Dose-dependent pharmacokinetics of caffeine in humans: Relevance as a test of quantitative liver function

Caffeine clearance was determined in 13 healthy control subjects and in 13 patients with histologically proven cirrhosis. On separate occasions, 70 mg, 200 mg, and 300 mg single doses of anhydrous caffeine were administered orally with decaffeinated coffee to each subject. Subjects were analyzed individually, acting as their own controls, thus reducing interindividual variability. The present study showed that caffeine exhibited dose-dependent pharmacokinetics, particularly in subjects who showed high initial clearance with the low dose (70 mg) of caffeine. There was a significant decrease in caffeine clearance with increasing dose from 70 mg to 300 mg ($n = 26$, $p < 0.01$, Dunnett's test), indicating saturable caffeine metabolism in the dose range tested. These findings imply that if caffeine is to be used as a guide to deteriorating liver function, serial caffeine clearance estimations should be performed in each individual subject, with use of the same dose of caffeine each time. (CLIN PHARMACOL THER 1990;47:516-24.)

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There has recently been increasing interest in the use of caffeine as a test substance for metabolic function of the liver because of its relative lack of toxicity, rapid absorption,[1,2] complete metabolism by the liver,[3,4] and its ready availability.

Patients with liver disease have been reported to have a higher fasting plasma caffeine concentration and reduced caffeine clearance compared to healthy control subjects,[5,6] although this could not be confirmed in a subsequent study.[7] A possible explanation for the discrepancy between the two studies was thought to be the difference in cumulative caffeine consumption in the two groups studied. It was subsequently suggested that the determination of plasma caffeine levels 12 hours after a loading caffeine dose of 140 mg after a period of abstinence would be a more reliable indicator of hepatic microsomal function.[8] Increasing oral doses of caffeine (140 to 366 mg) have since been used by different investigators in an effort to reduce the effects of environmental influences (such as smoking, caffeine consumption, and drugs) on caffeine clearance.

It has been claimed that caffeine is eliminated by first-order kinetics in humans.[1,2,9] Caffeine has been reported to follow linear kinetics up to 10 mg/kg.[1,2] In these studies, however, the subject numbers were relatively small and there was considerable interindividual variability in the reported clearance values. The study of Tang-Liu et al.[10] provides evidence to suggest that caffeine may exhibit dose-dependent pharmacokinetics in humans.[11] That report, together with the fact that theophylline (a close chemical relative of caffeine) is well documented as exhibiting dose-dependent pharmacokinetics,[12,13] prompted us to investigate whether there was any change in caffeine clearance rates with increasing doses in healthy subjects and in patients with cirrhosis. The bioavailability of oral caffeine was also studied in six of the healthy subjects because this has obvious relevance to the repeated use of caffeine in individual subjects to study variations in hepatic metabolism.

MATERIAL AND METHODS

Study design

After providing informed consent, subjects were administered three single oral doses of caffeine (70 mg, 200 mg, and 300 mg) on separate occasions, with intervals of 1 day between the 70 mg and 200 mg doses

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Table I. Patient data

Patient	*Age*	*Sex*	*Weight (kg)*	*Diagnosis*	*Creatinine mmol/L*	*PT (sec)*	*Albumin (gm/L)*
1	75	M	90	CAH	0.08	17	34
2	70	F	50	CAH	0.12	15	43
3	55	M	76	CAH (HBsAg + ve)	0.10	16	38
4	63	F	71	PBC	0.07	10	34
5*	64	F	70	PBC	0.04	16	36
6*	54	M	75	SHN	0.06	23	28
7†	62	M	72	HC	0.10	16	27
8	67	M	71	HC	0.09	16	47
9	59	M	68	HC	0.05	18	43
10	53	M	77	HC/ALD	0.06	23	30
11	63	M	68	ALD	0.16	19	28
12‡	67	M	77	ALD	0.18	16	28
13†	56	M	107	CC	0.08	17	42

PT, Prothrombin time; M, male; CAH, chronic active hepatitis; F, female; HBsAg + ve, hepatitis B surface antigen positive; PBC, primary biliary cirrhosis; SHN, subacute hepatic necrosis; HC, hemochromatosis; ALD, alcoholic liver disease; CC, cryptogenic cirrhosis.
*Patients receiving spiromolactone.
†Patients receiving β-blocker.
‡Patient receiving theophylline.

and approximately 1 week between the 200 mg and the 300 mg doses. Cirrhotic patients who exhibited a low clearance of a 70 mg dose of caffeine and those who had clinical evidence of hepatic decompensation were not administered the 300-mg dose. This study was approved by the Royal Brisbane Hospital Ethics Committee.

