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Disposition of Caffeine and Its Metabolites in Man[1]

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ABSTRACT

The disposition of caffeine and its metabolites was studied in six healthy subjects by use of sensitive and specific assays. The primary degradation of caffeine in man was found to be N-demethylation and/or ring oxidation to theophylline, paraxanthine, theobromine and 1,3,7-trimethyluric acid. These compounds were further degraded to dimethylated uric acids, monomethylxanthines and monomethyluric acids. About 3 and 6% of the drug was converted to theophylline and theobromine, respectively. The elimination of paraxanthine after its formation did not follow linear kinetics. A large urine recovery of 1-methylxanthine after caffeine administration in comparison with the amount recovered after administration of theophylline suggests an inhibitory effect on the degradation of this metabolite by either caffeine itself or another metabolite of caffeine. Caffeine and its primary metabolites, dimethylxanthines, were extensively reabsorbed in the renal tubule. Their renal clearances were highly urine flow-dependent and their urinary excretion varied with urine output during the study. About 70% of the dose was recovered in the urine. Postulated degradation pathways of caffeine are discussed.

Caffeine (137MX) is not only consumed extensively in the form of caffeine-containing beverages (Medvei, *et al.*, 1974; Marks and Kelly, 1973; Williams *et al.*, 1978), but is employed therapeutically in many prescription and nonprescription medications (Graham, 1978). Its pharmacologic effects have long been appreciated (Salter, 1959; Trendelenburg, 1912; Truitt, 1971). The pharmacokinetics and metabolic degradation pathways of caffeine, however, have not been well studied. An early report from Cornish and Christman (1957) concluded that the primary routes of caffeine elimination in man are demethylation to paraxanthine (17MX) and theophylline (13MX). These authors recovered about 70% of a caffeine dose in urine using colorimetric and gravimetric measurements of urinary metabolites.

Other investigators have suggested that caffeine disposition has unusual or variable characteristics. Warren (1969) observed that 7 days of abstention from caffeine were required in habitual coffee drinkers before blood caffeine concentrations declined below the detection limit, whereas in subjects who did not consume caffeine-containing products, caffeine concentrations fell to undetectable values within 3 hr after oral administration of a 500-mg dose. Bors *et al.* (1971) reported a significantly and consistently larger urinary recovery of intact caffeine (about 15%) than other investigators (about 2%).

One or more routes of caffeine metabolism may be saturable. After administration of a 300-mg dose of caffeine, Sved *et al.* (1976) observed that plasma levels of theophylline, a minor metabolite of caffeine, remained at plateau (approximately 0.1 mg/l) for 24 hr. Similar observations have been reported in the beagle dog and the rat (Aldridge and Neims, 1979; Welch *et al.*, 1977) for other metabolites. Aldridge *et al.* (1977) and Latini *et al.* (1978) also reported a disproportionate relationship between area under the plasma concentration time curve and dose in rats.

To define more precisely the kinetic relationships between caffeine and its metabolites, we explored the disposition of these compounds in man after normal dietary doses of the drug.

Materials and Methods

Materials. Caffeine for oral administration was obtained from the New York Quinine and Chemical Works, Inc. (New York, NY). Theophylline elixir, containing 80 mg of anhydrous theophylline per 15 ml, was obtained from Philips Roxane Laboratory, Inc. (Columbus, OH).

Study design. Six healthy subjects (one female and five males) between 24 to 32 years of age and weighing between 61 to 80 kg participated in the study. All study protocols were approved by the University of California, San Francisco, Committee on Human Research, and informed consent was obtained from the subjects. In all studies, subjects were asked to take no medications and to abstain from foods and beverages containing methylxanthines for 72 hr before and throughout the study.

A single dose of theophylline (7.5 mg/kg) was administered orally to each subject 1 hour after a light breakfast. Two weeks later, a single dose of caffeine (7.5 mg/kg) was administered in a similar manner.

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ABBREVIATIONS: 137MX, 1,3,7-trimethylxanthine; 17MX, 1,7-dimethylxanthine; 13MX, 1,3-dimethylxanthine; 37MX, 3,7-dimethylxanthine; 1MX, 1-methylxanthine; 1MU, 1-methyluric acid; 7MX, 7-methylxanthine; 7MU, 7-methyluric acid.

