PHARMACOKINETICS OF THEOPHYLLINE: A DOSE-RANGE STUDY

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- 1 Pharmacokinetics of theophylline were investigated in a group of healthy adult volunteers (non smokers and on xanthine-free diet) following single oral administration of 125, 250, 375 and 500 mg doses as tablets (Theodel®).
- 2 Absorption of theophylline was rapid and followed first-order kinetics. Plasma curves were fitted according to a one compartment open model.
- 3 There was a linear relationship ($P < 0.001$) between plasma $C_{\max}$ or AUC_x values and the administered dose. The analysis of variance showed that the pharmacokinetic parameters of theophylline ($t_{1/2}$ abs, $t_{\max}$, $t_{1/2}$ β , CL, CL_R , V_d and F) were not modified at any dose.
- 4 Absorption of the drug was complete since the recovery in urine of theophylline (13.7 to 16.8% of the dose) and its major metabolites, 1,3-dimethyluric acid (35 to 42%), 1-methyluric acid (21.3 to 26.7%) and 3-methylxanthine (11.5 to 13.7%), accounted for the administered dose. Some impairment of demethylation to 3-methylxanthine was observed in two subjects, however the percentage of theophylline and its major metabolites excreted in urine was constant for all the four doses.
- 5 On the basis of these results, after single oral administration, elimination of theophylline followed first-order kinetics in the range of doses investigated (1.62 to 10.42 mg/kg).

Introduction

Theophylline, 1,3-dimethylxanthine, was introduced into medical use several decades ago for its bronchodilator properties (Tuft & Brodsky, 1936; Hermann & Aynesworth, 1937).

Improvement of pulmonary function has been clearly related to theophylline plasma concentrations in excess of 8–10 mg/l (Jenne *et al.*, 1972; Mitenko & Ogilvie, 1973b; Levy & Koysooko, 1975; Pollock *et al.*, 1977), while serious adverse side effects involving the gastro intestinal system (vomiting, abdominal discomfort, diarrhoea), the central nervous system (dizziness, nausea, anorexia, anxiety) or the cardiovascular system (ventricular arrhythmias, tachycardia) have been shown to occur generally at plasma concentrations higher than 20 mg/l (Jenne *et al.*, 1972; Jacobs *et al.*, 1976; Hendeles *et al.*, 1977).

The therapeutic range of theophylline plasma concentrations is consequently narrow and the management of the drug in clinical practice is complicated by several factors which influence the disposition of theophylline: age, smoking habits, diet, disease, obesity and drugs all contribute to the wide inter-individual variability of theophylline clearance (Ogilvie, 1978; Kappas *et al.*, 1978; Jusko *et al.*, 1979;

Monks *et al.*, 1979; Staib *et al.*, 1980; Grygiel & Birkett, 1980; Feldman *et al.*, 1980). As a consequence, the monitoring of plasma concentration in patients on theophylline treatment is now current practice (Hendeles *et al.*, 1978; Ogilvie, 1980). After intravenous administration to healthy adults, the pharmacokinetics of theophylline in plasma are best described by a two compartment open model (Mitenko & Ogilvie, 1973a; Chrzanowski *et al.*, 1977); the biphasic disposition of the drug is characterised by a rapid distribution phase (half-life of 30 to 40 min) and a slower elimination phase (half-life of 4 to 12 h). After oral administration, the distribution phase of the drug is masked by the absorption and the kinetics can be adequately studied applying a one compartment model (Upton *et al.*, 1980). In healthy adults, binding of theophylline to plasma proteins is 53 to 65% and the volume of distribution is about 0.5 l/kg (Ogilvie, 1978). Theophylline is eliminated from the body mainly by metabolism and its major biotransformation products are 3-methylxanthine (3-MX), 1-methyluric acid (1-MU) and 1,3-dimethyluric acid (1,3-DMU) which are excreted in urine in a proportion of 70–90% of the dose, 5 to 15% is ex-

