Impaired Elimination of Caffeine in Cirrhosis

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The effect of cirrhosis on the disposition and elimination of caffeine was examined. Caffeine (250 mg) was administered orally to 15 healthy controls and eight patients with cirrhosis. The elimination half-life was prolonged from 5.2 ± 2.4 hr (mean ± SD) in controls to 6.1 ± 1.9 hr in cirrhotics, although this did not reach statistical significance. The plasma clearance, however, was significantly higher (1.4 ± 0.5 ml/min/kg) in controls as compared to cirrhotics (0.9 ± 0.3 ml/min/kg) (P < 0.05). The plasma binding of caffeine was also lower in cirrhotics (31.3 ± 1.8% vs 25.5 ± 4.0%, P < 0.01). The plasma clearance of unbound caffeine therefore was reduced from 2.0 ± 0.7 ml/min/kg in controls to 1.2 ± 0.4 ml/min/kg (P < 0.01) in cirrhotics, demonstrating impaired elimination of caffeine in cirrhosis.

Caffeine is extensively consumed both in prescription and nonprescription medications and in numerous beverages. The annual world consumption of coffee alone exceeds four million tons and caffeine is present in significant quantities in tea, cocoa, and many carbonated soft drinks. Caffeine is also present in many "over-the-counter" stimulant medications and analgesic mixtures. Caffeine has been shown to affect many organ systems; it is a central nervous system stimulant; it has numerous effects on the cardiovascular system including raising blood pressure, catecholamines, renin, and also free fatty acids (1-3).

In spite of the widespread consumption and numerous pharmacological effects, the pharmacokinetics of caffeine have not been extensively studied. In particular, the influence of disease states on the disposition of caffeine have not been examined. Parenchymal liver disease impairs the metabolism of a number of drugs (4), including theophylline, which is structurally very similar to caffeine (5). Statland et al (6) reported a single patient with liver disease who cleared caffeine very slowly and they suggested that caffeine may have played a role in the mental confusion seen in this patient. They subsequently reported in abstract form two further patients with hepatic insufficiency who had prolonged elimination half-lives of caffeine (7). We therefore examined in detail the effect of chronic parenchymal liver disease on the disposition and elimination of caffeine.

MATERIALS AND METHODS

Fifteen healthy male subjects, age range 18-71 years (13 nonsmokers), with normal clinical history, physical examination, and SMA_{12} profile were studied. Ten male patients with cirrhosis, age range 42-60 years (6 nonsmokers), were also studied. Six subjects had alcoholic cirrhosis and four had postnecrotic cirrhosis; the diagnosis was established by clinical and biochemical criteria and confirmed by percutaneous liver biopsy in nine. The clinical and laboratory data and current medications of the cirrhotic patients are listed in Table 1. All individuals gave written informed consent for the study, which was approved by the institutional committee for the protection of human subjects.

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TABLE 1. CHARACTERISTICS OF PATIENTS WITH CIRRHOSIS

Patients	Age (yr)	Weight (kg)	Total bilirubin (mg/100 ml) (0.15–1.0)†	Serum albumin (g/100 ml) (3.5–5.0)	Serum alkaline phosphatase (mU/ml) (30–85)	Serum glutamic oxalacetic transaminase (mU/ml) (7–40)	Prothrombin time Patient (sec)	Prothrombin time Control (sec)	Half-life (hr)	AUC* (μgm/hr/liters)	Caffeine clearance (ml/min/kg)	Other drugs	Other findings
1§	42	84	2.1	3.8	104	45	13.3	9.7	5.8	85.7	0.58	—	Distal splenorenal shunt
2§	42	74	1.5	4.8	124	24	12.9	11.0	3.2	38.3	1.48	Aldactone Lasix Lactulose	Ascites, prior encephalopathy
3§	46	70	2.8	4.4	193	32	—	—	8.3	87.3	0.67	Lasix Aldactone	Ascites
4§	56	66	2.5	2.5	189	31	12.5	11.5	5.9	73.8	0.85	—	
5§	48	84	1.1	4.1	90	45	12.7	11.0	6.1	53.3	0.93	Prednisone	Cirrhosis, chronic active hepatitis
6§	51	48	1.1	4.1	121	110	11.3	10.6	9.0	114.6	0.76	Aldactone Lactulose	Ascites
7§	60	67	1.3	2.7	132	631	10.1	10.8	6.7	45.6	1.36	Aldactone Hydrochlorothiazide	Clotted proximal splenorenal shunt
8§	52	79	1.0	3.8	96	55	12.4	11.3	4.0	56.2	0.94	Insulin	Ascites, diabetes
9‡§	44	86	1.6	3.2	94	65	14.1	10.8	—	382.5	—	Aldactone Lactulose	Alcoholic hepatitis, ascites, prior encephalopathy
10‡	65	90	2.0	4.1	102	46	—	—	—	358.1	—	Aldactone	Recurrent encephalopathy

*Area under plasma concentration/time curve (0–48 hr) value in controls 44.2 ± 16.9 (mean ± SD).
†Normal values.
‡Subjects with very prolonged elimination of caffeine (see text).
§Cirrhosis proved by liver biopsy.

