The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease

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1 Serum and salivary concentrations of caffeine (1,3,7-trimethylxanthine) and its dimethylxanthine metabolites were measured in 10 healthy control subjects and in 19 patients with cirrhosis, for up to 96 h following a 400 mg oral caffeine load.

2 Serum and salivary caffeine concentrations correlated significantly ($r = 0.954$; $P < 0.001$) and no significant differences were observed in the pharmacokinetic data derived from the respective concentration-time curves.

3 In the control subjects, basal salivary caffeine concentrations did not exceed 0.4 mg l^{-1}. The median (range) basal salivary caffeine concentrations in patients with compensated cirrhosis ($n = 10$), 0.2 (0–0.7) mg l^{-1} and decompensated cirrhosis ($n = 9$), 0.7 (0–5.8) mg l^{-1}, were not significantly different from control values, although three patients with decompensated cirrhosis had basal salivary caffeine values above 2.0 mg l^{-1}.

4 In the patients with compensated cirrhosis, the median peak salivary caffeine concentration, 10.9 (8.2–16.5) mg l^{-1} was significantly greater than in controls, 7.1 (4.7–11.8) mg l^{-1} ($P < 0.01$) and the median apparent volume of distribution was significantly reduced, 0.38 (0.19–0.49) *vs* 0.41 (0.23–0.63) l kg^{-1} ($P < 0.05$). In the patients with decompensated cirrhosis, the median peak salivary caffeine concentration, 12.4 (8.2–18.1) mg l^{-1} was greater than in controls, 7.1 (4.7–11.8) mg l^{-1} ($P < 0.02$) as were the median salivary caffeine half-life, 25.8 (9.8–150.5) *vs* 4.0 (2.1–8.1) h ($P < 0.001$) and the median area under the salivary caffeine concentration-time curve, 333.4 (226.7–2000) *vs* 78.3 (40.9–112.6) mg l^{-1} h ($P < 0.001$). The median elimination rate constant was significantly reduced in this patient group, 0.05 (0.01–0.07) *vs* 0.16 (0.09–0.33) h^{-1} ($P < 0.01$) as was the median total salivary caffeine clearance, 0.22 (0.01–0.61) *vs* 1.47 (0.87–2.43) ml min^{-1} kg^{-1} ($P < 0.001$).

5 There were significant correlations between the degree of hepatic dysfunction assessed by the Pugh's score rating and values for the salivary caffeine elimination half-life ($r_s = 0.859$; $P < 0.001$), the elimination rate constant ($r_s = -0.863$; $P < 0.001$) and the total salivary caffeine clearance ($r_s = -0.760$; $P < 0.001$). Patients with decompensated cirrhosis had caffeine elimination half-lives > 10 h, elimination rate constants of < 0.08 h^{-1}, 12 h salivary caffeine concentrations > 5.5 mg l^{-1} and total salivary clearance values of < 0.4 ml min^{-1} kg^{-1}. Kinetic data in the patients with compensated cirrhosis could not be distinguished in this way.

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6 Patients with well-compensated cirrhosis could not be differentiated routinely from control subjects on the basis of their caffeine pharmacokinetic data. Thus, use of the caffeine loading test to assess hepatocellular dysfunction confers no diagnostic advantage over clinical examination coupled with measurement of more readily available 'liver function tests'.

Introduction

Conventional liver function tests are of limited value for detecting and assessing the severity of hepatic dysfunction. Thus, in recent years, interest has been focused on developing methods to quantify hepatic function accurately. A number of such tests have been proposed, including measurement of fasting and 2 h post-prandial serum bile acid concentrations (Ferraris *et al.*, 1983), measurement of the rate of galactose elimination (Tygstrup, 1964) and the use of a variety of breath tests employing radio-labelled aminopyrine (Bircher *et al.*, 1976). In general these tests have not found favour, as they either confer no diagnostic benefit over more readily available laboratory tests or else they are costly, complex to perform or use test substances or procedures which are potentially harmful.