Subjects

Thirteen healthy volunteers (nine men and four women on the hospital staff) were recruited. The volunteers were between 20 and 50 years of age and weighed between 47 and 85 kg. None were taking any medications, and all had normal plasma biochemical profiles. Their normal caffeine intake ranged between 0 and 250 mg/day. Except for one volunteer who smoked 10 cigarettes a day, all others were nonsmokers. Eight of the volunteers were nondrinkers, and the other five consumed less than 50 gm alcohol a day. They were not restricted in their normal activities until the day before the study, when they were instructed to abstain from caffeine. Six of the same group of healthy subjects also received at least two doses (70 mg and 200 mg) of intravenous caffeine on another two separate occasions for estimation of the bioavailability of orally administered caffeine in these subjects. Three of these same healthy subjects also received 300 mg caffeine by intravenous infusion over 20 minutes.

Thirteen cirrhotic patients were also studied. Nine of these patients were nonsmokers, and the remaining four patients smoked fewer than 20 cigarettes a day. Data on these patients are presented in Table I. Nine patients were nondrinkers, and the remaining four consumed less than 50 gm alcohol a day. Patients were between the ages of 53 and 75 years and weighed between 50 and 107 kg. Their normal caffeine intake ranged from 50 to 500 mg a day. Two patients had decompensated cirrhosis, as assessed by the presence of ascites and hepatic encephalopathy, and these patients received 70 mg and 200 mg doses of caffeine only.

Caffeine-dosing method

Oral studies. Subjects were administered oral doses of 70 mg caffeine on the morning (between 8 and 9 AM) of the day before the caffeine pharmacokinetic study to provide uniformity of caffeine intake for the 24 hours preceding the study day. Subjects were provided with a list of caffeine-containing food or beverages and were instructed not to ingest any of these items until the end of the study. After an overnight fast, subjects were administered the appropriate oral dose of caffeine with decaffeinated coffee, and they fasted for at least 1 hour after dosing. Subjects remained in the sitting position during most of the study period. Blood samples were collected by way of an indwelling canula at 0, 10, 20, 30, and 60 minutes, and at 2, 4, 6, 12, and 24 hours for quantitation of serum caffeine concentrations. After collection, blood samples were centrifuged, the serum separated and stored at −20° C until the time of assay.

Intravenous studies. On separate occasions in six of our 13 healthy volunteers, single intravenous caffeine doses were infused into a peripheral forearm vein over a 20-minute period. All six subjects received 70 mg

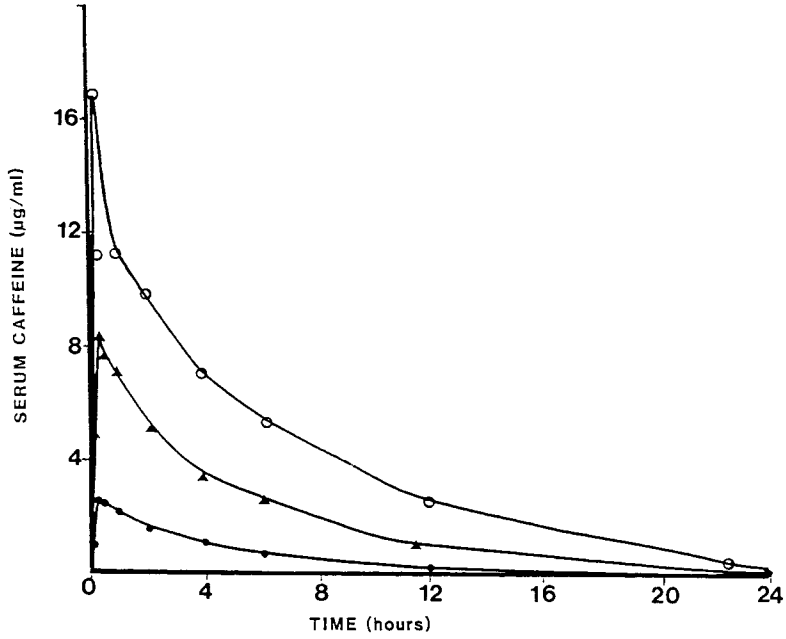

Fig. 1. Representative caffeine pharmacokinetics of an oral dose to a control subject. *Closed circles,* 70 mg; *triangles,* 200 mg; *open circles,* 300 mg.

and 200 mg intravenously, and three of the six also received 300 mg intravenously. Serial blood samples were collected for serum caffeine estimations from an indwelling canula in the arm opposite that used for caffeine dosing.

