Caffeine metabolism and coffee-attributed sleep disturbances

In six healthy subjects with a history of caffeine-induced wakefulness caffeine kinetics were compared to with those in six subjects not affected by caffeine. The data indicated that the former have a longer plasma t½ (mean 7.4 and 4.2 hr) and slower plasma clearance (mean 1.2 and 1.7 ml · min^{-1} · kg^{-1}) of caffeine. Plasma caffeine concentration at midnight, 8 hr after afternoon coffee, is higher in those with caffeine-attributed insomnia. Those reporting "coffee wakefulness" also tend to drink less coffee. We conclude that the rate of caffeine metabolism is a determinant of individual variation in the effect of drinking coffee on sleep.

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The world coffee production of about 5 · 10^9 kg/year, which equals about 100,000 tons of caffeine, makes this alkaloid the most widely consumed drug. Both the popularity of and abstention from coffee are principally accounted for by the stimulant action of caffeine on the CNS. Whether coffee does, in fact, disturb sleep, continues to be a matter of lively debate. When it comes to "what will you have to drink?," some people assert that a single cup of coffee in the evening, or even in the afternoon, disturbs their sleep; others may even habitually take coffee as a "nightcap." Such contradictory responses could mean that some beliefs about coffee effects are not well grounded in fact. In aggregate, however, they have been shown to reflect genuine differences in individual responses to caffeine.[1,6,10]

The individual variation of caffeine effect on sleep has been explained by differences in sensitivity of sites of action.[10] Another mechanism, common for many drugs, may be individual differences in kinetics, i.e., in absorption, distribution, and elimination. We thought this deserved further study.

We compared caffeine kinetics in six healthy subjects with a history of coffee-induced wakefulness with those in six subjects with no such history.

Subjects and methods

Our subjects were healthy students and hospital personnel ranging in age from between 22 and 45 yr (Table I). All were nonsmokers, took no drugs during the preceding month, and drank alcohol only casually. Histories were obtained on previous experience concerning the effect of coffee on sleep. The first six subjects who gave a history of having repeatedly experienced sleep disturbances, manifested mainly by delay in falling asleep after they drank coffee in the evening, were identified as group A and the first six subjects who asserted that coffee drinking in the evenings, or before bedtime, did not affect their sleep, were identified as group B. Blood chemistry (urea, albumin, globulin, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactic dehidrogenase, γ-glutamyl transpeptidase) was nor-

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Table I. *Subject characteristics and caffeine kinetic data after 260 to 350 mg caffeine*

Subject No.	*Sex/age*	*Weight (kg)*	*Coffee (cups)**	*t½ (hr)*	*$AUC^{0\rightarrow\infty}$ ($\mu g \cdot ml^{-1} \cdot hr$)*	*Clearance ($ml \cdot min^{-1} \cdot kg$)*	*aVd(β) (l/kg)*	*Protein binding (% free)*
Group A (reporting coffee wakefulness)								
1	F/45	60	2	4.9	76.1	1.3	0.54	62.4
2	M/43	85	1	12.2	99.7	0.7	0.73	64.7
3	M/47	85	2	8.2	70.3	1.0	0.69	55.6
4	F/29	63	2	7.7	80.9	1.1	0.76	60.5
5	M/22	75	0-1	4.1	28.8	2.0	0.71	52.9
6	F/31	46	2	7.4	99.3	1.0	0.61	57.4
Mean	36.2	69		7.4†		1.2‡	0.67	58.9
±SEM	4.2	6.3		1.2		0.2	0.03	1.8
Group B (coffee nonaffected)								
7	M/44	88	5-6	3.2	39.9	1.7	0.46	61.5
8	F/28	58	6	4.7	60.8	1.4	0.57	65.7
9	M/24	62	3-4	4.7	58.4	1.4	0.56	58.4
10	M/30	91	3-4	4.9	36.0	1.5	0.65	59.5
11	F/30	69	6	4.0	24.2	2.6	0.90	56.4
12	M/26	61	6	3.4	42.7	1.7	0.49	50.6
Mean	30.3	71.5		4.2†		1.7‡	0.61	58.7
±SEM	2.9	5.9		0.3		0.2	0.06	2.1

*Usual number of cups consumed daily.
†$P < 0.025$; ‡$P = 0.05$.

mal in all. The habitual daily coffee consumption was 0 to 2 cups in group A and 3 to 6 cups in group B (Table I).

