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Caffeine clearance and biotransformation in patients with chronic liver disease

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SUMMARY

1. The clearance and biotransformation of caffeine (1,3,7-trimethylxanthine) were investigated in eight healthy control subjects and 16 patients with cirrhosis, by measuring serial serum caffeine concentrations and recoveries of methylxanthine metabolites in urine for 48 h after a 400 mg oral caffeine load.

2. In the control group, the mean (±SD) serum caffeine clearance was 1.3±0.4 ml min^{-1} kg^{-1} and a mean of 56.4±16.5% of the administered caffeine was recovered from the urine over 48 h as methyluric acids and methylxanthines. The majority of the metabolites were excreted in the first 24 h period and only 2.0±1.4% of the administered caffeine was excreted unchanged.

3. Patients with compensated cirrhosis ($n=10$) metabolized caffeine similarly to the control subjects. Thus the mean serum caffeine clearance was 1.4±1.2 ml min^{-1} kg^{-1} and a mean of 57.2±11.7% of the administered caffeine was recovered from the urine over 48 h. The majority of the metabolites were excreted in the first 24 h; the pattern of metabolic excretion was unaltered and only 2.2±0.9% of the administered caffeine was excreted unchanged.

4. In the patients with decompensated cirrhosis ($n=6$), significant changes were observed in caffeine metabolism. The mean serum caffeine clearance (0.4±0.2 ml min^{-1} kg^{-1}) was significantly impaired compared with controls ($P<0.01$) and a significant delay was observed in metabolite excretion in the urine. Thus the mean recovery of metabolites in the urine during the first 24 h (25.0±11.2%) was significantly reduced compared with controls (44.1±12.4%, $P=0.03$), whereas the mean urinary metabolite recovery in the second 24 h (20.9±10.5%) was insignificantly increased compared with controls (12.3±7.8%). Overall, the mean recovery of metabolites in the urine in 48 h (45.9±15.4%) was similar to that in the control group. The overall recovery of unchanged caffeine was significantly greater than in controls (5.0±2.8% vs 2.0±1.4%, $P=0.04$), but the pattern of metabolite excretion was otherwise unchanged.

5. In the patients with liver disease there were significant linear correlations between the degree of hepatocellular dysfunction and the serum caffeine elimination half-life ($r=0.774$; $P<0.01$) and the total recovery of methylxanthine metabolites in the urine, in the 0–24 h ($r=0.702$; $P=0.002$) and 0–48 h ($r=0.581$; $P=0.018$) periods.

6. Caffeine clearance is impaired in patients with decompensated cirrhosis either because of a reduction in hepatic caffeine uptake or else because of a reduction in 'functioning hepatocyte mass'. However, the biotransformation of caffeine is unaltered in the presence of hepatic dysfunction.

Key words: caffeine, liver disease, metabolism, urine.

Abbreviations: 1-MU, 1-methyluric acid; 7-MU, 7-methyluric acid; 1,3-MU, 1,3-dimethyluric acid; 1,7-MU, 1,7-dimethyluric acid; 1,3,7-MU, 1,3,7-trimethyluric acid; 1-MX, 1-methylxanthine; 3-MX, 3-methylxanthine; 7-MX, 7-methylxanthine; 1,3-MX, 1,3-methylxanthine; 1,7-MX, 1,7-dimethylxanthine; 3,7-MX, 3,7-dimethylxanthine.

INTRODUCTION

Caffeine is a trimethylxanthine (1,3,7-trimethylxanthine) which, in man, is metabolized primarily by hepatic demethylation and oxidation under the influence of the hepatic microsomal cytochrome *P*-450-dependent mixed-

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function oxidase system. Only 1–3% of an administered dose is recovered unchanged from the urine [1–3]. The majority of administered caffeine is *N*-demethylated at the 7- and 3-positions producing 1-methylxanthine (1-MX) and its further metabolite 1-methyluric acid (1-MU) (Fig. 1). The other quantitatively important metabolites are 7-methylxanthine (7-MX), 1,7-dimethylxanthine (1,7-MX) and 1,7-dimethyluric acid (1,7-MU).