All subjects abstained from caffeine-containing beverages and medication for at least three days prior to the study. After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to three cups of coffee) in a capsule with 150 ml of water. Heparinized blood samples were subsequently collected at 15, 30, and 45 min and 1, 1½, 2, 3, 4, 6, 8, 24, 36, and 48 hr. The plasma was separated and stored at −20° C until analyzed.

Plasma levels of caffeine were determined by high-performance liquid chromatography (Waters Associates) as reported by Robertson et al (2). This assay is sensitive to a level of 100 nogs/ml. The plasma elimination half-lives ($T^1/_{2\beta}$) for caffeine were determined from the 1- to 48-hr data by linear regression of the logarithm of the plasma concentration and time. The total area under each curve was estimated by the trapezoidal rule, and this permitted calculation of the apparent oral plasma clearance (AUC_0) of caffeine from the ratio of the administered dose to the area under the plasma level-time curve (8). Although the drug was administered orally, two estimates were obtained of caffeine's apparent volume of distribution (V_d) with the realization that these calculations would be biased by the absorption process. The equations used for this purpose were:

$$V_d(\text{extrap}) = \frac{\text{Dose}}{C_p(0)} \qquad V_{d(\beta)} = \frac{\text{Dose } T^1/_2}{0.693\ AUC_0}$$

where $C_p(0)$ is the caffeine plasma concentration at zero time obtained by back extrapolation of the exponential disappearance curve, and AUC_0 is the total area under the caffeine plasma concentration–time curve.

The plasma binding of caffeine was determined by equilibrium dialysis using plasma collected immediately before the study. Equilibrium dialysis was at room temperature against 0.067 M phosphate buffer, pH 7.4, in an equilibrium dialyzing Teflon cell system (Spectrum Medical Industries, Inc., New York, New York.) with a cellulose membrane. Preliminary experiments indicated that 3 hr was sufficient time for equilibrium to be achieved, and binding was determined over the concentration range 2.5–10.0 μg/ml, using G-^{3}H-radiolabeled drug (Amersham) (specific activity 114 mCi/mg, purity greater than 98%).

Statistics. Statistical evaluations were performed with the two-tailed unpaired Student's *t* test, and linear regression analysis was performed to compare pharmacokinetic parameters and liver function tests. In both cases $P < 0.05$ was taken to be the minimal level of statistical significance.

RESULTS

The caffeine was rapidly absorbed with peak levels occurring between 30 and 60 min, after which time the concentration declined monoexponentially