At 4 P.M., after having been instructed to abstain from coffee for 16 hr, the subjects were requested to drink two cups of black coffee (estimated caffeine content, 300 mg). The amount consumed was measured and an aliquot of the beverage was assayed for caffeine. Dinner was served at 8 P.M. Venous heparinized blood samples (3 ml) were drawn just before drinking coffee and at about 1, 3, 5, 8, and 16 (8 A.M.) hr thereafter.

Plasma caffeine concentration was measured by an HPLC method.[11] Plasma binding of caffeine was determined by an ultrafiltration technique.

Data were analyzed on the assumption of a first-order one-compartment model. The plasma concentrations of caffeine were plotted semilogarithmically and the slope of the descending curve, i.e., the elimination rate constant (K_{el}), was calculated with the use of log-linear least square regression analysis. The plasma AUC was measured and the following equations were used: plasma $t½ = 0.693/K_{el}$; total plasma clearance (Cl) = Dose/AUC; and the apparent volume of distribution [$aVd(\beta)$] = Cl/K_{el}. Student's t test was used for statistical analysis.

Results

The individual plasma caffeine concentration–time curves are shown in Figs. 1 and 2 and the kinetic data are summarized in Table I. The plasma t½ of caffeine was longer (7.4 ± 1.2 SE hr) in subjects reporting wakefulness after coffee (group A) than in those not affected (group B) (t½ = 4.2 ± 0.3 SE hr; $P < 0.05$). Plasma clearance of caffeine was higher in group B ($P = 0.05$). No differences were noted between the groups in $aVd(\beta)$ or the degree of plasma protein binding of caffeine.

One subject who reported coffee wakefulness (No. 5) clearly deviated in kinetic characteristics from the other subjects in group A. He was the only subject in the group who did not report marked difficulty in falling asleep on the actual night of the study; subsequently he reported that he had no more sleep difficulties after drinking coffee.

In Table II serum plasma concentrations extrapolated to zero time and to 8 and 16 hr after

