theophylline faster than adults (Kadlec et al 1978) so greater fluctuations in theophylline levels and lower serum concentrations for equal doses of theophylline are to be expected compared with adults.

Another factor to be taken into account besides the food intake when assessing the pharmacokinetics of slow release theophylline products is the volume of fluid taken. Food in the stomach may absorb water. Welling et al (1975) and Pedersen (1984) have both shown that the absorption of theophylline is affected by the volume of water taken with the formulation (the volume of water taken

being a factor in gastric emptying). None of the studies conducted have taken the total water content of the food given into account. The volume of water given to swallow the tablet has been standardised but not the total fluid consumption. Certainly Pedersen (1984) showed that a dry meal prolonged t_{max} when compared with a wet meal in 10 children, although in this experiment there were wide inter-individual variations. Further experimentation relating the water content of the food to the absorption of theophylline would be worthwhile.

This present study showed that there were no statistically significant differences between Theo-Dur and Nuelin SA in any pharmacokinetic parameters measured. The peak to trough variations, in this work, were less for both Theo-Dur and Nuelin SA than those reported elsewhere for these products at steady state. Langaker et al (1981) reported peak to trough variations of 3.3 and 4.5 $\mu g\ ml^{-1}$ for Theo-Dur and Nuelin SA respectively and Talseth et al (1981) 3.4 and 3.9 $\mu g\ ml^{-1}$. This present experiment also showed that both of these sustained release formulations would retain reasonably consistent serum concentrations of theophylline with 12 hourly dosage when taken with food.

CHAPTER 5

A PHARMACOKINETIC STUDY USING THE RECOMMENDED DOSING SCHEDULES OF THEO-DUR AND UNIPHYLLIN

INTRODUCTION

Twice daily administration of sustained release theophylline preparations has become an established, effective and convenient means of controlling bronchodilation over a 24 hour period in patients with airway obstruction (Weinberger and Hendeles 1979). Sustained release formulations of theophylline have the potential to achieve uniform serum concentrations with longer dosing intervals than plain tablets (Dasta et al 1979, Fagerstrom et al 1981, Hendeles and Weinberger 1978). However, there are significant differences in the rate and extent of absorption among the available formulations, (Weinberger et al 1981) and the rate of absorption frequently has not been slow enough to allow the promotion of longer dosing intervals without excessive fluctuations in serum concentrations (Hendeles et al 1984).

A single nightly dose has potential advantages in patient compliance, control of nocturnal asthma and early morning breakthough. If formulations designed to be given twice daily were administered once daily in the same daily dose, it would be expected that a higher C_{max} would result with an associated increase in adverse effects; the peak to trough variation would be greater and, especially in fast eliminators, periods of inadequate serum concentrations of theophylline might occur. If a formulation was designed with a slow absorption rate, with normal daily doses an effective once a day preparation would exist without having the problems associated with higher doses of the conventional twice daily formulations.

Thompson et al 1982 demonstrated that a single dose of sustained release theophylline, Nuelin SA 250 mg given in a dosage of 5 - 12 mg Kg^{-1} day^{-1} taken at night (2100 h) achieved a therapeutic occupancy of 24 hours but with a mean C_{max} of 18.0 µg ml^{-1} and

a mean C_{min} of 9.1 μg ml^{-1}; the mean t_{max} was 10.0 ± 0.7 h. The level obtained was 26.5 μg ml^{-1}. This demonstrated the problems associated with once daily administration compared with conventional twice a day formulations.

In mid 1982 Napp Laboratories introduced into the United Kingdom a sustained release theophylline tablet, Uniphyllin, designed to be taken once daily. The recommended dosage regimen for patients under 70 Kg is 600 mg daily after an initial week of 400 mg once daily. If this product was to achieve its objective, it had to have a longer t_{max}, a minimum peak to trough variation and 24 hour therapeutic occupancy. In the first issue of manufacturer's literature, a serum concentration time profile was displayed showing 24 hour therapeutic occupancy over 5.0 μg ml^{-1} and a peak to trough variation of 6.0 μg ml^{-1}. t_{max} was 6 - 8 h after administration of a 600 mg dose. This t_{max} did not seem longer than many other sustained release formulations, especially if the products were given with food. (See chapter 1). Many patients would require higher levels of theophylline serum concentrations than cited in the manufacturer's literature to achieve adequate relief of their symptoms. If the range of C_{max} was large, toxic effects might be seen in some patients. Also, many conventional preparations already gave similar plasma concentrations when given twice daily with half the daily dose on each occasion.

The object of this study was to investigate the pharmacokinetic parameters of Uniphyllin at the recommended dosage compared with a conventional twice daily regimen of Theo-Dur at the same daily dosage. The peak to trough variation, therapeutic occupancy and the area under the serum concentration time curve over 24 hours would be measured. Medication was to be co-administered with food to reflect the normal clinical situation in some patients

who use meal times as a reminder for medicine taking. Any delay that might be caused by food would be advantageous for both once daily and twice daily preparations.

METHODS

Twelve healthy, non-smoking volunteers (7 female, 5 male) aged 19 - 34 years (mean 25.2 years), all weighing < 70 kg (mean 61.6 kg, range 53 - 69 kg), participated in the study. Using a randomised, open cross-over study design each volunteer received either Uniphyllin 400 mg as a single daily morning dose for 3 days, followed by 600 mg (1½ tablets) as a single daily morning dose for 4 days, or Theo-Dur 200 mg twice daily (morning and evening 12 h apart) for 3 days. On the eighth day, the day of sampling when steady-state kinetics would have been attained, a 600 mg dose of Uniphyllin or the first 300 mg dose of Theo-Dur was administered directly after a standard breakfast. The second dose of Theo-Dur 300 mg was given 12 h later directly after a standard evening meal. Since the Uniphyllin dosing schedule does not state whether administration should be morning or evening, Uniphyllin was taken in the morning to enable the drug to be administered with a standard breakfast. (Nolte and Newmann, 1982, have shown that there were no differences in absorption and elimination kinetics between morning and evening administration of Uniphyllin).

Blood samples were taken via an indwelling cannula immediately before the morning dose and at 2 hourly intervals thereafter for 24 hours.

Plasma was assayed immediately for theophylline by enzyme immunoassay (EMIT, Syva, UK). The between batch co-efficient of variation was 6.4%, and the lower limit of measurement was 1.0 $\mu g\ ml^{-1}$. The pharmacokinetic parameters (C_{max} and C_{min}), peak to trough differences over 24 h, t_{max}, the therapeutic occupancy and plasma half-lives were measured. The area under the plasma concentration curve (AUC_{0-24}) was calculated by the trapezoidal rule. Area under the curve, maximum and minimum theophylline levels and peak

to trough difference were analysed using analysis of variance. A paired t-test was used to determine the statistical significance of any differences in therapeutic occupancy.

Since two cycles of Theo-Dur were available, the means of the two peaks, two troughs and two peak trough differences in serum theophylline concentrations were used in the analyses.

RESULTS

Details of the volunteers are tabulated in table 12. The theophylline half life ranged between 3.6 and 11.2 h (mean 8.2 h) and the decay constants between 0.062 and 0.191 h^{-1} (mean 0.096 h^{-1}). The pharmacokinetic parameters measured are summarised in tables 10 and 11 and figures 12, 13 and 14. The mean AUC_{0-24} was 211.3 ($\pm$ 19.43 SEM) and 213.6 ($\pm$ 13.27 SEM) $\mu g\ ml^{-1}\ h$ for Theo-Dur and Uniphyllin respectively. No statistically significant differences were detected.

There were highly significant differences ($P < 0.001$) in both peak and trough theophylline concentrations between the drugs. Uniphyllin produced higher peaks, mean 13.9 ($\pm$ 0.93) $\mu g\ ml^{-1}$ with a range of 9.7 to 20.0 $\mu g\ ml^{-1}$ compared with 10.7 ($\pm$ 0.93) first peak and 10.7 ($\pm$ 0.88) $\mu g\ ml^{-1}$ second peak for Theo-Dur with ranges of 8.7 to 19.4 $\mu g\ ml^{-1}$ and 7.3 to 17.9 $\mu g\ ml^{-1}$ first and second peak respectively. Three volunteers on Uniphyllin 600 mg once daily had peak serum concentrations in the upper part of the therapeutic range (15 - 20 $\mu g\ ml^{-1}$), only one, volunteer 12, obtained equally high levels on Theo-Dur 300 mg twice daily.

There was a highly significant difference ($P < 0.001$) in peak to trough variation of 10.3 ($\pm$ 0.84 SEM) $\mu g\ ml^{-1}$ with a range of 6.9 to 17.0 $\mu g\ ml^{-1}$ for Uniphyllin. Theo-Dur, in comparison, had mean peak to trough variations of 3.6 ($\pm$ 0.33) and 3.8 ($\pm$ 0.28) $\mu g\ ml^{-1}$ for first and second peaks with a range of 2.4 to 6.0 and 2.5 to 5.7 $\mu g\ ml^{-1}$.

The mean t_{max} was approximately 1 hour earlier with Theo-Dur than with Uniphyllin. The t_{max} was earlier in seven out of twelve volunteers, later in one and the same in four, using a mean of two peaks for the Theo-Dur data. This difference failed to reach significance ($0.05 < P < 0.10$). There was no difference in t_{max}

between the first and second Theo-Dur peaks. Six volunteers had exactly the same t_{max} for both peaks (figure 12), four had an increase in the time to the second peak and two had a reduction in t_{max} for the second peak. The means were 7.33 ($\pm$ 0.38 SEM) and 7.58 ($\pm$ 0.38 SEM) h for the first and second peaks respectively.

By a paired t-test, it was found that the therapeutic occupancy (time in which theophylline concentrations lie between 5.0 and 20 $\mu g\ ml^{-1}$) was significantly different ($P < 0.05$). Eight volunteers achieved 24 hour therapeutic occupancy on Theo-Dur twice daily compared to four on Uniphyllin once daily. The mean therapeutic occupancy for Theo-Dur was 22.4 hours with a range of 13.7 to 24 hours compared with a mean of 20.4 hours with a range of 13.6 to 24 hours for Uniphyllin.

Table 10

SUMMARY OF PLASMA THEOPHYLLINE CONCENTRATIONS FOR UNIPHYLLIN

	Volunteer												Mean (± SEM)
	1	2	3	4	5	6	7	8	9	10	11	12	
AUC_{0-12} h	245.2	161.5	221.3	206.7	254.5	214.9	138.9	236.0	183.4	115.0	242.4	343.4	213.6(± 13.27)
Peak Plasma Concentrations ($\mu g\ ml^{-1}$)	14.3	9.7	12.6	13.6	16.8	18.8	10.5	14.1	12.4	10.6	13.6	20.0	13.9(± 0.93)
Trough Plasma Concentrations ($\mu g\ ml^{-1}$)	5.4	2.8	4.7	3.9	4.3	1.8	0.7	5.1	2.2	0.7	5.8	5.8	3.6(± 0.55)
Peak to Trough Variation ($\mu g\ ml^{-1}$)	8.9	6.9	7.9	9.7	12.5	17.0	9.8	9.0	10.2	9.9	7.8	14.2	10.3(± 0.84)
Time to Maximum Concentration (h)	10	10	7	8	8	10	8	10	6	8	8	8	8.4(± 0.38)
Therapeutic Occupancy (h)	24	17.6	23	21.8	23.3	18	13.6	24	18.3	13.2	24	24	20.4(± 1.18)

Table 11

SUMMARY OF PLASMA THEOPHYLLINE CONCENTRATIONS FOR THEO-DUR

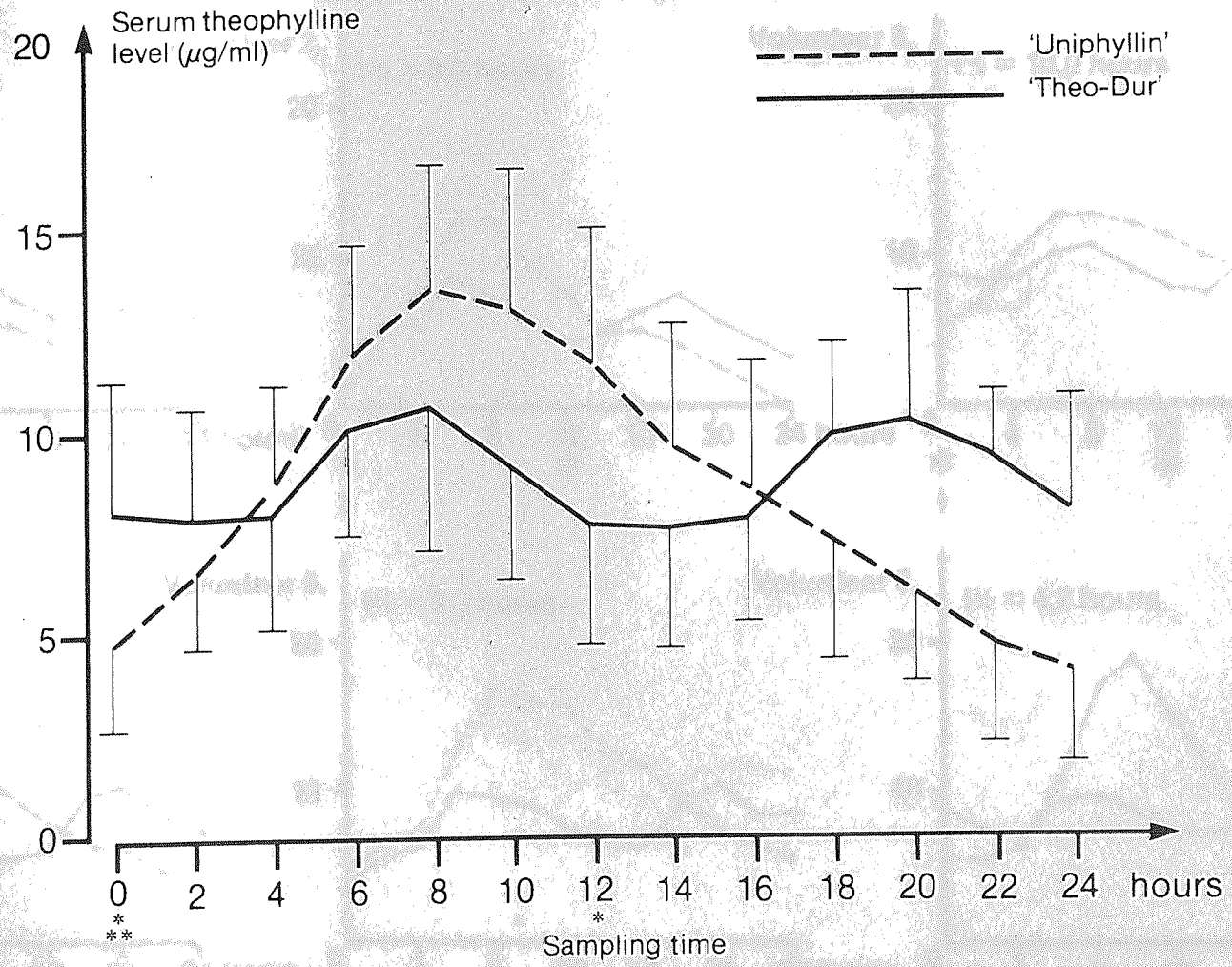
	Volunteers												Mean (± SEM)
	1	2	3	4	5	6	7	8	9	10	11	12	
AUC_{0-24} h	238.9	183.2	213.8	185.3	190.6	208.8	138.1	224.1	162.3	134.6	272.6	383.0	211.3(±19.43)
1st Peak Plasma Concs ($\mu g\ ml^{-1}$)	11.4	9.4	10.5	9.6	10.0	9.8	8.7	9.7	9.8	6.5	14.0	19.4	10.7(±0.93)
1st Trough Plasma Concs ($\mu g\ ml^{-1}$)	8.4	7.0	7.8	5.6	4.0	6.8	3.6	7.2	5.2	3.9	10.3	15.0	7.1(±0.92)
1st Peak to Trough Variation ($\mu g\ ml^{-1}$)	3.0	2.4	2.7	4.0	6.0	3.0	5.1	2.5	4.6	2.6	3.7	4.4	3.6(±0.33)
2nd Peak Plasma Concs ($\mu g\ ml^{-1}$)	11.7	8.3	10.0	10.5	10.4	11.9	7.5	13.2	7.3	7.6	11.8	18.0	10.7(±0.88)
2nd Trough Plasma Concs ($\mu g\ ml^{-1}$)	8.7	5.5	7.5	5.7	6.3	7.3	3.2	7.5	4.2	3.9	9.1	14.0	6.9(±0.04)
2nd Peak to Trough Variation ($\mu g\ ml^{-1}$)	3.0	2.8	2.5	4.8	4.1	4.6	4.3	5.7	3.1	3.7	2.7	4.0	3.8(±0.28)
Time to Reach Maximum Concentration (h)													
Peak 1	6	8	8	8	6	8	6	10	6	6	8	8	7.33(±0.38)
Peak 2	6	9	6	8	8	8	6	6	10	8	8	8	7.58(±0.38)
Therapeutic Occupancy (h)	24	24	24	24	23.2	24	19.9	24	20	13.7	24	24	22.4(±0.90)

