0270-9139/88/0803-0575$02.00/0
HEPATOLOGY

Vol. 8, No. 3, pp. 575–579, 1988
Printed in U.S.A.

Influence of Smoking on Caffeine Elimination in Healthy Volunteers and in Patients with Alcoholic Liver Cirrhosis

ROLF JOERES, HARTWIG KLINKER, HERMANN HEUSLER, JOHANNES EPPING, WALTER ZILLY AND ERNST RICHTER

Department of Internal Medicine, University of Würzburg, Würzburg, Federal Republic of Germany and Hartwaldklinik der BfA, Bad Brückenau, Federal Republic of Germany

The effect of smoking on caffeine elimination was measured in 7 healthy volunteers and in 18 smoking and in 30 nonsmoking patients with alcoholic liver cirrhosis following oral application of 366 mg caffeine. In an intraindividual experiment in smoking healthy probands, caffeine clearance decreased from 118 ± 33 to 77 ± 22 ml per min ($p < 0.05$) after abstaining cigarette smoking for 3 weeks. In a control group without liver disease (8 smokers, 15 nonsmokers), we found a caffeine clearance of 114 ± 40 ml per min in smokers and 64 ± 20 in nonsmokers ($p < 0.05$).

Smoking and nonsmoking patients with alcoholic liver cirrhosis did not differ with respect to clinical and laboratory data and hexobarbitone elimination. However, caffeine clearance was 63 ± 63 ml per min in smoking patients compared to 34 ± 49 ml per min in nonsmokers ($p < 0.05$).

Fasting plasma concentrations of caffeine were higher in nonsmokers (5.1 ± 6.2 μg per ml) than in smokers (2.1 ± 4.5 μg per ml, $p < 0.05$). We conclude that smoking habits have to be taken into account if caffeine is used as a model compound for measuring quantitative liver function.

In recent years, several model compounds have been proposed for measuring quantitatively the metabolizing capacity of the liver. However, test substrates as hexobarbitone (1), galactose (2), antipyrine (3), aminopyrine (4), indocyanine green (5) and sulfobromophthalein (6) are not well accepted in daily clinical practice. This may be explained by technical problems as well as the risk of adverse effects from the test drugs. Caffeine, however, does not produce severe side effects. Since it is almost completely absorbed after oral application and exclusively metabolized by the liver, it fulfills essential requirements of an ideal test substrate (7).

Several studies have demonstrated that caffeine plasma clearance can be used as a quantitative test of hepatic microsomal function in patients with liver disease (8–10). Earlier animal experiments have shown that caffeine elimination can be enhanced by cytochrome P-448 including agents like 3-methylcholanthrene (11). A comparable type of induction in man can be observed in smokers in whom caffeine clearance is enhanced in comparison with nonsmokers (12). If caffeine shall be used as a model compound for measuring liver function, the influence of smoking habits on this test must be defined more precisely.

Therefore, we first investigated the effect of smoking on caffeine elimination in six healthy volunteers in an intraindividual experiment. The second question was whether smoking can enhance caffeine metabolism in patients with liver cirrhosis who are known to have an impaired caffeine clearance.

MATERIALS AND METHODS

Caffeine was administered as caffeine monohydrate tablets (Cascan, Wiesbaden, Federal Republic of Germany) containing 183 mg caffeine. Hexobarbitone (Evipan®) was obtained from Bayer (Leverkusen, Federal Republic of Germany).

Subjects studied. The seven healthy male volunteers from the hospital staff aged from 25 to 45 years. All smoked 10 to 20 cigarettes daily. There was no interfering pharmacotherapy. The second group (Table 1) consisted of 18 smokers and 30 nonsmokers with clinically established and, in most patients, biopsy-proven alcoholic liver cirrhosis. Table 1 summarizes the clinical and laboratory data of the patients with liver cirrhosis separated by their smoking habits. Subjects were assigned to each subgroup according to the anamnestic data. Cigarette consumption ranged from 5 to 40 cigarettes daily in smokers.

Only five patients had relevant concomitant illness: one had pneumonia treated with ampicillin; one had urinary tract infection treated with norfloxacin; one was treated with rifampicin and pyracinamide for tuberculosis; one patient was treated for epilepsy with phenytoin, and one patient suffered from chronic obstructive bronchitis treated with theophylline. Drug treatment did not essentially differ in both subgroups (smokers: 5 with loop diuretics, 6 with aldactone and 1 with glibenclamide; nonsmokers: 2 with loop diuretics, 11 with aldactone and 1 with propranolol); all patients with cirrhosis were treated with lactulose and antacids.