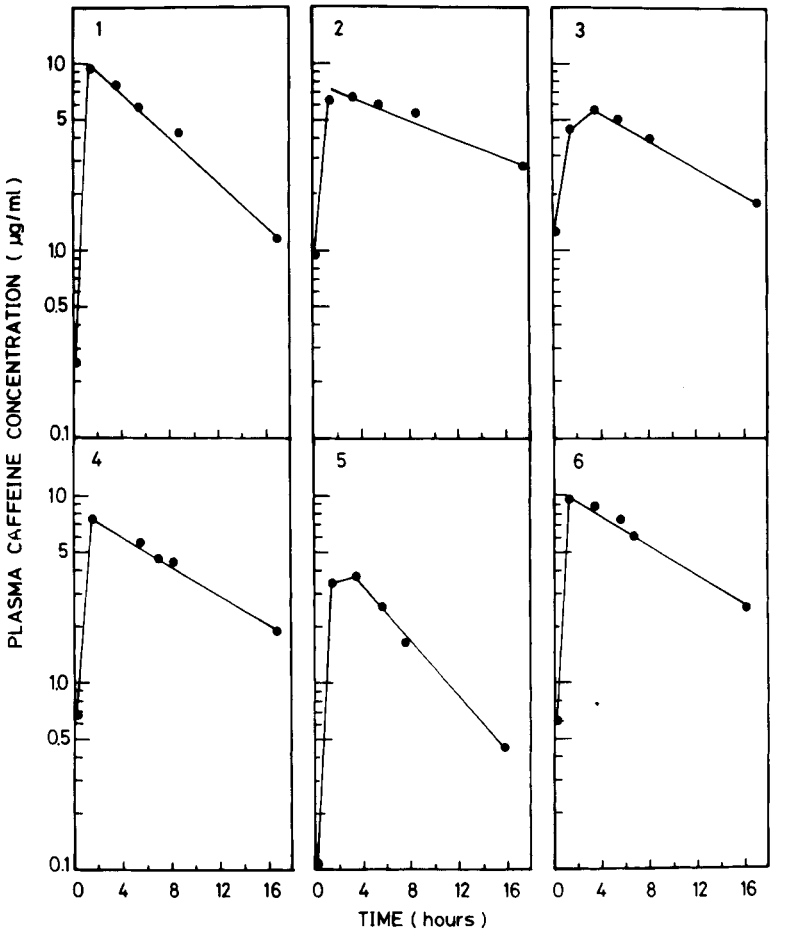

Fig. 1. Time course of plasma caffeine concentration after coffee in subjects with a history of wakefulness after coffee (group A).

coffee drinking are listed. Comparison of group A with group B subjects indicated similar means for the zero-time concentration, whereas values at the later time points were higher for group A. At midnight, in five of the group A subjects caffeine concentration was higher than 3.4 μg/ml, while in group B subjects all were lower.

There was no apparent correlation between the kinetics and age or sex.

Discussion

People who report coffee-induced wakefulness seem to eliminate caffeine from the plasma more slowly than those who state that they are not affected. They also seem to consume less coffee, which could be readily explained by their adverse experience. Since nonaffected subjects habitually drink more caffeine, it is also possible that, as with many other drugs, caffeine induces its own metabolism. Such a hypothesis is supported by the observation that caffeine can induce mixed-function oxidase activity toward certain substrates in animals.[13] Relative insensitivity of coffee drinkers to the sleep-disturbing action of caffeine has been reported[6,9] and was interpreted to represent an acquired cellular (CNS) tolerance.

We are aware of only one report on plasma levels of caffeine in relation to sleep latency.[10] Subjects were given decaffeinated coffee that contained, in random order, either caffeine (300

