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THEOPHYLLINE PHARMACOKINETICS IN ADVANCED AGE

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1 Theophylline kinetics following a single oral dose were characterized and compared in non-institutionalized ambulatory elderly and young gender-matched control subjects. Study design stressed stringent, yet realistic, control of several external factors known to influence theophylline metabolism.

2 Plasma levels of total drug were significantly higher in the elderly only at early sampling times (0.5 and 1 h) and at 36 h, while unbound theophylline levels were significantly higher ($P < 0.05$) at all sampling times resulting in a 45% greater AUC for unbound drug.

3 While no significant differences in volume of distribution (V_d) or overall plasma clearance were observed when calculations were based on total plasma theophylline, a 37% reduction in V_d ($P < 0.005$) and a 30% reduction in overall plasma clearance ($P < 0.02$) in the elderly became apparent when plasma protein binding was taken into account.

4 When urinary excretion patterns were compared, the elderly were found to have excreted a significantly higher fraction of the recovered dose as 1-methyluric acid ($P < 0.01$) and a lower fraction as unchanged theophylline ($P < 0.02$). A 47% reduction in the renal clearance of unbound theophylline ($P < 0.005$) was also observed in the elderly.

5 Results were consistent with less viable metabolism and renal excretion pathways for theophylline elimination in the elderly and serve to reemphasize the importance of including an assessment of plasma protein binding in studies of drug disposition in the elderly.

Introduction

Epidemiological studies indicate that the incidence of adverse drug reactions increases significantly with advancing age (Seidl *et al.*, 1966; Hurwitz, 1969). It is commonly accepted that many elderly patients can be satisfactorily treated with lower doses of drugs than their younger counterparts. It has become increasingly apparent that quantitative changes in drug disposition (pharmacokinetic changes) play a major role in producing these reactions and necessitating alterations in treatment regimens. Perhaps the most age-dependent aspect of drug disposition is elimination mediated by either the kidney or by metabolism in the liver. In concert, these processes not only determine how rapidly drug levels will diminish and thus the desired frequency of dosing, but also control the accumulation of potentially toxic unchanged drug and/or metabolites.

The metabolism of several drugs has been reported to be less efficient in the elderly (O'Malley *et al.*, 1980). The most commonly reported finding in previous studies has been a prolongation of plasma half-life, especially for drugs that are oxidized (hydroxylated) by liver microsomes. Unfortunately few studies have measured the most pharmacokinetically meaningful parameters describing drug elimination, corrected these for unbound fractions of drug in plasma where appropriate, or examined multiple metabolic pathways within the same individuals to assess possible differences in their decline with age.

When half-lives are used to quantitate the rates of metabolic processes, concurrent changes in drug distribution often obscure changes in the ability of the elderly person to metabolize drugs. A more meaningful measure of drug elimination is intrinsic clearance. This parameter takes distributive and binding changes into account, more directly evaluates the body's metabolic capability and provides a rational basis for the design of dosage regimens.