Caffeine assay

Serum caffeine assays were performed as described previously,[14,15] by use of high-performance liquid chromatography (HPLC). Standard curves were prepared by "spiking" control (methylxanthine-free) serum with known amounts of caffeine and internal standard. All serum samples and standards were assayed in duplicate. The coefficient of variation of the assay was 3.1% at the lower limit of detection and the assay was sensitive to a level of 0.1 µg/ml.

The caffeine metabolites were separated by extraction and chromatography, ensuring that the assay was specific for caffeine.

Pharmacokinetic analysis

The serum concentration–time data were fitted to an appropriate linear pharmacokinetic model by use of the Stemkinetics pharmacokinetic modeling program (Stemkinetics, User's Manual, Stemsoft, Brisbane, Australia), running on an IBM-compatible personal computer. Terminal elimination rate constants and $t_{1/2}$ values were calculated according to the following formula[16]:

$$t_{1/2} = \frac{0.693}{k}$$

in which k is the terminal elimination rate constant. Area under the curve (AUC) was calculated by trapezoidal rule integration from time 0 to t plus the addition of the area in the tail, which was calculated by the following equation:

$$AUC_{tail} = \frac{C_{last}}{k}$$

in which C_{last} = the last measured serum concentration.

If a nonzero value was measured for the zero time serum sample, the contribution of this residual amount of caffeine in the serum to the AUC was calculated according to the same formula as AUC_{tail}:

$$AUC_0 = \frac{C_0}{k}$$

in which C_0 is the zero time serum caffeine concentration.

The calculated AUC_0 was then subtracted from the AUC_{total} as follows:

$$AUC_{actual} = AUC(0\text{-}t) + AUC_{tail} - AUC_0$$

Seven of 13 patients had nonzero values measured in

Table II. Caffeine pharmacokinetic parameters in normal volunteers and cirrhotic patients

	Caffeine dose (mg)	$t_{1/2}$ *(hr)*	*Clearance (ml/min/kg)*	V_{area} *(L/kg)*
Normal subjects	70	4.5 ± 2.4	1.52 ± 0.61	0.51 ± 0.17
	200	6.0 ± 1.9	1.14 ± 0.33	0.54 ± 0.07
	300	6.4 ± 3.3	1.08 ± 0.29	0.55 ± 0.11
Cirrhotic patients				
CL > 1.0 ml/min/kg	70	3.9 ± 1.8	2.10 ± 1.00	0.60 ± 0.17
	200	4.3 ± 1.5	1.70 ± 0.56	0.52 ± 0.24
	300	5.9 ± 1.1	1.06 ± 0.30	0.53 ± 0.13
CL < 1.0 ml/min/kg	70	31.3 ± 17.9	0.37 ± 0.14	0.76 ± 0.34
	200	26.3 ± 6.7	0.35 ± 0.14	0.70 ± 0.15
	300	25.5 ± 4.4	0.33 ± 0.12	0.71 ± 0.17

$t_{1/2}$, Half-life; V_{area}, volume of distribution.

the zero time samples, ranging between 0.3 and 2.5 μg/ml. One exception was a decompensated patient who had a value of 7.3 μg/ml. Clearance (CL) was calculated by use of the formula:

$$CL = \frac{F \times Dose}{AUC}$$

in which F is the oral bioavailability (assumed to be 1), CL is the serum clearance, D is the dose, and AUC is the area under the serum concentration–time curve. Bioavailability was calculated by the formula:

$$F = \frac{AUC_{oral}}{AUC_{IV}} \times \frac{D_{IV}}{D_{oral}}$$

in which AUC_{IV} is the area under curve for intravenous caffeine, AUC_{oral} is the area under curve for the corresponding oral caffeine, D_{IV} is the dose given intravenously, and D_{oral} is the dose given orally.