In addition to routine laboratory tests, we measured hexobarbitone elimination in the cirrhotic patients after oral administration of 250 mg hexobarbitone according to a method described elsewhere (13).

Patients with liver cirrhosis were compared to an age-matched control group of 11 male and 12 female patients without liver disease and healthy volunteers after exclusion of interfering comedication (oral contraceptives, inducing agents as antiepileptic drugs and inhibitors like cimetidine). The pa-

Received May 20, 1987; accepted September 15, 1987.
Address reprint requests to: Rolf Joeres, M.D., Medizinische Universitäts-Klinik, Josef-Schneider-Str. 2, D-8700 Würzburg, Federal Republic of Germany.

TABLE 1. Clinical and laboratory data of 18 smoking and 30 nonsmoking patients with alcoholic liver cirrhosis (mean values ± S.D.; range)

	Age (yr)	M:F	Body weight (kg)	Bilirubin (mg/100 ml)	AST (IU/liter)	Alkaline phosphatase (IU/liter)	γ-Glutamyl transferase (IU/liter)	Conjugated bile acids (mmole/liter)	Albumin (gm/100 ml)	Hexobarbitone clearance	
										ml/min	ml/min/kg
Smokers	46	13:5	71	2.3	28	265	169	51	3.4	114	1.55
(n = 18)	±9		±14	±3.2	±19	±38	±181	±87	±0.8	±94	±1.29
	30–65		51–94	0.3–14.6	3–79	82–568	17–811	1–387	2.1–4.6	35–327	
Nonsmokers	51	21:9	75	2.8	31	198	112	30	3.8	104	1.32
(n = 30)	±6		±14	±4.7	±32	±104	±92	±31	±0.8	±55	±0.69
	40–66		48–100	0.7–26.3	7–174	86–628	14–344	3–113	1.8–5.3	37–230	
	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Normal range: bilirubin, 0.1–1.3; AST, 5–24; alkaline phosphatase, −200; γ-glutamyl transferase, −28; conjugated bile acids, 6; albumin, 3.5–5; hexobarbitone clearance, 216 ± 26. NS = not statistically significant.

tients in this group suffered from diabetes mellitus, arterial hypertension and compensated heart failure. Eight of them smoked 10 to 30 cigarettes daily (7 males, 1 female); the others were nonsmokers (11 males, 4 females). There was no difference between smokers and nonsmokers in comparison with patients with cirrhosis with regard to body weight and age [smokers: 47 ± 17 (29 to 72) years, 78 ± 8 (61 to 87) kg; nonsmokers: 52 ± 11 (28 to 64) years, 68 ± 13 (46 to 88) kg].

Experimental Design. Informed consent was obtained from all participants. They had to abstain from caffeine-containing beverages and food for at least 12 hr prior to the investigation. After an overnight fast, all probands received 366 mg caffeine in the form of 2 tablets containing 400 mg caffeine monohydrate orally. Blood samples were drawn before and at 1, 2, 3, 6, 12 and 24 hr after application of caffeine.

Seven healthy smokers were tested twice in an intraindividual experiment. The first time, they kept their usual smoking habits; the second test was performed after they had abstained from tobacco for 3 weeks. In all subjects of the control group and the patients with liver cirrhosis, caffeine elimination was measured once under the same conditions.

Blood samples were centrifuged (for 10 min at 4,000 rpm) and the plasma stored at −20°C until taken for analysis. Caffeine plasma concentrations were determined by gas chromatography. After centrifugation, mepivacaine was added as internal standard and the plasma extracted with chloroform at pH 9 to 9.5. After evaporation, the residue was dissolved in 200 μl absolute ethanol, and 0.5 to 1 μl was injected. We used a Hewlett-Packard gas-chromatography Model 5710 A equipped with a nitrogen selective detector (N-P-FID HP 18789 A), "on column" injection, a 15 m DB 17 fused-silica column (0.32 mm i.d.) and an integrator HP 3380 S. Conditions were as follows: inj. port, 250°C; oven temp, 160° to 230°C at 8° per min; det. temp., 300°C; carrier-gas was helium with a flow rate of 10 ml per min.