Many factors such as disease, diet, environmental

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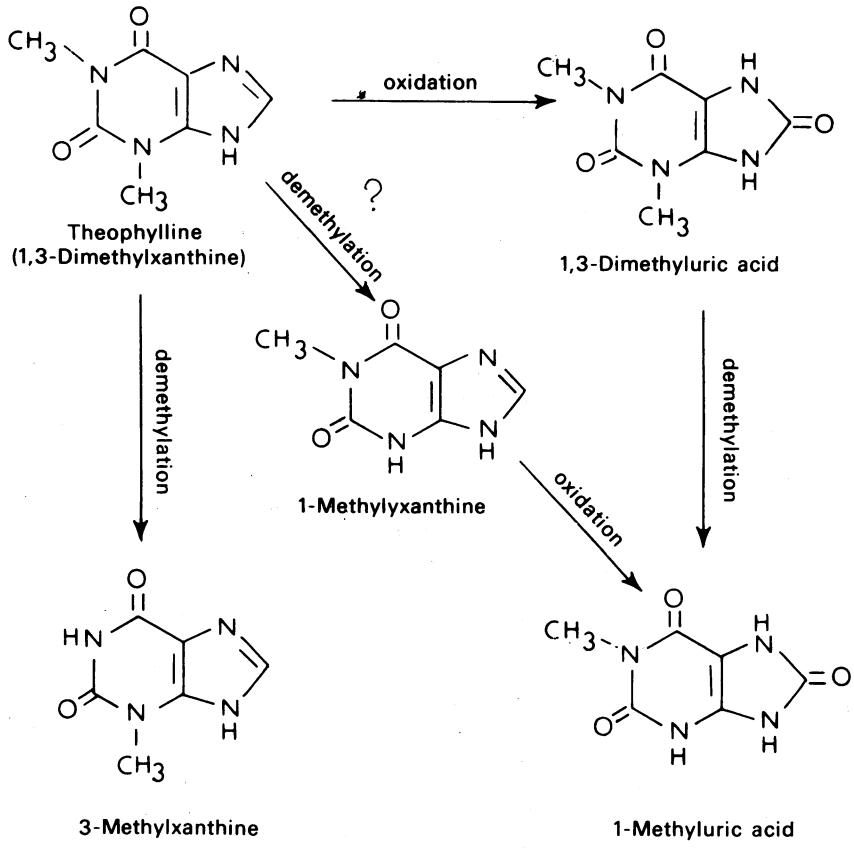

Figure 1 Pathway of theophylline metabolism in man.

insults and smoking can affect the rate of metabolism of drugs in man. Control of these factors, along with access to requisite analytical methodologies and appropriate subject populations presents a considerable obstacle to obtaining meaningful data. Theophylline is a drug that is both oxidized and dealkylated in man (Figure 1). It can be quantified as total and unbound drug in plasma and measured along with its metabolites in urine. Furthermore, of the available bronchodilators, theophylline and its salts appear to be the most widely prescribed agents in the United States for managing chronic pulmonary disorders in the aged (Physicians' Drug Prescribing Patterns in Skilled Nursing Facilities, 1976). The objective of the present study was to characterize and compare the single dose pharmacokinetics of theophylline in young control subjects and ambulatory elderly volunteers in an experimental setting that was realistic, yet amenable to control of many of the external factors influencing drug metabolism studies in man.

Methods

Subject selection

Fourteen ambulatory elderly (mean age 76, range 70–85 years; 13F, 1M) caucasians in independent community living were selected for the study. An equal number of young students (mean age 23, range 19–31 years), matched for gender and race, served as controls. Each volunteer was a non-smoker (cigarettes and marijuana) and non-drinker, the latter excluded those who habitually ingest more than the equivalent of 2 ounces of pure ethanol per week. Eligibility required normal renal and hepatic function for the subject's age as determined by SGOT, SGPT, bilirubin, serum albumin, BUN and creatinine clearance. All subjects were 'normal' volunteers in that they would not otherwise have been receiving theophylline. While some of the elderly suffered chronic ailments common among their age group, all were required to have the ability to shop unaided as an

indication of general overall health and none had cardiac failure or any other disease deemed likely to affect theophylline disposition. All medications were screened for possible interactions with theophylline disposition and assay and all non-essential ones were discontinued for the duration of the study. Many elderly subjects were taking medication chronically and continued to do so during the study since these medications were considered a necessary part of their treatment. These drugs included hydrochlorthiazide, frusemide, digoxin and reserpine. While studies are lacking that would definitely exclude the possibility of an interaction between these agents and theophylline, there is no evidence to suggest that the drugs involved would interfere with either the plasma protein binding or metabolism of theophylline.

Study design

The study protocol, including dietary restrictions, drug administration and sampling times is depicted in Figure 2. During the period from 4 days prior to the administration of theophylline to 3 days thereafter, subjects were forbidden from ingesting food and beverages containing methylxanthines and foods known to affect the rate of microsomal drug metabolism. Caffeine-containing beverages, cruciferous vegetables (Brussels sprouts, etc.) and char-broiled foods were specifically forbidden. Beginning 2 days prior to drug administration, elderly subjects were housed around-the-clock in a country inn being used as a clinical research facility. All meals were provided by the investigators and their content was stringently controlled. The arrangement permitted extremely close surveillance of subjects and enabled the investigators to insure complete urine collection and dietary compliance. While it was not feasible to sequester the control subjects, their dietary restrictions were identical to those of the elderly and urine collections were scrupulously monitored.