Statistical analysis

Statistical analyses were performed by use of paired Wilcoxon tests (because the data were not normally distributed) and the Dunnett's test for group differences in a population.

RESULTS

Oral caffeine administration

Eleven healthy volunteers (control subjects) and nine patients completed three pharmacokinetic studies using single doses of oral caffeine—namely, 70 mg, 200 mg, and 300 mg. Intrasubject variability did not exceed 5% in each of three normal subjects. A representative set of control pharmacokinetic studies is shown in Fig. 1. Four of the patients and three of the control subjects completed only two of the three studies. In the cirrhotic patients (whose clearance of a 70 mg dose of caffeine was >1.0 ml/min/kg), as well as in the healthy volunteers, caffeine exhibited dose-dependent pharmacokinetics.

Pharmacokinetic data on normal volunteers and patients with cirrhosis are presented in Table II. In the control group, mean (±SD) caffeine clearance decreased significantly ($p < 0.05$) from 1.52 ± 0.61 ml/min/kg to 1.14 ± 0.33 ml/min/kg when the oral caffeine dose was increased from 70 mg to 200 mg. The clearance decreased further to 1.08 ± 0.29 ml/min/kg when the caffeine dose was increased to 300 mg (Fig. 2), although this did not reach statistical significance ($p > 0.05$). The mean (±SD) terminal half-life of caffeine increased significantly from 4.5 ± 2.4 hours to 6.0 ± 1.9 hours, when the caffeine dose was increased from 70 to 200 mg. After the caffeine dose was increased to 300 mg, an additional increase in the mean caffeine elimination half-life was observed, namely, 6.4 ± 3.3 hours, although this was not significantly different ($p > 0.05$) from that obtained after the 200-mg dose. The volume of distribution of caffeine remained relatively constant at a value of 0.5 L/kg across the dose range studied (70 to 300 mg).

In cirrhotic patients with serum caffeine clearance values of 1 ml/min/kg or greater after ingestion of 70 mg caffeine, mean (±SD) caffeine clearance decreased significantly ($p < 0.05$) from 2.10 ± 1.00 ml/min/kg to 1.06 ± 0.30 ml/min/kg when the caffeine dose was increased from 70 mg to 300 mg. Similarly, the mean (±SD) terminal half-life of caffeine increased significantly ($p = 0.05$) from 3.9 ± 1.8 hours to 5.9 ± 1.1 hours when the caffeine dose was increased from 70 mg to 300 mg. The volume of distribution of caffeine in this group of patients did not alter significantly ($p >$