The effects of liver disease on caffeine elimination have been studied by monitoring plasma clearance of oral or intravenously administered caffeine [4–6] and by measurement of $^{14}CO_2$ in expired breath after intravenous injection of [3-*methyl*-^{14}C]caffeine [6, 7]. The results of these studies have shown, that in patients with cirrhosis, plasma caffeine clearance is significantly reduced and its elimination half-life is significantly prolonged [4–6]. Less significant changes are found in patients with non-cirrhotic liver disease [5].

The impaired clearance of caffeine in patients with chronic liver disease is usually attributed to a reduction in 'functioning hepatocyte mass' [6]. However, the delayed elimination may reflect specific alterations in the biotransformation of caffeine. Changes in the disposition of caffeine have been reported after the administration of allopurinol [8] and oral contraceptives [9], during pregnancy [10] and in the newborn infant [11].

In the present study the effects of chronic liver disease on the clearance and biotransformation of caffeine were investigated by comparing serum caffeine concentrations and recoveries of metabolites in urine in healthy control subjects and in patients with cirrhosis, after an oral caffeine load.

METHODS

Sixteen patients with biopsy-proven cirrhosis and eight healthy control subjects were studied. The patients with liver disease were divided into two groups on the basis of their degree of hepatic dysfunction which was determined by a number of clinical and biochemical variables and the Pugh's scoring system [12]. The first group consisted of ten hospital outpatients, three males and seven females, aged 40–71 years, with Pugh's scores of 7 or less and thus well-compensated liver disease. The second group consisted of six hospital inpatients, three males and three females, aged 41–68 years, with Pugh's scores of 8–12 and thus decompensated liver disease (Table 1). Although serum creatinine concentrations tended to be higher in the patients with decompensated cirrhosis, 24 h urine outputs were normal and there was no evidence to suggest that individuals in this group had impaired renal function.

Patients with alcohol-related liver disease had been abstinent from alcohol for a minimum of 3 weeks, which was confirmed by random monitoring of breath alcohol values. None of the patients with non-alcohol-related cirrhosis consumed alcohol in excess of 5 g daily; five patients with liver disease were regular smokers. All but essential medication was stopped for 24 h before the study and for its duration.

The control group comprised eight healthy volunteers, four males and four females, aged 24–36 years. None of the control subjects consumed alcohol in excess of 5 g daily and none was a regular smoker. None had taken drugs likely to interfere with caffeine metabolism in the 2 weeks before the study nor did so during the study period.