Following an overnight fast and a 12-h pre-drug urine collection, a single 200 mg rapid-release theophylline tablet (Slophylline®, Dooner Labs, Lot 11808C) was administered. Toast and cereal were provided 3 h post-dose. Blood was sampled at 0, 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 24, and 36 h and plasma samples frozen at −20°C until assay. Urine was collected for up to 72 h after dosing as indicated in Figure 2.

Analytical methods

Plasma or ultrafiltrate theophylline concentrations were analyzed by a reversed phase HPLC method (Miksic & Hodes, 1979). This method resolves theophylline from its isomer, paraxanthine, a metabolite of caffeine. β-Hydroxyethyltheophylline (500 ng in 50 μl water) was added as an internal standard to a 100 μl sample aliquot which was then extracted with a 1 ml aliquot of chloroform: isopropanol (1:1). The organic phase was evaporated to dryness under N_2 at 65°C, reconstituted in 50 μl of methanol and 20 μl were chromatographed. The chromatographic system consisted of a Model M-45 solvent delivery system, Bondapak C_{18}/Corasil pre-column (3.9 mm i.d. × 5 cm) and μBondapak C_{18} column (3.9 mm i.d. × 30 cm, Waters Associates, Milford, MA USA). Detection was achieved with a variable wavelength UV detector (Laboratory Data Control, Riviera Beach, Florida, USA) set at 280 nm. Mobile phase was a mixture of methanol: tetrahydrofuran: sodium acetate (4:1:95, 0.01 M, pH 5) flowing at 2.0 ml/min. Column temperature was maintained at 25°C using a water bath. Calibration curves of peak height ratio of drug/internal standard concentration were linear (r^2 = 0.999) over the 0.2–10 μg/ml concentration range studied. The lower limit of quantitative reliability was 0.2 μg/ml.

Theophylline and its metabolites were determined in urine by direct injection of a specimen (diluted 1:1 with an aqueous solution of 0.028 M sodium tetraborate at 5.8% NaCl) onto the system described above using sulphadiazine as an internal standard.

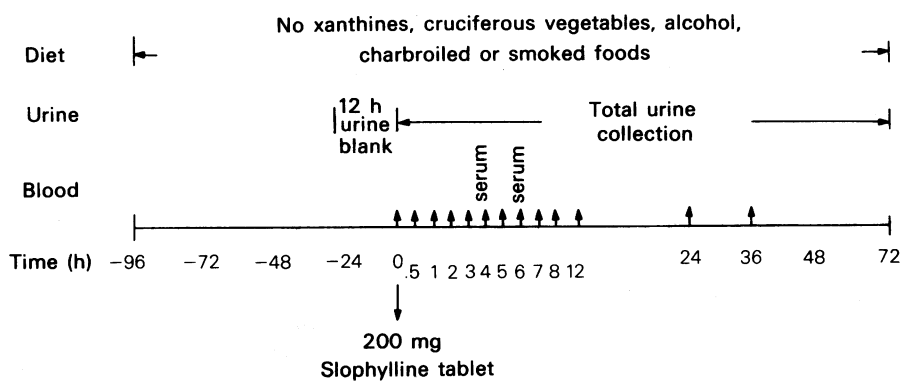

Figure 2 Protocol for drug administration, dietary restriction and sampling.

Mobile phase was acetonitrile: methanol: sodium acetate (1:1:98, 0.01 M, pH 4). Column temperature was set at 50°C and mobile phase flow rate was 1.2 ml/min. The lower limit of quantitative reliability for the determination of each metabolite was 1 μg/ml. All concentrations were determined by comparison of peak height ratios of drug/internal standard with those obtained for standard solutions. Spiked urine samples and aqueous standard solutions yielded identical calibration curves.

Protein binding

Protein binding of theophylline in plasma was determined by the micro-ultrafiltration method of Shah, Wallace & Riegelman (1974). Circular discs cut from Centriflo 2100 CF-50 ultrafilter cones (Amicon Corp., Lexington, MA) served as the ultrafilters. No adsorptive losses to the ultrafilter could be detected and the filters retained 99.8% of the protein. Approximately 7% of the applied sample was actually collected as ultrafiltrate in an attempt to minimize any protein concentration effects above the membrane.