Table 12

VOLUNTEER CHARACTERISTICS
FOR THEO-DUR VERSUS UNIPHYLLIN STUDY

VOLUNTEER NUMBER	ORDER GROUP	KEL	$t_{\frac{1}{2}}$ (h)	AGE (YEARS)	WEIGHT (Kgs)	SEX
1	1	0.062	11.2	21	68.0	FEMALE
2	2	0.078	8.9	34	63.0	MALE
3	2	0.069	10.0	25	69.0	MALE
4	1	0.069	10.0	26	62.5	FEMALE
5	1	0.076	9.1	22	60.0	FEMALE
6	1	0.164	4.2	23	55.0	FEMALE
7	2	0.120	5.8	29	53.0	FEMALE
8	1	0.074	9.4	19	69.0	MALE
9	2	0.113	6.1	27	53.5	MALE
10	1	0.191	3.6	26	67.5	MALE
11	2	0.074	9.4	24	66.0	FEMALE
12	2	0.067	10.3	27	53.0	FEMALE

ORDER GROUP 1 = UNIPHYLLIN/THEO-DUR
2 = THEO-DUR/UNIPHYLLIN



CONCENTRATION

$\mu g\ ml^{-1}$

* Theo-Dur taken — 300mg theophylline ** Uniphyllin taken — 600mg theophylline

Figure 12 Steady-state serum theophylline levels (mean ± 1S.D) over 24 hours in 12 volunteers

Figure 13 **Serum theophylline levels over 24 hours at steady-state following dosing with Theo-Dur (300mg 12 hourly) and Uniphyllin (600mg 24 hourly) for each of 12 volunteers**

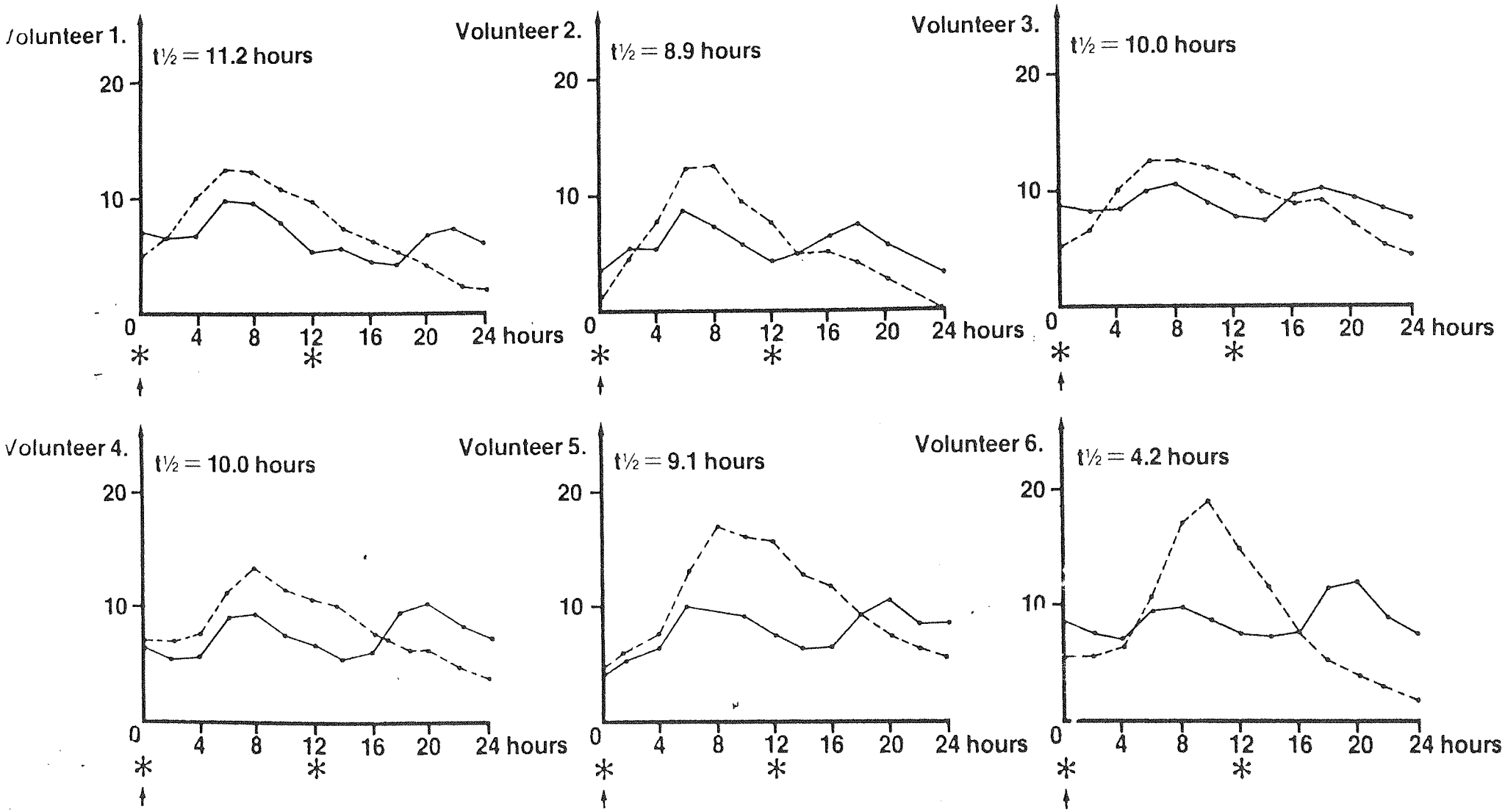
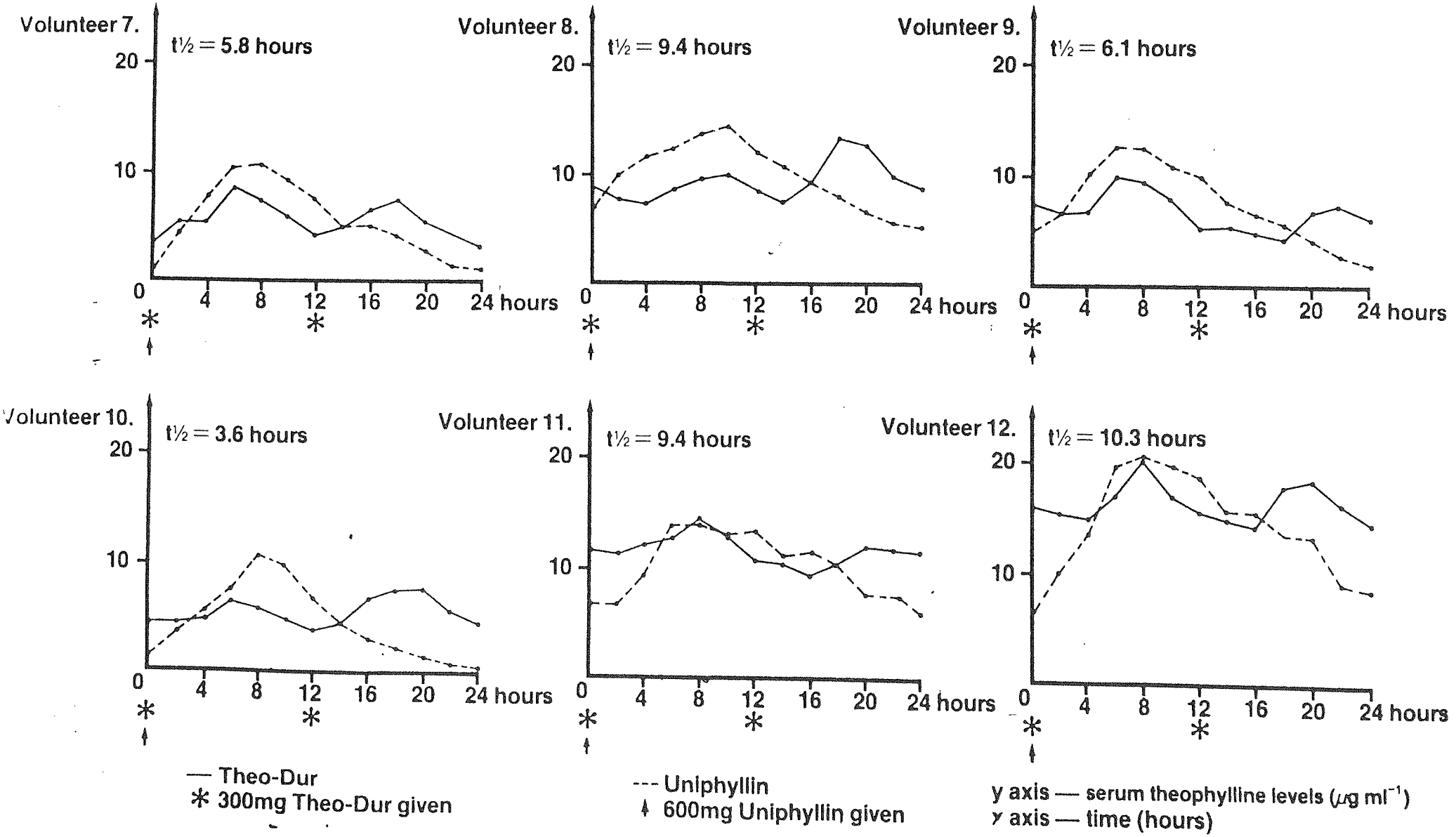


Figure 14 (contd) **Serum theophylline levels over 24 hours at steady-state following dosing with Theo-Dur (300mg 12 hourly) and Uniphyllin (600mg 24 hourly) for each of 12 volunteers**



DISCUSSION

This study has shown that administration of Uniphyllin once daily produced significantly greater peak to trough variation than twice daily administered Theo-Dur at an equal daily dose. This agrees with the later work of Nolte and Newmann (1982) who found patients receiving a mean of 9.7 mg kg^{-1} per day of theophylline had a peak to trough variation of 11.3 µg ml^{-1} when given once daily Uniphyllin. In contrast, the works by Lasseter and Shambler (1984), Cohen (1982) and Cohen (1984) have not demonstrated such a marked peak to trough variation. Lasseter and Shambler reported a mean peak to trough variation of 8.42 µg ml^{-1} in 18 patients receiving 800 mg of Uniphyllin as a single daily dose. Cohen (1984) obtained the same results in 12 patients on an 800 mg single daily dose, reporting a peak to trough variation of 8.34 µg ml^{-1}. However, Cohen (1982) found a peak to trough variation of 5.2 µg ml^{-1} in patients with obstructive airways disease and 4.9 µg ml^{-1} in normal subjects receiving 800 mg of Uniphyllin once daily. Dosing for a drug like theophylline with an elimination half life of 3 to 10 hours means that there is usually a greater fluctuation with once daily dosing than conventional twice daily dosage forms. Because of limitations of gastro-intestinal transit time, it is unlikely that the absorption rate can be altered sufficiently to counteract the unfavourable ratio of elimination half life to dosage interval without greater peak to trough variation. It is interesting to note the t_{max} in these conflicting studies:

Reference	t_{max}
Nolte and Newmann (1982)	6.0 h
Cohen (1982)	6.0 h
Lasseter and Shambler (1984)	8.82 h
Cohen (1984)	7.5 h
This study	8.4 h

In neither the Nolte and Newmann nor in the Cohen studies was the drug given with food. In the Lasseter and Cohen studies and this research medication was taken with food. It would appear from these reports that food may cause a delay in t_{max} as postulated by Leeds (1982) and others. This should help to minimise the peak to trough variation. In the Lasseter and Cohen report this occurred but it was not confirmed in this study. Leeds (1982) showed that 300 mg Theo-Dur tablets taken immediately after a standard breakfast produced peak serum concentrations 8 h after administration. This data is similar to this present research where the mean peak concentrations were 7.58 and 7.33 h after the administration of 300 mg of Theo-Dur immediately after a standard breakfast and evening meal respectively. In the Lasseter and Shambler (1984) report, 2 tablets of Theo-Dur 200 mg gave a t_{max} at 6.9 h and the peak to trough variation was 7.53 $\mu g\ ml^{-1}$, a fluctuation that has not been reported in any other study with Theo-Dur given twice daily (Fox et al 1984, Gonzalez and Golub 1983 amongst others) in patients or volunteers. The difference between this research and a similar study by lasseter and Shambler (1984) was the selection of volunteers. Lasseter and Shambler advertised in the Miami Herald Newspaper and although selected to be healthy, I doubt if volunteers selected in this manner could be as reliable as student and NHS workers who formed the volunteers in this research whose commitment to accuracy and compliance would be greater. The mean weight was greater, 73 kg, but to compensate the dose 800 mg was higher, otherwise the methodology of both studies was identical but the results are very different.

The significant difference in therapeutic occupancy demonstrates the problem of once daily dosing. For all patients, any of the available products will produce greater fluctuations in plasma concentration if given once daily than if the same product is given twice daily. Patients with rapid elimination, such as smokers,

are likely to have a decreased therapeutic affect with once daily compared with twice daily dosing with the same patient. Administration of once daily theophylline will increase variability of blood levels due to the larger dose given. In this study volunteer 10 failed to achieve 24 h therapeutic occupancy on either drug, (13.2 h on Uniphyllin and 13.7 h on Theo-Dur). The peak concentration obtained for volunteer 10 on Uniphyllin was 10.6 $\mu g\ ml^{-1}$ compared with 6.5 $\mu g\ ml^{-1}$ on Theo-Dur. If 24 h therapeutic occupancy was to be achieved in volunteer 10 and the dose increased, higher levels possibly close to the toxic level would have to be achieved on Uniphyllin rather than on Theo-Dur where the dose is divided during the day. Only four volunteers achieved 24 hour occupancy on both drugs, all had long decay half lives, volunteer 8, 9.4 h, volunteer 11, 9.4 h, volunteer 12, 10.3 h and volunteer 1, 11.2 h. It would appear from this study that to obtain 24 h occupancy on Uniphyllin a half life of 9.4 h or greater is required at the recommended dosage, whereas volunteer 6 on Theo-dur obtained 24 h therapeutic occupancy with a half life of 4.2 h (tables 10 and 11). The same volunteer (volunteer 6) on Uniphyllin had a therapeutic occupancy of 18 h with a C_{max} of 18.8 $\mu g\ ml^{-1}$. Assuming first order kinetics, to achieve 24 h occupancy serum concentrations over 20.0 $\mu g\ ml^{-1}$ would be obtained, and a dose increase of 200 mg would result in a concentration of 25.0 $\mu g\ ml^{-1}$. It is interesting to note that 3 out of 4 volunteers who achieved 24 h therapeutic occupancy on both drugs were female.

Whether a single daily dose should be administered at night or in the morning has been of interest since some workers, Lesko et al (1980) and MacLeod et al (1982) have found differences in the pharmacokinetics of theophylline during the day and night time. Lesko et al (1980) found significantly higher trough concentrations of theophylline in the morning compared with the evening in fourteen volunteers taking twice daily sustained release theophylline.

Lesko postulated that diurnal changes in hepatic microsomal oxidase may alter the drug disposition. MacLeod et al (1982) measured the rate of elimination between day time and night time. The night time elimination rate was significantly greater than the day time. Up to 40% differences were found by Macleod between night time and day time serum concentrations. The amount of Theo-Dur absorbed at night was measured at 86.8% whereas other workers, Spangler et al (1978), Weinberger et al (1978) and Fagerstrom et al (1981), had all shown Theo-Dur to be 100% bioavailable. MacLeod stated that the evening time concentration profile was altered by decreased absorption and increased clearance at night. MacLeod's study was conducted using children with a mean age of 9.3 years. It is known that the metabolism of theophylline in children can be increased compared with adults (Sommer et al 1981, Jusko et al 1979) and greater fluctuations in serum concentrations are more frequent in children than adults (Hendeles 1984). Lesko et al (1980) used adult volunteers with an age range of 21 - 40 years and hence the variation in metabolism of theophylline between adults and children may explain the conflicting results between the studies.

Taylor et al (1983) found no difference in overall bioavailability or rates of absorption and elimination between day and night administration of intravenous aminophylline or oral liquid theophylline given to eight healthy volunteers. Birkett et al (1982) similarly found no difference between day or night time administration of intravenous aminophylline, but found a significant 2.6 fold difference in the morning and evening trough concentrations with a sustained release formulation, Nuelin SA, the 9 pm trough concentration being the lowest. Birkett suggested that this difference between morning and evening trough concentrations was due to a period in the afternoon and evening of low absorption alternating with periods of rapid dissolution and absorption in the early morning related

to gastric motility. In a later study Birkett et al (1984) examined three sustained release formulations for differences in peak to trough variation during the day and night. The mean fluctuation over the dosage interval was 7.5 $\mu g\ ml^{-1}$ for all three formulations, the fluctuation being the greatest for Theo-Dur, less so with Nuelin SA and non-existent for Somophyllin.

In the present study the mean morning and evening trough concentrations of theophylline for Theo-Dur were 7.1 ($\pm$ 0.92) and 6.9 ($\pm$ 0.04) $\mu g\ ml^{-1}$ respectively, a difference of only 0.2 $\mu g\ ml^{-1}$.