creted in urine as unchanged drug (Jenne *et al.*, 1976; Monks *et al.*, 1979; Jonkman *et al.*, 1981; Tang-Liu *et al.*, 1982). The elimination kinetics of theophylline have been assumed to follow first-order kinetics at the doses usually administered during chronic treatment, however, the possibility of dose-dependent kinetics has been evoked (Lesko, 1979). Renal excretion of theophylline is flow dependent (Levy & Koysooko, 1976) but this is only a minor pathway of elimination in man. Furthermore, the fraction of theophylline recovered in urine is linearly related to serum concentrations of the drug (Jenne *et al.*, 1976), indicating that the renal excretion of theophylline is not saturable. Changes of metabolic clearance due to saturation of one metabolic pathway could affect the disposition of theophylline and in this respect elimination of 3-MX, 1-MU and 1,3-DMU in urine has been found to follow Michaelis-Menten zero-order elimination kinetics (Monks *et al.*, 1979; Jonkman *et al.*, 1981; Tang-Liu *et al.*, 1982). In addition, apparent saturation (zero-order) kinetics of theophylline have been observed during cases of intoxication when the plasma concentrations were well above the therapeutic window (Weinberger & Ginchansky, 1977; Sarrazin *et al.*, 1980).

In this context it is surprising that a well controlled dose-range pharmacokinetic study has not yet been carried out. The objective of this paper was, therefore, to investigate the pharmacokinetics of theophylline and its major metabolites, 3-MX, 1-MU and 1,3-DMU following single oral administration of four doses to a group of healthy adults.

Methods

Protocol

This study, approved by the local Ethics Committee, was carried out at the 'Hôpital Cantonal' of Geneva, under the direction of Prof. A. Donath. Eight healthy adult caucasian volunteers received four single oral doses of Theodel® (Theolande® in R.F.A. and Theovina® in Belgium), a new theophylline scored tablet (batch 7, prepared in the Dept. of Pharmaceutical Development of Delalande Research Centre) according to a cross-over design. The four doses contained 125 mg (½ tablet), 250 mg (1 tablet), 375 mg (1 + ½ tablet) and 500 mg (2 tablets) of theophylline. The subjects were fasted for 10 h before and 4 h after each administration. Two days before and during the study, they observed a diet free of xanthines. The drug was administered with 150 ml of water. Lean body weight was determined with a whole body counter (Wenger & Soucas, 1964), by measuring the radioactivity due to the natural abundance of radioactive potassium [⁴⁰K]. The assumption made is that

potassium content per unit of lean body weight is constant.

Blood samples (7–10 ml) were collected by venipuncture from a forearm vein into heparinised test tubes before administration, then at 0.25, 0.5, 1, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 24, 28, 32, 36 and 48 h. Plasma was immediately separated by centrifugation (20 min × 1000 g), transferred into a second tube and frozen at –20°C until analysed. Urines were collected the morning before administration, then at 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, 36–48 and 48–72 h. The volume excreted at each interval and the pH were recorded and a 50 ml aliquot of each fraction was frozen at –20°C until analysed. A 2 week period was allowed between each administration to the subjects.

Chemicals and reagents

Theophylline (Batch R966, Finorga, Chasse s/Rhône, France); 3-MX, 1,3-DMU, 7-β-hydroxypropyltheophylline, 8-chlorotheophylline, caffeine, theobromine, paraxanthine and hypoxanthine (Sigma, St Louis, USA); 1-MU kindly supplied by Prof. R.L. Smith (St Mary's Hospital, London, UK); 1,3,7-trimethyluric acid, 7-methyluric acid and 3-methyluric acid (Fluka AG, Buchs, Switzerland). Anhydrous sodium acetate, sodium hydroxide, sodium carbonate, sodium bicarbonate, ammonium sulphate, hydrochloric and acetic acid all of analytical grade (Merck); tetrabutyl ammonium hydrogen sulphate (TBA) (Aldrich, Beerse, Belgium); acetonitrile UV grade (Rathburn Chem. Ltd. UK); chloroform and isopropanol RPE (Carlo Erba, Milano, Italy).