Liver volume determination

Liver volumes were determined in each subject using both transverse and longitudinal ultrasonic scans taken at 1 cm intervals. Cross-sectional areas of each scan were determined by a computer analysis which digitalizes the images through the use of a tracer and sensor plate. Individual areas were then converted to volumes and summed.

To check the accuracy of the determinations, a calf liver was suspended in an aquarium of water. Taking precautions to exclude air from the system, transverse and longitudinal scans were then made as described above. The *in vitro* determination was able to ascertain the true volume of the liver (as determined by displacement of water) to within ± 5%.

Pharmacokinetic and statistical analysis

Single dose theophylline plasma level data were fitted to a one-compartment open model by the nonlinear least squares regression program NONLIN (Metzler, Elfring & McEven, 1974). The exponential stripping program CSTRIP (Sedman & Wagner, 1976) was used to obtain initial polyexponential parameter estimates. It was not possible to distinguish the two compartment characteristics generally ascribed to theophylline following intravenous doses of the drug. Areas under the plasma level-time curve (AUC) up to the last sampling point were computed using the linear trapezoidal rule. Terminal areas were calculated from the last measured plasma level divided by the overall elimination rate constant. Log trapezoidal determinations of AUC were found to differ from the linear determinations by only about 3%.

The mole fraction of the dose excreted by each individual metabolic or renal pathway was estimated by dividing the molar amount of a particular metabolite excreted by the total molar quantity eliminated. Although urinary collections were sometimes discontinued prior to recovery of the entire absorbed dose, mole fraction of the dose recovered was empirically found to become independent of urine collection time beyond 36 h. Figure 3 shows the results in two such subjects.

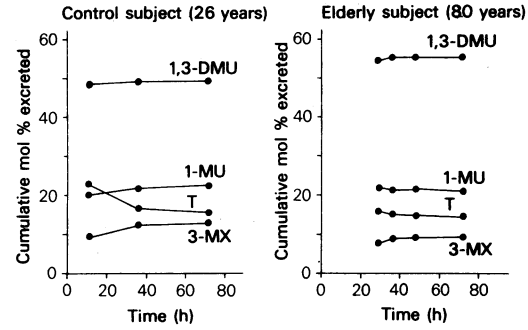

Figure 3 Cumulative mol % of theophylline (T) and its major metabolites in urine as a function of total urine collection period.

Apparent oral clearance (total plasma clearance) was calculated by the model independent equation:

$$\text{Total plasma clearance} = \frac{F\,(\text{Dose})}{AUC}$$

where AUC is the area under the plasma level-time curve for total (bound + unbound) theophylline. The results were found to be identical to those obtained from the product of the best fit model parameters ($K\ V_d$). Bioavailability (F) was taken as unity based on studies conducted by Upton showing it could not be claimed with 95% confidence that the brand of theophylline used in the present study was less than 95% bioavailable in man (Upton *et al.*, 1980). Intra-individual differences in theophylline disposition would, in all probability, exceed the 5% difference between F = 1 and F = 0.95.

Plasma clearance was multiplied by the reciprocal of the fraction of unbound drug in plasma (f) to determine unbound (intrinsic) clearance. Since the protocol was designed for the analysis of plasma concentrations only, no reliable data were available for the distribution of the drug between plasma and erythrocytes. Our calculations were thus based on a partition coefficient of one, an assumption supported by the results of Peat & Jennison (1977) and Sheehan & Haythorn (1976), both of whom found that the blood:plasma ratio for theophylline is indeed unity.

Table 1 Subject characteristics

	Control	*Elderly*
Age (years)	23.1 ± 3.4	76.2 ± 4.4
Body weight (kg)	57.1 ± 9.4	71.8 ± 13.4
Liver volume (l/kg)	0.031 ± 0.009	0.031 ± 0.011
Serum albumin (g/100 ml)	4.4 ± 0.20	3.9 ± 0.44
Creatinine clearance (ml/min)	95.6 ± 19.8	52.4 ± 14.1

All values expressed as mean ± s.d.