The range of differences between volunteers in the present study was small, the highest difference being 2.3 $\mu g\ ml^{-1}$ for volunteer 5. Only 3 out of 12 volunteers had a difference between morning and evening troughs concentrations greater than 1.0 $\mu g\ ml^{-1}$. No difference at all was found between peak concentrations of Theo-Dur. The mean peak concentration was 10.7 $\mu g\ ml^{-1}$ for both first and second peaks. Similarly, with Uniphyllin the morning and evening mean trough concentrations were 4.69 and 4.08 $\mu g\ ml^{-1}$ respectively, a difference of only 0.61 $\mu g\ ml^{-1}$ and again the range between volunteers was small, 3.9 to 0.5 $\mu g\ ml^{-1}$ (tables 10 and 11).

This study concurs with Nolte and Newmann (1982) who found identical serum concentration profiles when Uniphyllin was given at 0800 h and 1800 h as a single daily dose. No difference in morning or evening trough levels were found for either Theo-Dur twice daily or Uniphyllin once daily. From this study it would appear that sustained release theophylline formulations are not affected by diurnal variation.

It appears that not until the rate of metabolism of theophylline is high does any possible diurnal influence occur. Likewise, unless there are going to be changes in gastric motility, very little effect is going to be seen upon the release of theophylline from

its formulation at different times of the day. The conflict of reports on diurnal variation highlights, yet again, the problems of investigating a drug which has such variable kinetics in studies with such small numbers. To obtain a valid population for experimentation either the criteria for selection have to be extremely exacting or the number of volunteers has to be much larger, if reasonable conclusions that are absolutely unequivocal are to be made.

CONCLUSION

Theo-Dur 300 mg twice daily obtained significance ($P < 0.05$) greater 24 h therapeutic occupancy than Uniphyllin 600 mg once daily. Uniphyllin once daily had a highly significant ($P < 0.001$) greater peak to trough variation than Theo-Dur twice daily. No significant difference was found in t_{max} between the two formulations.

CHAPTER 6

THE EFFECTS OF GASTRIC MOTILITY AND FOOD ON THE RELEASE OF THEOPHYLLINE FROM A MULTIPELLET AND A MATRIX SLOW-RELEASE PREPARATION IN VOLUNTEERS

INTRODUCTION

Food influences the bioavailability of a large number of drugs. It interferes with tablet disintegration, drug disposition and drug transit through the gastro-intestinal tract (Melander 1978). The effects of food can be due to its composition eg, high fat, the physical presence of the food in the stomach delaying gastric emptying or the induction of digestive enzymes and bile production. The absorption of theophylline from Tedral plain uncoated tablets was investigated by Welling et al (1975). Absorption was faster when the drug was taken with a high protein meal compared with a high fat meal. The fatty meal was thought to decrease gastric emptying and increase the residence time of the tablet in the stomach. The effect of food composition on gastric emptying is fat > protein > carbohydrate.

A number of workers have investigated the effects of food composition on the absorption of theophylline from sustained release products (Kappas et al 1976, Feldman 1980 and Thompson et al 1983). Thompson confirmed Welling's results, that a high protein diet resulted in lower peak serum concentrations than a high carbohydrate diet. Thompson thought the reason for this effect was multifactorial, where dietary components could affect the absorption of theophylline. He cited Gillespie et al (1973) as evidence that proteins and amino acids can block the mucosal absorption of Levodopa and could have a similar action with other drugs including theophylline. Kapas et al (1976) postulated a metabolic effect, a high protein diet having a similar effect in man as in rats, where cytochrome P450 and P448 are induced when fed on a continuous high protein diet. In rats, protein has been shown to increase the rate of metabolism of phenobarbitone, strychnine and aminopyrine. Feldman et al (1980) showed the same effect of a high protein diet in children as in adults. Feldman offered no explanation for the dietary effects of food on

theophylline but cited Kappas's work as a possible explanation.

Pedersen (1981), Leeds et al (1982) and others have all shown that co-administration of food with some sustained release theophylline products increases t_{max} and reduces C_{max}. The only exception to this has been recent work by Hendeles et al (1985) who found "dose dumping" with a multipellet formulation, Theo-24, when taken with a large breakfast in four out of eight volunteers. Hendeles put forward the explanation that alkaline salts or pancreatic enzymes or both, secreted following a meal, were affecting the coating on the multipellet allowing the release of theophylline to be more rapid than intended. In this study an abnormally large meal consisting of 50% carbohydrate containing 900 Kcal was used.

Theophylline is formulated in two main sustained release forms, matrix and multipellet. The multipellet is said to have an advantage that it is not affected by co-administration with food, the pellets being small enough to pass through the pyloric sphincter when closed, as in the presence of food, and behave similarly to a sustained release liquid preparation (Bachgard and Nielsen, 1978).

In the UK the Wellcome Foundation marketed "Provent", a multipellet formulation, claiming that it was not affected by food. The purpose of this study was, therefore,

1) to ascertain whether gastric emptying alone is a component in the delayed absorption of theophylline separate from the presence of food and,

2) to observe whether the absorption of a multipellet formulation "Provent" is affected by food.

Nimmo et al (1973) used a technique of altering gastric emptying by employing metoclopramide 10 mg intravenously to increase gastric emptying time and propantheline 30 mg intravenously to delay gastric emptying time and demonstrated that the absorption of paracetamol

was dependent on the speed of gastric emptying.

Stevens (1982) investigated the effect of oral metoclopramide on the release of Theo-Dur 300 mg sustained release tablets. Unfortunately, he failed to take into account that oral metocloparamide has a large inter-individual variation in bioavailability (Bateman 1983) and to achieve maximum gastric emptying metoclopramide has to have food present in the stomach (personal communication, Wellcome Foundation 1983).

This experiment was designed to investigate the effects of altering gastric motility on the absorption of theophylline over a 12 hour dosage interval, from a multipellet slow release product, Provent. Theo-Dur was used as a comparator product.

METHODS

Twenty healthy non-smoking male (11) and female (9) volunteers, aged 18 - 40 years, weighing 55 to 65 kg (female) and 65 to 75 kg (male) were randomised into two groups of 10. There was no difference between groups in age, weight or sex distribution. One group took Provent 600 mg as a single morning dose, with 50 ml of water on each of four treatment days, the other group took Theo-Dur 600 mg in an alike manner. In addition, the Provent group attended a fifth study day when 150 mg of liquid theophylline was administered. The same treatment was administered to all volunteers on each study day.

Treatment Groups

STUDY DAY	1	2	3	4	5
GROUP A	Fasting and Provent	Food and Provent	Food and Metoclopramide and Provent	Fasting and Propantheline and Provent	150 mg of oral Liquid Theophylline 8 volunteers only
GROUP B	Fasting and Theo-Dur	Food and Theo-Dur	Food and Metoclopramide and Theo-Dur	Fasting and Propantheline and Theo-Dur	No Treatment

All volunteers fasted overnight before each study day, abstaining from caffeine containing beverages. On study days 2 and 3 the food eaten prior to administration of the theophylline was a standard breakfast of cornflakes, ½ pint of milk, 2 pieces of toast, a pat of butter and a marmalade portion in total containing 63% carbohydrate, 14% protein and 23% fat. On the fasting study days 1, 4 and 5, no food was taken until six hours after the administration of the theophylline. This consisted of a light salad.

The slow-release theophylline preparation was administered 30 minutes after intravenous metoclopramide 10 mg and propantheline 30 mg on study days 3 and 4. At least 7 days washout occurred between treatments.

3 to 5 ml of blood was sampled at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after theophylline administration by an indwelling catheter. On the fifth study day no 9 or 11 hour samples were taken. The plasma produced was assayed immediately for theophylline by enzyme immunoassay, the lower limit of assay being 1.0 $\mu g\ ml^{-1}$ and in this experiment the co-efficient of variation between kit batches was 5.2%.

The absorption rate constant was determined for 8 out of 10 volunteers taking Provent by comparison with 150 mg of oral liquid theophylline. The t_{max}, C_{max} and AUC_{0-12} were subjected to an analysis of variance using the SPSS-X programme on the University of Sheffield Prime Computer.

The absorption rate constant was obtained using the Wagner-Nelson method (Wagner and Nelson, 1964).

RESULTS

Five comparisons can be considered for each drug in this experiment,

1) Fasting vs food

2) Fasting vs metoclopramide with food

3) Food vs metoclopramide with food

4) Fasting vs propantheline fasting

5) Food vs propantheline fasting

No statistically significant differences were seen in the Provent or Theo-Dur fasting versus food groups between any of the parameters measured. There was a non-significant trend towards a longer t_{max} in the Provent group - eight out of ten volunteers had an increase in t_{max} when Provent was taken with food compared with the fasting state. The reverse was seen in the Theo-Dur group - a non-significant trend was to a reduced t_{max}, where seven out of ten volunteers had a shorter t_{max}. One volunteer showed no difference and 2 had a more prolonged t_{max} when the drug was taken with food.

When volunteers who had taken the drug with no food were compared with metoclopramide, again no statistically significant differences were seen in any of the parameters measured. Seven out of ten volunteers in the Provent group had a reduced C_{max}, one showed no difference and two had a slight increase when given metoclopramide and food compared with fasting but failed to reach significance.

There was a significant difference, ($F = 0.000$), in t_{max} when the food versus metoclopramide groups were compared with Provent. Eight out of ten volunteers had a reduced t_{max} when given metoclopramide. This effect failed to reach significance in the Theo-Dur group, with seven out of ten having an increased t_{max} when given metoclopramide compared with food alone. C_{max} between the two groups showed no

statistical difference, although all volunteers taking Theo-Dur with metoclopramide had a reduction in C_{max} compared with taking it with food.

In the fourth comparison, fasting Vs propantheline, there was a significant difference in the t_{max} ($F = 0.000$), and the rate of absorption ($P < 0.01$) in the Provent group. All ten volunteers had an increase in t_{max}, as measured by the maximum serum concentration recorded in the 12 hours interval. Six out of eight volunteers had a reduced rate of absorption, (table 14). These results were again not mirrored in the Theo-Dur group where six out of ten volunteers had an increased t_{max}, in four of these the increase was marginal and hence failed to reach significance.

No significant differences were found in the fifth comparison, food versus propantheline, in any of the parameters measured, although t_{max}, ($F = 0.019$) was close to reaching significance. This is reflected when nine out of ten in the Theo-Dur group and seven out of ten in the Provent group had an increased t_{max}.

An analysis of variance showed that in t_{max}, C_{max} and AUC_{0-12} a significant difference, $F = 0.000$ occurred between Theo-Dur and Provent. The AUC_{0-12} was higher for Theo-Dur than for Provent, the mean of all four study days being 99.36 $\mu g\ ml^{-1}\ h$ compared with 73.72 $\mu g\ ml^{-1}\ h$ for the Provent group. In all study groups the C_{max} for Theo-Dur was higher than for Provent, 12.9 $\mu g\ ml^{-1}$ compared with an average of 8.65 $\mu g\ ml^{-1}$ respectively. Similarly, on three out of four study days, the t_{max} was higher for the Theo-Dur groups (table 13).

The mean data is displayed in figures 15 and 16.

Table 13

THE EFFECTS OF FASTING CONDITIONS, FOOD, METOCLOPRAMIDE AND PROPANTHELINE ON THE ABSORPTION OF PROVENT AND THEO-DUR

(MEAN PHARMACOKINETIC DATA ± STANDARD DEVIATION)

TREATMENT		FASTING	WITH FOOD	METOCLOPRAMIDE PLUS FOOD	PROPANTHELINE FASTING
PROVENT	C_{max} $\mu g\ ml^{-1}$	8.77 ± 1.84	8.66 ± 1.84	8.08 ± 1.83	9.1 ± 2.25
	t_{max} h	7.2 ± 1.75	8.7 ± 1.49	6.9 ± 2.08	10.8 ± 1.81
	AUC_{0-12} $\mu g\ ml^{-1}$ h	78.97 ± 15.37	74.14 ± 12.57	73.07 ± 14.85	68.90 ± 13.66
	K_a h^{-1}	0.292 ± 0.055	0.245 ± 0.025	0.269 ± 0.071	0.194 ± 0.055
THEO-DUR	C_{max} $\mu g\ ml^{-1}$	12.35 ± 2.82	13.98 ± 3.57	11.89 ± 2.64	13.38 ± 2.80
	t_{max} h	9.0 ± 1.76	7.1 ± 1.45	9.2 ± 1.55	9.3 ± 1.89
	AUC_{0-12} $\mu g\ ml^{-1}$ h	97.0 ± 17.5	106.02 ± 23.35	98.7 ± 21.96	95.71 ± 21.08

Table 14

EFFECT OF GASTRIC MOTILITY ON THE ABSORPTION OF THEOPHYLLINE FROM THE PROVENT FORMULATION

SUBJECT	ABSORPTION RATE CONSTANT (hr^{-1})			
	FASTING	FOOD	METOCLOPRAMIDE	PROPANTHELINE
1	0.333	0.248	0.244	0.195
2	0.373	0.232	0.393	0.169
3	0.340	0.291	0.276	0.167
4	0.268	0.224	0.290	0.310
5	0.307	0.250	0.242	0.126
6	0.248	0.260	0.186	0.158
7	0.249	0.246	0.333	0.206
8	0.124	0.208	0.185	0.217
Mean	0.292	0.245	0.269	0.194
SD	0.055	0.025	0.017	0.055
CV (%)	18.9	10.2	26.4	28.5