Determination of theophylline in plasma

Plasma (0.5 or 1 ml) was added to a conical tapered tube with 0.1 ml of the internal reference standard 8-chlorotheophylline (aqueous solution of 2.0 or 24.0 mg/l) and 0.2 ml of HCl 4N. The solution was extracted with 4.5 or 9 ml of chloroform-isopropanol (95/5, v/v) for 20 min on a rock'n roll shaker (Luckham Ltd, UK). The organic phase after centrifugation (5 min × 1000 g) was separated with a hydrophobic paper (1 PS Whatman, UK) and the aqueous phase discarded. The organic phase was evaporated to dryness at 35°C (water bath) under a stream of nitrogen, the dry residue was dissolved in 0.9 ml of distilled water and 0.5 ml was injected into the high performance liquid chromatograph. A Micromeritics 750 liquid chromatograph, equipped with a 725 automatic injector and a 786 UV detector, was used. The stainless steel column 15 × 0.46 cm was packed with Spherisorb ODS 5μ (Phase Sep. Queensferry, UK) and the mobile phase was acetonitrile/sodium acetate-acetic acid (0.010M, pH 4.0) 10/90, v/v at a flow rate of 1 ml/min at 20°C. The UV detector was set at 273 nm. Quantification of theophylline was obtained by the

peak height ratio method (height theophylline/height 8-chlorotheophylline) and the calibration curves gave a linear response for plasma concentrations of theophylline ranging from 0.05 to 2.00 mg/l (1 ml plasma) and from 0.50 to 20 mg/l (0.5 ml plasma). The retention times were 6.0 and 11.4 min for theophylline and the internal standard; the recovery of theophylline from plasma was $85 \pm 5\%$ and the lower limit of sensitivity was 0.02 mg/l. The main theophylline metabolites (3-MX, 1-MU and 1,3-DMU), caffeine, theobromine, hypoxanthine, 3-methyluric acid, 1,3,7-trimethyluric acid and 7-methyluric acid did not interfere with the assay. The retention time of paraxanthine, a metabolite of caffeine, was close to that of theophylline (5.85 min), therefore, this compound could interfere with the analysis if present at high concentration. This problem, however, was avoided since the subjects abstained from xanthine intake during the study.

Determination of theophylline and its major metabolites in urine

The methodology used is derived from that described by Muir *et al.* (1980).

Theophylline, 3-MX, 1-MU and 1,3-DMU were extracted from urine (0.25–0.5 ml sample) with chloroform/isopropanol 85/15, v/v (8.5 ml). After centrifugation (5 min $\times$ 1000 g) the organic phase was filtered through a hydrophobic paper and evaporated to dryness in a water bath at 35°C, under a stream of nitrogen. The dry residue was dissolved in 5 ml of TBA 0.05 M and sodium acetate 0.01 M (vortex 1 min) and the pH of the solution adjusted to 4.75 by NaOH 10 M. 0.5 ml was injected into the high performance liquid chromatograph. A Micrometrics 750 liquid chromatograph equipped with a 725 automatic injector, a 753 ternary solvent gradient and 786 UV detector was used (280 nm). The stainless steel column (25 $\times$ 0.46 cm) was packed with Spherisorb ODS 5 μ , and, in order to avoid loss of resolution, a precolumn (4 $\times$ 0.46 cm) packed with Co-Pell ODS 30–38 μ was used. Theophylline and its metabolites were eluted from the h.p.l.c. column by a solvent gradient of sodium acetate 0.01 M-TBA 0.005 M pH 4.75 (NaOH 10M) and acetonitrile with an initial proportion of acetonitrile of 4% v/v to a final proportion of 15%. Each analysis was performed in $\approx$ 30 min. Quantification of theophylline and metabolites was obtained by the peak height ratio method and the calibration curves were linear for concentrations between 1 and 30 mg/l (theophylline and 3-MX) or between 1 and 60 mg/l (1-MU and 1,3-DMU). The recovery from urine was: $93 \pm 5\%$ for theophylline, $81 \pm 5\%$ for 3-MX, $57 \pm 6\%$ for 1-MU and $80 \pm 3\%$ for 1,3-DMU. The retention times were 5.8 min (3-MX), 7.0 min (1-MU), 8.6 min (1,3-DMU), 11.2 min (theophylline) and 14.4 min (7- β -hydroxypropyl-theophylline).

Pharmacokinetics

The pharmacokinetic analysis of plasma and urine data was carried out using the G-PHARM interactive program with a Tektronix 4052 desk computer (Gomeni & Gomeni, 1978).