Blood samples were drawn through an indwelling needle placed in an antecubital vein into heparinized Venoject Vacuum tubes (Kimble-Terumo, Inc., Elkton, MD) just before and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 28, 32, 36 and 48 hr after each dose. Complete urine collections were made between blood sampling times and up to 60 hr after each dose. Samples were stored at −20°C until analysis.

Analytical procedures. Concentrations of methylxanthines and methyluric acids in plasma and urine samples were determined by reversed-phase high-performance liquid chromatographic assays (Tang-Liu *et al.*, 1982b; Tang-Liu and Riegelman, 1982).

Data analysis. The rate of formation of a metabolite of caffeine ($dA_{M,F}/dt$) is related to the plasma concentration of its precursor (C_P) by the metabolite formation clearance ($CL_{P\to M}$):

$$\frac{dA_{M,F}}{dt} = CL_{P\to M} \cdot C_P \quad (1)$$

The rate of metabolite elimination ($dA_{M,E}/dt$) is determined by the plasma metabolite concentration (C_M) and the metabolite elimination clearance (CL_M):

$$\frac{dA_{M,E}}{dt} = CL_M \cdot C_M \quad (2)$$

The rate of change of the amount of metabolite in the body at any time (dA_M/dt) is the difference between these two rates (equations 1 and 2):

$$\frac{dA_M}{dt} = CL_{P\to M} \cdot C_P - CL_M \cdot C_M. \quad (3)$$

Because no metabolite exists in the body at zero and infinite time after a single dose of the parent compound, integration of equation 3 (assuming linear kinetics) gives:

$$\frac{AUC_M}{AUC_P} = \frac{CL_{P\to M}}{CL_M} \quad (4)$$

where AUC_M and AUC_P are the areas under the concentration-time curves of the metabolite and its precursor, respectively.

Defining f_M as the fraction of the precursor converted to the metabolite ($f_M = CL_{P\to M}/CL_P$). Equation 4 may be rewritten:

$$\frac{AUC_M}{AUC_P} = f_M \cdot CL_P/CL_M \quad (5)$$

The area under the plasma concentration time curve ($AUC_{0\to t_n}$) for caffeine and its metabolites was estimated by the trapezoidal rule to the last sampling time (t_n). The area beyond this time ($AUC_{t_n\to\infty}$) was approximated by dividing the value of the final measured concentration by the terminal rate constant (k). Total $AUC_{0\to\infty}$ was the sum of $AUC_{0\to t_n}$ and $AUC_{t_n\to\infty}$. The rate constant, k, was determined by linear regression of the logarithm of the plasma concentration with time from 2 to 24 hr after dose administration. Apparent $T_{1/2}$ was calculated as the product of the reciprocal of k and ln2. The apparent volume of distribution (Vd) was obtained by dividing the dose of caffeine or theophylline by the plasma concentration extrapolated to zero time. Absorption of both theophylline and caffeine is rapid and complete (Chvasta and Cooke, 1971; Marks and Kelly, 1973; Burg, 1975; Ogilvie, 1978). Apparent total clearance (CL) for each drug was therefore determined as the dose divided by the appropriate $AUC_{0\to\infty}$. The fraction (f_M) of caffeine converted to theophylline or theobromine was calculated by use of the ratios of clearances and AUCs (equation 5).