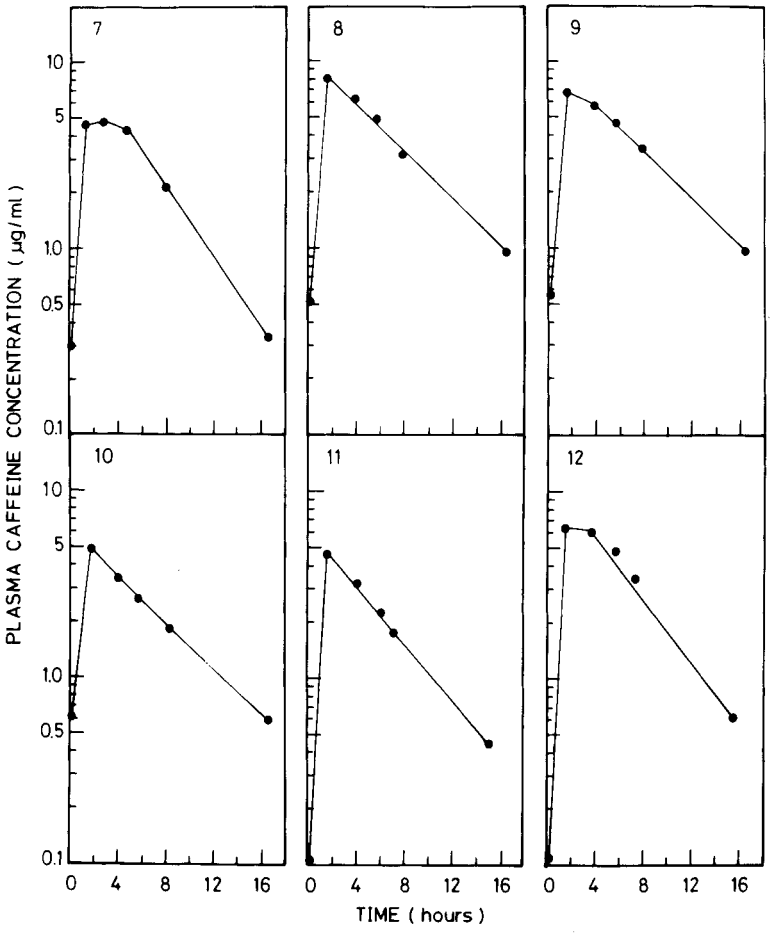

Fig. 2. Time course of plasma caffeine concentration after coffee in subjects in whom sleep is not affected by coffee (group B).

mg) or lactose, 1 hr before bedtime. The following morning, they estimated how long it had taken them to fall asleep. The difference between the mean placebo and caffeine times for successive nights ranged between 1.8 and 32 min. In 10 subjects caffeine plasma concentration was measured 1, 2, and 3 hr after drinking coffee. The authors stated that plasma levels decline at much the same rates in all subjects, although our analysis of their data shows β values for the slope to range from -0.311 to -0.04. Their data do not permit analysis of the correlation between sleep latency and kinetic differences. Thus the often-quoted conclusion that individual differences in response to caffeine must reflect varying sensitivity in sites of action can be questioned.

Sleep laboratory studies based on computer-monitored electroencephalogram-electroculograms demonstrated, on the whole, a delay in the onset of sleep and an effect on the depth of sleep after caffeine.[5,14] These effects were dose related.[12] Only one study failed to identify an effect of caffeine (450 mg) on sleep. Caffeine exposure consisted of the drinking of six 12-oz cans of Coca Cola between noon and bedtime (about one to three t½ of caffeine.)[17]

One study evaluated histories of the effect of coffee on sleep in 11 pairs of identical twins.[1] Only one pair was discordant. In this connection, it should be noted that the rate of drug metabolism is a concordant feature in identical twins.[19]

Caffeine undergoes hepatic metabolism by

Table II. *Plasma caffeine concentration in subjects with a history of wakefulness induced by coffee (group A) and those in whom sleep was not affected by coffee (group B)*

	Plasma caffeine concentration (μg/ml)					
	*Estimate of zero time**		*8 hr after coffee*		*16 hr after coffee*	
	Group A†	*Group B*	*Group A*	*Group B*	*Group A*	*Group B*
	12.3	11.4	4.0	2.1	1.3	0.4
	6.9	10.2	5.0	3.3	3.2	1.0
	6.5	10.2	3.9	3.3	2.0	1.0
	8.2	5.4	3.4	1.9	1.3	0.6
	6.1	6.0	1.6	1.6	0.4	0.5
	11.0	13.8	5.5	2.8	2.6	0.6
Mean	8.5	9.5	3.9	2.5	1.8	0.68
±SEM	1.05	1.32	0.56	0.30	0.41	0.10
	$P > 0.05$		$P < 0.05$		$P < 0.025$	

*Extrapolated value (C°p) less the actual concentration before coffee.
†Subject order as in Table I.

successive demethylation to dimethyl- and monomethylxanthines and by oxidation to dimethyl- and monomethyluric acids. Less than 1% of a caffeine dose appears in the urine in its native form.[4,7] The plasma t½ therefore represents the rate of hepatic metabolism. The caffeine t½ was reported to vary between 1.5 to 15 or more hr. It was shown to be shorter in smokers[15] and prolonged by the use of oral contraceptive steroids[16] or idrocilamide (a muscle relaxant).[4] In patients with alcoholic or postnecrotic cirrhosis, t½ values have ranged up to 168 hr.[8,18] These changes probably reflect modulation of the hepatic cytochrome P_1-450 system.[2]

Caffeine is absorbed rapidly after ingestion and is distributed in the body in proportion to the water content of the tissue.[3] This may explain the finding,[16] also noted by us, of a larger aVd(β) of caffeine in women. Caffeine elimination appears to be independent of age and sex.[16]

We suggest that the rate of hepatic caffeine metabolism is slower in people who experience sleep disturbances after drinking coffee than in those who do not. This may be due to either an inherent capacity or an inductive effect of caffeine itself on hepatic enzymes. This effect may be dose related; if so, those who habitually drink large amounts of coffee may reduce their likelihood of experiencing sleep disturbance.