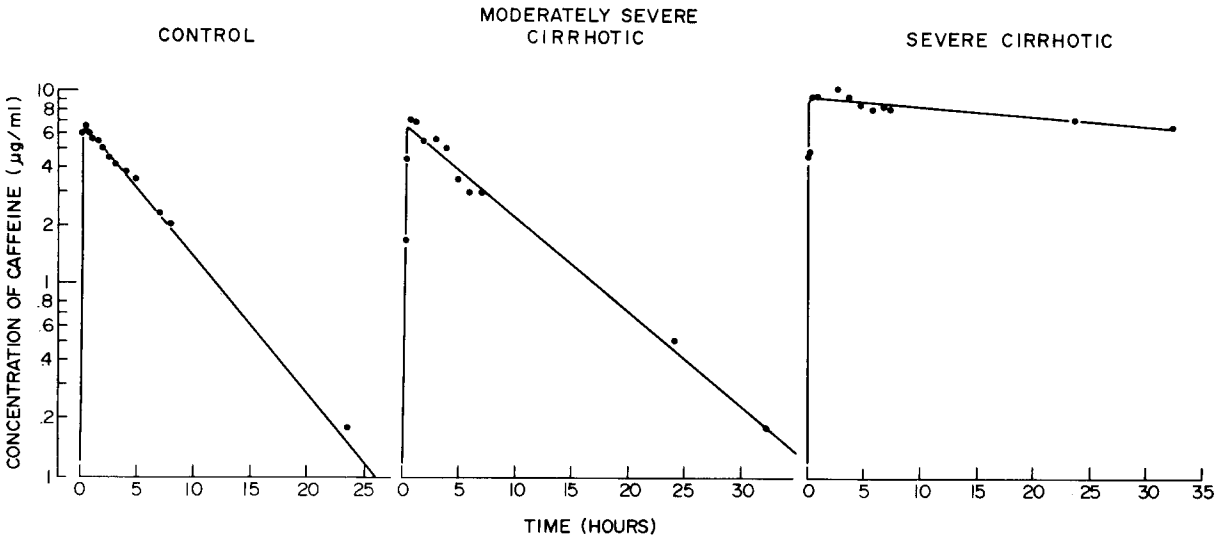

Fig 1. Representative caffeine plasma concentration/time profiles of a control (left panel), moderately severe cirrhotic patient (middle panel), and a severe cirrhotic patient (right panel).

(Figure 1). There were no age-related differences in the half-life, volume of distribution, or clearance in the normal subjects. In four normal subjects the study was repeated on a second occasion, and there was less than 10% variation from the mean plasma clearance determinations. There were two subjects (nos. 9 and 10, Table 1) among the cirrhotic patients who had caffeine present in their zero (precaffeine) sample although apparently being off caffeine for three days, and the level rose after the administration of the caffeine capsule but did not significantly decline over 48 hr (Figure 1). Clinically these subjects had the most severe liver disease and both had had repeated episodes of encephalopathy. These patients were obviously very poor metabolizers of caffeine; however, their data were not sufficient to define kinetic parameters. The kinetic parameters from the other eight patients with cirrhosis and the normal controls are listed in Table 2. The half-life of elimination was larger in the cirrhotics, but this did not reach statistical significance. The volume of distribution calculated either as $V_{d(\beta)}$ or V_d (extrap) was slightly smaller in the cirrhotics. The plasma clearance, however, was significantly reduced in the cirrhotics compared to controls. The plasma binding of caffeine was lower in cirrhotics, and binding correlated well with serum albumin (Figure 2). Accordingly the clearance of unbound drug (clearance of unbound drug = plasma clearance/unbound fraction of drug) was also significantly reduced. There were no significant correlations between any of the routine liver "function" tests and the plasma clearance of caffeine in the patients with cirrhosis.

Another statistical analysis was also carried out, including the two cirrhotics with the most abnormal caffeine disposition. Assigning the most impaired values to these two patients and using the nonparametric Wilcoxon nonpaired rank sum test, the statistical differences from controls were similar to the parametric statistical analysis with P values for half-life >0.05, for clearance/kg = 0.015, volume of distribution >0.05, binding = 0.001, and clearance of unbound drug/kg = 0.007.

DISCUSSION

It has been demonstrated previously that caffeine is rapidly and completely absorbed after oral admin-

TABLE 2. EFFECT OF CIRRHOSIS ON DISPOSITION AND ELIMINATION OF CAFFEINE (MEAN ± SD)

	Normal (N = 15)	*Cirrhosis (N = 8)*
$T\,1/2_{(\beta)}$ (hr)	5.2 ± 2.4	6.1 ± 1.9
$V_{d(\beta)}$ (liters/kg)	0.54 ± 0.17	0.47 ± 0.16
$V_{d(extrap)}$ (liters/kg)	0.54 ± 0.13	0.49 ± 0.09
Plasma clearance (ml/min/kg)	1.4 ± 0.5	0.9 ± 0.3*
Plasma binding (%)	31.3 ± 1.8	25.5 ± 4.0**
Plasma clearance of unbound drug (ml/min/kg)	2.0 ± 0.7	1.2 ± 0.4**

*$P < 0.05$.
**$P < 0.01$.

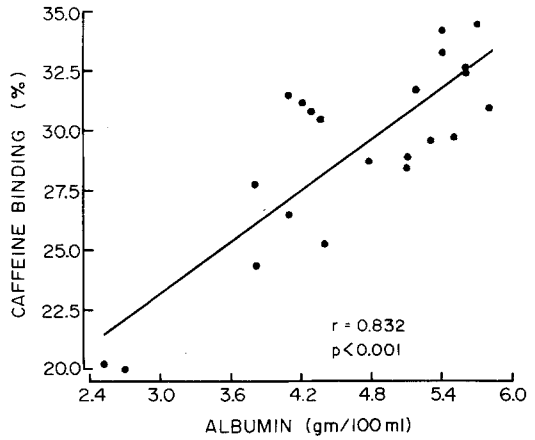

Fig 2. Correlation of caffeine plasma binding and serum albumin in all the subjects studied.

istration (9). The present study confirms this rapid absorption with peak levels occurring at a mean of 40 min after drug ingestion. There was a marked variation in the elimination half-life and clearance values within the normal subjects; however, the results obtained in these normal subjects are similar to other reported studies (9, 10). There was no difference in the time to peak level and the peak level between cirrhotics and controls, suggesting that differences in absorption do not play a factor in the altered pharmacokinetic parameters seen in cirrhotics. Furthermore, in the 15 control subjects with an age range of 18–71 years there were no age-related changes in any of the pharmacokinetic parameters, and therefore all these subjects were used for comparison to the cirrhotic subjects.