Results

Average urinary recoveries of caffeine and its metabolites obtained in this study along with those from Cornish and Christman (1957) are listed in table 1. Figure 1 shows the plasma concentration-time profiles of caffeine and its dimethylxanthine metabolites after a single dose of caffeine. Pharmacokinetic parameters calculated for caffeine (137MX) and theophylline (13MX) appear in table 2. The values of $T_{1/2}$, Vd and CL values for caffeine and theophylline are comparable to literature values previously reported (Burg, 1975; Parsons and Neims, 1978; Patwardhan *et al.*, 1980). Table 3 lists the $AUC_{0\to\infty}$ ratios of caffeine and its three primary metabolites, theophylline (13MX), theobromine (37MX), and paraxanthine (17MX). To calculate f_M values for these metabolites, their clearances must be known (equation 5). The clearance of theophylline was determined from the theophylline dose administered in this study for each subject. The clearance of theobromine was taken from a report of Drouillard *et al.* (1978). The fractions of caffeine metabolized to theophylline and theobromine are therefore included in table 3 for each subject. Because literature values for paraxanthine clearance are not available, estimated values of f_M for this metabolite are not shown in values of f_M for this metabolite are not shown in table 3.

The relationship between the elimination rate of paraxanthine (approximated by the sum of the excretion rates of 1MX, 1MU, 7MX, 7MU, 17MX and 1,7-dimethyluric acid) and its plasma concentration appeared to be convex ascending (fig. 2). This relationship suggests that paraxanthine clearance decreases as its concentration increases (equation 2).

The renal clearances of caffeine and the three dimethylxanthines were urine flow-dependent (fig. 3). The order of increasing values of renal clearance at any urine flow rate is: caffeine, theophylline, paraxanthine and theobromine.

Discussion

Caffeine and its metabolites undergo oxidative N-demethylation and ring oxidation to methylxanthines and methyluric acids. Their metabolism is enhanced by polycyclic aromatic hydrocarbons in animals (Aldridge *et al.*, 1977; Aldridge and Neims, 1979; Welch *et al.*, 1977; Betlach and Tozer, 1980) and by cigarette smoking in man (Parsons and Neims, 1978; Ogilvie, 1978). These data suggest involvement of cytochrome P-448 in the metabolism of caffeine. Additional studies have shown that of all the methylxanthines, only 1MX is a substrate of xanthine oxidase (Bergmann and Dikstein, 1956; Lohmann and Miech, 1976; Grygiel *et al.*, 1979).

There are 14 possible methylxanthines and methyluric acids

TABLE 1

Urinary recoveries[a] of caffeine and its metabolites after a single oral dose of caffeine

3MX, 3-methylxanthine; 13MU, 1,3-dimethyluric acid; 17MU, 1,7-dimethyluric acid; 137MU, 1,3,7-trimethyluric acid.

Dose	N	1MX	1MU	3MX	7MX	7MU	13MX	13MU	37MX	17MX	17MU	137MX	137MU	Total
1 g[b]	2	19	28	—[c]	6.6	—	—	9.4	—	4.7	—	1.2	—	69
7.5 mg/kg[d]	6	10	21	2.3	4.0	4.7	0.8	2.9	1.2	7.1	7.3	3.7	2.5	67
		(3)	(8)	(0.3)	(1.6)	(2.3)	(0.6)	(1.0)	(0.5)	(1.7)	(1.0)	(1.0)	(1.6)	(8)

[a] Percentage of caffeine dose on a molar basis.
[b] Data of Cornish and Christman (1959); urine collected to 48 hr (mean).
[c] Not reported.
[d] Data of this study; urine collected to 60 hr (mean with S.D. in parentheses).