Theophylline plasma data were analysed using a one compartment open model; urine data of theophylline and its major metabolites 3-MX, 1-MU and 1,3-DMU were analysed by the excretion rate method. The pharmacokinetic parameters were optimized by a Gauss-Newton iterative procedure where each data point was weighed by the reciprocal of the square of the observed value. The parameters were calculated as follows:

Plasma (theophylline)

Dose = dose administered (mg/kg)

t_{lag} = lag-time (h)

$t_{1/2 \text{ abs}}$ = half life of the absorption phase (h)

t_{max} = time of the peak plasma concentration (h)

C_{max} = peak plasma concentration (mg/l)

$t_{1/2 \beta}$ = half life of the elimination phase (h)

$\text{AUC}_x = \text{AUC}_{48} + C_{48}/\beta$ area under the plasma concentration/time curve extrapolated to infinity, determined by the trapezoidal rule ($\text{mg l}^{-1} \text{ h}$)
 AUC_{48} and C_{48} represent the area and the plasma concentration values at 48 h. β is the slope of the elimination phase.

$\text{CL} = \text{F} \cdot \text{Dose}/\text{AUC}_x$ = plasma clearance ($1 \text{ h}^{-1} \text{ kg}^{-1}$)
 where F is the fraction of the dose absorbed.

$V_d = \text{CL}/\beta$ = apparent volume of distribution (l/kg).

Urine (theophylline + metabolites)

$t_{\text{max}u}$ = time of the maximum excretion rate in urine (h)

$(\text{d}U/\text{d}t)_{\text{max}}$ = maximum excretion rate in urine (mg/h)

$t_{1/2u}$ = half life of excretion in urine (h)

Ae_x = amount excreted in urine (mg)

$f = \text{Ae}_x/\text{Dose}$ = fraction of the dose excreted in urine. For the metabolites, f was determined on a molar basis.

$\text{CL}_R = \text{Dose} \cdot f/\text{AUC}_x$ = renal clearance ($1 \text{ h}^{-1} \text{ kg}^{-1}$).

Statistical analysis

A two way (formulation, subject) analysis of variance (ANOVA) of the pharmacokinetic parameters obtained from the eight subjects after each dose, and least-squares regression analyses were carried out on a Tektronix 4052 desk computer.

Results

Routine laboratory analyses gave normal results for the eight adult subjects: they were normotensive (BP 120/80 mm Hg and HR 65 ± 10 beats/min), with values normal for hepatic (SGOT 10 u/l, SGPT 10 ± 1 u/l and alkaline phosphatase 28 ± 5 u/l) and renal

(blood urea 5.8 ± 0.9 mm and creatinine clearance 119 ± 8 ml/min) function. Their characteristics are given in Table 1. Theophylline was well tolerated after a 125 and 250 mg dose. After doses of 375 and 500 mg (Table 2), various side effects were observed (anorexia, anxiety, dizziness, vertigo, dry mouth, headache, nausea, tiredness and lassitude).

Table 1 Characteristics of the eight subjects participating in the study.

Subject	Sex	Age (years)	Weight (kg)	Lean body weight (kg)
1	M	25	64	58
2	F	27	61	46
3	M	22	77	65
4	F	32	52	33
5	M	35	68	57
6	F	30	62	44
7	M	31	64	57
8	F	28	48	38
Mean	—	29	62	50
$\pm$ s.d.	—	4	9	11

Figure 1 Mean plasma concentration (semi-logarithmic and linear plots) of theophylline from eight subjects after single oral administration of 125 mg (Δ), 250 mg ($\square$), 375 mg ($\bullet$) and 500 mg (∇) tablets.

Table 2 Incidence of side effects in the eight subjects receiving 4 single oral doses of theophylline. No side effects after the 125 and 250 mg doses.