It has been suggested that caffeine (1,3,7-trimethylxanthine, 137MX) might be an ideal test substance for assessing hepatic function, as it is rapidly and completely absorbed after oral ingestion (Blancharad & Sawers, 1983) and is metabolised primarily by the hepatic cytochrome P-450 dependent mixed function oxidase system (Arnaud & Welsch, 1981). Indeed it has been shown that plasma caffeine clearance is significantly reduced in patients with cirrhosis and its elimination half-life is significantly prolonged (Desmond *et al.*, 1980; Wietholtz *et al.*, 1981; Renner *et al.*, 1984; Wang *et al.*, 1985). Although caffeine loading tests are inexpensive, simple to perform and safe, the test procedure has yet to be standardised and there are few guidelines as to how the test results should be interpreted.

In the present study, caffeine pharmacokinetics were assessed in control subjects and in patients with cirrhosis, in order to define values for kinetic variables which might distinguish between healthy subjects and patients with liver disease of varying severity.

Methods

Nineteen patients with cirrhosis, which had been confirmed histologically, and ten 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 Pugh's scoring system (Pugh *et al.*, 1973). The first group comprised ten patients, 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 comprised nine patients, five males and four females, aged 41–78 years with Pugh's scores of 8–12 and thus decompensated liver disease (Table 1). Serum creatinine concentrations tended to be higher in the patients with decompensated cirrhosis but 24 h urinary 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. 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 48 h before the study and for its duration.

The control group comprised ten healthy volunteers, seven males and three females, aged 24–48 years. None of the control subjects consumed alcohol in excess of 5 g daily; one of the control subjects smoked an average of five cigarettes per day. None had taken drugs likely to interfere with caffeine metabolism in the 2 weeks before the study nor did so during the study period.

Average, daily caffeine intakes were estimated in all subjects using standardised reference values for each of the major sources of caffeine (Barone & Roberts, 1984). 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 salivary samples were obtained after an overnight fast. Salivary samples, 1–2 ml

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

Subject	Sex	Age (years)	Weight (kg)	*Liver disease	Plasma bilirubin **(5–17) (mmol l⁻¹)	Serum ***AST (17–40) (u l⁻¹)	Plasma albumin (30–50) (g l⁻¹)	Serum creatinine (60–120) (μmol l⁻¹)	+PT (11–14) (s)	++Ascites (0,+,++)	°Encephalopathy (0–IV)	°°Pugh's score (5–15)	Smoking (cigarettes/day)	Daily caffeine intake (mg)	Medication
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	6–8
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
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	+	0	8	–	220	1,5,17–21
13	F	63	41	PBC	228	152	34	151	12	0	I–II	9	–	320	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	–	160	5,20
16	M	64	70	AC	41	48	27	105	20	++	II	12	–	0	1,11,18,19,27,29,30
17	M	62	60	AC	33	27	33	157	18	++	I	10	–	0	1,18,19,24,31
18	M	78	56	PBC	132	214	23	100	14	++	III	12	–	300	5,18,20,32,33
19	F	59	59	PBC	444	150	38	120	19	+++	II–III	12	–	150	5,13,18,20,34,35

*AC-Alcoholic cirrhosis, PBC-primary biliary cirrhosis; **-Laboratory reference range; ***AST-aspartate transaminase; +PT-prothrombin time; ++Ascites 0-nil, +-slight, ++-moderate; °Encephalopathy assessed using West Haven criteria (Conn et al., 1977); °°Pugh et al., 1973.

1 Folic acid	2 Vitamin E	3 Indomethacin	4 Lorazepam
6 Potassium chloride	7 Allopurinol	8 Chlorazepate potassium	9 Orovite
11 Ferrous sulphate	12 Cimetidine	13 Prednisolone	14 Domperidone
16 Hydroxyapatite compound	17 D-penicillamine	18 Lactulose	19 Thiamine
21 Tripotassium dicitrate bismuthate	22 Phenoxybenzamine hydrochloride	23 Stanozolol	24 Paracetamol
26 Danthrox	27 Cholestyramine	28 Nystatin	29 Frusemide
31 Ampicillin	32 Nitrofurantoin	33 Quinine sulphate	34 Cefoxitin

5 Spironolactone
10 Malotilate
15 Glibenclamide
20 Ranitidine
25 Magnesium trisilicate
30 Amiloride
35 Metronidazole

in volume, were expectorated, without stimulation, into a glass tube. Blood samples were withdrawn through an indwelling catheter and the serum separated after centrifugation. Subjects were then given 400 mg of anhydrous caffeine in a gelatine capsule with approximately 150 ml of water. Serial serum and salivary samples were collected at 20 min, 40 min, 1, 2, 3, 4, 6, 8, 12, 24 and 48 h. Further samples were collected from the patients with decompensated cirrhosis at 72 h and when possible at 96 h. All samples were stored at $-20°$ C until analysed.