NS

NS NS P < 0.01

NS P < 0.01

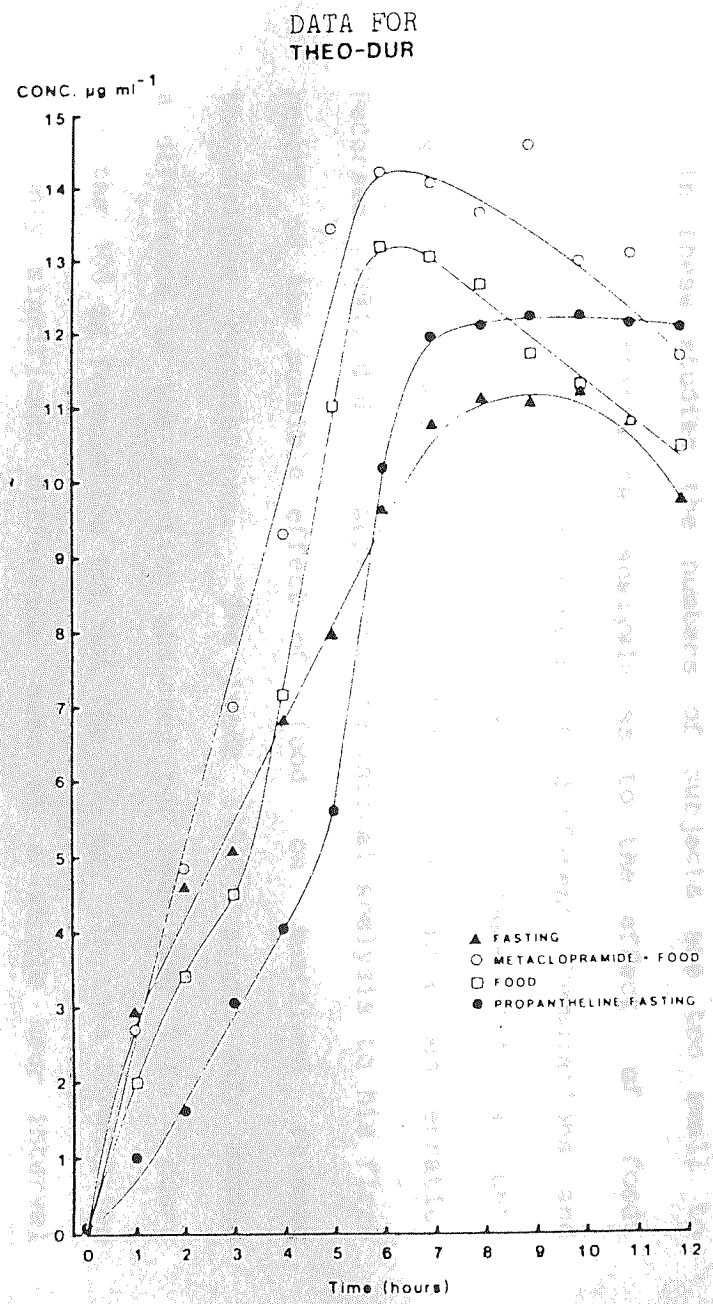


Fig 15 MEAN PLASMA CONCENTRATION FOR THEO-DUR

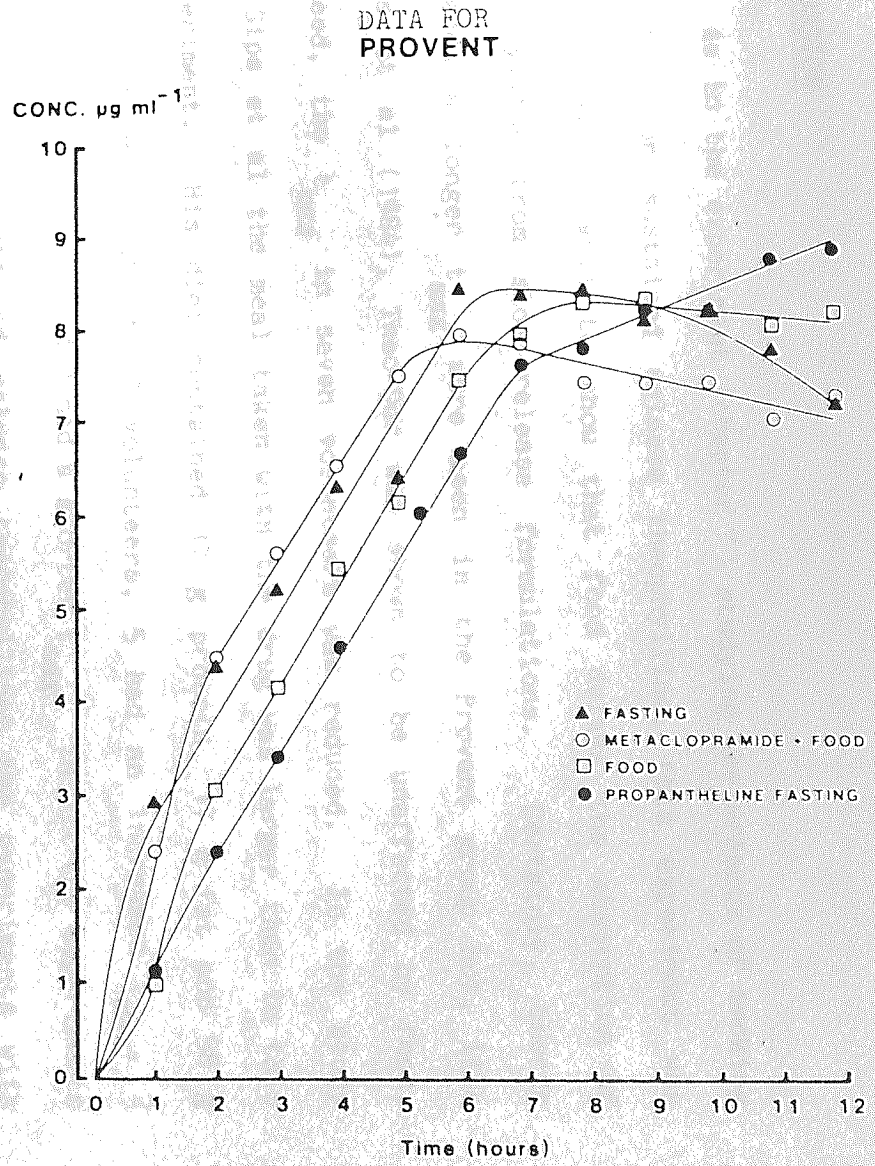


Fig 16 MEAN PLASMA CONCENTRATION DATA FOR PROVENT

DICUSSION

As in the experiment (chapter 7) studying the effects of smoking and food on sustained release theophylline, this experiment was statistically unable to show that food delays the absorption of theophylline from slow release formulations. Certainly, trends towards a longer t_{max} were seen in the Provent group but, like Sips et al (1984), Theo-Dur was shown to be unaffected by food; indeed, the t_{max} in seven volunteers was reduced. In the study by Sips et al the meal taken with the drug was larger than in this experiment. His diet contained 17 g protein, 17 g fat and 58 g carbohydrate. Out of 10 volunteers, 5 had an increased t_{max}, 2 showed no difference and 3 had a shorter t_{max}. In all the experiments conducted on sustained release theophyllines the experiments with and without food, the number of patients or volunteers has been small, Feldman et al (1980), 14, Pedersen (1981), 10, Leeds et al (1982), 6, Thompson et al (1983), 8, Pedersen (1984), 10, Birkett et al (1984), 10 and Sips et al (1984), 10.

In these studies the numbers of subjects are too small to give reliable statistical analysis as to the effect of food, especially when the large number of different formulations and individual variation of pharmacokinetics is taken into account. This study has shown, once again, that this effect is at best erratic. Pedersen (1981) did not apply any statistical analysis to his first report on the possible effect of food on sustained release theophylline formulations. The Leeds (1982) study only showed a difference in the fraction absorbed per hour over 1 to 4 hours for the 100 mg formulation but not the 300 mg. In this formulation the only significant difference seen at a single hour interval was that at the 4 hour point.

Thompson et al (1983) carried out a Student's paired t-test using a diet of 68% carbohydrate, 15% protein and 17% fat compared with fasting and found a significant difference at 1, 3, 4 and 8 hours after administration but not after 0.5, 2, 6, 12 or 24 hours. The literature indicates that food may be implicated in delaying theophylline absorption from sustained release formulations but it does not prove it. The results of my own experiments and those of others already cited have been unable to prove convincingly any statistically valid effect. The fraction absorbed per hour would be the ideal measurement for proving this but the design of the experiment must concentrate on blood sampling over the first few hours when the effect is going to be the greatest. Sampling at every 15 minutes over the first two hours, then at 30 minutes up to 4 hours would be necessary to obtain accurate data. To obtain meaningful rates of elimination, administration or oral theophylline or intravenous theophylline would be essential.

There were several design faults in this study. After four study days is was difficult to persuade volunteers to return some time later to take oral liquid theophylline. Only 8 out of the 10 in the Provent group were willing to do this and one in the Theo-Dur group. The dose of oral liquid theophylline given was too small. Caution trying to avoid toxic levels was uppermost, but at the cost of low levels of theophylline measured. Higher plasma concentrations would have been obtained if a 300 mg dose of oral liquid had been used and more accurate elimination rate constants could have been calculated.

Volunteer 1 exhibited marked differences in theophylline pharmacokinetics following administration of the liquid formulation. Close examination of the data pertaining to volunteer 1 indicates that the half life associated with the terminal phase of the plasma

concentration time profile is not consistent with the k_{el} reported in the literature whereas that associated with the initial phase is. The data associated with the terminal phase appears to be an artefact or assay error due to the concentration of theophylline measured being close to the limits of the assay instrument. In this volunteer the data on the terminal phase was disregarded.

Stevens et al (1982) found no significant differences in the pharmacokinetics of Theo-Dur 300 mg tablets when the drug was given with oral metoclopramide 10 mg after overnight fasting. However, as described above, there is a large individual variation of bio-availability in metoclopramide and the presence of food is necessary for optimal activity.

In this experiment, when metoclopramide with food was compared with those volunteers fasting, no significant differences were seen. In the Provent group, 7 out of 10 had a reduced C_{max} but in both the Provent and the Theo-Dur groups the t_{max} was altered at random. The absorption rate constants were increased in only 4 out of the 8 volunteers measured in the Provent groups. The mean values were slightly higher for the absorption rate in the fasting volunteers. If the concept of food delaying absorption is correct, then the fact that no significant differences were seen between the metoclopramide with food and fasting groups was negated by metoclopramide, but as this delay by food was unable to be demonstrated in this experiment, no such deduction can be made.

When food is compared with metoclopramide with food, 8 out of 10 in the Provent group and 6 out of 10 in the Theo-Dur group had a decreased t_{max} but this and other pharmacokinetic parameters failed to reach statistical significance. Certainly, the addition of metoclopramide to either of the formulations, whether fasting or

non-fasting, failed to have any demonstrable effect on the absorption of theophylline. Metoclopramide has been shown to have an effect on paracetamol absorption when given intravenously and tetracycline absorption when given orally, (Nimmo et al 1973). Using Pivampicillin (Gothi et al 1972) and alcohol (Finch et al 1974 and Kreel et al 1972) metoclopramide has been shown to have a greater effect on gastric emptying when the gastric emptying time is more prolonged, as it is in women. In this study, no sex difference was seen in the response to metoclopramide amongst the volunteers.

As the rate of absorption of theophylline from sustained release formulations is governed primarily by the release and absorption from the formulation in the duodenum, it would not be unreasonable to expect very little effect between the fasting and the metoclopramide with food groups, as no delay in absorption was established with food alone, likewise, comparing food with metoclopramide and food alone.

There was an alteration in this absorption on the study days when propantheline was administered with sustained release theophylline. When fasting was compared with propantheline fasting groups a significant difference was seen in t_{max} and rate of absorption in the Provent volunteers but not in the Theo-dur taking volunteers. Unfortunately, it was not possible to measure the Theo-Dur group due to the inability to persuade volunteers to return after the propantheline study day. It could be that the rate-determining step when Provent is in the stomach (where the motility is reduced by propantheline) is the release of the multipellets from the gelatine capsule which encloses them. Hunter et al (1982) demonstrated that the emptying of multipellets from a gelatine capsule was dependent upon the pyloric contractions of the stomach.

The dispersal of pellets was prolonged when the capsule was taken after a meal. Unlike the channels in the matrix formulation which can start to leach theophylline straight away into the solution, the gelatine capsule multipellet formulation can be affected by gastric stasis to prolong this dispersal phase.

The theory of multipellet trickle (Bechgaard and Neilson 1978) is that due to incomplete pyloric closure, pellets can trickle from the stomach into the duodenum (the multipellet product having been formulated for release in the alkaline environment of the duodenum). If this theory is correct, reduced solution of the pellets in the acid media of the static stomach could explain the delay in absorption seen with propantheline in the multipellet Provent formulation compared with the matrix Theo-Dur preparation. Hendeles et al (1985) demonstrated that when Provent's sister formulation, Theo-24 (a multipellet formulation designed by the same person and available in the United States) was given with a large meal up to half the dose was "dumped" once the pellets were exposed to the influence of alkaline bile salts and pancreatic enzymes of the duodenum. But before this rapid absorption took place, initially the absorption was reduced due to the delay of the pellets in the stomach caused by the large meal. This underlines the problem of the formulation of sustained release theophylline products, each is a different drug due to its formulation and an effect on one formulation cannot be easily transposed to another.

When the fifth comparison was made between food and propantheline fasting, no statistical differences were seen. In the design of this experiment, if the expected delay with food had occurred, it could have been stated that the effect of propantheline is similar to the delay seen with food alone. Unfortunately, as

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this was not demonstrated in this experiment, this comparison is not valid even though no statistically significant differences were seen, indeed, a non-significant trend to an increased t_{max} was seen in both Provent (9 out of 10) and Theo-Dur (7 out of 10) groups which could indicate that propantheline had a greater effect than food alone on the rate of absorption of theophylline. In the Provent volunteers, where rate of absorption was able to be measured, 6 out of 8 volunteers had a reduced rate of absorption. If the volunteer numbers had been larger, it is possible that some significance could have been demonstrated. This means that no correlation between the effects of food and propantheline can be made. Propantheline does affect the release of theophylline from Provent and other similar drugs such as dicyclomine would also be expected to act in a similar way but the clinical implications of this are limited.

When comparisons were made between the drugs, analysis of variance showed significant differences in t_{max}, C_{max} and AUC_{0-12}. Theo-Dur had a higher C_{max}, longer t_{max} and larger AUC_{0-12} on most study days. Unpublished work by Hadizija and Wargin (personal communication, Wellcome laboratories 1984) has shown Provent to have a t_{max} of 8 hours and a C_{max} of 4.39 $\mu g\ ml^{-1}$ for a 300 mg dose, with 98.39% absorption after 12 hours. The AUC_{0-12} from the Hadizija and Wargin work was 43.148 $\mu g\ ml^{-1}\ h$. This compares favourably with the data in this experiment. Assuming first order kinetics, to account for twice the dose compared with the Hadizija and Wargin experiment, the t_{max} is 7.2 h, C_{max} 8.77 $\mu g\ ml^{-1}$ and the AUC_{0-12} 78.97 $\mu g\ ml^{-1}\ h$. However, the advantages of more uniform release proclaimed for the multipellet formulation compared with the matrix formulation of Theo-Dur have not been confirmed in this experiment. Indeed it might be affected more than the matrix formulation by loss of gastric motility.

CHAPTER 7

THE EFFECT OF SMOKING AND FOOD ON

PHYLLOCONTIN FORTE AND THEO-DUR

SUSTAINED RELEASE THEOPHYLLINE FORMULATIONS

INTRODUCTION

A number of authors, Jenne et al (1975), Hunt et al (1976), Powell et al (1977), Jusko et al (1979) and Horai et al (1983) have reported the effects of cigarette smoking on theophylline clearance, (table 15).

Table 15

COMPARISON OF NON-SMOKER/SMOKER PHARMACOKINETIC DATA

	Number of Subjects	Theophylline Clearance (L/h/kg ± SD)	Half life (h ± SD)	Volume of Distribution (L/kg ± SD)
Non-Smokers				
Jenne (1975)	14		7.2 ± 1.8	
Hunt (1976)	8	0.038 ± 0.010	7.0 ± 1.7	0.038 ± 0.04
Powell (1977)	15	0.04 ± 0.008	8.3	0.47 ± 0.08
Horai (1983)	6	0.035 ± 0.004		
Smokers				
Jenne (1975)	10		4.1 ± 1.0	
Hunt (1976)	8	0.086 ± 0.037	4.3 ± 1.4	0.5 ± 0.06
Powell (1977)	7	0.063 ± 0.019	5.4	0.5 ± 0.06
Horai (1983)	6	0.051 ± 0.006		

Three of the above authors demonstrated an increase in theophylline clearance and a decreased half life. Hunt et al (1976) found a significant increase in the apparent volume of distribution in heavy smokers, 0.50 ± 0.12 L/kg, compared with 0.38 ± 0.04 L/kg in non-smokers, (table 15). However, this increase was not comfirmed by Powell et al (1977) who found no difference in the volume of distribution between smokers and non-smokers. Hunt et al (1976)

tried to explain the difference by suggesting that in their experiments smokers were leaner and contained less body fat than non-smokers: when their data is corrected for estimated ideal body weight the values for volume of distribution are 0.492 L/kg for smokers compared with 0.403 L/kg for non-smokers. Hunt et al (1976) commented on the fact that smoking may affect bioavailability and hence the volume of distribution calculations. This suspected reduction of bioavailability was also commented upon by Horai et al (1983) who found a non-significant trend towards reduced bioavailability of theophylline from sustained release formulations in a small group of six smokers when compared with six non-smokers. In that study, one formulation had 16% less absolute bioavailability in smokers and a second formulation 13% less than in non-smokers. However, no explanation and no further details were given in those experiments.

The established increase in theophylline clearance in smokers has important clinical implications. Higher doses or increased frequency of administration are needed to maintain therapeutic concentrations of theophylline in smokers compared with non-smokers. If no allowance is made for increased clearance, the smokers could experience greater peak to trough variation, ineffective concentrations and failure of theophylline treatment.

This clinical implication has led Hendeles and Weinberger (1983) to claim that in adult smokers and other fast eliminators, Slobid, Sustaire (products not available on the UK market) and Theo-Dur are the only slow-release theophylline formulations that are completely absorbed at a rate to allow maintenance of serum concentrations within the therapeutic range for a 12 hour dosing interval. Of these, Hendeles and Weinberger (1983) demonstrated that Theo-Dur was the most effective (at a dose of 12.8 mg/kg).

Theo-Dur was the only slow-release product tested that maintained plasma concentrations within the therapeutic range of 10 - 20 $\mu g\ ml^{-1}$ for the 12 hour dosage interval. Hendeles, Iafrate and Weinberger (1984) stated "that in slow eliminators of theophylline clinically relevant differences between brands are not apparent. However, in patients with rapid elimination, ie, children, cigarette smokers, only some formulations, ie, Slo-Bid Gyrocaps and Theo-Dur can maintain serum concentrations within the therapeutic range for an entire 12 hour dosing interval". Hendeles et al (1984), based this on the mean fraction absorbed-time profile, calculated from a modification of the Wagner-Nelson equation, a process-independent method of comparing rates of absorption of different products after a single dose (see Appendix 3). They then used this data to predict steady state plasma profiles with each formulation. It is interesting to note that using this method, Hendeles et al (1984) used a single value of volume of distribution for smokers and non-smokers of 0.45 l/kg. When applied to children, Hendeles showed that the predicted values for Theo-Dur from the modified Wagner-Nelson equation correlated with measured serum theophylline concentrations and when given every twelve hours, Theo-Dur maintained serum levels within the therapeutic range. Although not shown, Hendeles predicted serum concentrations for adult smokers where the mean half life of elimination was 4 hours or less. He suggests these would be similar to the average child so that in adult smokers Theo-Dur would maintain therapeutic concentrations. Any preparation with faster absorption would not maintain the desired concentration. Phyllocontin Forte (350 mg of aminophylline), a continuous slow-release delivery system was introduced by Napp Laboratories in November 1983 and marketed primarily for the treatment of smokers. As food has been shown by a number of workers to reduce the absorption

of theophylline [Feldman et al (1982), Pedersen (1981), Leeds et al (1982)], increase t_{max} and lower C_{max}, it was of interest to investigate whether a slow-release formulation such as Phyllocontin Forte 350 mg taken with food would exhibit a more prolonged absorption so that at steady state there might be a minimal peak to trough variation in cigarette smokers, allowing serum concentrations to be held within an effective range throughout the dosing interval.

This experiment was designed to compare the pharmacokinetic profile of Phyllocontin Forte with Theo-Dur in smokers and non-smokers in fasting and non-fasting states.