Dose (mg)	Number of subjects	Anorexia	Anxiety	Dizziness	Dry mouth	Headache	Lassitude	Nausea	Tiredness	Vertigo
375	8	2	1	8	4	—	2	4	3	8
500	8	3	1	8	6	3	5	7	6	8

Theophylline was detectable in plasma from 0.25 to 48 h after each administration. The metabolites 3-MX, 1-MU and 1,3-DMU were detectable only after the higher doses (375 and 500 mg); their plasma concentrations did not exceed 1–2 mg/l and the data were unacceptable for pharmacokinetic analysis. Mean plasma concentration/time curves of theophylline after the 4 single doses are given in Figure 1. The absorption of theophylline was rapid ($t_{1/2\text{abs}}$ from 0.07 to 1.37 h) and plasma t_{max} was reached between 0.5 and 3.0 h; the variability of $t_{1/2\text{abs}}$ and t_{max} was due to the subjects and not to dose. The disposition of theophylline from plasma ($t_{1/2\beta}$) was mono-exponential at all doses and there was a highly significant correlation ($P < 0.001$) between C_{max} or AUC_x and the dose (mg/kg) calculated in terms of total weight or lean body weight (Figure 2).

The plasma clearance ranged from 0.041 ± 0.007 to $0.043 \pm 0.012 \text{ l h}^{-1} \text{ kg}^{-1}$ the apparent volume of distribution was estimated to be between 0.46 ± 0.07 to $0.54 \pm 0.07 \text{ l/kg}$ according to dose. Mean pharmacokinetic parameters obtained at the 4 doses are compared in Table 3.

13.7 to 16.8% of the dose was excreted in urine as unchanged theophylline, 11.5 to 13.7% as 3-MX, 21.3 to 26.7% as 1-MU and 35.0 to 42.0% as 1,3-DMU. The elimination of theophylline from the body was obtained principally by metabolism, and renal clearance accounted for only 13.3 to 16.6% (0.0057 ± 0.0017 to $0.0068 \pm 0.0020 \text{ l h}^{-1} \text{ kg}^{-1}$) of the total clearance.

The urinary excretion data for theophylline, 3-MX, 1-MU and 1,3-DMU together with their urinary pharmacokinetic parameters are compared in Figure 3. There was a linear correlation (Figure 4) between the dose and the maximum excretion rate ($\text{dU}/\text{dt}_{\text{max}}$) for theophylline and 1,3-DMU ($P < 0.001$), 3-MX ($P < 0.01$) and 1-MU ($P < 0.05$). Analysis of variance showed no significant difference for the plasma ($t_{1/2\text{abs}}$, t_{max} , $t_{1/2\beta}$, CL and V_d) or for the urine (CL_R , f , $t_{\text{max}u}$ and $t_{1/2u}$) pharmacokinetic parameters obtained for the four doses in the group of subjects investigated.

Discussion

Theophylline was rapidly absorbed from all four doses. Side effects were observed only after administration of the 375 and 500 mg doses, their incidence and intensity were more pronounced after the larger dose, however, there was no apparent relationship between side effects and plasma C_{max} values.

Despite the high intraindividual and interindividual variations of the rate of absorption of the drug, plasma t_{max} values were unchanged at any dose. This shows that absorption of theophylline followed first-order kinetics. The virtually complete recovery from urine of the given dose after each administration (Figure 3) indicates the good absorption of the drug from this new theophylline tablet.

The linear relationship between plasma C_{max} or

Figure 2 Relationship between C_{max} or AUC_x and the dose. TBW = total body weight, LBW = lean body weight.

Table 3 Plasma pharmacokinetic parameters of theophylline from eight subjects following 4 single oral administrations of the drug.

	125 mg		250 mg		375 mg		500 mg	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
t_{lag} (h)	0.11	0-0.21	0.09	0-0.16	0.09	0-0.20	0.07	0-0.21
$t_{1/2\text{ abs}}$ (h)	0.31	0.07-0.99	0.44	0.14-1.21	0.29	0.09-0.53	0.55	0.10-1.37
t_{max} (h)	1.6	1.0-2.0	1.8	1.0-3.0	1.6	0.5-3.0	2.0	0.5-3.0
C_{max} (mg/l)	4.1	3.0-6.7	8.0	5.0-12.1	10.5	6.7-15.0	15.1	10.7-20.5
$t_{1/2\beta}$ (h)	8.6	6.5-10.8	8.1	5.9-10.4	9.3	7.0-11.3	8.8	6.6-12.4
	52	31-94	106	69-172	161	75-272	210	136-373
AUC_{∞} (mg l ⁻¹ h)	0.043	0.026-0.061	0.041	0.028-0.048	0.042	0.029-0.065	0.041	0.026-0.051
CL (l h ⁻¹ kg ⁻¹)	0.0057	0.0033-0.0080	0.0067	0.0039-0.0078	0.0067	0.0029-0.0082	0.0068	0.0031-0.0102
V_d (l/kg)	0.53	0.40-0.72	0.46	0.38-0.57	0.54	0.46-0.60	0.52	0.38-0.74