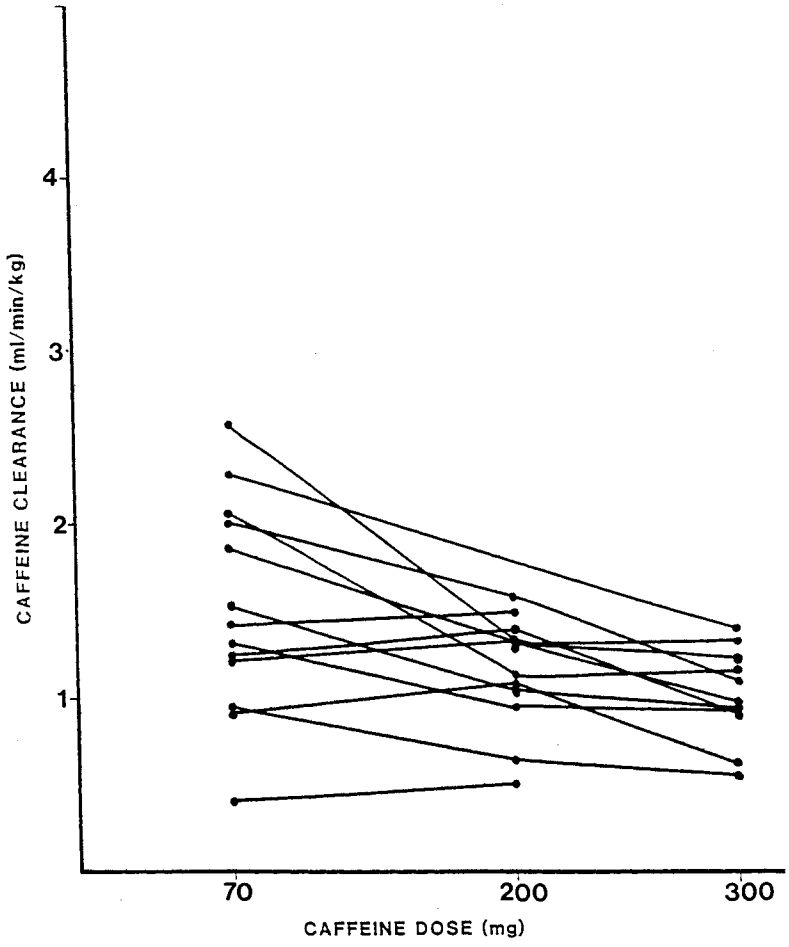

Fig. 2. Serum caffeine clearance with increasing oral caffeine doses in control subjects.

0.05) with the dose, and it was not significantly different from the value of 0.5 L/kg observed in the healthy control subjects.

In those cirrhotic patients with low clearance (<1.0 ml/min/kg) of a 70 mg dose of caffeine, there was no significant change ($p > 0.05$) in the mean (±SD) caffeine clearance value of 0.37 ml/min/kg as the caffeine dose was increased from 70 mg to 300 mg, reflecting saturation of caffeine metabolism, even at low caffeine doses (Fig. 3). In these same patients, the mean terminal half-life of caffeine was relatively unchanged at approximately 26 hours across the dose range studied, with this value being approximately 5 times that observed in the healthy control subjects and in those cirrhotic patients with high (>1.0 ml/min/kg) clearance of a 70 mg dose of caffeine (Fig. 4). The volume of distribution of caffeine in these patients remained relatively constant (0.75 L/kg) as the caffeine dose increased from 70 to 300 mg, with this value being approximately 50% greater than that observed in heal volunteers or in cirrhotic patients with high clearan of 70 mg caffeine.

It was interesting to note that conventional liver function tests did not correlate with caffeine clearance.

Intravenous caffeine administration

The mean (±SD) oral bioavailability of caffeine was 0.93 ± 0.16 for the 70 mg dose; 0.99 ± 0.16 for the 200 mg dose, and 1.01 ± 0.13 for the 300 mg dose. There was no statistically significant difference between the bioavailability values obtained at each dosing level ($p > 0.05$, Dunnett's test). Thus we concluded that the oral bioavailability of caffeine is close to 100% across the dosage range studied.

DISCUSSION

Although dose-dependent pharmacokinetics of caffeine has been documented in animals,[4,5] several pre-