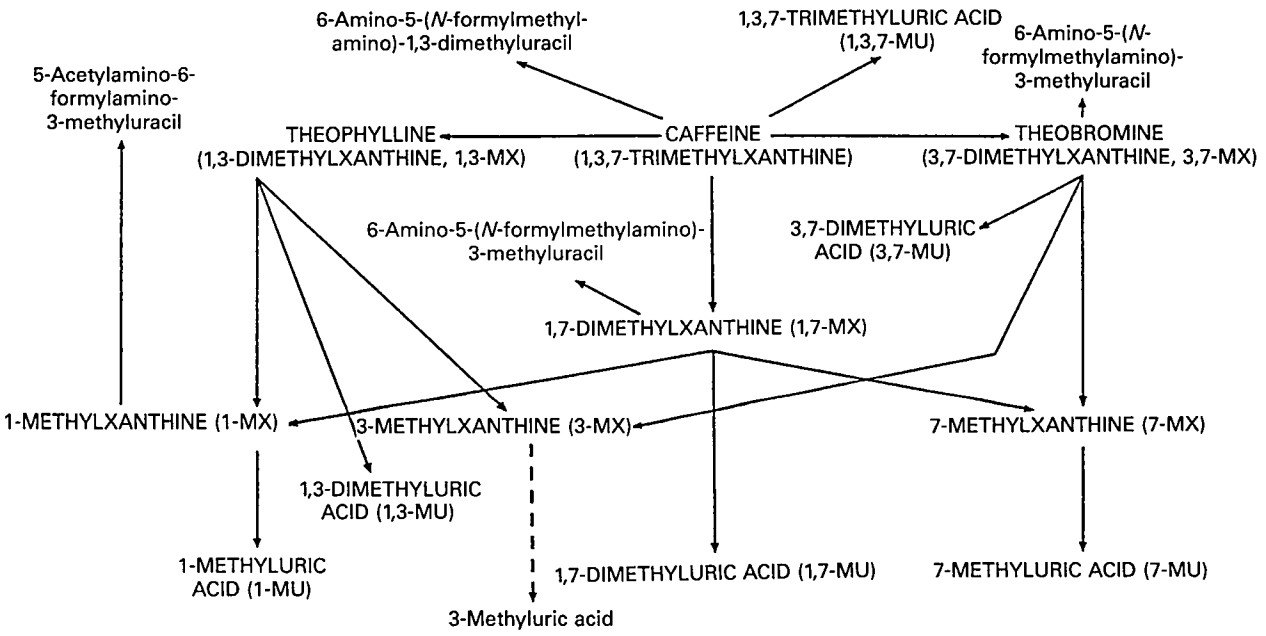

Fig. 1. Metabolic pathway of caffeine. In the present study metabolites in uppercase letters were measured in the urine in control subjects ($n = 8$) and patients with cirrhosis ($n = 16$), for 48 h after a 400 mg oral caffeine load.

Table 1. Details of clinical and laboratory findings in cirrhotic patients given an oral dose of 400 mg of caffeine

Degree of ascites: 0, nil, +, slight, + +, moderate. Encephalopathy was assessed using the West Haven criteria [13]. Abbreviations: AST, aspartate transaminase; AC, alcoholic cirrhosis; PBC, primary biliary cirrhosis. Medication: 1, folic acid; 2, vitamin E; 3, indomethacin; 4, lorazepam; 5, spironolactone; 6, potassium chloride; 7, allopurinol; 8, chlorazepate potassium; 9, orovite; 10, malotilate; 11, ferrous sulphate; 12, cimetidine; 13, prednisolone; 14, domperidone; 15, glibenclamide; 16, hydroxyapatite compound; 17, D-penicillamine; 18, lactulose; 19, thiamine; 20, ranitidine; 21, tripotassium dicitrate bismuthate; 22, phenoxybenzamine hydrochloride; 23, stanozolol; 24, paracetamol; 25, magnesium trisilicate; 26, danthrox; 27, cholestyramine; 28, nystatin; 29, frusemide, 30, amiloride.

Subject	Sex	Age (years)	Weight (kg)	Liver disease	Plasma bilirubin (μmol/l) (5–17 μmol/l)*	Serum AST (units/l) (17–40 units/l)*	Plasma albumin (g/l) (30–50 g/l)*	Serum creatinine (μmol/l) (60–120 μmol/l)*	Prothrombin time (s) (11–14 s)*	Ascites	Encephalopathy (0–IV)	Pugh's score [12] (5–15)	Smoking (cigarettes/day)	Caffeine intake (g/day)	Medication
Compensated cirrhosis															
1	F	52	56	AC	6	14	47	70	12	0	0	5	15	540	1
2	F	56	56	AC	7	20	46	64	12	0	0	5	—	130	2
3	M	52	73	AC	18	76	45	85	13	0	0	5	3	330	3
4	F	40	70	AC	19	24	40	71	17	0	0	5	15	350	4
5	F	43	54	AC	8	27	46	50	12	0	0	5	25	1290	5
6	F	54	56	AC	7	17	46	65	15	0	0	5	40	380	5
7	M	60	67	AC	15	15	44	82	15	0	0	5	—	490	6, 7, 8
8	F	68	78	AC	5	33	39	69	14	0	0	5	—	500	1, 9, 10
9	F	71	72	AC	21	27	38	70	15	0	0	5	—	220	5, 6, 11–14
10	M	53	66	AC	52	45	43	57	17	0	0	7	—	230	1, 9, 15
Mean		54.9	64.8	—	15.8	29.8	43.4	68.3	14.2	—	—	5.2	—	446	
±SD		9.2	8.2		13.3	17.8	3.1	9.9	1.8			0.6		308	
Decompensated cirrhosis															
11	F	42	90	AC	67	100	29	62	15	0	0	8	—	320	5, 9, 13, 16
12	M	68	69	PBC	67	64	33	98	12	+	II	8	—	220	1, 5, 17–21
13	F	63	41	PBC	228	152	34	151	12	0	I–II	9	—	—	4, 9, 18, 20, 22–26
14	F	41	55	PBC	396	247	36	90	12	+	I–II	9	—	180	5, 9, 16, 20, 27, 28
15	M	64	73	AC	312	103	28	104	19	+	I–II	11	—	150	5, 20
16	M	64	70	AC	41	48	27	105	20	+ +	II	12	—	—	1, 11, 18, 19, 27, 29, 30
Mean		57.0	66.3	—	185.1	119.0	31.2	101.7	15.0	—	—	9.5	—	145	
±SD		11.1	15.2		136.0	66.0	3.3	26.4	3.4			1.5		115	

*Laboratory reference range.