Calculations. Caffeine elimination was considered to be a first-order process, and the elimination rate constant (k_e) was calculated from the log-linear part of the plasma concentration time curve under the assumption of a one-compartment open model and complete absorption. The apparent volume of distribution (V_D) of caffeine was calculated by the following equation: V_D = dose p.o./(C_{OEX} − C_{OF}), where the extrapolated caffeine concentration at time O (C_{OEX}) was corrected by subtraction of the fasting plasma levels of caffeine (C_{OF}) before application of the test dose (9). Plasma clearance of caffeine was calculated from CL = $V_D \times k_e$ and elimination half-life from $t_{½} = LN\ 2/k_e$. It should be noted that the model-independent method (CL = dose p.o./AUC), including correction for the fasting caffeine plasma levels, provides comparable results ($r = 0.91$, $p < 0.05$).

All results are given as mean ± S.D. and range. Comparisons are based on the Mann-Whitney test ($p < 0.05$ was regarded as statistically significant).

RESULTS

Caffeine Clearance in Smoking Volunteers (Table 2). The 2-fold caffeine test in seven healthy smokers, who abstained from smoking for 3 weeks, revealed the intraindividual influence of smoking on caffeine elimination. Caffeine clearance was reduced from 118 ± 33 to 77 ± 22 ml per min (1.61 ± 0.43 vs. 1.05 ± 0.28 ml per min per kg) in the absence of the inducing effect of smoking ($p < 0.05$). The apparent volume of distribution (43 ± 6 l vs. 35 ± 6 l, 0.58 ± 0.08 vs. 0.46 ± 0.08 liters per kg, NS) remained unchanged, and caffeine plasma half-life increased from 257 ± 356 to 356 ± 131 min ($p < 0.05$). This effect was observed in 6 of the 7 probands, whereas pharmacokinetic parameters did not change in one person.

Caffeine Elimination in the Control Group (Table 3, Figure 1). Caffeine clearance was higher in smokers than in nonsmokers without liver disease (104 ± 40 vs. 64 ± 20 ml per min, 1.43 ± 0.54 vs. 0.96 ± 0.34 ml per min per kg, $p < 0.05$). However, due to a greater but insignificant difference in the volume of the distribution (37 ± 11 l vs. 29 ± 8 l; 0.51 ± 0.13 vs. 0.41 ± 0.07 liters per kg, NS), the difference in elimination half-life did not reach statistical significance (286 ± 76 vs. 363 ± 134 min, $p < 0.10$).

TABLE 2. Pharmacokinetic parameters of caffeine in seven healthy volunteers before and after abstaining for 3 weeks from smoking (mean values ± S.D.; range)

	Cleafance		$t_{½}$ (min)	V_D	
	ml/min	ml/min/kg		liters	liters/kg
Smoking	118	1.61	257	43	0.58
	±33	±0.43	±48	±6	±0.08
	90–176		195–334	33–50	
Abstinent	77	1.05	356	35	0.46
	±22	±0.28	±131	±6	±0.08
	58–107		199–516	30–43	
	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS	NS

NS = not statistically significant.

TABLE 3. Pharmacokinetic parameters of caffeine in 8 smoking and 15 nonsmoking healthy volunteers and patients without liver disease (mean values ± S.D.; range)

	Clearance		$t_{½}$ (min)	V_D	
	ml/min	ml/min/kg		liters	liters/kg
Smokers (n = 8)	104[a] ±40 65–176	1.43 ±0.54	286[a] ±76 198–402	37 ±11 22–50	0.51 ±0.13
Nonsmokers (n = 15)	64[b] ±20 28–102	0.96 ±0.35	336[b] ±134 159–662	29 ±8 17–46	0.41 ±0.07
	$p < 0.05$	$p < 0.05$	NS	NS	NS

NS = not statistically significant.
[a] $p < 0.05$ vs. smoking cirrhotics.
[b] $p < 0.05$ vs. nonsmoking cirrhotics.

TABLE 4. Pharmacokinetic parameters of caffeine in 18 smoking and 30 nonsmoking patients with alcoholic liver cirrhosis (mean values ± S.D.; range)

	Clearance		$t_{½}$ (min)	V_D		C_O (μg/ml)
	ml/min	ml/min/kg		liters	liters/kg	
Smokers (n = 18)	63 ±63 1–230	0.90 ±0.85	899 ±683 161–2,390	37 ±15 16–62	0.53 ±0.22	2.1 ±4.5 0.1–18.4
Nonsmokers (n = 30)	34 ±49 1–270	0.47 ±0.67	1,415 ±1,328 148–5,542	40 ±20 19–73	0.55 ±0.26	5.1 ±6.1 0.1–23.0
	$p < 0.05$	$p < 0.05$	NS	NS	NS	$p < 0.05$

NS = not statistically significant.