The concentrations of caffeine and of its major dimethyl metabolites, theophylline (1,3-dimethylxanthine, 13MX), paraxanthine (1,7-dimethylxanthine, 17MX) and theobromine (3,7-dimethylxanthine, 37MX) were measured in serum and saliva using a reversed-phase, high performance liquid chromatography procedure (Scott *et al.*, 1984). The overall sensitivity of the method was 200 ng ml^{-1} for caffeine and 100 ng ml^{-1} for its dimethylxanthine metabolites. Mean overall coefficients of variation for within batch and between batch precision, determined on serum and salivary samples 'spiked' with 4 mg l^{-1} and 8 mg l^{-1} amounts of caffeine and paraxanthine were 3.4% (range 3.1–4.1) and 3.5% (2.0–4.6), respectively.

Pharmacokinetic data were calculated for caffeine and its dimethylxanthine metabolites using the computer-based 'NONLIN' program supplied by Upjohn Ltd, Crawley, Sussex, UK. This system fits a polyexponential equation to concentration-time data by a weighted, non-linear, least-square regression algorithm. The areas under the concentration-time curves following oral caffeine were calculated by the trapezoidal method with extrapolation to infinity.

Comparisons between the measured and derived pharmacokinetic variables in the control subjects and patient groups were made using the Mann Whitney U test. Correlations between caffeine and paraxanthine concentrations in serum and saliva were measured using linear regression analysis while correlations between standard liver function test results, the Pugh's score and pharmacokinetic variables were assessed using the Spearman Rank test. A value of $P = 0.05$ or less was considered significant.

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

Results

The average median daily caffeine intake, before the study, in the patients with decompensated cirrhosis, 180 mg (range 0–320) was significantly lower than in the control subjects, 380 mg (0–800) ($P < 0.05$) and in the patients with compensated cirrhosis, 365 mg (132–1290) ($P < 0.02$).

Pharmacokinetics of caffeine in serum and saliva

Significant linear correlations were observed between serum and salivary caffeine concentrations, following the oral caffeine load, in both the control subjects ($r = 0.965$; $P < 0.001$) and in the patients with compensated ($r = 0.953$; $P < 0.001$) and decompensated cirrhosis ($r = 0.928$; $P < 0.001$). The pharmacokinetic data derived from the serum and salivary caffeine concentration-time curves did not differ significantly in either the control subjects or the two patient groups. Only the salivary data are included in this report.

In the control subjects, the median basal salivary caffeine concentration was 0.1 (0–0.4) mg l^{-1}. The corresponding concentrations in the compensated, 0.2 (0–0.7) mg l^{-1} and decompensated cirrhotic groups, 0.7 (0–5.8) mg l^{-1} were not significantly different from the control value. However, three patients with decompensated cirrhosis (15, 18 and 19) had basal salivary caffeine concentrations greater than 2.0 mg l^{-1}.

Differences were observed in the salivary caffeine concentration-time curves (Figure 1) and in the measured and derived pharmacokinetic data (Table 2, Figure 2) in the control subjects and patient groups. In patients with compensated cirrhosis, the median peak concentration of caffeine in saliva 10.9 (8.2–16.5) mg l^{-1} was significantly greater than in controls 7.1 (4.7–11.8) mg l^{-1} ($P < 0.01$) and the mean apparent volume of distribution was significantly reduced, 0.38 (0.19–0.49) *vs* 0.41 (0.23–0.63) l kg^{-1} ($P < 0.05$) (Table 2, Figure 2).