All subjects studied provided written informed consent. The study was approved by the Royal Free Hospital Ethics Committee.

Average daily caffeine intakes were estimated in all subjects using standardized reference values for each of the major sources of dietary caffeine [14]. All study participants were given a list of caffeine-containing beverages, foods and medications, and were asked to avoid them for 72 h before the study and during the study period.

Basal serum and urine samples were obtained after an overnight fast. Subjects were then given 400 mg of anhydrous caffeine in a gelatin capsule with approximately 150 ml of water. Serial serum samples were collected at 20 min, 40 min, 1, 2, 3, 4, 6, 8, 12, 24 and 48 h. Where possible, further samples were collected at 72 and 96 h. All samples were stored at −20°C until analysed. Total urine outputs were collected for the time intervals 0–24 h and 24–48 h. The urine volumes were recorded and 30 ml aliquots were stored at −20°C until analysed.

The concentrations of caffeine in serum were measured using a reversed-phase h.p.l.c. procedure previously described [15]. The overall sensitivity of the method was 200 ng/ml. The mean overall coefficients of variation for within-batch and between-batch precision were 3.9% and 4.6%, respectively.

Concentrations of caffeine and 11 of its metabolites were measured in urine using a previously described h.p.l.c. procedure [16]. These compounds were resolved using a Hypersil 5 μm octadecylsilane column (250 mm × 4.5 mm, Shandon U.K.) eluted with 0–12% acetonitrile in a 10 mmol/l acetate buffer, pH 4.8, containing 1% tetrahydrofuran. A flow rate of 1.5 ml/min was maintained throughout. Urine samples were prepared for chromatography using an ion-pair extraction procedure [17]. A 200 μl aliquot of centrifuged urine, 50 μl of internal standard [proxyphylline (7β-hydroxypropyltheophylline) 200 mg/l], 200 μl of 0.1 mol/l tetrabutylammonium hydrogen sulphate and 100 μl of buffer (0.1 mol/l sodium carbonate–0.1 mol/l sodium bicarbonate, 90:10, v/v, pH 11) were vortex-mixed for 30 s in a stoppered tube, before and after the addition of approximately 0.5 g of ammonium sulphate. The mixture was then extracted by vortex-mixing with 5 ml of a solution containing ethylacetate–chloroform–propan-2-ol (45:45:10, by vol.) for at least 1 min. After centrifugation for 5 min at 2000 rev./min (1500 *g*), a 4 ml aliquot of the organic layer was transferred to a clean tube and evaporated to dryness at 45°C in a stream of air. The residue was dissolved in 500 μl of 1% tetrahydrofuran at pH 4.8 and 50 μl of the solution was injected on to the column. The eluted metabolites were detected by u.v. monitoring at 280 nm and quantified by comparing the peak height ratios of metabolite and internal standard with those from appropriately prepared standard solutions. The overall sensitivity of the procedure was 0.6 mg/l with values ranging from 0.3 mg/l for caffeine to 1.4 mg/l for theophylline (1,3-dimethylxanthine, 1,3-MX). Mean overall coefficients of variation for within-batch and between-batch precision were 8.1% and 8.0%, respectively.

Caffeine, tetrahydrofuran (AR), ethylacetate (AR), chloroform (AR) and propan-2-ol (AR) were purchased from BDH Chemicals Ltd, Poole, Dorset, U.K.; 1,3-MX, 3,7-dimethylxanthine (theobromine, 3,7-MX), proxyphylline (7-β-hydroxypropyl-theophylline), 1-MU, 1,7-MX and tetrabutylammonium hydrogen sulphate from Sigma Chemical Co. Ltd, Poole, Dorset, U.K.; 7-methyluric acid (7-MU), (7-MX), 3-methylxanthine (3-MX), 1-MX, 1,3-dimethyluric acid (1,3-MU), 1,7-MU and 1,3,7-trimethyluric acid (1,3,7-MU) from Adams Chemical Co., Round Lake, Illinois, U.S.A. Acetonitrile (h.p.l.c. grade) was obtained from Rathburn Chemicals Ltd, Walkerburn, Scotland, U.K.