METHOD

Two groups of volunteers comprising 10 non-smokers and 10 cigarette smokers (more than 10 cigarettes a day) participated in the study. Each group contained 2 females and 8 males; mean age in the smoking group was 24 years, and 26 years in the non-smoking group. The volunteers weighed between 50.5 - 77 Kg, the mean weight for the smokers being 71.5 Kg compared with 62.5 Kg for the non-smokers. All volunteers fasted overnight and were told to avoid xanthine containing foods and drinks for the experimental period.

On four separate days using a randomised, open, cross-over design, each volunteer received either 2 x 350 mg tablets of Phyllocontin Forte or 2 x 300 mg tablets of Theo-Dur, with a standard breakfast of cereal, toast, marmalade and milk (containing 17 g protein, 27 g fat and 76 g carbohydrate) or no breakfast. Each study day was separated by at least seven days.

STUDY GROUPS IN SMOKERS AND NON-SMOKERS

Phyllocontin forte 700 mg with food	Phyllocontin Forte 700 mg fasting	Theo-Dur 600 mg with food	Theo-Dur 600 mg fasting

The drug was administered as a single morning dose swallowed with 50 ml of water. volunteers in receipt of breakfast took the tablet immediately after eating. Lunch was eaten 5 hours after breakfast and consisted of a normal uncontrolled meal.

Blood samples (3 - 5 ml) were taken via an indwelling cannula immediately before the morning dose and at 1, 2, 3, 4, 5, 6, 7, 10, 12, 16, 20 and 24 hours afterwards. Plasma was assayed immediately for theophylline by enzyme immunoassay.

Pharmacokinetic parameters, C_{max}, t_{max} were measured, AUC_{0-24} was calculated by the trapezoidal rule and extrapolated to infinity

to give $AUC_{0-\infty}$. The decay constant was calculated by regression analysis and elimination half life calculated from the equation

$$t_{\frac{1}{2}} = \frac{0.693}{k_{el}}$$

Statistical analysis was made using analysis of variance, using the SPSSX programme on the University of Sheffield Prime computer.

Informed consent was obtained from all volunteers and the study was approved by Aston University and the Central Birmingham Health Authority Ethical Committees.

RESULTS

The results showed a highly statistical difference in AUC_{0-24}, K_d, $t_{\frac{1}{2}}$, C_{max} and t_{max} between smokers and non-smokers (tables 17-21). The mean AUC_{0-24} was between 40 to 60% greater in non-smokers than in smokers. C_{max} and t_{max} were statistically significantly higher (table 16) in non-smokers under all conditions studied.

Figures 17 to 20 show the effects of smoking on Phyllocontin Forte and Theo-Dur profiles. The AUC_{0-24} can clearly be seen to be less in smokers with a reduction in t_{max}. The slope of the absorption phase is identical in figures 17 and 18 for Theo-Dur but the slope of the absorption phase is different in figures 19 and 20 for Phyllocontin whereas in smokers, graphically, the absorption of theophylline is slower.

Figures 21 to 24 show the significant reduction in $t_{\frac{1}{2}}$, t_{max}, AUC_{0-24} and C_{max} between smokers and non-smokers. All values are less in smokers with lower standard deviations, especially in figure 23.

In this experiment no significant differences were shown between volunteers taking sustained release theophylline with or without food. In smokers, 12 out of 20 total volunteer profiles studied showed an increase in t_{max}, 2 showed no effect and 6 showed a reduction in t_{max} when given the formulation with food. 2 of these reductions occurred in the Phyllocontin group, 4 in the Theo-Dur group (figure 27) Three of the four in the Theo-Dur group showed a substantial and unexpected reversal of the established concept that food prolongs t_{max}. In non-smokers 9 out of 20 volunteers had a prolonged t_{max}, 6 showed no effect and 5 showed a reduction when co-administration of food took place (see figure 28). In both smokers and non-smokers the mean t_{max} with food was higher than when fasting but failed to reach significance.

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The mean C_{max} for Phyllocontin Forte in both smokers and non-smokers was reduced when given with food but with Theo-Dur it was increased (figures 25 and 26). In the Phyllocontin Forte groups 14 volunteers had a reduction and 6 had an increase in C_{max}. In the Theo-Dur groups 8 showed a decrease, 1 showed no difference and 11 a substantial increase in C_{max} when given food. Of these, 4 showed an increase of 3.7, 4.2, 3.2 and 4.8 $\mu g\ ml^{-1}$.

The AUC_{0-24} for Phyllocontin Forte or Theo-Dur was not statistically affected by the presence of food (figures 24, 30, 31 and 32). In Phyllocontin Forte, the AUC_{0-24} was higher when fasting than with food (table 16) but was not significant. Theo-Dur was not consistent, in non-smokers with food a larger AUC_{0-24} was recorded than when fasting.

When drug to drug comparisons were made there was a significant difference in t_{max} between Phyllocontin forte and Theo-Dur, ($F = 0.000$). The mean t_{max}s for Phyllocontin Forte fasting and with food were 6.0 h and 6.6 h compared with Theo-Dur fasting and with food of 8.1 h and 7.5 h in smokers. In non-smokers Phyllocontin Forte fasting and with food had t_{max} values of 7.3 h and 7.4 h compared with 8.9 and 9.3 h for Theo-Dur fasting and with food respectively. All other parameters when compared drug with drug failed to reach significance (tables 17 to 21). Figures 33 and 34 show the difference in the rate of absorption when the two fasting situations are compared in smokers for Phyllocontin Forte but the t_{max} being identical with the C_{max}, only 0.55 $\mu g\ ml^{-1}$ apart.

Figures 35 and 36 show the effect when Phyllocontin forte, fasting and with food, is compared with Theo-Dur with food in smokers. The much slower absorption profile of Theo-Dur can be seen.

The EMIT kit batch to batch co-efficient of variation for this experiment was 4.2%.

Table 16

COMPARISON OF MEAN ($\pm$ STANDARD DEVIATION) DATA FOR SMOKERS AND NON-SMOKERS

	Time to Maximum Concentration (h)	Maximum Concentration (mg ml^{-1})	Rate of Decay (h^{-1})	AUC_{0-24} ($\mu g\ ml^{-1}\ h$)	$AUC_{0-\infty}$ ($\mu g\ ml^{-1}\ h$)	Half Life (h)
SMOKERS						
Phyllocontin fasting	6.0 $\pm$ 0.9	9.3 $\pm$ 1.5	0.08 $\pm$ 0.022	134.8 $\pm$ 13.83	167.7 $\pm$ 28.7	9.3 $\pm$ 2.4
Phyllocontin with food	6.6 $\pm$ 1.3	8.4 $\pm$ 1.2	0.08 $\pm$ 0.022	115.4 $\pm$ 26.85	152.3 $\pm$ 48.6	9.7 $\pm$ 4.2
Theo-Dur fasting	8.1 $\pm$ 2.4	9.3 $\pm$ 2.6	0.075 $\pm$ 0.031	130.0 $\pm$ 11.15	182.2 $\pm$ 47.1	11.05 $\pm$ 5.24
Theo-Dur with food	7.5 $\pm$ 1.2	9.6 $\pm$ 2.0	0.098 $\pm$ 0.032	122.19 $\pm$ 17.92	147.6 $\pm$ 32.5	7.7 $\pm$ 2.15
NON-SMOKERS						
Phyllocontin fasting	7.3 $\pm$ 1.2	11.5 $\pm$ 1.9	0.058 $\pm$ 0.024	187.79 $\pm$ 42.93	299.4 $\pm$ 133.2	14.1 $\pm$ 6.1
Phyllocontin with food	7.4 $\pm$ 1.3	10.9 $\pm$ 2.9	0.046 $\pm$ 0.019	178.15 $\pm$ 45.99	309.8 $\pm$ 103.3	17.1 $\pm$ 5.4
Theo-Dur fasting	8.9 $\pm$ 1.8	10.6 $\pm$ 3.5	0.05 $\pm$ 0 015	174.92 $\pm$ 53.35	304.1 $\pm$ 125.0	14.9 $\pm$ 5.1
Theo-Dur with food	9.8 $\pm$ 1.8	11.3 $\pm$ 3.1	0.053 $\pm$ 0.018	180.36 $\pm$ 46.98	322.2 $\pm$ 136.3	13.9 $\pm$ 3.9

Table 17

ANALYSIS OF VARIANCE
SPSS-X (Sheffield) release 1.0 PRIME 9950

* * * A N A L Y S I S O F V A R I A N C E * * *

BY	TMAX	TIME TO MAXIMUM CONCENTRATION
	SMOKER	SMOKER OR NO-SMOKER
	DRUG	DRUG USED
	FOOD	FOOD OR FASTING

SOURCE OF VARIATION	SUM OF SQUARES	DF	MEAN SQUARE	F	SIGNIF OF F
MAIN EFFECTS	96.300	3	32.100	13.375	0.000
SMOKER	33.800	1	33.800	14.083	0.000*
DRUG	61.250	1	61.250	25.521	0.000
FOOD	1.250	1	1.250	0.521	0.473
2-WAY INTERACTIONS	2.700	3	0.900	0.375	0.771
SMOKER DRUG	1.250	1	1.250	0.521	0.473
SMOKER FOOD	1.250	1	1.250	0.521	0.473
DRUG FOOD	0.200	1	0.200	0.083	0.774
3-WAY INTERACTIONS	5.000	1	5.000	2.083	0.153
SMOKER DRUG FOOD	5.000	1	5.000	2.083	0.153
EXPLAINED	104.000	7	14.857	6.190	0.000
RESIDUAL	172.800	72	2.400	6.190	0.000
TOTAL	276.800	79	3.504		

80 CASES WERE PROCESSED
0 CASES (0.0 PCT) WERE MISSING

* Significant value

Table 18

ANALYSIS OF VARIANCE
SPSS-X (Sheffield) release 1.0 PRIME 9950

* * * A N A L Y S I S O F V A R I A N C E * * *

BY	CMAX	MAXIMUM CONCENTRATION
	SMOKER	SMOKER OR NO-SMOKER
	DRUG	DRUG USED
	FOOD	FOOD OR FASTING

SOURCE OF VARIATION	SUM OF SQUARES	DF	MEAN SQUARE	F	SIGNIF OF F
MAIN EFFECTS	83.309	3	27.770	4.226	0.008
SMOKER	82.013	1	82.013	12.480	0.001*
DRUG	0.145	1	0.145	0.022	0.883
FOOD	1.152	1	1.152	0.175	0.677
2-WAY INTERACTIONS	18.741	3	6.247	0.951	0.421
SMOKER DRUG	6.272	1	6.272	0.954	0.332
SMOKER FOOD	0.145	1	0.145	0.022	0.883
DRUG FOOD	12.325	1	12.325	1.875	0.175
3-WAY INTERACTIONS	0.512	1	0.512	0.078	0.781
SMOKER DRUG FOOD	0.512	1	0.512	0.078	0.781
EXPLAINED	102.562	7	14.652	2.229	0.041
RESIDUAL	473.166	72	6.572		
TOTAL	575.728	79	7.288		

80 CASES WERE PROCESSED
0 CASES (0.00 PCT) WERE MISSING

* Significant value

Table 19

ANALYSIS OF VARIANCE
SPSS-X (Sheffield) release 1.0 PRIME 9950

* * * A N A L Y S I S O F V A R I A N C E * * *

BY T.5 HALF LIFE
SMOKER SMOKER OR NO-SMOKER
DRUG DRUG USED
FOOD FOOD OR FASTING

SOURCE OF VARIATION	SUM OF SQUARES	DF	MEAN SQUARE	F	SIGNIF OF F
MAIN EFFECTS	624.067	3	208.022	10.164	0.000
SMOKER	614.386	1	614.386	30.019	0.000*
DRUG	8.646	1	8.646	0.422	0.518
FOOD	1.035	1	1.035	0.051	0.823
2-WAY INTERACTIONS	110.681	3	36.894	1.803	0.154
SMOKER DRUG	5.995	1	5.995	0.293	0.590
SMOKER FOOD	30.381	1	30.381	1.484	0.227
DRUG FOOD	74.305	1	74.305	3.631	0.061
3-WAY INTERACTIONS	0.066	1	0.066	0.003	0.955
SMOKER DRUG FOOD	0.066	1	0.066	0.003	0.955
EXPLAINED	734.815	7	104.974	5.129	0.000
RESIDUAL	1473.605	72	20.467		
TOTAL	2208.420	79	27.955		

80 CASES WERE PROCESSED
0 CASES (0.00 PCT) WERE MISSING

* Significant value

Table 20

ANALYSIS OF VARIANCE
SPSS-X (Sheffield) release 1.0 PRIME 9950

* * * A N A L Y S I S O F V A R I A N C E * * *

BY KD RATE OF DECAY
SMOKER SMOKER OR NO-SMOKER
DRUG DRUG USED
FOOD FOOD OR FASTING

SOURCE OF VARIATION	SUM OF SQUARES	DF	MEAN SQUARE	F	SIGNIF OF F
MAIN EFFECTS	0.020	3	0.007	11.202	0.000
SMOKER	0.020	1	0.020	32.759	0.000*
DRUG	0.000	1	0.000	0.322	0.572
FOOD	0.000	1	0.000	0.523	0.472
2-WAY INTERACTIONS	0.003	3	0.001	1.738	0.167
SMOKER DRUG	0.000	1	0.000	0.162	0.688
SMOKER FOOD	0.001	1	0.001	2.395	0.126
DRUG FOOD	0.002	1	0.002	2.657	0.107
3-WAY INTERACTIONS	0.000	1	0.000	0.057	0.812
SMOKER DRUG FOOD	0.000	1	0.000	0.057	0.812
EXPLAINED	0.023	7	0.003	5.554	0.000
RESIDUAL	0.043	72	0.001		
TOTAL	0.066	79	0.001		

80 CASES WERE PROCESSED
0 CASES (0.0PCT) WERE MISSING.

* Significant value

Table 21

ANALYSIS OF VARIANCE
SPSS-X (Sheffield) release 1.0 Prime 9950

* * * A N A L Y S I S O F V A R I A N C E * * *

BY AUC AREA UNDER PLASMA TIME CURVE 0-24
SMOKER SMOKER OR NO-SMOKER
DRUG DRUG USED
FOOD FOOD OR FASTING

SOURCE OF VARIATION	SUM OF SQUARES	DF	MEAN SQUARE	F	SIGN OF F
MAIN EFFECTS	61336.662	3	20445.554	15.773	0.000
SMOKER	60036.690	1	60036.690	46.317	0.000*
DRUG	85.822	1	85.822	0.066	0.798
FOOD	1214.149	1	1214.149	0.937	0.336
2-WAY INTERACTIONS	1727.908	3	575.969	0.444	0.722
SMOKER DRUG	212.356	1	212.356	0.164	0.687
SMOKER FOOD	646.726	1	646.726	0.499	0.482
DRUG FOOD	868.826	1	868.826	0.670	0.416
3-WAY INTERACTIONS	18.012	1	18.012	0.014	0.906
SMOKER DRUG FOOD	18.012	1	18.012	0.014	0.906
EXPLAINED	63082.582	7	9011.797	6.952	0.000
RESIDUAL	93327.944	72	1296.221		
TOTAL	156410.525	79	1979.880		