In patients with decompensated cirrhosis, the median peak salivary caffeine concentration, 12.4 (8.2–18.1) mg l^{-1} was greater than in controls, 7.1 (4.7–11.8) mg l^{-1} ($P < 0.02$) but the median time to peak salivary caffeine concentration was not significantly different. Significant increases were also observed in the median salivary caffeine half-life, 25.8 (9.8–150.5) *vs* 4.0 (2.1–8.1) h ($P < 0.001$) and in the median area under the salivary caffeine concentration-time curve, 333.4 (226.7–2000) *vs* 78.3 (40.9–112.6) mg l^{-1} h ($P < 0.001$). The median apparent volume of distribution in this group, 0.48 (0.35–0.58) l kg^{-1} was comparable with the control value, 0.41 (0.23–0.63) l kg^{-1}. The median elimination rate constant was significantly reduced compared with controls, 0.05 (0.01–0.07)

vs 0.16 (0.09–0.33) h^{-1} ($P < 0.001$) as was the median total salivary clearance, 0.22 (0.01–0.61) *vs* 1.47 (0.87–2.43) ml min^{-1} kg^{-1} ($P < 0.001$).

In the cirrhotic patients there was no significant relationship between the salivary caffeine kinetic data and the results of the standard liver function tests. However, there were significant linear correlations between the degree of hepatic dysfunction assessed by the Pugh's score rating (Pugh *et al.*, 1973) and values for salivary caffeine elimination half-life ($r_s = 0.859$; $P < 0.001$), the elimination rate constant ($r_s = -0.863$; $P < 0.001$) and total salivary caffeine clearance ($r_s = -0.760$; $P < 0.001$). Patients with decompensated cirrhosis had caffeine elimination half-lives > 10 h, elimination rate constants of < 0.08 h^{-1}, 12 h salivary caffeine concentrations > 5.5 mg l^{-1} and total salivary clearance values of < 0.4 ml min^{-1} kg^{-1}.

There were no significant relationships between the salivary caffeine kinetic data and any feature of the patients' demography, or their average daily caffeine intake before the study. Similarly there was no significant relationship between the salivary caffeine kinetic data and smoking habits. Thus, in the patients with compensated cirrhosis no significant differences were observed between the smokers ($n = 5$) and non-smokers ($n = 5$) in

Figure 1 Salivary caffeine concentration-time curves in control subjects (▲— —▲), $n = 10$) and in patients with compensated (■———■, $n = 10$) and decompensated cirrhosis (●—·—●, $n = 9$) following a single 400 mg oral caffeine load at time zero. Values expressed as mean ± s.e. mean.

the median salivary caffeine half-life, 3.3 (1.1–4.8) *vs* 4.3 (2.9–8.4) h, the median elimination rate constant, 0.21 (0.15–0.61) *vs* 0.16 (0.08–0.24) h^{-1}, or the median total salivary caffeine clearance, 1.2 (0.9–4.5) *vs* 0.9 (0.5–2.1) ml min^{-1} kg^{-1}.

Dimethylxanthine metabolites in serum and saliva

In the majority of subjects studied, theophylline (1,3-dimethylxanthine, 13MX) and theobromine (3,7-dimethylxanthine, 37MX) were not detected in basal serum and salivary samples. Following the oral caffeine load only minimal amounts of these metabolites were detected in serum and saliva. However, in three patients with decompensated cirrhosis (15, 18 and 19) basal serum and salivary theobromine concentrations exceeded 1.5 mg l^{-1} and remained elevated following the oral caffeine load.

Basal paraxanthine (1,7-dimethylxanthine, 17MX) concentrations were less than 0.3 mg l^{-1} in all subjects studied. However, discernible amounts of this metabolite were detected in serum and saliva after the oral caffeine load in all but two subjects (15, 16).

Significant linear correlations were observed between serum and salivary paraxanthine concentrations following the oral caffeine load, in both the control subjects and in the patients with compensated and decompensated cirrhosis. The overall mean ± s.d. correlation coefficient was 0.89 ± 0.08 (range 0.76–0.99). Since the pharmacokinetic data derived from the serum and salivary paraxanthine concentration-time curves did not differ significantly in either the control subjects or the two patient groups only the salivary data are included in this report.