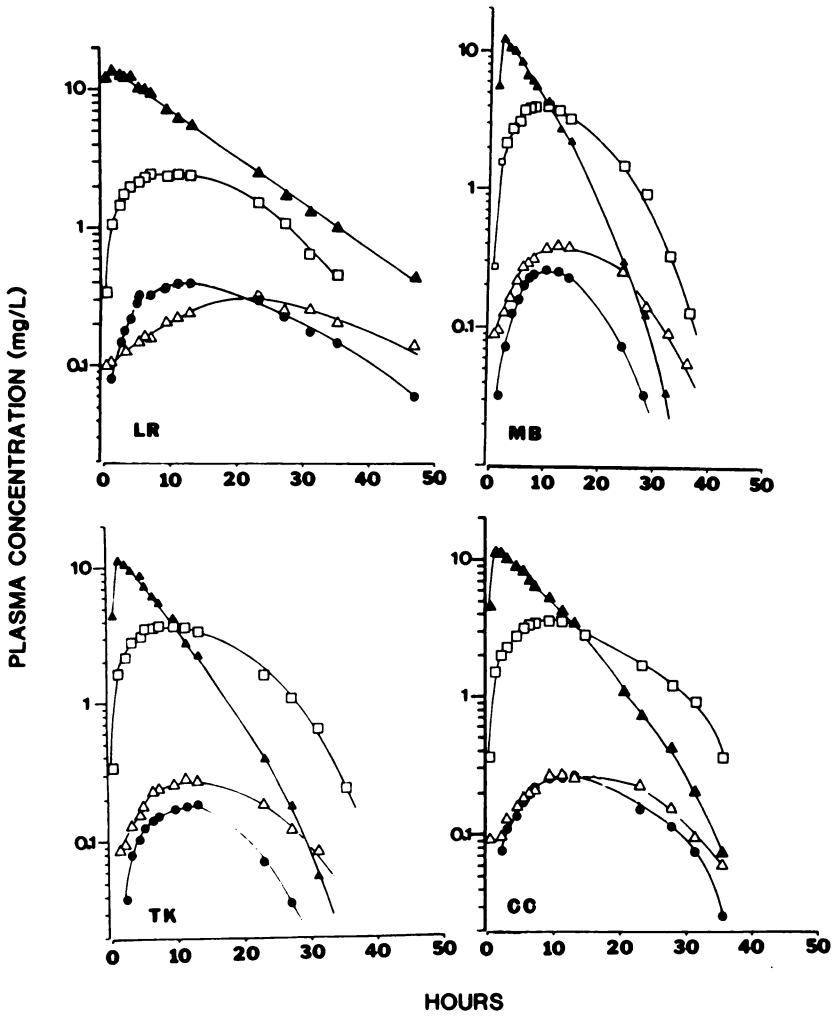

Fig. 1. Plasma concentrations of caffeine (▲) and its metabolites: theophylline (△), theobromine (●) and paraxanthine (□) after a single oral dose of caffeine. Data are shown for four subjects (LR, MB, TK and CC).

TABLE 2

Pharmacokinetic parameters of caffeine and theophylline

Subject	Body Wt.	Caffeine[a, c]			Theophylline[b, c]		
		Vd	$T_{1/2}$	CL	Vd	$T_{1/2}$	CL
	kg	l/kg	hr	l/hr	l/kg	hr	l/hr
LR	61	0.46	9.9	2.3	0.40	7.5	2.4
SB	80	0.48	3.5	9.2	0.42	5.8	4.6
CC	68	0.52	6.3	4.4	0.43	8.9	2.5
JM	74	0.52	2.8	15.0	0.50	4.0	5.0
TK	79	0.53	4.8	6.2	0.54	8.4	3.8
MB	77	0.58	5.3	5.9	0.50	7.0	3.6
Mean	73	0.52	5.4	0.096[d]	0.47	6.9	0.049[d]
S.D.	7.4	0.04	2.5	0.058[d]	0.06	1.8	0.012[d]

[a] Obtained from a single dose of caffeine.
[b] Obtained from a single dose of theophylline.
[c] The values of volume of distribution (Vd), $T_{1/2}$ and clearance (CL) are approximations of linear kinetics. For their methods of calculation, see "Materials and Methods."
[d] Expressed in liters per hour per kilogram.

TABLE 3

Derived parameters for each subject

Subject	$\frac{AUC_{13MX}}{AUC_{137MX}}$	$\frac{AUC_{37MX}}{AUC_{137MX}}$	$\frac{AUC_{17MX}}{AUC_{137MX}}$	f_{13MX}[a]	f_{37MX}[a, b]
LR	0.053	0.059	0.305	5.6	8.9
SB	0.045	0.115	0.818	2.2	5.6
CC	0.050	0.060	0.659	2.9	5.3
JM	0.137	0.186	1.065	4.6	5.1
TK	0.035	0.033	0.803	2.1	2.4
MB	0.047	0.099	0.778	2.9	8.2
Mean	0.061	0.092	0.738	3.4	5.9
S.D.	0.038	0.055	0.259	1.4	2.3