Plasma clearance or intrinsic clearance multiplied by the fraction of the recovered dose excreted as unchanged theophylline yielded corresponding renal clearances of total and unbound drug.

Volumes of distribution were calculated as the plasma or intrinsic clearance divided by the overall elimination rate constant, K. Plasma clearance of unbound theophylline to 3-methylxanthine (3-MX) and total methylurates (MU = 1,3-dimethyluric acid (1,3-DMU) + 1-methyluric acid (1-MU)) was calculated by multiplying intrinsic clearance by the mol % of the dose excreted as metabolite:

$$\text{Plasma clearance (unbound theophylline} \rightarrow \text{3-MX)} = \text{Intrinsic clearance} \times \text{Mol \% of dose excreted as 3-MX}$$

$$\text{Plasma clearance (unbound theophylline} \rightarrow \text{MU)} = \text{Intrinsic clearance} \times \text{Mol \% of dose excreted as MU}$$

Statistical comparisons of elderly and control groups were made using the 2-tailed Student's *t*-test for unpaired data.

Results

Physical characteristics of the subjects participating in the study are summarized in Table 1. Liver volumes as a percentage of body weight did not differ between elderly and control subjects while serum albumin and creatinine clearance were significantly lower in the elderly ($P < 0.005$). Creatinine clearances normalized for body surface area were even more markedly diminished in the elderly because of this group's larger body surface areas.

Figures 4a and 4b depict the mean semilogarithmic plasma level-time profiles for total and unbound theophylline, respectively, following the single 200 mg oral dose. Aside from a significant difference at the 36 h sampling time, total plasma levels differed significantly ($P < 0.05$) only at very early sampling times (0.5 and 1 h). These differences are more clearly seen in Figure 5 which plots the early sample points on rectangular coordinates. In contrast, unbound theophylline levels were significantly higher

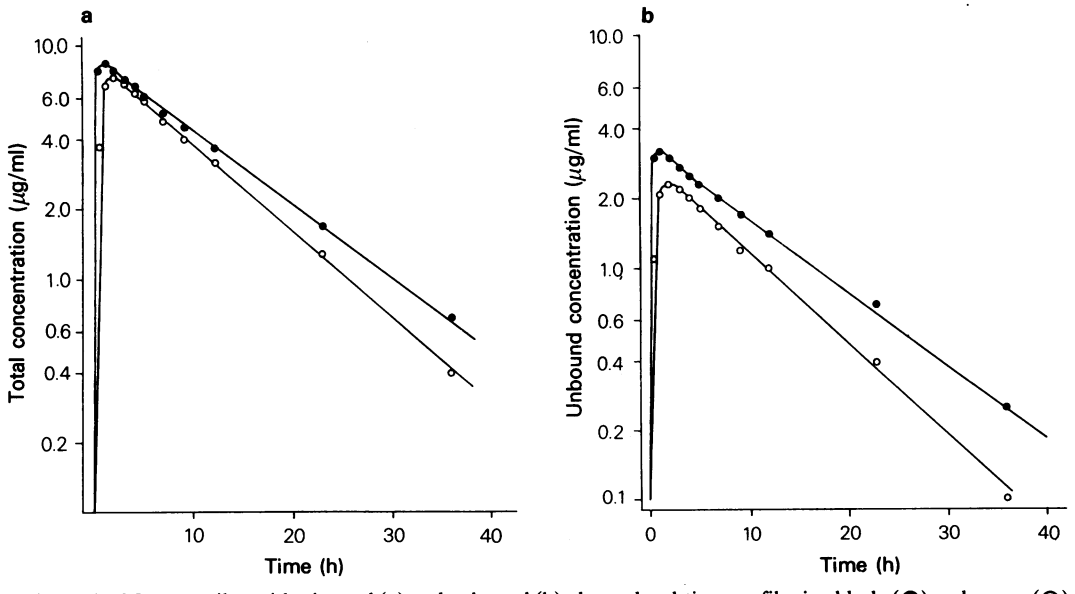

Figure 4 Mean semilogarithmic total (a) and unbound (b) plasma level-time profiles in elderly (●) and young (○) volunteers following a single 200 mg oral dose of theophylline.