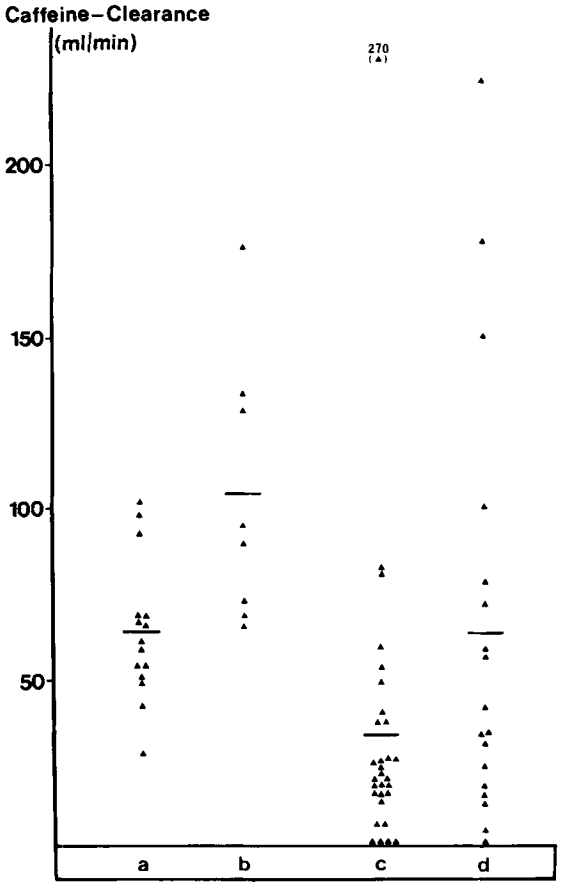

FIG. 1. Caffeine clearance in the smoking (b) and nonsmoking (a) control group in comparison to smoking (d) and nonsmoking (c) patients with alcoholic liver cirrhosis (mean values represented by *bar*).

Caffeine Clearance in Patients with Alcoholic Liver Cirrhosis (Table 4, Figure 1). We could not find differences in the clinical and laboratory data of smoking and nonsmoking patients with alcoholic liver cirrhosis (Table 1). Hexobarbitone elimination was 114 ± 94 ml per min (1.55 ± 1.29 ml per min per kg) in smoking patients and 104 ± 55 ml per min (1.32 ± 0.69 ml per min per kg) in abstinent patients (NS) with a half-life of 711 ± 352 and 787 ± 459 ml per min (NS) and a volume of distribution of 86 ± 28 liters (1.21 ± 0.41 liters per kg) and 106 ± 37 liters (1.41 ± 0.47 liters per kg) (NS), respectively. Hexobarbitone elimination was reduced to about 50% in comparison with healthy volunteers, if compared to data published elsewhere (14).

In contrast to these results, in smokers, caffeine clearance was significantly higher than in nonsmokers (63 ± 63 vs. 34 ± 49 ml per min, 0.90 ± 0.85 vs. 0.47 ± 0.67 ml per min per kg, $p < 0.05$). Due to a great standard deviation, the difference in the elimination half-lifes narrowly missed statistical significance (899 ± 683 vs. 1,415 ± 1,328 min, $p < 0.10$). The volume of distribution was not different in both subgroups (37 ± 15 vs. 40 ± 20 liters, 0.53 ± 0.22 vs. 0.55 ± 0.26 liters per kg). That the influence of smoking and caffeine clearance is not an artificial effect of the experimental conditions can be derived from the fasting caffeine plasma concentrations that are lower in smoking than in nonsmoking patients (2.1 ± 4.5 vs. 5.1 ± 6.1 μg per ml, $p < 0.05$).

Both smoking and nonsmoking patients with liver cirrhosis had a significantly lower caffeine clearance and higher elimination half-life compared to the corresponding subgroups of the controls without liver disease. Volume of distribution, however, did not differ significantly in all subgroups.

DISCUSSION

Caffeine is consumed extensively in the form of caffeine-containing beverages and food, and is also therapeutically administered in many medications. Several publications have pointed out the advantages of caffeine as a tool for the estimation of quantitative liver function (9, 10). It produces serious side effects very rarely, can be administered orally, is almost entirely metabolized by the liver and can be measured accurately in serum.