[a] Calculated from equation 5, expressed as percentage.
[b] Value of CL_{37MX} = 0.056 l/hr/kg (Drouillard *et al.*, 1978).

which could be formed from caffeine (fig. 4). Because these compounds are structurally related, with intact purine ring and similar UV absorbance, sensitive and specific assays are necessary to separate and quantify the potential metabolites of caffeine in man. Using assays developed in the laboratory of Dr. Sidney Riegelman that possess the necessary specificity and sensitivity, we demonstrate in this study that the primary degradation of caffeine in man is by oxidative N-demethylation to theobromine (37MX), paraxanthine (17MX), theophylline (13MX) and by direct ring oxidation to 1,3,7-trimethyluric acid. These compounds are further metabolized to dimethyluric acids, monomethyluric acids and monomethylxanthines (fig. 4). With the exception of 3-methyluric acid and 3,7-dimethyluric acid, all other methylxanthines and methyluric acids were detected in the urine in this study. We speculate that 3-methylxanthine and 37MX are not metabolized to the corresponding uric acids by xanthine oxidase nor other oxidases at any measurable rates due to substrate specificity of these enzymes.

Caffeine is extensively metabolized with only 3% of a dose excreted unchanged in the urine (table 1). Because we recovered only 70% of the caffeine dose from the urine in this study, other routes of elimination of caffeine must exist (assuming complete bioavailability), for example: 1) complete demethylation to xanthine or uric acid; 2) ring cleavage of methylated uric acids to allantoins; 3) reduction of methylated uric acids to methylated dihydrouric acids; and 4) biliary excretion of caffeine. Although we did not quantify the urinary elimination of xanthine and uric acids in this study, Cornish and Christman (1957), failing to observe an increase in the excretion of xanthine or uric acid after caffeine administration, concluded that demethylation of caffeine in man does not go beyond monomethylated species of xanthine or uric acid. Ring cleavage of 1,3,7-trimethyluric acid, a metabolite of caffeine, to 3,6,8-trimethylallantoin has been reported in the rat (Rao *et al.*, 1973). Although this reaction requires uricase enzymes not found in humans, it may nonetheless occur in man through the action of intestinal flora which do possess these enzymes. 1,3,7-Trimethyldihydrouric acid has been recovered in the urine of the rat after caffeine administration (Rao *et al.*, 1973). Allantoins,

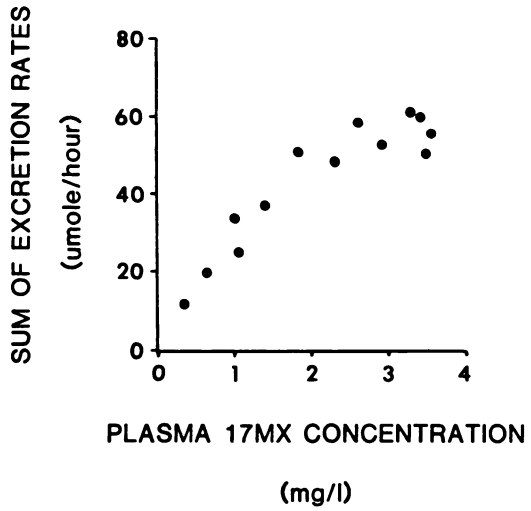

Fig. 2. Sum of urinary excretion rates of 1MX, 1MU, 7MX, 7MU, 17MX, and 1,7-dimethyluric acid as a function of plasma 17MX (paraxanthine) concentration after a single dose of caffeine in a representative subject.