AUC_{∞} values and the dose ($P < 0.001$) was observed for the individual data as well as for the grouped data and the intercepts of these plots were not significantly different from zero. As previously observed (Pierson *et al.*, 1974), the difference between total weight and lean body weight was higher for women than for men (Table 1). Plasma curves (Figure 1) and pharmacokinetic parameters (Table 3) showed that the theophylline elimination rate from plasma, plasma clearance and the apparent volume of distribution remained unchanged for all four doses. The results obtained from this study are in agreement with those reported in the literature for healthy adult non-smokers (Ogilvie, 1978). The interindividual variation of the pharmacokinetic parameters obtained in this study remain high despite the fact that the study has been carried out in a selected group of subjects who were non-smokers and followed a xanthine-free diet.

From urine data in Figure 3, it can be seen that plasma clearance was principally due to metabolism and that renal clearance of theophylline represented only 10-15% of total clearance. The major metabolic pathways of theophylline were 8-hydroxylation to 1,3-DMU, 3-demethylation and 8-hydroxylation to 1-MU and 1-demethylation to 3-MX.

As already observed by Jenne *et al.* (1976) there was no relationship between urinary excretion of theophylline and 1,3-DMU, whereas as shown in Figure 5, excretion of theophylline was inversely related to that of 3-MX ($P < 0.001$) and 1-MU ($P < 0.01$). The lack of correlation between the excretion of 1,3-DMU and 1-MU would indicate that 1-MU is formed by oxidation of 1-methylxanthine (1-MX), rather than by demethylation of 1,3-DMU. It has been demonstrated, in fact, that when allopurinol (a xanthine oxidase inhibitor) is given together with theophylline, the excretion of 1-MU decreases with a consequent increase of 1-MX (Lohmann & Miech, 1976; Grygiel *et al.*, 1979). The positive correlation ($P < 0.001$) between urinary excretion of 1-MU and 3-MX (Figure 5) supports the hypothesis of Grygiel *et al.* (1980) that both 1-MU and 3-MX formation are probably regulated by the same form of cytochrome P-450, the 1-MX formed is then converted by a xanthine oxidase to 1-MU. Contrary to their observations, however, we did not find any correlation between the urinary excretion of 1,3-DMU and those of 3-MX and 1-MU, indicating that there was no competition between 8-hydroxylation of 1,3-DMU and N-demethylation of theophylline.

The analysis of urine data relative to the excretion of theophylline and its three major metabolites gave conflicting results. In fact, the analysis of variance showed that t , t_{maxu} and $t_{1/2u}$ were unchanged at the four doses, but if compared to the values of theophylline, the t_{maxu} of metabolites was delayed and $t_{1/2u}$ was prolonged (Figure 3). t_{maxu} was determined

Figure 3 Urine pharmacokinetic parameters from eight subjects following single oral doses of theophylline (T) (mean values $\pm$ s.d.). ■ 125 mg, ▨ 250 mg, ▤ 375 mg and ▩ 500 mg.