Pharmacokinetic data were calculated for caffeine in serum using a computer-based kinetics program. The computer system consisted of an intelligent user interface linked to the 'NONLIN' program supplied by Upjohn Ltd, Crawley, Sussex, U.K. With this system a polyexponential equation was used to fit the serum concentration–time data by weighted, non-linear, least-squares regression algorithm. Metabolite recoveries in the urine were expressed as a percentage of the administered dose of caffeine.

The data were analysed using Student's *t*-test, the Mann–Whitney *U*-test and linear regression analysis. A value of *P* of 0.05 or less was considered significant.

Table 2. Serum caffeine kinetics in control subjects and in patients with compensated and decompensated cirrhosis after a 400 mg oral caffeine load

Values are expressed as means ± SD. Abbreviations: β, elimination constant; $t_{1/2}$, half-life; V_d, apparent value of distribution; Cl, total clearance. Significance of difference between values in control subjects and patients: $^*P < 0.01$.

Subject group	β (h^{-1})	$t_{1/2}$ (h)	V_d (litres kg^{-1})	Cl (ml min^{-1} kg^{-1})
Controls ($n=8$)	0.18 ± 0.07	4.4 ± 1.9	0.44 ± 0.09	1.3 ± 0.4
Compensated cirrhosis ($n=10$)	0.19 ± 0.15	5.2 ± 2.7	0.38 ± 0.09	1.4 ± 1.2
Decompensated cirrhosis ($n=5$)	0.05 ± 0.02*	39.5 ± 61.8*	0.48 ± 0.10	0.4 ± 0.2*

RESULTS

There were no significant differences in average daily caffeine intakes before the study in the control subjects (mean ± SD 278 ± 153 mg, range 0–500 mg) and in the patients with compensated (446 ± 308 mg, range 130–1290 mg) and decompensated (145 ± 115 mg, range 0–320 mg) cirrhosis.

No significant differences were observed in the measured and derived pharmacokinetic data for caffeine (Table 2) in the patients with compensated cirrhosis compared with the control subjects (Table 2), indicating that in this patient group caffeine clearance is essentially unimpaired. However, significant differences were observed in kinetic variables between the patients with decompensated cirrhosis and control subjects (Table 2), indicating significant impairment of caffeine clearance in this patient group.

No appreciable traces of xanthine metabolites were detected in basal urine samples in any of the subjects studied. After the oral caffeine load, recoveries of metabolites in urine in the control subjects were quantitatively and qualitatively similar to those reported previously [1–3]. The principal metabolites were 1-MU, 1-MX and 1,7-MU (Table 3).

The mean total recoveries of metabolites in urine in patients with compensated cirrhosis for the periods

Table 3. Caffeine metabolite recoveries in control subjects and in patients with chronic liver disease after a 400 mg oral dose of caffeine

Values are expressed as means ± SD. *P* values are significance of difference between results in control subjects and in the patients with liver disease. Abbreviation: NS, not significant.