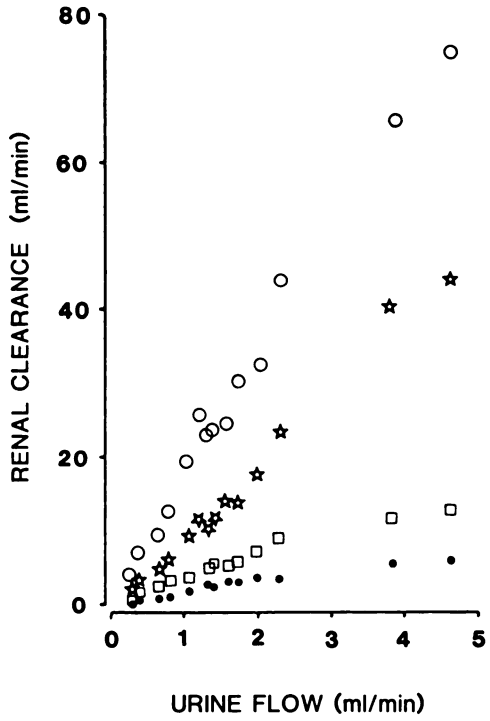

Fig. 3. Relationship between urine flow and the renal clearance of caffeine (●), theophylline (□), paraxanthine (☆) and theobromide (○) in a representative subject after a single dose of caffeine.

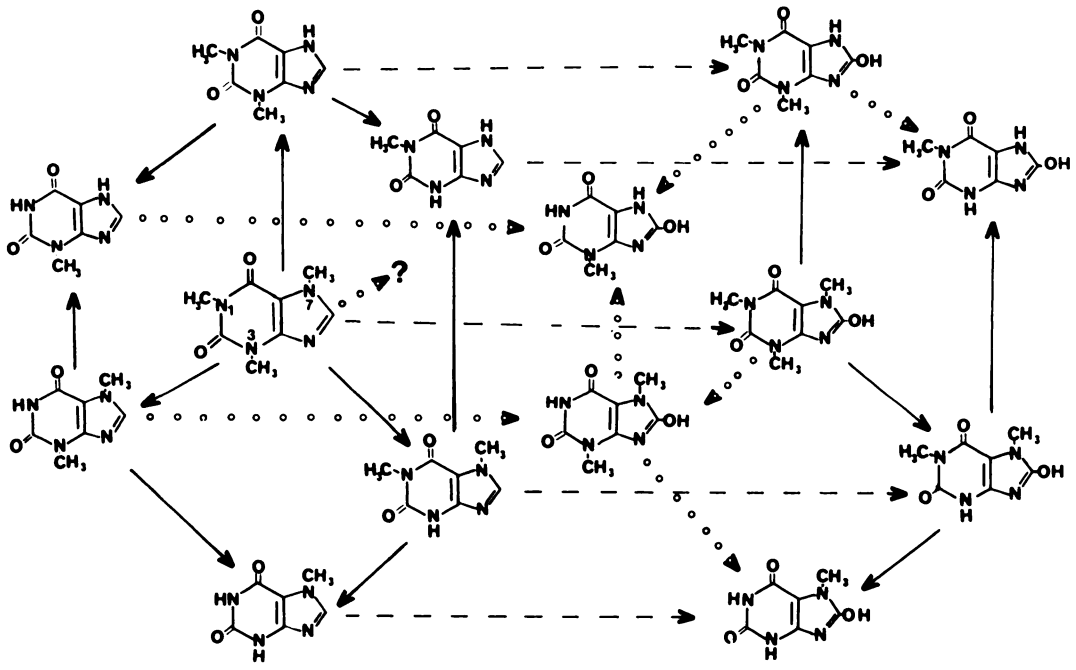

Fig. 4. Proposed metabolism patterns of caffeine and its metabolites in man. Demethylation processes (⟶), ring oxidation processes (- - - →) and undetected pathways (∘ ∘ ∘ ∘ ∘→) are also illustrated.

dihydrouric acids and their degradation products are hard to detect with a high-performance liquid chromatographic assay-UV detector because of low absorbance and are not identified in this study. Because we did not collect feces in this study, we cannot comment on the biliary excretion of caffeine.