80 CASES WERE PROCESSED
0 CASES (0.0 PCT) WERE MISSING.

* Significant value

Figure 17

THEO - DUR FASTING

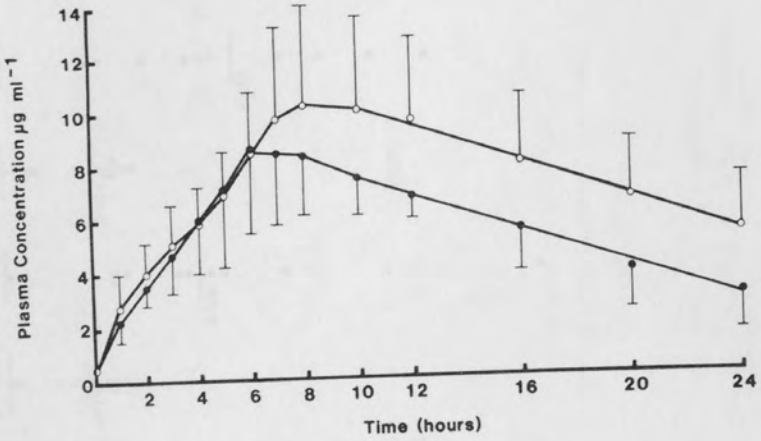


Figure 18

THEO - DUR WITH FOOD

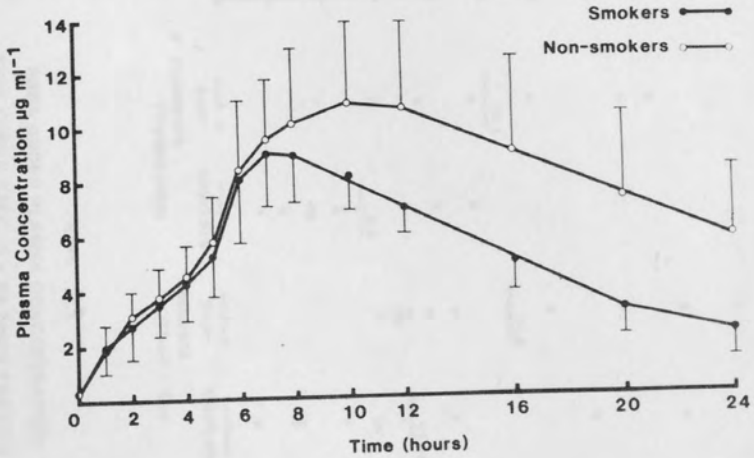


Figure 19

PHYLLOCONTIN WITH FOOD

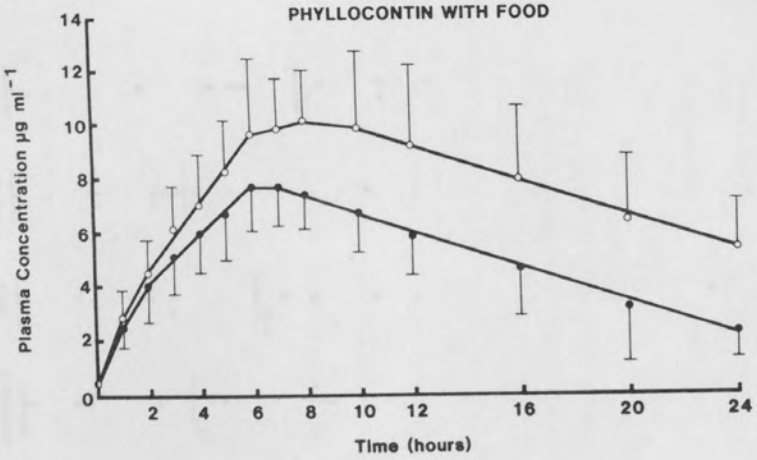


Figure 20

PHYLLOCONTIN FASTING

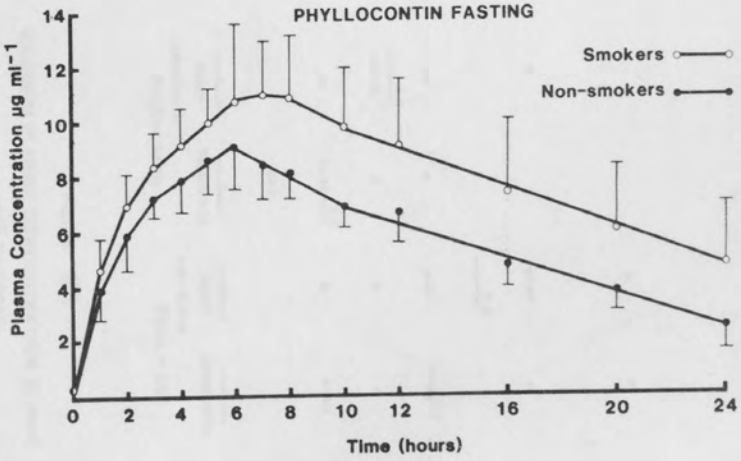


Figure 21

HALF LIFE ($t_{\frac{1}{2}}$) HOURS FASTING

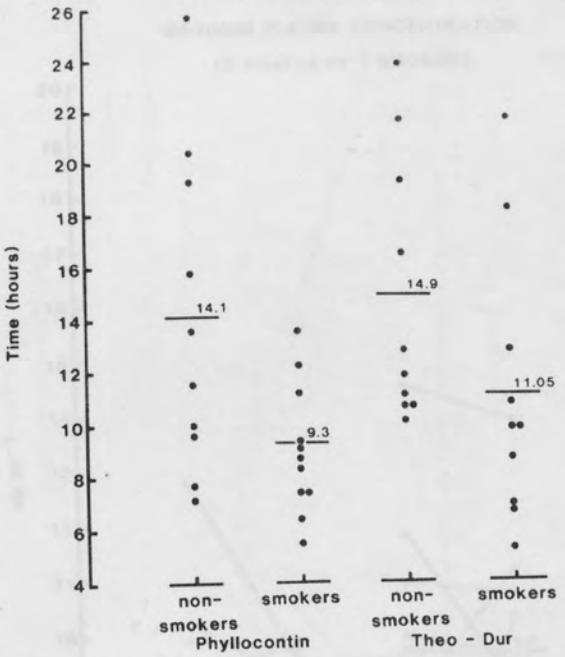


Figure 22

TIME TO MAXIMUM CONCENTRATION

(t max) HOURS FASTING

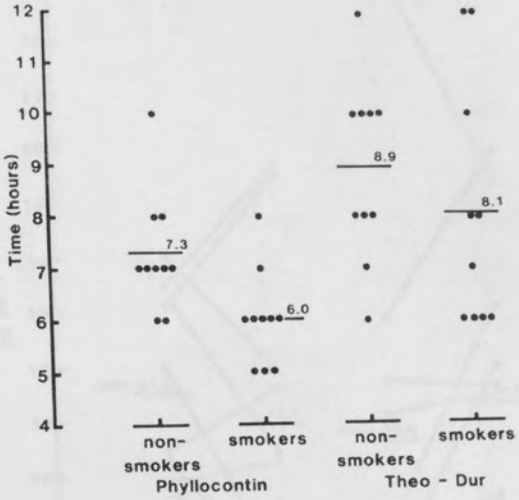


Figure 23

AREA UNDER PLASMA CONCENTRATION

TIME CURVE A.U.C. 0 - 24 hours FASTING

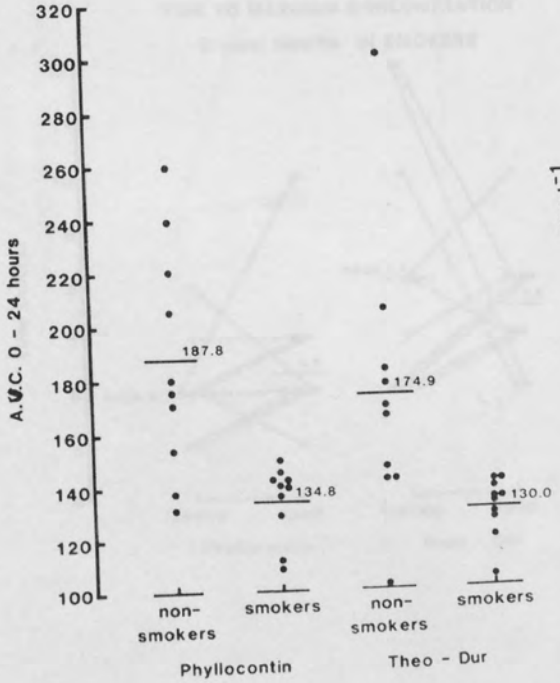


Figure 24

MAXIMUM PLASMA CONCENTRATION (C max)