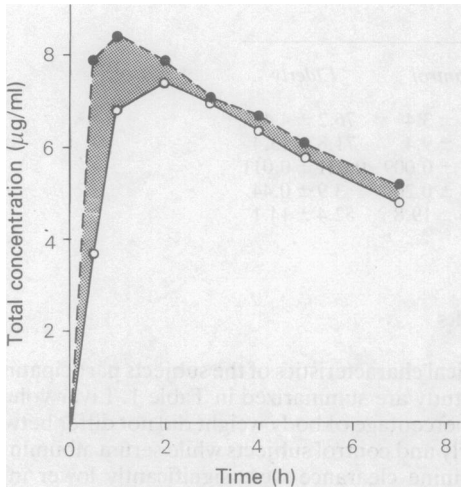

Figure 5 Comparison of mean total plasma level profiles at early times following a single 200 mg oral dose of theophylline to elderly (●) and young (○) volunteers.

in the elderly ($P < 0.05$) at all sampling times resulting in a 45% increase in total AUC for unbound drug. This is a reflection of the fact that the mean percent plasma protein bound was found to be 68.8 ± 3.6% in the control subjects compared with only 62.5 ± 5.2% in the elderly ($P < 0.01$).

Urinary excretion patterns for theophylline and its metabolites are compared between elderly subjects and controls in Table 2. Values are expressed as the mol percent of the *recovered* dose excreted as each specie. When these excretion patterns were compared by *t*-test analysis, the elderly were found to have excreted a significantly higher fraction of the recovered dose as 1-MU ($P < 0.01$) and a significantly lower fraction as unchanged theophylline ($P < 0.02$).

Disposition parameters calculated from plasma theophylline levels are summarized in Table 3. When calculations were based on total plasma theophylline, no significant differences were found in volume of distribution or total plasma clearance. When these parameters were based on *unbound* theophylline in plasma, elderly subjects were found to have significantly lower values of these two parameters.

Table 4 summarizes the apparent metabolic clearances of unbound theophylline for each of several pathways and the renal clearance of unchanged drug in the elderly and control groups. Attempts to correlate liver volume with total plasma clearance or any of its component parts were unsuccessful. Instead of decreasing the coefficient of variation of the data, normalization of clearances for liver volume resulted in additional scatter of the value obtained. We have, therefore, reported uncorrected clearances throughout. Elderly subjects had significantly lower renal clearance of theophylline and intrinsic metabolic clearance resulting in 3-MX. The mean MU clearance was 20% lower in the elderly, but the difference only achieved statistical significance at the 90% confidence level. The renal clearance of unbound theophylline was well correlated ($r = 0.61$, $P < 0.001$) with creatinine clearance as shown in Figure 6. Interestingly, renal clearance of unchanged theophylline was the only clearance parameter measured that showed greater variability in elderly than in young control subjects (C.V. 88% *v* 23%).

Discussion

Ideally studies of the effects of age on drug disposition should be conducted longitudinally with *changes* in relevant parameters assessed over time within a given subject. Because such studies require many years to complete and are rarely feasible, age effects are generally reported as *differences* between elderly subjects and young controls. Frequently the elderly are institutionalized, often with multiple pathologies, while the controls are in independent and community living. Swift *et al.* (1978) have shown that metabolic rates can be significantly dependent on such environmental differences. Even when differences in lifestyle and pathology are minimized, a multitude of environmental and genetic factors such as smoking, drinking,

Table 2 Urinary excretion of theophylline metabolites

	Control	*Elderly*	
Mol % of dose recovered	80.4 ± 8.1	69.2 ± 15.9	NS
Mol % of dose recovered excreted as:			
3-methylxanthine	12.5 ± 2.4	11.2 ± 3.0	NS
1,3-dimethyluric acid	50.1 ± 5.7	52.1 ± 7.0	NS
1-methyluric acid	20.9 ± 4.2	25.3 ± 3.9	$P < 0.01$
Theophylline	16.4 ± 4.0	11.4 ± 5.9	$P < 0.02$

All values expressed as mean ± s.d.