However, there are some limitations to the concept of caffeine as an "ideal" test substrate. In contrast to previously published data (15), we found an age-dependent decrease of caffeine elimination in patients without liver disease (16). On the other hand, no influence of sex on caffeine elimination could be demonstrated in these 61 patients. Several drugs and possible comedications as idrocilamide (17), cimetidine (18), furafylline (19) and mexiletine (20), impair caffeine clearance to a different, sometimes remarkable extent. It is doubtful whether the

number of possible interactions is limited to those compounds previously listed.

Earlier studies in the rat with 3-methylcholanthrene as inducing agent led to the assumption that caffeine degradation is at least partially mediated by the cytochrome P-448 (11).

Since tobacco smoke contains inducers of the same type, Parsons and Neims (12) could demonstrate an increased caffeine elimination in smokers in comparison with a group of nonsmokers. We could confirm this observation in an intraindividual experiment in seven smoking volunteers who stopped smoking for 3 weeks. Abstinence led to a reduction of caffeine clearance to about 33% after this interval. Furthermore, this inducing effect could also be demonstrated in our control group of smoking and nonsmoking individuals without liver disease and after exclusion of other factors compromising caffeine elimination.

However, it should be noted that the clearance values in our control group are lower than those published by some other groups. As a possible explanation, an effect of the administered dose on caffeine elimination has to be considered. Data derived from literature (7, 9, 10, 12, 18, 21–23) give the impression that with doses below about 3 mg per kg body weight, caffeine clearance tends to be higher than with doses in the range of 4 to 7 mg per kg (Figure 2). It should be pointed out, that our plasma concentration vs. time curves gave no indication of nonlinear caffeine elimination. Thus, we did not find any evidence that the elevated fasting plasma levels of caffeine contribute to the impaired biotransformation by autoinhibition, which could be suspected theoretically from the known theophylline-caffeine interaction. Furthermore, the caffeine clearance in our control group is in the same range as in other studies with a comparable dosage regimen.

Patients with liver cirrhosis are known to have a reduced capacity to eliminate caffeine with a decrease in clearance and consecutive increase in caffeine fasting

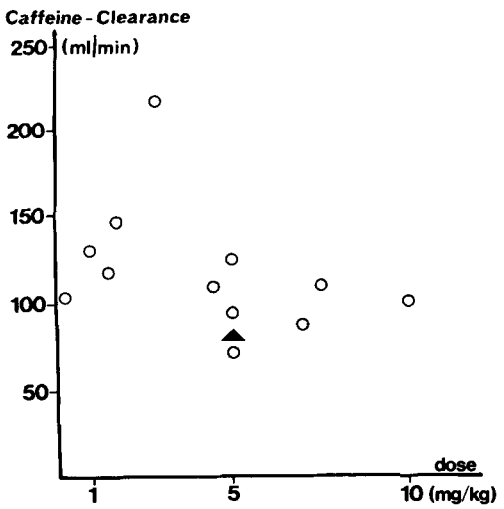

FIG. 2. Relationship between the administered caffeine dose and caffeine clearance in probands without liver disease [○ = data derived from Refs. (7, 9, 10, 12, 17, 20, 21, 23); ▲ = own results].

levels (8–10). This was confirmed by our data if smoking habits were taken into account in the comparison of patients with liver cirrhosis with the control group. Remarkably, there was no difference between smoking cirrhotics and nonsmoking patients without liver disease. Other groups found a greater difference between cirrhotic patients and individuals without liver disease (9, 10) than we could demonstrate. At least partially, this may be explained by differences in the severity of the liver disease. On the other hand, the control groups were not age-matched in these studies.

Despite the impairment of liver function in cirrhosis, the organ is still sensitive to the inducing effect of smoking, apparently to a similar extent as a normal liver. In the case of smoking, this seems to be a rather specific effect on the cytochrome P-448 system (3-methylcholanthrene-inducible) measured in terms of caffeine clearance. In the same group of patients, hexobarbitone elimination, which is thought to be cytochrome P-450 (pheonbarbitone-inducible)-dependent, was not influenced by smoking habits (24).

Therefore, we draw the conclusion that caffeine clearance measures only a small but nevertheless important sector of the drug metabolizing capacity of the liver with regard to the multiplicity of the mixed-function oxygenase system. Further studies have to reveal the clinical relevance of this parameter not only as a diagnostic tool, but also for the prognostic evaluation of liver disease (25).