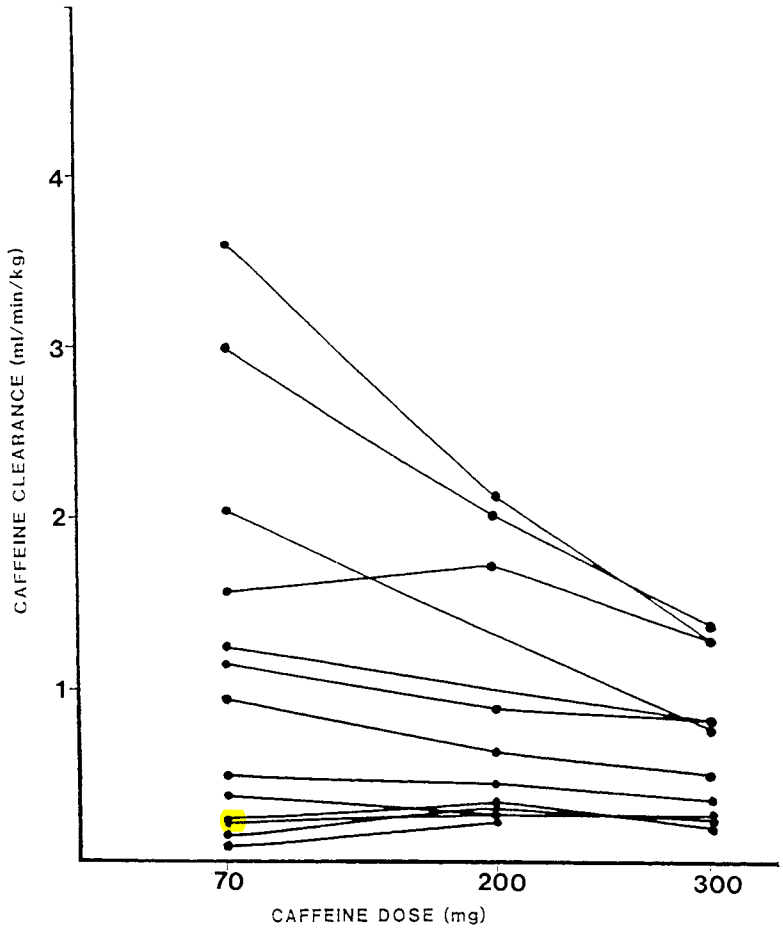

Fig. 3. Serum caffeine clearance with increasing oral caffeine doses in patients with cirrhosis.

vious studies in humans have suggested that caffeine might be eliminated by linear kinetics.[1,2,9] However, Tang-Liu et al.[10] reported that after a single oral dose of caffeine (7.5 mg/kg), the plasma concentrations of the caffeine metabolites—paraxanthine (1,7-MX), theophylline (1,3-MX), and theobromine (3,7-MX)—remained relatively constant for at least 10 hours. In the same study, the plasma-caffeine concentration decayed in a nonlinear fashion, decreasing in a convex manner at low concentrations. Using a C^{14} caffeine breath test, Kotake et al.[11] showed that the rate of $^{14}CO_2$ excretion increased with increasing dose up to 5 mg/kg, after which there was no further increase during the first 2 hours, suggesting saturation of caffeine metabolism.

The present study demonstrated that caffeine does exhibit dose-dependent pharmacokinetics in both healthy volunteers and cirrhotic patients whose serum clearance of a 70 mg dose of caffeine was >1.0 ml/min/kg. Our findings indicated that caffeine is subject to saturable metabolism in the dose range tested.

In patients with low initial caffeine clearance, there was little change in clearance with increased dose because the major metabolic pathway has apparently already been saturated at the low dose (70 mg). The elimination half-life of caffeine was five times longer (approximately 26 hours) in these patients than that observed in healthy controls or in cirrhotic patients with high initial caffeine clearance, reflecting the low metabolic capacity in this group of patients. (These results are similar to those obtained by other workers) (Table III). The volume of distribution of caffeine in this same group was 0.75 L/kg—50% higher than that observed in healthy volunteers and cirrhotic patients with high initial caffeine clearance. The increased volume of distribution of caffeine observed in these patients may be explained by the considerable ascites present in these patients. It appears that administration of more than 70

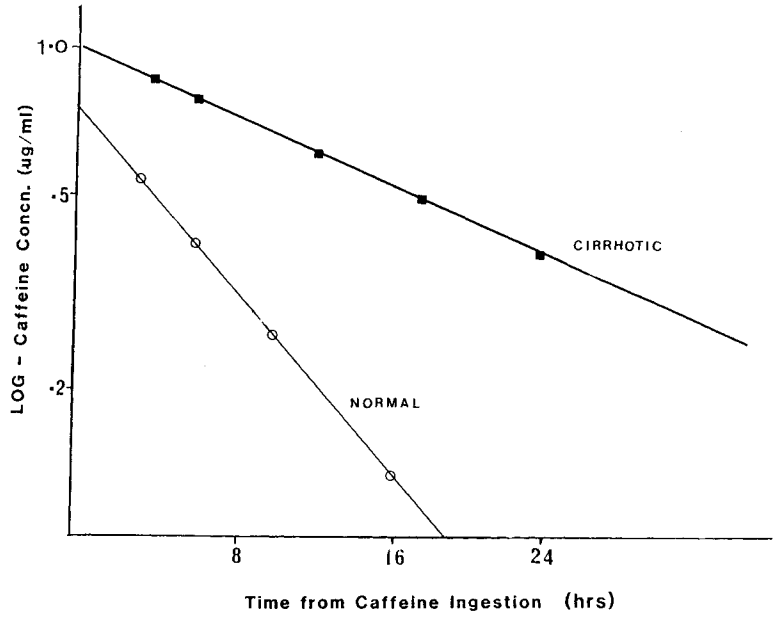

Fig. 4. Representative caffeine elimination in a control subject and in a patient with cirrhosis.