$\mu g\ ml^{-1}$ FASTING

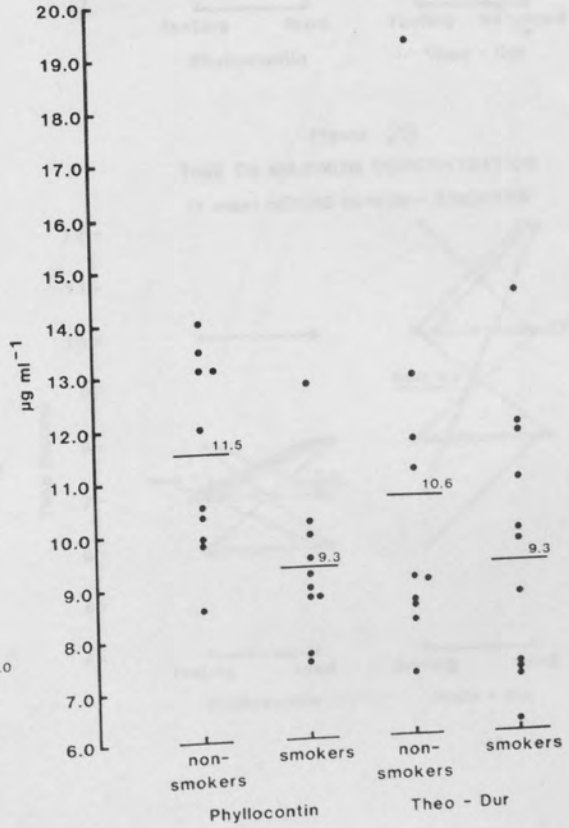


Figure 25

MAXIMUM PLASMA CONCENTRATION

(C max) μg ml^{-1} SMOKERS

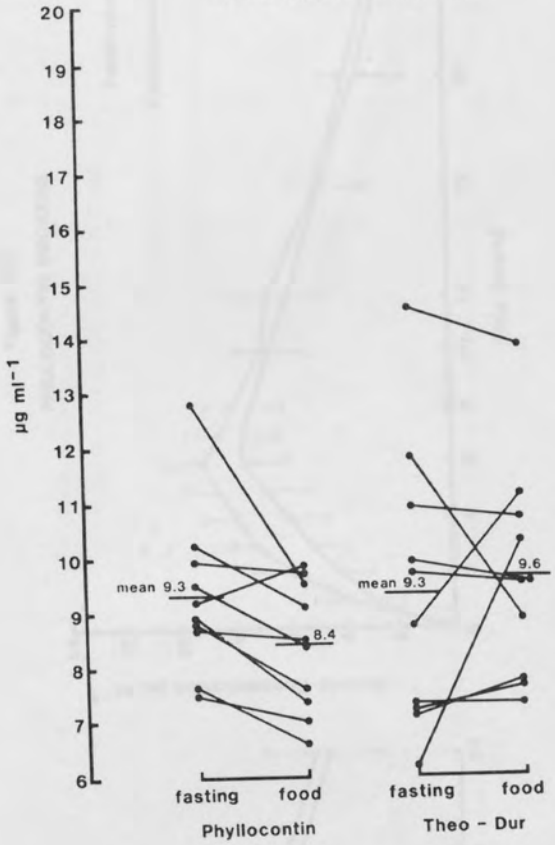


Figure 26

MAXIMUM PLASMA CONCENTRATION

(C max) μg ml^{-1} NON - SMOKERS

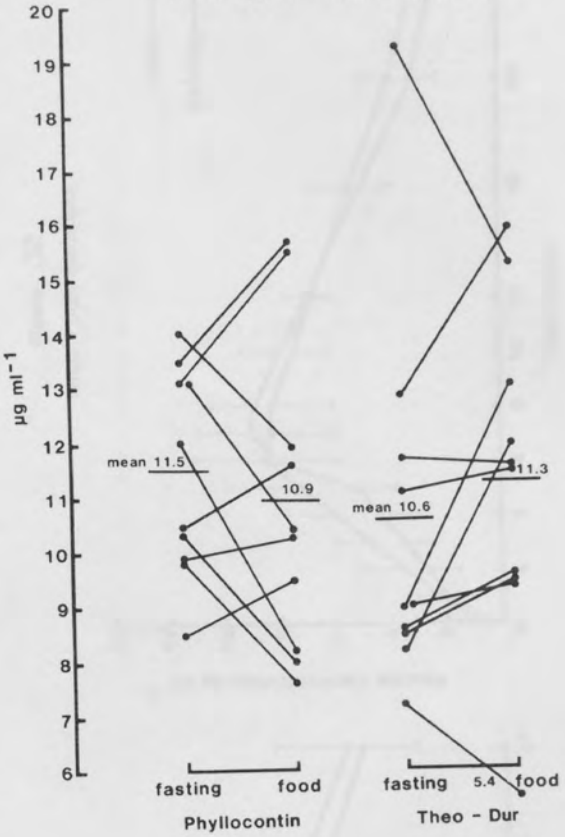


Figure 27

TIME TO MAXIMUM CONCENTRATION

(t max) HOURS IN SMOKERS

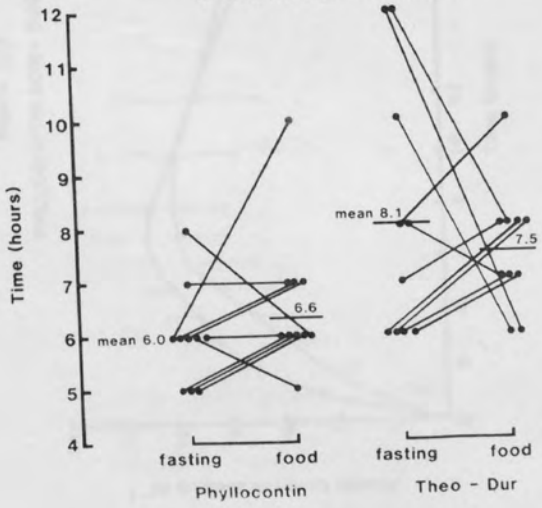


Figure 28

TIME TO MAXIMUM CONCENTRATION

(t max) HOURS IN NON - SMOKERS

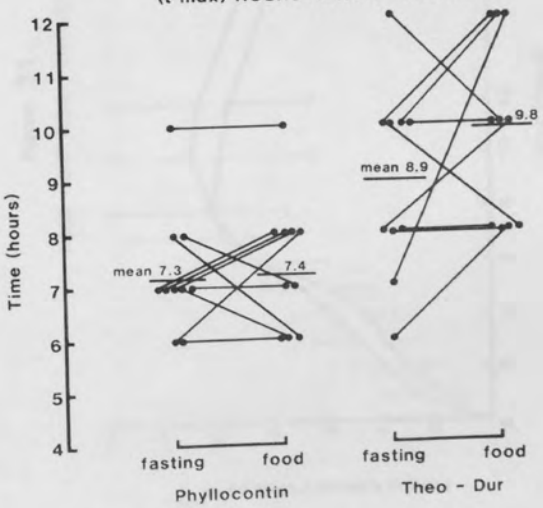


Figure 29

PHILLOCONTIN NON - SMOKERS

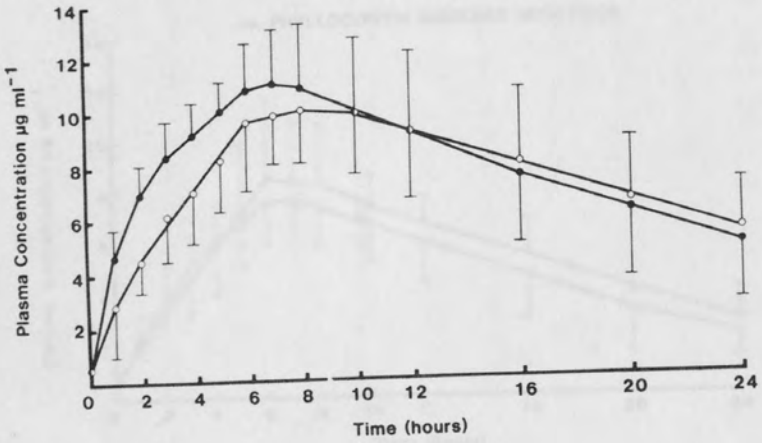


Figure 30

PHILLOCONTIN SMOKERS

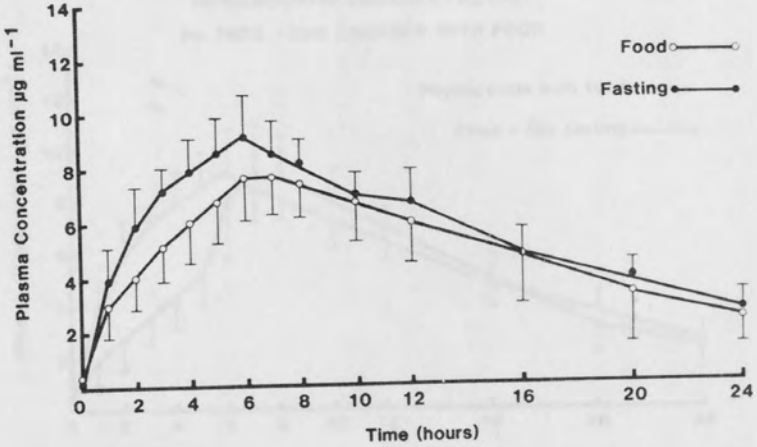


Figure 31

THEO - DUR NON - SMOKERS

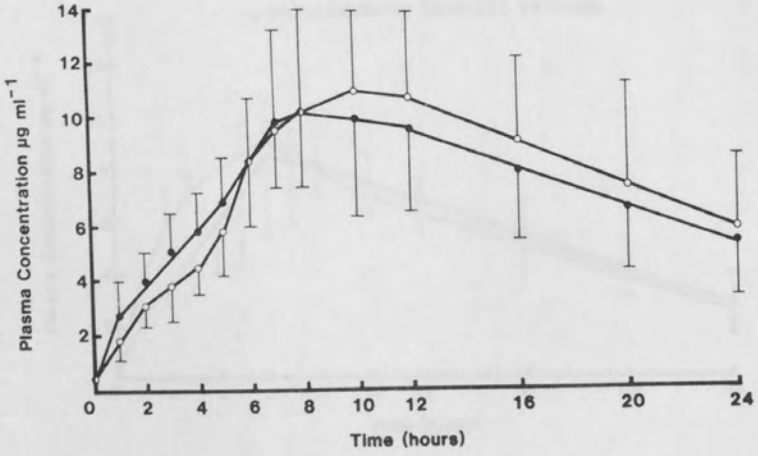


Figure 32

THEO - DUR SMOKERS

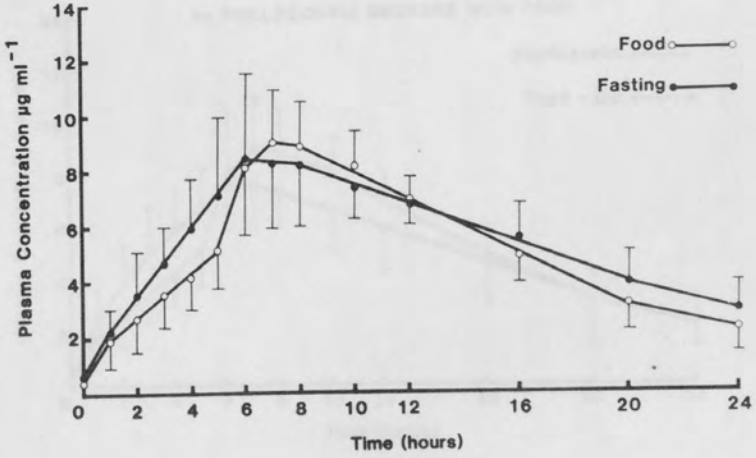


Figure 33

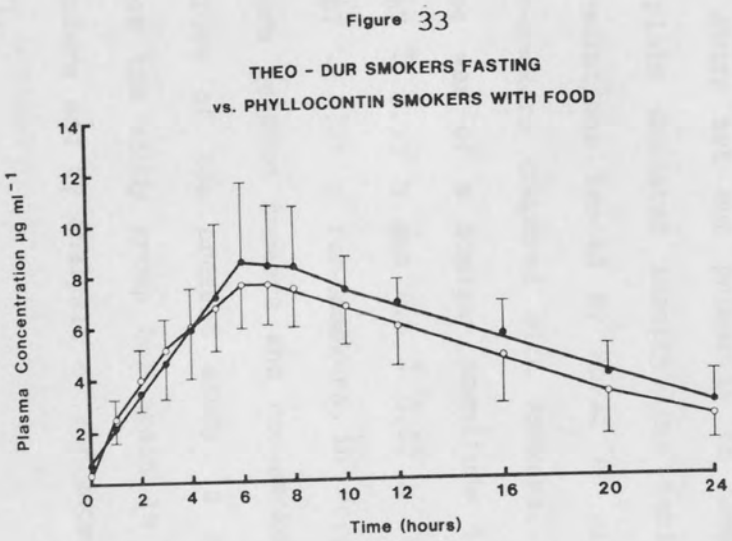


Figure 34

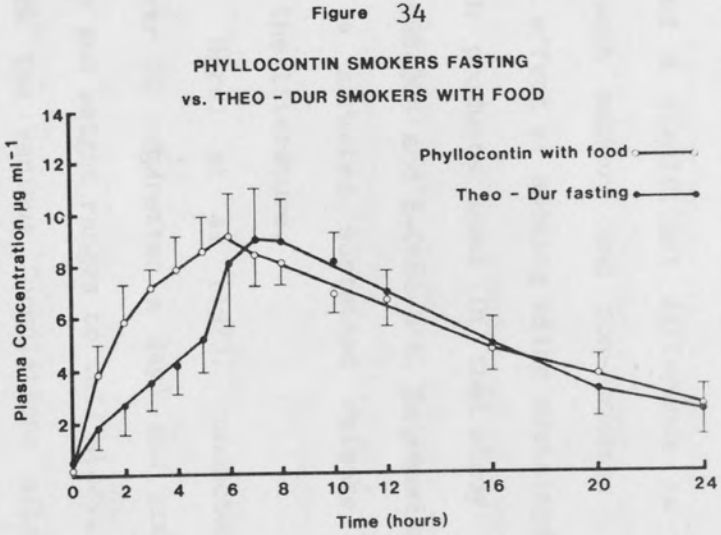


Figure 35

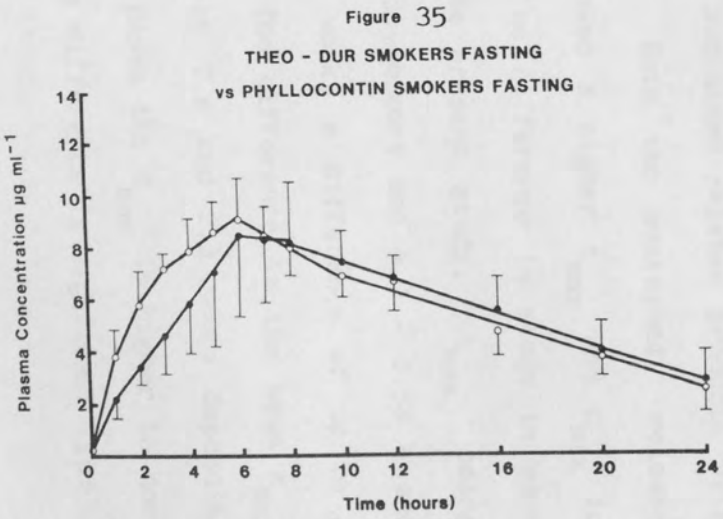
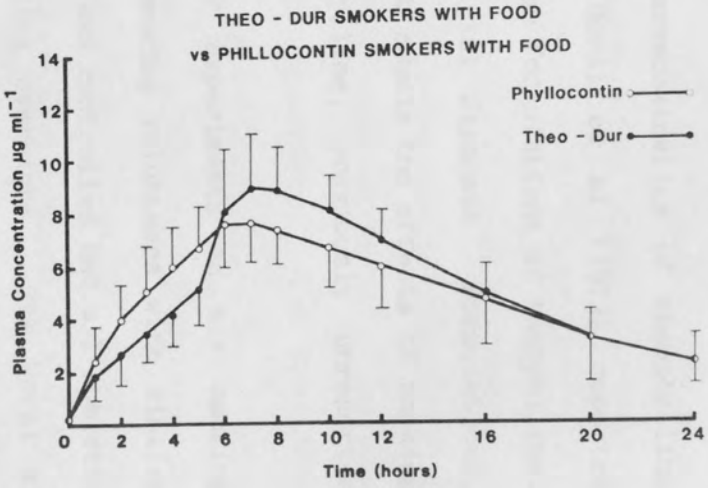


Figure 36



DISCUSSION

The results of this experiment are consistent with the findings of Horai et al (1973), Hunt et al (1976) and Powell et al (1977) who found a significant difference in the pharmacokinetics of theophylline between smokers and non-smokers. Only Horai et al (1973) reported the effect of smoking using sustained release formulations of theophlline. Both products used in that study were trial Japanese formulations, E-0686-004 and E-0686-016. The present experiment details the effects of smoking on a marketed sustained release theophylline, previously unreported in the literature.

Horai et al (1973) conducted their experiments on six smoking (over 20 cigarettes a day) and six non-smoking volunteers with similar age and weight ranges to this study. Diet was controlled and all subjects took the various formulations after fasting overnight. The Horai et al study set out primarily to compare sustained release products with a plain uncoated theophylline tablet. Both the sustained release formulations tested by Horai et al showed a higher t_{max} and C_{max} in non-smokers compared with smokers. The difference in means in each case was of a similar magnitude to the present study, t_{max} being 5.67 $\pm$ 0.33 h and 4.8 $\pm$ 0.02 h for non-smokers and 4.0 $\pm$ 0.58 h and 4.67 - 0.21 h for smokers in Horai's work, a difference of up to 2 hours between smokers and non-smokers. The difference in the mean t_{max} values of the present study is between 0.8 and 2.3 hours depending upon the study group but again in all cases the t_{max} is higher in non-smokers and by analysis of variance this difference is signficant (table 17).

Similar comparisons of C_{max} between Horai's and this study can also be made. In both experiments, C_{max} was higher in non-smokers

and the differences of means are of the same magnitude when dosage differences between the two studies are taken into account. In Horai's study, significance between smokers and non-smokers was not reported but in this study the difference in C_{max} for both sustained release products tested between smokers and non-smokers was significant (table 18).

Horai et al measured the absolute bioavailability of the sustained release products tested. There was a trend, although not statistically significant, for the bioavailability from both sustained release formulations to be less in smokers than non-smokers. The mean AUCs were significantly smaller in smokers than in non-smokers, ($P < 0.05$), and this was reproduced in my own study. Absolute bioavailability was not determined but there was a significantly smaller AUC_{0-24} in smokers when compared with non-smokers possibly indicating a reduced bioavailability in smokers. This would be a clinically significant effect, when determining dosage of theophylline in smokers. It is now common to take into account the increased drug clearance in smokers but no-one takes into account reduced bioavailability.

The reduced C_{max} and half life in cigarette smokers can in part be explained by the induced cytochrome P-450 mediated path way of theophylline metabolism. Grygiel and Birkett (1981) produced evidence that cigarette smoking induced the cytochrome P-450 mediated path ways of theophylline metabolism, although it was thought that N-demethylation might be increased to a greater extent than 8-hydroxylation (Introduction). Smoking may be affecting the process of absorption from the gut to the blood compartment. Nicotine stimulates the parasympathetic ganglia, resulting in increased tone and motor activity of the bowel. Nausea, vomiting and diarrhoea are observed following systemic absorption of nicotine. The results of the present experiment may be explained by an increase in transit time of the sustained

release formulation by increasing gastric motility, decreasing the time available for the theophylline to be absorbed. Certainly, some of the clinical implications of these effects have been reported. Pfeifer and Greenblatt (1978) in a study of 2,766 patients on theophylline found a reduced incidence of side effects in smokers, 7%, than in non-smokers, 13%. As side effects of theophylline correlate well with plasma concentrations (Weinberger and Hendeles 1976), it would indicate that smokers do have lower concentrations of theophylline than non-smokers. This formerly had always been assumed to be due to induced metabolism of theophylline resulting in increased drug clearance, but reduced bioavailability could be an important additional effect of smoking. All the literature on the effects of smoking on drugs concentrates on the problems related to drug clearance (D'Arcy 1984). Drugs which are not metabolised do not seem to be mentioned. A further study to measure absolute bioavailability in smokers compared with non-smokers taking sustained release theophylline would be worth while, as such a study has not appeared in the literature.

A significant increase in rate of decay and a reduced half life was shown in smokers. The alteration of rate of decay in this study was between 25 and 50%, which is similar to other studies reporting increased theophylline clearance.

Other workers have not reported the elimination half life of sustained release theophylline in smokers but, as expected, this was reduced in smokers, eg, between 26 and 46%.

This reduction of half life has been anticipated by Hendeles and Weinberger (1983) in that they comment that "even when patients are on the more slowly released products, such as Theo-Dur, some smoking patients may require eight hour dosing to prevent repeated breakthrough of asthmatic symptoms prior to the next dose." The half life for both Phyllocontin Forte and Theo-Dur in smokers was greater than reported in non-smokers for other sustained release formulations (Chapter 1).

When the sustained release formulation was given on fasting and non-fasting volunteers this study was unable to show any statistically significant difference between the two groups in any of the parameters measured. The principle that food does delay absorption by reducing C_{max} and increasing t_{max} has been proposed by Pedersen (1981), Feldman et al (1980) and Leeds et al (1982). In the Phyllocontin groups and smoker and non-smoker groups there was a trend towards a lower C_{max} (figures 29 and 30) but no effect on t_{max} when taken with food. The Theo-Dur groups showed the reverse, (figures 31 and 32). There was a trend to longer t_{max} but in both smokers and non-smokers, C_{max} was higher when the drug was given with food.

The differences that occurred with food could not be traced to any single volunteer. The response to food appeared to be random amongst the volunteers. Volunteer 18 had a decrease in C_{max} of 4.0 $\mu g\ ml^{-1}$ with Theo-Dur but an increase of 2.2 $\mu g\ ml^{-1}$ with Phyllocontin Forte between fasting and non-fasting conditions whereas volunteer 12 had a decrease of 2.4 $\mu g\ ml^{-1}$ with Phyllocontin and an increase of 4.1 $\mu g\ ml^{-1}$ with Theo-Dur.

This intra and inter-variation in theophylline pharmacokinetics has been commented upon by Szeflet et al (1984) who conducted a study comparing the profiles of Slo-Phyllin Gyrocaps with Theo-Dur in a cross-over single dose study, each study day separated by a week. He found that some subjects showed little variation but others showed

considerable differences between drugs and study days. Dederich et al (1981) in a similar study comparing the same sustained release formulations as Szefler with eight volunteers also found a wide range of intra-subject pharmacokinetic parameters. Upton et al (1982) confirmed statistically that 39 out of 60 participating individuals in a study varied in their disposition rate on the different occasions, each was required to take a dose during the course of a cross - over bioavailability trial. Fluctuations as much as 60% were seen and changes were not confined to sex, smokers or non-smokers or to heavier or lighter individuals. Upton et al (1982) found no explanation for the intra-individual variability. Pollack et al (1984) commented in a comparison study between a sustained release tablet and a beaded capsule, that the tablet formulation showed considerably more intra-subject variation for absorption profiles than the capsule formulation. Pedersen (1984) also reported variability in absorption profiles of theophylline from Theo-Dur sprinkle when ten asthmatic children in a study took the formulation with a wet meal, dry meal or fasting. One child had no detectable serum theophylline levels three hours after taking the drug but then an abrupt absorption occurred with peak levels 12 hours after intake. There is no doubt that intra and inter-variation in theophylline absorption occurs from sustained release formulations and reporting of mean data in the literature has, I feel, often disguised this effect.

Dederich et al (1981) listed gastric emptying, intestinal motility and food transit time as some of the possible factors to explain this variability, Pollack et al (1984) attributed these individual differences to gastro-intestinal physiology. Differences in food composition (Welling et al 1975) and fluid have been shown to affect theophylline absorption. Pedersen (1984) concluded that various meals may have different effects upon sustained release theophylline. But in a

standardised study such as this one where all volunteers took identical food with the sustained release preparation swallowed with a measured 50 ml of water, it seems unlikely that this has had a major influence. It must be related to a major individual variable such as gastric emptying, muscle tone, or the subject being tensed or relaxed. These must have an individual effect that is greater or can override the mean effect of delayed t_{max}, slowed absorption that food produces. It would be interesting to repeat such experiments with mood altering or gastric emptying modifying drugs to see if some of these variables could be identified. Certainly, in those authors where intra/inter-subject variation has not been admitted and mean data alone has been presented, critical evaluation of the conclusions cannot be easily made.

The complexity of theophylline absorption from sustained release formulations cannot be explained by variations in gastro-intestinal physiology alone. Certainly, in the initial absorption phase, circadian variation may play a role. MacLeod et al (1983) and Birkett et al (1984) have all commented upon this effect of theophylline disposition. MacLeod et al suggested that there could be as much as a 40% increase in nocturnal elimination compared with diurnal elimination. Opposing this, Birkett et al (1984) and Nolte and Newman (1980) found no difference in resulting blood levels of theophylline between morning and evening doses of sustained release theophyllines. In this present study, some of the volunteers often arrived later in the study day. Due to the lateness of arrival these volunteers took the morning dose of drug as quickly as possible. On a number of occasions minutes may have elapsed between being asleep and starting the study day. In this case the effect of the nocturnal circadian variation may have had some influence on the initial absorption phase of the sustained release preparation studied. Other volunteers always arrived having

been awake for some hours. This was in the most part random, and hence could in part explain some of the differences in individual variations that occurred between study days. In future studies it may be important to start the study day well into the morning so all volunteers or patients are in the diurnal mode.

The lack of effects of food on the absorption characteristics in this study could be overridden by the greater effect of smoking. The effects of food on the absorption profile in smokers has not previously been demonstrated. Previous studies were on children, (Pedersen 1981 and Feldman et al 1980) and healthy non-smoking males, Leeds (1982).

It is possible that the effect of food is not always of the magnitude that will constitute a major modification of theophylline absorption from sustained release products in patients where other more influential variables may be present such as smoking, circadian variations and gastric physiology. It may be one factor to be taken into account and certainly Pedersen (1981) and Thompson et al (1983) are correct to suggest that theophylline sustained release products should be taken with food. Although Hendeles (1985) has shown that dose dumping can occur when Theo-24 is taken with a large meal.

When the drug to drug comparison is made in this study, a significant difference (table 17) occurs between Phyllocontin Forte and Theo-Dur in the time to maximum concentration. No other significant differences are seen in any of the other pharmacokinetic parameters measured. In all study groups the t_{max} for Theo-Dur was greater than for Phyllocontin Forte. This does indicate that the rate of absorption is more prolonged in Theo-Dur. When the plasma concentration time profiles are compared (figures 33 to 36) differences can be seen only in the absorption phase. When Theo-Dur fasting and Phyllocontin Forte with food in smokers are compared (figure 33) almost identical plasma

concentration time profiles result. At steady state it would be anticipated that very little difference would be seen between the two drugs formulations in peak to trough variation if Phyllocontin Forte is adminstered with food.

Hendeles's (1984) statement that Theo-Dur is the most suitable slow-release product for fast eliminators, such as children and smokers, was verified by experimentation in children but not in smokers. This experiment has substantiated that Phyllocontin Forte when given with food is similar to Theo-Dur given either fasting or with food. If both are taken on an empty stomach, Theo-Dur does maintain better absorption characteristics as measured by plasma concentration time profiles (figure 35). It also emphasises that studies on sustained release theophyllines must be carried out on smokers as well as non-smokers, as Pedersen (1984) has also suggested, with different diets to ascertain the full implication of these formulations in patients, especially as theophylline has such variable pharmacokinetics.