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References

1. Abe K: Reaction to coffee and alcohol in monozygotic twins. J Psychosomat Res **12:** 199-203, 1968.
2. Aldridge A, Parsons WD, Neims AH: Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. Life Sci **21:**967-974, 1977.
3. Axelrod J, Reichenthal J: The fate of caffeine in man and a method for its estimation in biological material. J Pharmacol Exp Ther **107:**519-523, 1952.
4. Brazier JL, Descotes J, Lehry N, Ollagnier M, Evreux JCL: Inhibition by idrocilamide of the disposition of caffeine. Eur J Clin Pharmacol **17:**37-43, 1980.
5. Brezinova V: Effect of caffeine on sleep: EEG study in late middle age people. Br J Clin Pharmacol **1:**203-208, 1974.
6. Colton T, Gosselin RE, Smith RP: The tolerance of coffee drinkers to caffeine. CLIN PHARMACOL THER **9:**31-39, 1968.
7. Cornish HH, Christman AA: A study of the metabolism of theobromine, theophylline, and caffeine in man. J Biol Chem **228:**315-323, 1957.
8. Desmond PV, Patwardhan RV, Johnson RF, Schenker S: Impaired elimination of caffeine in cirrhosis. Dig Dis Sci **25:**193-197, 1980.
9. Goldstein A: Wakefulness caused by caffeine. Naunyn-Schmiedebergs Arch Pharmacol **248:** 269-278, 1964.
10. Goldstein A, Warren R, Kaizer S: Psychotropic effects of caffeine in man. I. Individual differences in sensitivity to caffeine-induced wakefulness. J Pharmacol Exp Ther **149:**156-159, 1965.
11. Gotz VP, Drayer DE, Schned ES, Reidenberg MM: Unusual cause of theophylline toxicity. NY State J Med **79:**1232-1234, 1979.
12. Karacan I, Thornby JI, Anch AM, Booth GH,

Williams RL, Salis PJ: Dose-related sleep disturbances induced by coffee and caffeine. CLIN PHARMACOL THER **20:**682-689, 1976.

13. Mitoma C, Lombrozo L, Le Valley SC, Dehn F: Nature of the effect of caffeine on the drug-metabolizing enzymes. Arch Biochem Biophys **134:**434-441, 1969.
14. Muller-Limmroth W: Der Einfluss von coffeinhaltigem und caffeinfreiem kaffee auf den schlaf des menschen. Z Ernahrungswiss **14**(suppl.): 46-53, 1972.
15. Parsons WD, Neims AH: Effect of smoking on caffeine clearance. CLIN PHARMACOL THER **24:**40-45, 1978.
16. Patwardhan RV, Desmond PV, Johnson RF, Schenker S: Impaired elimination of caffeine by oral contraceptive steroids. J Lab Clin Med **95:**603-608, 1980.
17. Saletu B, Allen M, Itil TM: The effect of Coca-Cola, caffeine, anti-depressants, and C chlorpromazine on objective and subjective sleep parameters. Pharmakopsychiatria **254:** 307-321, 1974.
18. Statland BE, Demas TJ: Serum caffeine half-lives, healthy subjects vs. patients having alcoholic hepatic disease. Am J Clin Pathol **73:**390-393, 1980.
19. Vesell ES: Polygenic factors controlling drug response. Med Clin North Am **58:**951-963, 1974.