Table III. Caffeine pharmacokinetic data from other studies in the literature

Reference	*Caffeine dose (mg)*	$t_{1/2}$ *(hr)*	*Clearance (ml/min/kg)*	V_{area} *(L/kg)*
Desmond et al.[6]				
Normal subjects	250	5.2 ± 2.4	1.4 ± 0.5	0.54 ± 0.17
Cirrhotic patients	250	6.1 ± 1.9	0.9 ± 0.3	0.47 ± 0.16
Renner et al.[5]				
Normal subjects	125	3.8 ± 0.9	2.02 ± 0.68	0.64 ± 0.13
Cirrhotic patients	125	4.7 ± 2.1	1.52 ± 0.48	0.55 ± 0.07
Bonati et al.[1]				
Normal subjects (5 mg/kg)	350	6.3	1.01	0.56
Joeres et al.[18]				
Normal subjects				
Smokers	366	4.3 ± 0.8	1.43 ± 0.54	0.51 ± 0.13
Nonsmokers		5.9 ± 2.2	0.96 ± 0.35	0.41 ± 0.07
Cirrhotic patients				
Smokers	366	15.0 ± 11.4	0.90 ± 0.85	0.53 ± 0.22
Nonsmokers		23.6 ± 22.1	0.47 ± 0.67	0.55 ± 0.26

$t_{1/2}$, Half-life; V_{area}, volume of distribution.

mg caffeine to this group of patients provided no advantage in the evaluation of the full capacity of the liver to metabolize caffeine. Hence, discrimination of patients was better at the low dose. This finding could also be useful in the prevention of side effects resulting from accumulation of caffeine and its metabolites in these patients—a recommendation can be made that they avoid ingesting caffeine-containing foods and beverages as a lifestyle change.

In control subjects and in cirrhotic patients with a relatively high clearance of 70 mg caffeine, a 200 mg or 300 mg dose was needed to at least partially saturate the major metabolic pathways of caffeine.

The previous studies in humans, which examined the

effect of dose magnitude on the pharmacokinetics of caffeine, involved the use of relatively small numbers of subjects, and the doses used were much higher than in the present study. Some of the subjects had adverse effects, such as headache, palpitation, and flushing,[9] and only two of the four subjects in the second study[2] were subjected to the high dose because of side effects.

In addition to the small number of subjects studied, there was also considerable interindividual variability in the caffeine clearance values reported.[2,9] In this study, we have investigated caffeine kinetics at three different doses in 13 healthy volunteers and in 13 cirrhotic patients. The findings from each group show a statistically significant decrease in caffeine clearance ($p < 0.001$) when the dose is increased from 70 mg to 300 mg.

Considerable variability in the calculated clearance values was noted in both control subjects and patients, particularly in those individuals with high clearance of 70 mg caffeine. This may in part be a result of the influence of environmental factors on caffeine clearance,[14,15,17-21] or of genetic differences in the metabolism of caffeine.[22] The observed interpatient variability in caffeine clearance means that if caffeine clearance is to be used as a quantitative test for assessment of liver function, then serial estimations are required, with each patient acting as his or her own control.

Six of the 13 patients in this study had serum caffeine clearances >1 ml/min/kg after 70 mg caffeine. Three of these patients had hemochromatosis. One patient had chronic active hepatitis treated with prednisolone and another had primary biliary cirrhosis. All these patients had documented histologic evidence of cirrhosis. This would tend to suggest some functional reserve of metabolic capacity in the liver. Thus it would appear that considerable hepatocyte loss may be required before functional liver impairment is manifested.

In conclusion, our study has shown that caffeine exhibits dose-dependent pharmacokinetics, particularly in subjects with caffeine clearance greater than 1 ml/min/kg after a low dose (70 mg) of caffeine. This finding is consistent with the results of Tang-Liu et al.[10] and Kotake et al.,[11] which provided indirect evidence to support the hypothesis that caffeine may follow dose-dependent pharmacokinetics. The finding of dose-dependent caffeine pharmacokinetics in this study and the marked interindividual variability in caffeine clearance make serial estimations of caffeine clearance in individual patients with the same dose essential, if caffeine is to be used as an indicator of the residual liver function of an individual.

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