Table 3 Pharmacokinetic parameters derived from unchanged plasma theophylline

	Control	*Elderly*	
$T_{½}$ (h)	8.51 ± 2.00	9.81 ± 4.10	NS
V_d total (l/kg)	0.43 ± 0.06	0.32 ± 0.05	NS
$V_{d\ unbound}$ (l/kg)	1.38 ± 0.23	0.86 ± 0.14	$P < 0.005$
Total plasma clearance (ml/min)	34.9 ± 12.0	29.4 ± 9.99	NS
Unbound plasma clearance (ml/min)	113.5 ± 39.5	79.8 ± 29.7	$P < 0.02$

All values expressed as mean ± s.d.

diet, gender and race, to name but a few, can make substantial contributions to drug disposition – especially for drugs such as theophylline that are primarily eliminated by metabolism in the liver. Cusack *et al.* (1980) in a recent report on theophylline kinetics in relation to age, concluded that 'studies must be designed to ensure that comparable groups are employed minimizing the contribution of environmental factors which readily modify results and confound interpretation of data'.

We have studied theophylline metabolism in a group of functionally independent, non-institutionalized elderly. They were considered to be more representative of the elderly as a whole since this type of individual comprises an estimated 95% of the elderly population (Kovar, 1980). The daily functioning of these independent elderly was indicative of an adequacy of organ system function which was validated by both clinical and laboratory testing. While it is impossible to control all external factors and probably undesirable to do so, we have matched our comparison groups for race and gender and controlled diet, smoking habit, alcohol intake and urine collection in a realistic fashion.

While some of our results do not differ substantially from those of Cusack *et al.* (1980) who compared healthy young controls with elderly patients in a long-term care setting, our conclusions are substantially different, primarily because age effects appear to have been masked by differences in plasma protein binding. While they reported that ageing *per se* did not affect the absorption, distribution or elimination kinetics of single dose oral theophylline in non-smokers, we found significant differences in several parameters when measurements were based on unbound plasma theophylline determinations.

While the purpose of the present study was not to evaluate the effect of age on the oral absorption of theophylline, the significantly higher total and unbound theophylline levels at 0.5 and 1.0 h are suggestive of a faster rate of absorption for this brand of theophylline in this group of elderly. These early plasma levels are confounded, however, by distributive processes and without intravenous data it is impossible to unequivocally ascribe the differences to absorption *per se*. It should be noted that Cusack *et al.* (1980) reported a similar trend in their data although the observed difference did not achieve statistical significance.

The lower degree of plasma protein binding of theophylline in our elderly may have been due to lower plasma albumin levels in this group as has been the case for other drugs with diminished binding in advanced age (O'Malley *et al.*, 1980). Although unbound concentrations of theophylline were significantly higher at all sampling points in the elderly, total theophylline levels were, for the most part, identical.

One area where differences were noted between elderly subjects and controls was that of renal excretion of unchanged theophylline. A 30% reduction in the fraction of theophylline excreted unchanged was seen in the elderly sample and the

Table 4 Clearance of unbound theophylline

	Control	*Elderly*	
Metabolic clearance (ml/min)			
3-Methylxanthine	14.7 ± 7.5	9.17 ± 4.25	$P < 0.05$
Total methylurate	76.0 ± 35.0	61.2 ± 21.2	$P < 0.1$
Renal clearance (ml/min)	17.7 ± 4.08	9.35 ± 8.19	$P < 0.005$

All values expressed as mean ± s.d.

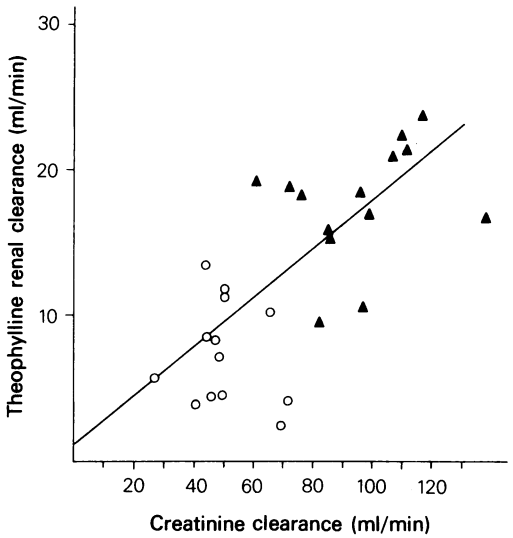

Figure 6 Relationship between unbound theophylline renal clearance and creatinine clearance in elderly (○) and young (▲) volunteers. $r = 0.611$, $P < 0.001$.