	Control subjects ($n=8$)	Compensated cirrhosis ($n=10$)	*P*	Decompensated cirrhosis ($n=6$)	*P*
	Caffeine metabolite recovery 0–24 h (% of dose)				
7-MU	0.8 ± 0.5	0.6 ± 0.3	NS	0.8 ± 0.5	NS
7-MX	2.2 ± 0.7	1.9 ± 0.9	NS	1.4 ± 0.8	0.04
1-MU	15.6 ± 7.4	14.3 ± 6.6	NS	6.9 ± 6.6	NS
3-MX	0.9 ± 0.5	1.0 ± 0.5	NS	0.6 ± 0.6	NS
1-MX	9.2 ± 4.4	8.9 ± 3.1	NS	3.1 ± 2.2	0.005
1,3-MU	0.9 ± 0.4	0.8 ± 0.4	NS	0.7 ± 0.4	NS
3,7-MX	1.7 ± 0.7	1.7 ± 1.5	NS	1.1 ± 0.7	NS
1,7-MU	6.1 ± 1.3	5.6 ± 2.1	NS	4.5 ± 3.1	NS
1,7-MX	3.5 ± 1.7	3.5 ± 1.4	NS	1.9 ± 1.6	NS
1,3-MX	0.4 ± 0.4	0.6 ± 0.2	NS	0.3 ± 0.3	NS
1,3,7-MU	0.9 ± 0.7	0.5 ± 0.4	NS	0.6 ± 0.5	NS
Caffeine	1.9 ± 1.5	1.7 ± 0.7	NS	3.3 ± 1.5	NS
Total	44.1 ± 12.4	41.3 ± 11.4	NS	25.1 ± 11.2	0.03
	Caffeine metabolite recovery 24–48 h (% of dose)				
7-MU	0.4 ± 0.4	0.6 ± 0.6	NS	0.6 ± 0.5	NS
7-MX	1.2 ± 0.8	1.4 ± 0.6	NS	1.3 ± 0.5	NS
1-MU	4.3 ± 2.9	4.0 ± 2.6	NS	6.5 ± 4.2	NS
3-MX	1.1 ± 0.6	0.8 ± 0.3	NS	0.6 ± 0.3	NS
1-MX	2.0 ± 1.4	3.2 ± 2.5	NS	2.6 ± 1.7	NS
1,3-MU	0.7 ± 0.5	0.6 ± 0.7	NS	0.5 ± 0.4	NS
3,7-MX	0.7 ± 0.5	1.0 ± 1.2	NS	1.1 ± 0.4	NS
1,7-MU	1.3 ± 1.1	1.9 ± 1.5	NS	3.7 ± 2.7	NS
1,7-MX	0.5 ± 0.6	1.4 ± 1.5	NS	1.9 ± 2.2	NS
1,3-MX	0.2 ± 0.3	0.4 ± 0.3	NS	0.8 ± 0.7	NS
1,3,7-MU	0.1 ± 0.2	0.4 ± 0.6	NS	0.5 ± 0.6	NS
Caffeine	0.1 ± 0.2	0.5 ± 0.4	NS	1.7 ± 1.6	0.003
Total	12.3 ± 7.8	15.9 ± 10.9	NS	20.9 ± 10.5	NS
	Total caffeine metabolite recovery 0–48 h (% of dose)				
7-MU	1.2 ± 0.6	1.2 ± 0.8	NS	1.5 ± 0.5	NS
7-MX	3.4 ± 1.2	3.4 ± 0.9	NS	2.6 ± 1.0	NS
1-MU	19.8 ± 8.5	18.3 ± 6.0	NS	12.7 ± 9.1	NS
3-MX	2.0 ± 1.0	1.8 ± 0.6	NS	1.2 ± 0.5	NS
1-MX	11.3 ± 4.9	12.1 ± 2.8	NS	5.7 ± 2.8	NS
1,3-MU	1.6 ± 0.6	1.4 ± 0.9	NS	1.2 ± 0.8	NS
3,7-MX	2.4 ± 0.6	2.7 ± 1.7	NS	2.2 ± 0.9	NS
1,7-MU	7.4 ± 2.0	7.5 ± 3.0	NS	8.1 ± 5.0	NS
1,7-MX	4.0 ± 2.0	5.0 ± 2.1	NS	3.8 ± 3.8	NS
1,3-MX	0.6 ± 0.5	0.9 ± 0.4	NS	1.1 ± 0.7	NS
1,3,7-MU	1.0 ± 0.7	0.9 ± 0.7	NS	1.1 ± 1.0	NS
Caffeine	2.0 ± 1.4	2.2 ± 0.9	NS	5.0 ± 2.8	0.04
Total	56.4 ± 16.5	57.2 ± 11.5	NS	45.9 ± 15.4	NS

0–24 h, 24–48 h and 0–48 h after caffeine ingestion were similar to those in control subjects (Table 3). No significant differences were observed in the mean recoveries of individual metabolites or in the overall pattern of metabolite excretion in this patient group.