Figure 4 Relationship between the maximum excretion rate of theophylline and its metabolites $(dU/dt)_{\max}$ and the dose.

in the 2 h-urine fractions whereas $t_{1/2}$ was estimated including the data obtained from the 12 h-urine fractions. Therefore, the longer elimination half-life of metabolites in urine compared to that of theophylline could be explained by the fact that collection of urine samples was too infrequent. In fact, the low plasma concentrations of 3-MX, 1-MU and 1,3-DMU (< 1–2 mg/l), in view of their volumes of distribution which are unlikely to be higher than that of theophylline, implies that the metabolites were quickly excreted in urine. The limiting step would therefore appear to be the formation of the metabolites rather than their excretion. The same conclusions were drawn after a single 320 mg dose of theophylline to 6 healthy adults (Jonkman *et al.*, 1981). Monks *et al.* (1979) have shown that urinary excretion of 3-MX follows Michaelis-Menten zero-order kinetics during the first 12 h after i.v. injection of [14 C]-theophylline. Jonkman *et al.* (1981) have confirmed this hypothesis and from their urinary excretion rate data it appears that also 1-MU and 1,3-DMU showed capacity-limited kinetics. Since they observed a log-linear decline of theophylline plasma concentration/time curves, they suggest the possibility that this apparent first-order process is the result of two non-linear processes: the metabolic clearance of theophylline and its renal clearance. When metabolic clearance is low, the renal clearance of theophylline is elevated. Similar results were obtained also by Tang-Liu *et al.* (1982), following a single intravenous dose of aminophylline (4.3 to 8.6 mg/kg) to a group of healthy adults. In addition, these authors found also a non-linear log plasma concentration decay of theophylline and showed that the three metabolic pathways of theophylline to 3-MX, 1-MU and 1,3-DMU were capacity-limited as shown by plots of the urinary excretion of the metabolites against theophylline plasma concentrations at mid-interval of urine collection.

If the metabolism is saturated this will be reflected in a reduction of theophylline clearance by the saturated route which will result in an increase in metabolism by other routes and/or an increase in the excretion of unchanged drug. From our data, these parameters were unchanged by dose, however, a critical analysis of the excretion in urine shows that if the relationship between $(dU/dt)_{\max}$ and the dose was highly significant for theophylline and 1,3-DMU ($P < 0.001$), for 3-MX ($P < 0.01$) and 1-MU ($P < 0.05$) the correlation was more scattered (Figure 4).

The plots of the excretion rate in urine of theophylline, 3-MX, 1-MU and 1,3-DMU against theophylline plasma concentrations at mid-intervals for each subject at the four doses were drawn. Since the drug was administered by the oral route only the data points after the 4–6 h interval were considered, i.e. after a complete distribution of theophylline. From these data we observed a linear relationship for 1,3-DMU, 1-MU and theophylline (Figure 6), although

Figure 5 Relationship between urinary excretion (% dose excreted) of theophylline, 3-MX and 1-MU.

for theophylline there was a trend towards higher excretion rate at the highest plasma concentrations of theophylline, particularly in subjects 5 and 8. For 3-MX, in the majority of the subjects, the excretion rate in urine increased linearly with theophylline plasma concentration, however, in subjects 4 and 6 the correlation coefficients of the linear regression ($r = 0.67$ and $r = 0.88$ respectively for a degree of freedom $df = 18$) were similar to those derived from the Hanes plots ($r = 0.67$ and $r = 0.81$ respectively). This would suggest that demethylation to 3-MX could

Figure 6 Relationship between urinary excretion rate of theophylline, 3-MX, 1-MU and 1,3-DMU ν theophylline plasma concentration in subject 1.

be impaired at the higher theophylline plasma concentrations, i.e. at the higher doses.

Nevertheless, the percentage of 3-MX excreted in urine was constant at any dose (11.5 to 13.7% of the dose). Furthermore, this metabolic pathway is less important than those leading to the formation of 1,3-DMU and 1-MU. During repeated administration of the drug when steady state plasma concentrations are achieved, saturation of theophylline metabolism should be observed, particularly if the dose is increased. However, a recent study in a group of healthy adults (Koeter *et al.*, 1981) has shown that theophylline followed linear pharmacokinetics during 1 week repeated oral administration of Theodur® (300 and 900 mg/day), a sustained release

preparation. This observation is confirmed in our study in which there was no clear evidence that the kinetics of theophylline could be saturated. Although in two subjects some impairment of demethylation at the higher doses was observed, plasma and urine pharmacokinetic data were unchanged by dose. The conclusion of our study is, therefore, that after a single oral administration the elimination of theophylline follows first-order kinetics in the range of doses from 1.62 to 10.42 mg/kg.

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