Hendeles and Weinberger (1983) also state "that it is misleading to compare products in non-smoking adults where elimination on the average, is slow. Dosing recommendations based upon such comparisons do not accurately reflect differences between products that can become clinically important for most children, smoking adults and about 25% of non-smoking adults with more rapid than average elimination."

This statement by Hendeles and Weinberger itself fails to take into account other variations that can occur, certainly if, as indicated, the reduced bioavailability of theophylline from sustained release formulations in smokers can be substantiated by further experimentation.

CONCLUSION

This experiment has shown that when Phyllocontin Forte and Theo-Dur sustained release theophylline preparations are administered to smoking and non-smoking, healthy volunteers, significant differences occur in the pharmacokinetic parameters of t_{max}, C_{max}, $t_{\frac{1}{2}}$, K_d and AUC_{0-24} between smokers and non-smokers.

In both smokers and non-smokers, the t_{max} of Theo-Dur is significantly greater than Phyllocontin Forte.

When administered with food no significant differences occur in the pharmacokinetic parameters of t_{max}, C_{max}, $t_{\frac{1}{2}}$, K_d and AUC_{0-24} between the sustained release formulations in both smoking and non-smoking volunteers. Comparison of plamsa concentration profiles show that when Phyllocontin Forte is administered with food in smokers it has a similar profile to Theo-Dur whether Theo-Dur is given with food or fasting.

It is apparent that if Phyllocontin Forte is adminstered with food in smoking patients, similar therapeutic responses to those seen with Theo-Dur will occur. Phyllocontin Forte is a suitable sustained release preparation for use in smokers.

GENERAL DISCUSSION

It is important to the patient prescribed theophylline to have a drug which will obtain sufficient therapeutic concentration to relieve or reduce the symptoms of bronchial airway obstruction without intolerable side effects. Almost invariably a sustained release theophylline will be prescribed in a standard dose in addition to other bronchodilator therapy. All theophylline formulations on the UK market demonstrate sustained release characteristics (see chapter 1) and when administered in a sufficient dose at regular intervals will achieve theophylline concentrations within the therapeutic range and be acceptable to the majority of patients. However, the numerous influences on the absorption, distribution, metabolism and clearance of theophylline make theophylline therapy unpredictable. Patient variability can be the cause of either inadequate therapy or unacceptable side effects. This thesis set out to examine the influence of some of these variables especially the effect of food on the release and absorption of theophylline from sustained release formulations.

The evidence that food has an effect on the absorption of theophylline from sustained release formulations is as follows.

Welling et al (1975) was the first to investigate the problems of co-administration of food with theophylline-containing drugs. He conducted a study on six healthy male volunteers with a narrow age and weight range. After the required overnight fasting and abstinence from caffeine-containing beverages, each subject received one of six treatments on separate days taking Tedral tablets containing 130 mg of theophylline, 8 mg of phenobarbitone and 24 mg of ephedrine. Significant differences, as analysed by the paired t-test, were found in the first 2 h after administration between the serum concentrations of theophylline in volunteers fasting

and those taking the drug with a meal containing a high carbohydrate, high fat, or high protein composition. On close examination Welling's data at 2 h showed the maximum difference in serum concentrations to be 0.5 $\mu g\ ml^{-1}$ between the high fat and high carbohydrate diet, 1.5 $\mu g\ ml^{-1}$ between the high fat and high protein diet and 0.8 $\mu g\ ml^{-1}$ between the high carbohydrate and high protein diet. These are relatively small differences and the assay method used was the Schack and Waxler (1949) spectrophotometric assay. This assay has subsequently been shown to be interfered with by phenobarbitone and the metabolites of theophylline (Hendeles et al 1978), phenobarbitone being an ingredient of Tedral. Hendeles et al (1980) showed that this method of analysis had a co-efficient of variation of 27%. These slight differences in a small number of volunteers with a non-specific, unreliable assay method raised the question, with hindsight, as to whether Welling's conclusions were valid.

Another paper to use the Schack and Waxler assay method was Kappas et al (1976). The six volunteers studied were allowed to use aspirin, another drug which interferes with this assay method (Hendeles et al 1978). Kappas measured the difference in elimination half lives of the six volunteers on diets of different compositions of protein and carbohydrate. A high carbohydrate-low protein diet increased the mean half life by 2.4 h and a high protein-low carbohydrate diet decreased the half life by 2.9 h. Upton et al (1982) demonstrated that 39 out of 60 individuals varied in their terminal disposition rate constants β, between different study days 3 to 4 days apart. Fluctuations of 60% were seen and changes of 30% or greater were common. Kappas's subjects had different diets for two week periods over 8 weeks. If Upton is correct, changes in half life of this magnitude could take place at random. The method of statistical analysis applied to the results was not stated.

The effect of order was not considered over this period of time. This could have a bearing on the legitimacy of the results.

Feldman et al (1980) continued on this theme of varying the protein and carbohydrate components of meals in 14 children aged 7 to 14. Feldman reported the mean half life on a high protein diet was decreased by 2 h and on a high carbohydrate diet increased by 11.3 h and the percentage of protein and carbohydrate was similar to the Kappas et al (1976) study. In a following issue of the Journal of Paediatrics (1981, **68**, 600 - 601), a letter by Weinberger severely critisized the method Feldman had used to calculate the volume of distribution and the elimination rate constant. When the half lives were re-calculated using the appropriate method for multiple dose studies, the differences were a decrease of 0.8 h for a high protein diet and an increase of 1.2 h for a high carbohydrate diet. As Weinberger pointed out, the disproportionately long half lives of elimination reported by Feldman et al during the high carbohydrate diet do not correspond to the clearance values and are probably fictitious due to the prolonged absorption of the theophylline formulation.

In 1983 Thompson et al used high protein, high carbohydrate diets to see if the pharmacokinetics of Nuelin SA were altered. No effect of diet composition was seen on the elimination half life in eight patients when their diet was changed from high protein to a high carbohydrate diet.

In a letter to the British Journal of Clinical Pharmacology, Pedersen (1981) reported a dramatic prolongation of t_{max} in children given Nuelin SA with a standardisied breakfast. No statistical analysis was carried out by Pedersen on the reported data and only mean data was included in the letter. Later in 1984, Pedersen and Moeller-Petersen confirmed these results. Using a theophylline

formulation, Nuelin SA, known to have pH-dependent dissolution (Jonkman 1981) Pedersen was able to demonstrate a prolongation of t_{max} in children but not in adults during the same study.

Thompson et al (1983) confirmed Pedersen's finding in adults. Using Nuelin SA he found no statistically significant difference in C_{max} and t_{max} between fasting and non-fasting conditions in 18 adult asthmatics. He did, however, find a decrease in peak to trough variation of 40% ($P < 0.001$) between the fasting and non-fasting conditions. The effect of food on another product, Theo-Dur, was investigated by Leeds et al (1982) and Sips et al (1984). Leeds et al only found signficant differences in the fraction of theophylline absorbed between fasting and non-fasting conditions at 1 to 4 h post dose using a rapid release formulation, Theo-Dur 100 mg. only at one sampling point, 4 h, did Leeds show any signficant difference in the fraction of drug absorbed from Theo-Dur 300 mg. Sips et al (1984) reported food having no effect on the absorption of theophylline from Theo-Dur 300 mg, although this study could be suspect due to peculiar non-fasting conditions.

When comparing the bioequivalence of sustained release formulations on the UK market taken in a single dose with food (chapter 1) no one single formulation behaved signficantly different from another. Nuelin SA had the longest half life of the products tested but this was found to be non-significant. This may have been due to the small number of volunteers. The long half life of Nuelin SA in this experiment would fit into the general concept that the pH-dependent dissolution of this formulation would make it the most likely, of all the formulations, to be affected by food (chapter 3). Likewise, when the effect of food on the release of theophylline from Phyllocontin forte and Theo-Dur was investigated in smokers and non-smokers (chapter 7), no significant effects

were seen. Indeed the effect of food appeared to be random in both smokers and non-smokers. This random effect on t_{max} and C_{max} could be due to other random variables that occur during theophylline therapy. This lack of effect of food on sustained release formulations was again reproduced in the modification of gastric motility with metoclopramide and propantheline (chapter 6). Although significant effects were seen in both the rate of absorption and t_{max} with Provent when administered with propantheline, co-administration with food alone produced no significant effect compared with fasting with either Provent or Theo-Dur. There is no doubt that food is not a major influence on the absorption of theophylline from sustained release products, unless the formulation has a design fault as demonstrated by Hendeles et al (1985) with dose dumping of theophylline from Theo-24 or the pH-dependent dissolution of Nuelin SA (Jonkman 1981).

The design faults in release mechanisms as highlighted by Hendeles et al (1985) and Jonkman (1981) could be expected to be elucidated by in vitro studies. It certainly would be interesting to conduct dissolution testing on Theo-24 and Provent, the British sister formulation, to observe their behaviour in gastric fluids and not whether rapid dissolution takes place in a prolonged acid pH. In the evaluation of a new sustained release formulation in vitro testing prior to in vivo testing would be advantageous. Volunteer studies are expensive to conduct and often, with hindsight, the methods could be improved to obtain more worthwhile information. Of the experiments conducted in this thesis, most, in retrospect, could have been greatly improved. The pharmacokinetic parameters to be measured could have been more relevant. It is the fraction of drug absorbed with time in the first hours of absorption that will be the crucial parameter to measure to positively conclude

the effect of food, pH or gastric motility on sustained release theophylline products. In this method to accurately obtain an elimination rate constant is a problem in sustained release formulations, since it is difficult to assess when absorption stops to allow accurate measurement of elimination.

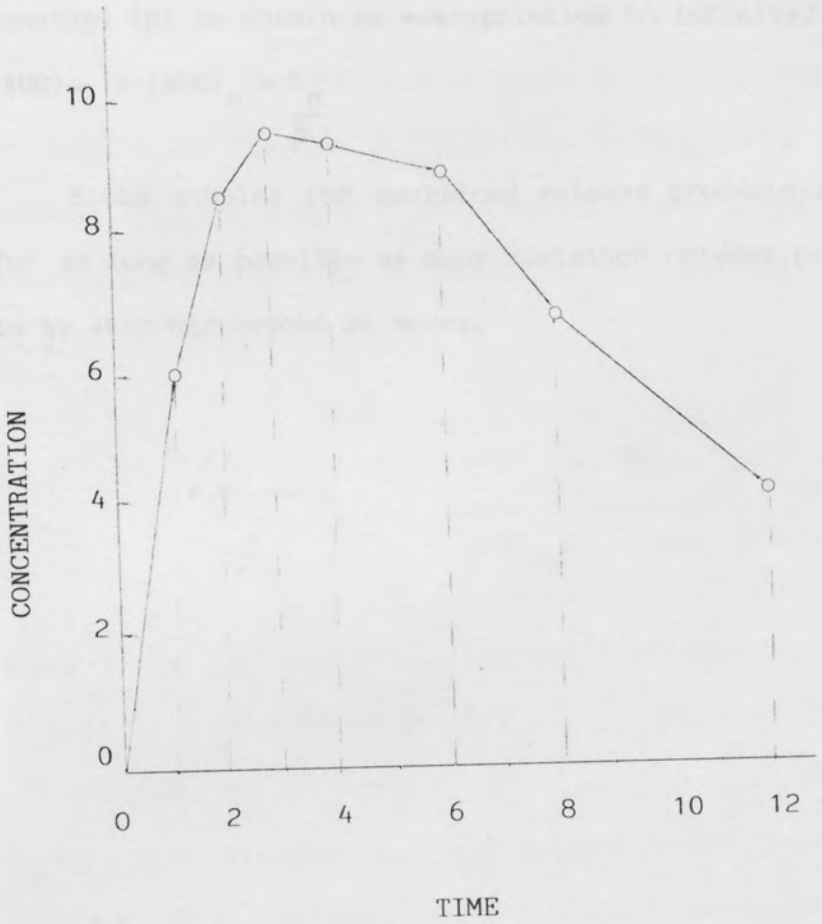
In single dose studies, measurement after 24 hours may be necessary to ensure elimination without absorption of theophylline is taking place. However, after 24 hours the amount of drug that can be measured in the serum or plasma is often below the limit of accuracy of the assay method. The assumption that subjects will have the same elimination rate when given intravenous or oral liquid theophylline some days after or before administration of sustained release theophylline, in order to obtain an elimination rate constant, may not be valid as theophylline elimination has been reported to vary over even short periods of time (Szefler 1984).

As already discussed, to obtain the statistical power to detect variations in theophylline kinetics, a sufficient number of subjects must take part in a study. How a trialist can obtain sufficient subjects is difficult to solve. Although multicentre trials themselves have a number of problems with standardisation, it may be the only way to overcome the problem. Another approach is to look at a specific population, eg fast metabolisers (Mucklow and Kuhn 1985). The work on children and smokers is a reflection of this, if only the data so gathered was not used to substantiate cases in different populations such as non-smoking adults. How relevant data is obtained from a specific population and interpreted in the clinical situation is difficult to assess. To conduct meaningful controlled studies on a drug with such variable pharmacokinetics as theophylline presents a dilemma. As the drug in the clinical

situation is commonly misprescribed and is of dubious merit (Cochrane 1984) it may be better to discourage the use of theophylline. Indeed if β_2 stimulants had been available in the USA at the same time as the UK the might of the American pharmaceutical industry would not have been used to excessively promote this drug and it would now probably be obsolete.

APPENDIX 1

DETERMINATION OF AREA UNDER THE CURVE BY THE TRAPEZOIDAL RULE



Drug concentration (μg/ml) as a function of time (hr) after oral administration. The data points are connected by straight line segments, rather than a smooth curve, to apply the trapezoidal rule. The area of each trapezoid is delineated (Gibaldi 1982).

A serum concentration time curve can be described by a series of trapezoids that are determined by each concentration time point. The area bound by the trapezoid approximates the area under the curve, the greater the number of data points, the closer is the approximation.

$$\text{Area} = (\tfrac{1}{2})(C_1 + C_2)(T_2 - T_1) + (\tfrac{1}{2})(C_2 + C_3)(T_3 - T_2) + (\tfrac{1}{2})(C_{n-1} + C_n)(T_n - T_{n-1})$$

Where C denotes drug concentration, T denotes time and the subscript referes to the sample number.

The area from the last data point C_n to infinity is estimated from the quotient of that concentration and the elimination rate constant (β) to obtain an extrapolation to infinity.

$$(AUC)_{\infty} = (AUC)_n + \frac{C_n}{\beta}$$

Blood samples for sustained release products should be collected for as long as possible as many sustained release products may continue to be absorbed beyond 24 hours.

APPENDIX 2

DETERMINATION OF THE ELIMINATION RATE CONSTANT

The elimination rate constant (β) is determined from the log linear slope of the elimination phase serum concentration measurements of the rapid release theophylline fitted to a straight line by a least squares regression technique. The total AUCs of both the references and the study products are normalised for difference in dose, as follows:

$$F = \frac{(AUC_{pro})\ (Dose_{ref})}{(AUC_{ref})\ (Dose_{pro})}$$

where F is the total fraction of dose absorbed, ref is the dose of reference formulation and the $Dose_{pro}$ is that of the study product.

Calculation of extent of absorption in this manner assumes first order elimination. In practice, the true elimination rate constant of a sustained release product cannot be determined, since absorption may continue for an extended time and the terminal portion of the serum concentration time curve cannot be unequivocally identified. Thus the elimination rate determined with the rapidly absorbed reference formulation is assumed to be unchanged when the sustained release product is administered. Intra-subject variation in theophylline elimination can, therefore, be a source of error.

APPENDIX 3

RATE AND EXTENT OF ABSORPTION

A modification of the Wagner-Nelson (1963) method of calculating the fraction of an oral dose absorbed over time is a useful method to compare both rate and extent of absorption. The cumulative fraction of the dose absorbed at each serum concentration following a single dose is calcaulted by dividing the amount absorbed at that time point by the dose given:

$$FA_1 = \frac{(X_A)_t}{(X_A)_\infty} = \frac{(AUC)_t + \frac{C_t}{\beta}}{(AUC)_\infty}$$

Where $(X_A)_t$ = the cumulative amount absorbed at time t, $(X_A)_\infty$ = the total amount of drug available for absorption (ie, the dose), C_t = serum concentration at time t, β = elimination rate constant determined from the reference product, $(AUC)_t$ = the area under the serum concentration time curve for the sustained release formulation from zero to time t and $(AUC)_\infty$ = the total area under the serum concentration time curve for the reference product.

The fraction of drug absorbed is usually plotted on the y axis against time on the x axis to graphically represent comparison of the rate and extent of absorption of one sustained release product with another.

GLOSSARY OF ABBREVIATIONS

$AUC_{0-\infty}$	Area under the plasma concentration time curve from zero to infinity
AUC_{0-t}	Area under the plasma concentration time curve from zero to time t
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
t_{max}	Time to maximum concentration
t_{min}	Time to minimum concentration
K_a	Absorption rate constant
K_d	Rate of decay constant
K_{el}	Elimination rate constant
$t_{\frac{1}{2}}$	Elimination half life

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