Knowing clearances and AUCs for caffeine and its primary metabolites, f_M of a specific metabolite can be calculated (equation 5). Caffeine and metabolite AUC ratios were obtained in this study for theophylline, theobromine and paraxanthine (table 2). By using caffeine and theophylline clearances determined in each subject directly and a value for theobromine clearance obtained from the literature, we estimate that approximately 3 and 6% of total caffeine plasma clearance is accounted for, respectively, by biotransformation to theophylline and theobromine (table 3). Because we were not able to administer paraxanthine in this study nor are literature values for its clearance in man available, we cannot estimate the fraction of caffeine metabolized to paraxanthine. However, the value of $f_M \cdot CL_{137MX}/CL_M$ for paraxanthine is about 10 times greater than the corresponding ratios for theobromine and theophylline (table 3). If the clearance of paraxanthine is approximately the same as that of theophylline and theobromine, approximately 37% (equation 5) of a caffeine dose is biotransformed to paraxanthine.

Several aspects of the data in this study indicate that caffeine, like theophylline, may exhibit dose-dependent pharmacokinetics. After single oral doses of caffeine, plasma concentrations of the dimethylxanthines all remained relatively constant for at least 10 hr before declining (fig. 1). Although this observation may be attributed to the occurrence of longer elimination $T_{1/2}$s of these metabolites than the elimination $T_{1/2}$ of caffeine, it could also suggest that the formation of the dimethylxanthine metabolites of caffeine may be saturable. In addition, plasma caffeine concentration decayed in a nonlinear fashion, becoming convex-descending at low concentrations (fig. 1). This nonlinear decline in caffeine plasma concentrations, which denotes that clearance of caffeine increases at lower concentrations, is also consistent with capacity-limited metabolism. Because theophylline and theobromine are minor metabolites of caffeine, the contribution from these two compounds to the formation of 1MX, 1MU, 7MX and 7MU is very small. If the assumption is made that the sum of the excretion rates of 1MX, 1MU, 7MX, 7MU and 17MX (paraxanthine) and 1,7-dimethyluric acid approximate the elimination rate of paraxanthine, then the slope of a line relating this excretion rate and paraxanthine plasma concentration provides an estimate of plasma paraxanthine clearance. The data in figure 2 depicting this relationship suggests that paraxanthine clearance declines at higher caffeine concentrations. This observation provides additional evidence for the capacity-limited metabolism of caffeine.

After a single dose of theophylline, negligible amounts of 1MX are recovered in the urine, indicating that the metabolism of 1MX to 1MU in man is essentially complete and rapid (Tang-Liu *et al.*, 1982b). In this study, we recovered up to half as much 1MX as 1MU after the same dose of caffeine (table 1). 1MX should be metabolized completely by the same enzyme(s) whether it is derived from theophylline or paraxanthine. The large urinary recovery of 1MX in this study after caffeine suggests that caffeine or its metabolites may inhibit xanthine oxidase.

Most lipophilic compounds are reabsorbed passively in the renal tubule. The degree of reabsorption depends on the lipophilicity of the compound as well as on the luminal flow rate (Tang-Liu *et al.*, 1982a). The more lipophilic the compound, the more it is reabsorbed and the smaller its renal clearance. The renal clearances of caffeine, theophylline, paraxanthine and theobromine in this study were all smaller than glomerular filtration rate and all exhibited urine flow dependence (fig. 3). The more polar monomethylated xanthines and methyluric acid metabolites exhibited clearances larger than glomerular rate and were relatively insensitive to changes in urine flow (Tang-Liu *et al.*, 1982b). The clearances of methyluric acids are greater than glomerular filtration rate and renal secretory mechanisms are likely to be involved in their elimination.

The data in this investigation indicate that caffeine is eliminated in man primarily by metabolic transformation to several methylated xanthine and uric acid metabolites. Other metabolic or nonmetabolic routes of elimination are possible. At least one and possibly more routes of elimination of caffeine may be saturable and caffeine and/or its metabolites may inhibit xanthine oxidase. Renal clearance of less polar dimethylxanthine metabolites and caffeine itself are, in accordance with theoretical considerations, sensitive to changes in urine flow. Its more polar metabolites are not sensitive to urine flow. The methylxanthines and methyluric acids are similar in structure and are eliminated by similar pathways. Interactions among these compounds in the processes of distribution, metabolism and excretion are therefore likely to occur. We are in the process of exploring the effect of caffeine and its metabolites on the disposition of theophylline, a widely used bronchodilator.

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