Significant differences were observed in the recoveries of metabolites in urine after oral caffeine in the patients with decompensated cirrhosis compared with the controls (Table 3). In the first 24 h after caffeine ingestion there was a significant reduction in the mean total recovery of metabolites in urine in this group (25.1 ± 11.2% vs 44.1 ± 12.4%, $P=0.03$). The mean urinary recoveries of all metabolites, with the exception of 7-MU, were reduced, although only the reductions in 7-MX (1.4 ± 0.8 vs 2.2 ± 0.7%, $P=0.04$) and 1-MX (3.1 ± 2.2 vs 9.2 ± 4.4%, $P=0.005$) recoveries were significant. In the second 24 h after caffeine ingestion, mean recoveries of metabolites in urine in three cirrhotic patients were insignificantly increased compared with controls. Overall, the mean total recovery of metabolites in the urine during the 48 h after caffeine ingestion in this group (45.9 ± 15.4%) was similar to the control mean (56.4 ± 16.5%). The mean recoveries of unchanged caffeine were greater in patients with decompensated cirrhosis than in controls in the 0–24 h (3.3 ± 1.5 vs 1.9 ± 1.8%, NS), 24–48 h (1.7 ± 1.6 vs 0.1 ± 0.2%, $P=0.003$) and 0–48 h (5.0 ± 2.8 vs 2.0 ± 1.4, $P=0.04$) periods.

In the patients with liver disease there were significant linear correlations between the degree of hepatic dysfunction assessed by the Pugh's scoring system [12] and values for serum caffeine elimination half-life ($r=0.774$; $P=0.001$) and the total recovery of metabolites in the urine, in the 0–24 h ($r=0.702$; $P=0.002$) and 0–48 h ($r=0.581$; $P=0.018$) periods (Fig. 2) Significant correlations were also observed between the total recovery of metabolites in the urine in the 0–24 h period and the serum caffeine elimination constant ($r=0.583$; $P=0.04$) and the elimination half-life ($r=0.724$; $P=0.002$). No significant relationships existed between the caffeine kinetic variables in serum or the recoveries of methylxanthine metabolites in urine and any feature of the patients' demography, their smoking habits or their average daily caffeine intake before the study.

DISCUSSION

The major factors which determine the ability of the liver to clear drugs are the hepatic blood flow, the activity of the hepatic drug-metabolizing enzymes, the anatomical arrangement of the portal blood supply and the extent to which the drug is protein-bound. In patients with liver disease, the clearance of a number of drugs may be impaired because of changes in these variables [18, 19]. Caffeine is only 30% protein-bound [4] and has a low hepatic extraction ratio. Thus its hepatic clearance is largely indepedent of liver blood flow but will be affected by reductions in the activity of the hepatic drug-metabolizing enzymes and in the 'functioning hepatocyte mass'.

In the patients with well-compensated cirrhosis in the present study, serum kinetic data and recoveries of