Differences were observed in the salivary paraxanthine concentration-time curves (Figure 3) and in the measured and derived pharmacokinetic data in control subjects and in both patient groups. In patients with compensated cirrhosis, the median peak salivary paraxanthine concentration, 2.7 (1.5–4.0) mg l^{-1} was significantly greater than in controls, 1.8 (1.2–3.6) mg l^{-1} ($P < 0.02$), while the median peak paraxanthine concentration in patients with decompensated cirrhosis, 1.2 (0.5–1.8) mg l^{-1} was significantly reduced ($P < 0.03$). The median times to peak paraxanthine concentrations in the control subjects, 6.0 (2.0–12.0) h and in the patients with compensated cirrhosis, 6.0 (2.0–12.0) h were comparable, whereas the median time to peak salivary paraxanthine concentration in the decompensated cirrhotics, 12.0 (1.0–48.0) h was significantly delayed ($P < 0.01$). In the majority of patients with decompensated cirrhosis, the salivary paraxanthine pharmacokinetic data in-
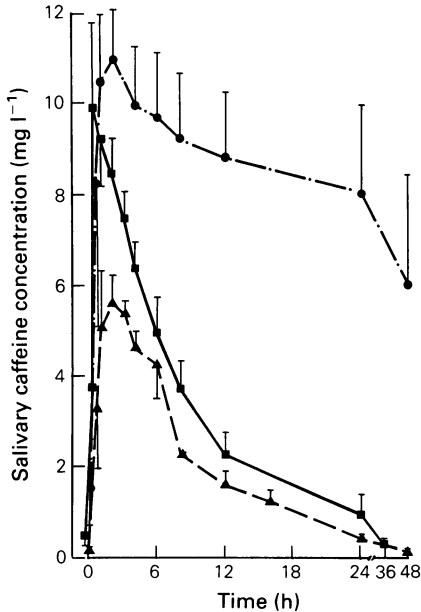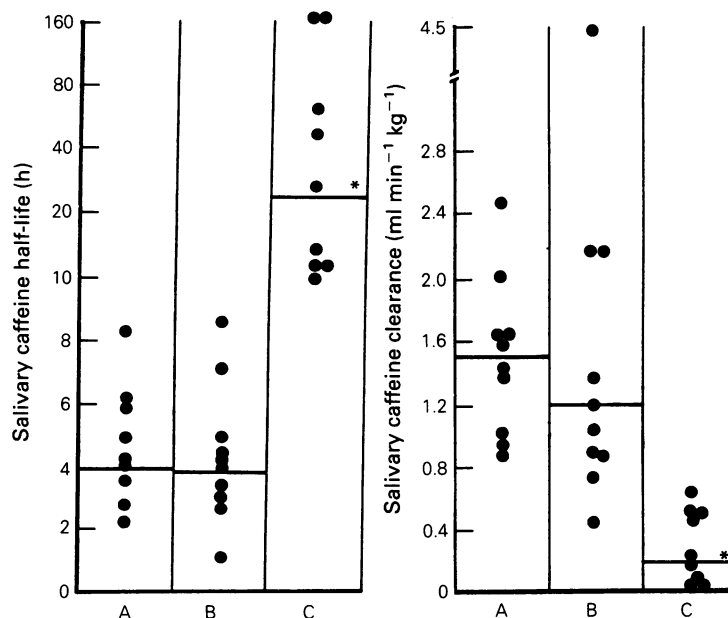
Figure 2 Salivary caffeine half-lives and total salivary caffeine clearance values in A) control subjects (*n* = 10) and in patients with B) compensated (*n* = 10) and C) decompensated cirrhosis (*n* = 9) following a single 400 mg oral caffeine load at time zero. ——— = group median values; * significance of the difference between values in patients with decompensated cirrhosis and control subjects *P* < 0.001.

Table 2 Salivary caffeine kinetics in control subjects and in patients with compensated and decompensated cirrhosis following a 400 mg oral caffeine load. Values expressed as median (range)

Subject group (n)	C_{max} (mg l^{-1})	t_{max} (h)	k (h^{-1})	$t_{1/2}$ (h)	V (l kg^{-1})	AUC (mg l^{-1} h)	CL (ml min^{-1} kg^{-1})
Controls (10)	7.1 (4.7–11.8)	2.0 (1.0–6.0)	0.16 (0.09–0.33)	4.0 (2.1–8.1)	0.41 (0.23–0.63)	78.3 (40.9–112.6)	1.47 (0.87–2.43)
Compensated cirrhosis (10)	10.9[+] (8.2–16.5)	1.0 (0.3–3.0)	0.18 (0.08–0.61)	3.9 (1.1–8.4)	0.38* (0.19–0.49)	76.2 (29.3–201.7)	1.19 (0.46–4.52)
Decompensated cirrhosis (9)	12.4** (8.2–18.1)	2.0 (0.5–6.0)	0.05[++] (0.01–0.07)	25.8[++] (9.8–150.5)	0.48 (0.35–0.58)	333.4[++] (226.7–2000)	0.22[++] (0.01–0.61)