Parenchymal liver disease impairs the elimination of a number of drugs metabolized by the mixed-function oxidase enzymes. Caffeine is a trimethylxanthine and is metabolized by demethylation and oxidation mainly to methyluric acids and methylxanthines (11). Therefore the impaired clearance of caffeine in cirrhosis is not unexpected. The total clearance of caffeine was reduced by 35% in cirrhotics compared to controls. The elimination half-life was prolonged in cirrhotics compared to controls, but this did not reach statistical significance. The impaired elimination of caffeine in cirrhosis is further emphasized by the two subjects with severe liver disease who did not eliminate the caffeine significantly over the time of the study and were excluded from the analysis.

Caffeine was only about 30% bound to plasma proteins in controls; however, it was even less bound (25%) in patients with cirrhosis. The lowered plasma binding was presumably related to a significantly lower albumin in the cirrhotics (5.4 ± 0.2 vs 3.8 ± 2.7 g/100 ml); indeed there was an excellent correlation between plasma binding and albumin when all subjects are considered (Figure 2). This correlation is also strong when only the cirrhotics are compared ($r = 0.812$, $P = 0.002$). The reduced clearance of caffeine is even more marked when binding is taken into consideration and clearance of unbound drug is calculated. The clearance of unbound drug more closely reflects the metabolizing capacity of the liver (8) for caffeine and therefore more strongly demonstrates the reduced eliminating capacity in cirrhosis. It has been shown that smoking induces the metabolism of caffeine (10), and in the present study four cirrhotics and two normal subjects smoked; however, this would tend to reduce the differences between controls and cirrhotics.

The implications of these findings are that patients with cirrhosis would have elevated levels of caffeine in their plasma for a longer period of time than controls after ingestion of caffeine. Moreover, the clearance of a drug determines its steady-state concentration in plasma with chronic administraton; thus in moderate or heavy consumers, caffeine will accumulate in the cirrhotic subjects and also it will be eliminated more slowly. Caffeine has extensive pharmacological effects (1–3): it is a cerebral stimulant, increases cardiac muscle contraction, raises blood pressure, dilates smooth muscle, raises catecholamines, and elevates free fatty acids. The influence of the elevated caffeine levels in cirrhotic patients on these pharmacologic effects was not addressed in this study, although it is reasonable to presume that the effects should be more marked in the cirrhotics.

In summary, this study demonstrates that subjects with cirrhosis have impaired elimination of caffeine and it would be reasonable to advise these patients to moderate their intake of caffeine-containing beverages and medications.

REFERENCES

1. Ritchie JM: Central nervous system stimulants. *In* The Pharmacological Basis of Therapeutics, 4th ed. LS Goodman and A Gilman (eds). New York, Macmillan, 1970, pp 358-370
2. Robertson D, Frolich JC Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA: Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N Engl J Med 298:181-186, 1978

3. Bellet S, Kershbaum A, Finck EM: Response of free fatty acids to coffee and caffeine. Metabolism 17:702–707, 1968
4. Roberts RK, Desmond PV, Schenker S: Drug prescribing in hepatobiliary disease. Drugs 17:198–212, 1979
5. Mandione A, Imhoff TE, Lee RV, Shum LY, Jusko WJ: Pharmacokinetics of theophylline in hepatic disease. Chest 73:616–622, 1978
6. Statland BE, Demas T, Danis M: Caffeine accumulation associated with alcoholic liver disease. N Engl J Med 295:110–111, 1976
7. Demas T, Statland BE: Prolonged half-life of serum caffeine in patients with hepatic insufficiency. Clin Chem 23:1156, 1977
8. Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377–390, 1975
9. Axelrod J, Reichenthal J: The fate of caffeine in man and a method for its estimation in biological material. J Pharmacol 107:519–523, 1953
10. Parsons WD, Neims AH: Effect of smoking on caffeine clearance. Clin Pharmacol Ther 26:40–45, 1978
11. Burg AW: Physiological disposition of caffeine. Drug Metab Rev 4:199–228, 1975