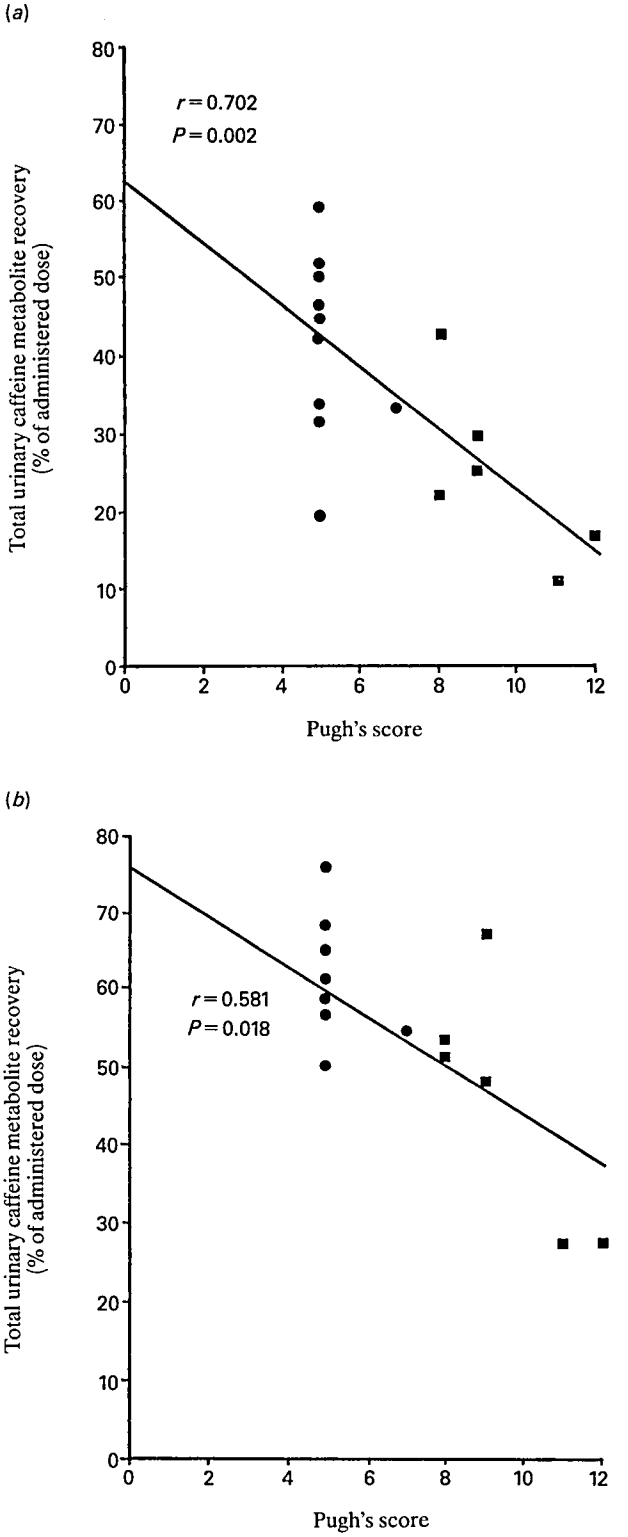

Fig. 2. Relationship between the degree of hepatocellular dysfunction, assessed by the Pugh's scoring system [12], and the total recovery of metabolites in the urine for the periods 0–24 h (*a*) and 0–48 h (*b*) after ingestion of 400 mg of anhydrous caffeine, in 10 patients with compensated (●) and six patients with decompensated (■) cirrhosis.

metabolites in urine after an oral caffeine load were similar to those in control subjects. In both these groups approximately 60% of the administered caffeine was recovered from the urine, predominantly in the first 24 h, as methyluric acids and methylxanthines; approximately 2% of the ingested dose was recovered as unchanged caffeine. The remaining 40% of the administered caffeine was probably excreted as acetylated uracil derivatives.

In the patients with decompensated cirrhosis there was a generalized impairment of caffeine metabolism reflected by the serum kinetic data and by the recoveries of metabolites in the urine. Thus, although the mean total recovery of metabolites in urine over 48 h was similar to that in the control group, there was a significant delay in metabolite excretion. As a result, the total recovery of metabolites in urine in the first 24 h after the caffeine load was significantly reduced and significantly more caffeine was excreted unchanged, accounting for some 5% of the administered load. It is likely, that in this group, excretion of caffeine metabolites continued beyond the 48 h study period. The caffeine not accounted for in this way was probably excreted as acetylated uracil derivatives.

Although caffeine metabolism was impaired in the patients with decompensated cirrhosis, the overall pattern of metabolite excretion in this group was not significantly altered. This indicates that the biotransformation of caffeine is unaffected even in the presence of severe liver disease. It has been suggested that the impaired clearance of theophylline (1,3-MX) observed in patients with liver disease might be associated with a decrease in 1-*N*-demethylation [20], but this does not appear to be the case in patients given caffeine. Smoking has been shown to increase caffeine clearance because it causes induction of hepatic acylhydrocarbon hydroxylase activity [21]. However, the recoveries of metabolites in urine in the smokers and non-smokers in this study were not significantly different.

In the patients with liver disease there was a significant relationship between the degree of impairment of caffeine metabolism and the degree of hepatocellular dysfunction assessed by the Pugh's score rating [12]. Significant reductions in hepatic concentrations of cytochrome *P*-450 and in the activities of the drug-metabolizing enzymes have only been observed in patients with severe and extensive hepatocellular necrosis [22]. It is, therefore, unlikely that the impairment of caffeine clearance observed in our patients with decompensated cirrhosis resulted from a reduction in hepatic enzyme activity as all had inactive cirrhosis on liver biopsy. The impairment in caffeine clearance observed in this study most likely results from a reduction in the hepatic uptake of caffeine or else a reduction in 'functioning hepatocyte mass'.

Thus, although caffeine clearance is impaired in patients with chronic liver disease, there is no evidence that the biotransformation of caffeine is altered in the presence of hepatic dysfunction.

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