renal clearance of that unbound theophylline which was excreted unchanged was reduced by 47%. This reduction is probably due to the decreased filtration capability of the elderly kidney as suggested by a mean 45% reduction in creatinine clearance and the significant correlation between the renal clearances of theophylline and creatinine depicted in Figure 6.

Our observation that plasma clearance of total theophylline is unchanged in the elderly agrees with previously published results (Cusack *et al.*, 1980). Unbound (intrinsic) clearance was, however, reduced by 30% in old age in our study, a finding that is probably more reflective of the actual level of metabolic activity in the two age groups. The result is consistent with the currect recommendation that aminophylline infusion rates be reduced by 25% in older patients (Jusko *et al.*, 1977).

Since theophylline undergoes both *N*-1-demethylation and C-8-oxidation in man, it was of interest to see whether advanced age affected these pathways similarly. The intrinsic clearance for the *N*-1-demethylation of theophylline to 3-MX was reduced by 37% in our elderly group ($P < 0.05$). There was no evidence of saturation of this pathway since the fraction of the dose excreted as 3-MX in the urine was the same for both age groups. The products of the C-8-oxidation of theophylline are methylurates (1,3-DMU and 1-MU). We noted a 20% reduction in the elderly in that portion of theophylline's intrinsic clearance that results in methylurate formation. The difference did not reach statistical significance at the 95% level because of a large variability about the mean.

Although Figure 1 depicts a postulated pathway for the production of methylurate through an *N*-3-demethylation of theophylline, there is evidence that this pathway is insignificant in man. Ogilvie (1978) recently reviewed the pharmacokinetics of theophylline in man and concluded that the pathway is questionable and probably non-existent. 1-MX has not generally been detected as a metabolite of theophylline in man, and its postulated existence stems from studies of theophylline conversion by rat liver slices *in vitro* (Lohmann & Miech, 1976). We looked for 1-MX in our samples and could find no evidence of its presence. Grygiel *et al.* (1979) did find what appeared to be about 1% of the total dose of theophylline recovered in the urine as 1-MX and this fraction rose dramatically when the xanthine oxidase inhibitor allopurinol was administered. Unfortunately, the subjects were on a xanthine-restricted diet for only 24 h prior to the study. Since 1-MX is a major metabolite of caffeine in man, residual caffeine could well have been producing the reported levels of 1-MX. It should also be noted in this regard that the kinetic study of Cusack in the elderly (Cusack *et al.*, 1980) only withheld caffeine for 12 h prior to dosing. We have found that a washout period of 48 h or longer is a necessity if accurate results are to be obtained. To the extent that the assumption of a negligible 1-MX pathway is valid, one may infer that the reduced clearance of theophylline to MU reflects an impairment of C-8-oxidation. Thus, it would appear that both *N*-1-demethylation and C-8-oxidation pathways for theophylline metabolism may be less viable in the elderly.

The results of the present study serve to re-emphasize the importance of including an assessment of plasma protein binding in studies of drug disposition in the elderly. Age-related changes in drug metabolism may not be evident when total (unbound plus bound) drug levels are measured, since changes in protein binding with age may mask differences in intrinsic clearance. Estimates of V_d and clearance must be appropriately corrected for unbound fraction to yield the more relevant parameters of unbound V_d and intrinsic clearance. The same conclusion was drawn by Greenblatt & Shader (1980) in a recent review of the effects of age on benzodiazepine kinetics. While theophylline is not as highly bound to plasma proteins as the benzodiazepines, it has a rather small therapeutic index and the differences reported here between young and old could prove to be of clinical significance, especially in such high risk situations as the intravenous use of theophylline in the management of acute bronchospasm in the elderly (Jusko *et al.*, 1977).

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