C_{max} maximum concentration; t_{max} time to peak salivary concentration; k elimination rate constant; $t_{1/2}$ elimination half-life; V apparent value of distribution; AUC area under curve; CL total clearance. Significance of difference between values in control subjects and patients *P* < 0.05; **P* < 0.02; [+]P* < 0.01; [++]P* < 0.001.

dicated that both the formation and clearance of this metabolite were substantially impaired so that it could be detected in significant concentrations in the saliva 48 h after the oral caffeine load.

Discussion

In the present study, no significant differences were observed in the pharmacokinetic data derived from either the serum or the salivary caffeine concentration-time curves following the oral caffeine load. This finding confirms the suitability of salivary caffeine measurements for determining pharmacokinetic data (Newton *et al.*, 1981; Zylber-Katz *et al.*, 1984). However, some difficulty was encountered in collecting salivary samples from seriously ill patients and from patients with primary biliary cirrhosis and Sjorgren's syndrome (Epstein *et al.*, 1980).

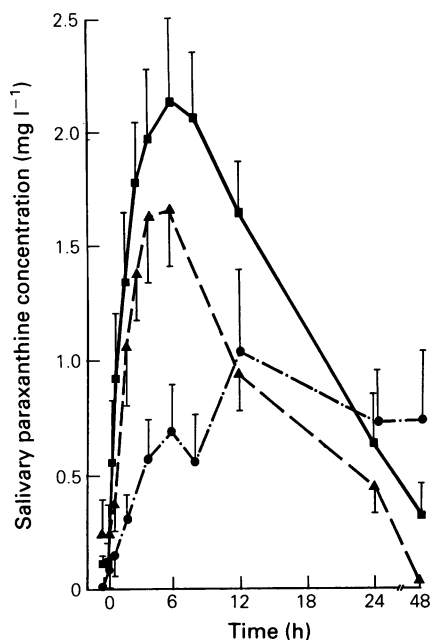The kinetic data obtained for caffeine in the present study were similar to those obtained in

Figure 3 Salivary paraxanthine concentration-time curves in control subjects (▲— —▲, $n = 10$) and in patients with compensated (■——■, $n = 10$) and decompensated cirrhosis (●—·—●, $n = 9$) following a single 400 mg oral caffeine load at time zero. Values expressed as mean ± s.e. mean.

control subjects and in patients with liver disease in previously published studies (Desmond *et al.*, 1980; Renner *et al.*, 1984; Wang *et al.*, 1985), although a direct comparison of the data is not possible because of differences in experimental design.

Caffeine is rapidly and completely absorbed from the gastrointestinal tract (Blancharad & Sawers, 1983) and in the present study peak caffeine concentrations were attained in all subjects within 3 h of ingesting the caffeine load; thereafter caffeine concentrations declined monoexponentially. The median peak caffeine concentration was increased in patients with compensated cirrhosis probably reflecting the decrease in the median apparent volume of distribution observed in this group, which is unexplained. The median peak caffeine concentration was also increased in patients with decompensated cirrhosis, undoubtedly as a result of a reduction in hepatic caffeine uptake most likely due to a reduction in hepatocellular function.

The total body clearance of a drug or xenobiotic compound is the sum of its metabolic clearance

and its renal clearance. In healthy volunteers only 1–3% of an administered caffeine load is excreted unchanged in the urine (Arnaud & Welsch, 1981; Callahan *et al.*, 1982; Scott *et al.*, 1988) and its biotransformation is unchanged in patients with chronic liver disease (Scott *et al.*, 1988). Caffeine is extensively metabolised by the hepatic cytochrome P-450 drug metabolising system; thus, for all practical purposes the total clearance of caffeine, calculated from pharmacokinetic variables, is equivalent to its hepatic clearance.

In the present study, caffeine clearance values were comparable in healthy controls and in patients with compensated cirrhosis. However, caffeine clearance was significantly impaired in patients with decompensated cirrhosis. As the hepatic extraction of caffeine is low, its clearance is not significantly affected by changes in hepatic blood flow and the first pass elimination effects are minimal. Clearance values are, however, affected by changes in the activity of the hepatic drug metabolising enzymes and in 'functioning hepatocyte mass'. In our patients with liver disease there was a significant relationship between the degree of impairment in caffeine clearance and the degree of hepatocellular dysfunction assessed by the Pugh's score rating (Pugh *et al.*, 1973). As the hepatic concentration of cytochrome P-450 isozymes and the activities of the drug metabolising enzymes are only reduced in individuals with severe hepatocellular necrosis (Farrell *et al.*, 1979), it is unlikely that the impaired caffeine clearance observed in our patients with decompensated cirrhosis resulted from a reduction in the activity of the mixed function oxidase enzyme system, as they all had inactive cirrhosis on liver biopsy. The impairment in caffeine clearance in these patients must reflect a reduction in 'functioning hepatocyte mass'.

Our patients with decompensated cirrhosis ingested significantly less caffeine than either the control subjects or the patients with compensated cirrhosis probably because their fluid intake was restricted. It is possible that this may have biased the clearance values in this group although overall there was no statistical relationship between pre-study caffeine intakes and any of the pharmacokinetic variables. Caffeine clearance has been shown to increase in smokers (Parsons & Neims, 1978). In the present study, none of the patients with decompensated cirrhosis smoked and in the patients with compensated cirrhosis, no significant differences were observed in kinetic variables between the smokers and non-smokers. However, the median caffeine clearance was higher in the smokers and this may have biased the results in the compensated group. Similarly,

many of the patients were taking drugs, such as cimetidine and allopurinol which might have affected oxidation rates (Roberts *et al.*, 1981; Grant *et al.*, 1986). Where possible all medication was stopped 48 h before the study but the effects of the drugs on the oxidation rate might have persisted, at least to a degree, in the patients with decompensated disease. These effects if present, however, cannot be quantified.

Approximately 75% of ingested caffeine undergoes 3-demethylation to form paraxanthine (Arnaud & Welsch, 1981; Callahan *et al.*, 1982). In the majority of subjects studied, significant amounts of this dimethyl metabolite of caffeine were detected in serum and saliva following the oral caffeine load. In the patients with compensated cirrhosis, the median peak paraxanthine concentration was increased, possibly reflecting a decrease in the median apparent volume of distribution in this group. In the patients with decompensated cirrhosis, the formation and clearance of paraxanthine were impaired reflecting the general impairment in caffeine metabolism.

It has been suggested that caffeine concentrations in the plasma after an overnight fast (Renner *et al.*, 1984) or else plasma concentrations determined 12 h after an oral caffeine load (Wang *et al.*, 1985) might serve as a simple guide to the severity of hepatic dysfunction. In the present study, basal serum and salivary caffeine concentrations after 72 h without caffeine were higher in our patients with liver disease than in the control subjects, but only three patients with decompensated cirrhosis had values in excess of 2 mg l^{-1}. The concentrations of caffeine present in specimens collected from patients with decompensated cirrhosis 12 h after the oral caffeine load were clearly distinguishable from those in the other two groups of subjects but there was considerable overlap between 12 h caffeine levels, in serum and saliva, in control subjects and patients with compensated cirrhosis.

All our patients with decompensated cirrhosis had caffeine half-times > 10 h, elimination rate constants of < 0.08 h^{-1}, 12 h caffeine concentrations > 5.5 mg l^{-1} and total clearance values of < 0.4 ml min^{-1} kg^{-1}. Using these criteria, patients with decompensated cirrhosis could be readily distinguished from control subjects and patients with compensated cirrhosis. However, no such distinction could be made between control subjects and patients with compensated cirrhosis on the basis of kinetic variables. These individuals were, by definition, clinically well and the majority of their biochemical test results were within laboratory reference ranges. It is not surprising, therefore, that the oxidation of caffeine was relatively normal in this group. In this respect the caffeine kinetic data is accurately reflecting liver function. However, as these patients could not be distinguished from control subjects on the basis of their caffeine kinetic data the value of the caffeine loading test for the detection of chronic liver disease must be limited.

The results of this study suggest that the use of the caffeine loading test to assess hepatocellular dysfunction confers no diagnostic advantage over clinical examintion coupled with the measurement of 'routine liver function tests'.

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