REFERENCES

1. Breimer DD, Zilly W, Richter E. Pharmacokinetics of hexobarbital in acute hepatitis and after apparent recovery. Clin Pharmacol Ther 1975; 18:433–440.
2. Tygstrup N. Determination of the hepatic elimination capacity of galactose by single injection. Scand J Clin Lab Invest 1966; 18(Suppl 92):118–125.
3. Andreasen PB, Ranek L, Statland BE, et al. Clearance of antipyrine-dependence of qualitative liver function. Eur J Clin Invest 1974; 4:129–134.
4. Bircher J, Kupfer A, Gikalow S, et al. Aminopyrine demethylation measured by breath analysis in cirrhosis. Clin Pharmacol Ther 1976; 20:484–492.
5. Paumgartner G. The handling of indocyanine green by the liver. Schewiz Med Woschenschr 1975; 105:5–30.
6. Haecki W, Bircher J, Preisig R. A new look at the plasma disappearance of sulfobromophtaleine (BSP): correlation with BSP transport maximum and the hepatic plasma flow in mean. J Lab Clin Med 1976; 88:1019–1031.
7. Tang-Liu DD, Williams R, Riegelman S. Disposition of caffeine and its metabolites in man. J Pharmacol Exp Ther 1983; 224:180–185.
8. Desmond PV, Patwardhan RV, Johnson RF, et al. Impaired elimination of caffeine in cirrhosis. Dig Dis Sc 1980; 25:193–197.
9. Renner E, Wietholtz H, Huguenin P, et al. Caffeine: a model compound for measuring liver function. Hepatology 1984; 4:38–46.
10. Wang T, Kleber F, Stellaard F, et al. Caffeine elimination. A test of liver function. Klin Woschenschr 1985; 63:1124–1128.
11. Aldridge A, Parsons WD, Neims AH. Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. Life Sci 1977; 21:967–974.
12. Parsons WD, Neims AH. Effect of smoking on caffeine clearance. Clin Pharmacol Ther 1978; 24:40–45.
13. Breimer DD, van Rossum JM. Rapid and sensitive gaschromatographic determination of hexobarbital in plasma of man using a nitrogen detector. J Chromatogr 1974; 88:235–243.

14. Breimer DD, Honhoff C, Zilly W, et al. Pharmacokinetics of HB in man after intravenous infusion. J Pharmacokin Biopharm 1975; 3:1–11.
15. Blanchard S, Sawers SJA. Comparative pharmacokinetics of caffeine in young and elderly men. J Pharmacokinetics Biopharm 1983; 11:109–126.
16. Joeres R, Heusler H, Hofstetter G, et al. Einfluss des Alters auf die hepatische Elimination von Coffein, Hexobarbital und Lidocain in einem internistischen Patienten-Kollektiv. In: Rietbrock N, Woodcock BG, eds. Clinical pharmacology in the aged. Methods in clinical pharmacology, Braunschweig, West Germany: Vieweg, 1987.
17. Brazier SL, Descotes S, Lery N, et al. Inhibition by idrocilamide of the disposition of caffeine. Eur J Clin Pharmacol 1980; 17:37–43.
18. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. Br J Clin Pharmac 1981; 12:155–159.
19. Tarrus E, Cami S, Roberts DJ, et al. Accumulation of caffeine in healthy volunteers treated with furafylline. Br J Clin Pharmacol 1987; 23:9–18.
20. Joeres R, Klinker H, Heusler H, et al. Influence of mexiletine on caffeine elimination. Pharmacol Therap 1987; 33:163–169.
21. Blanchard J, Sawers SJA. The absolute bioavailability of caffeine in man. Eur J Clin Pharmacol 1983; 24:93–98.
22. Bonati M, Latini R, Galletti F, et al. Caffeine disposition after oral doses. Clin Pharmacol Therap 1982; 32:98–106.
23. Holstege A, Staiger M, Haag K, et al. Untersuchungen zum Koffein-Metabolismus und zur Galaktose-Eliminationskapazität bei Patienten mit Lebercirrhose in Abhängigkeit von der Child-Klassifikation (Abstract). Z Gastroenterol 1987; 25:1.
24. Miyano K, Fujii T, Toki S. Stereoselective hydroxylation of hexobarbital enantiomers by rat liver microsomes. Drug Metab Disp 1980; 8:104–110.
25. Joeres R, Hofstetter G, Klinker H, et al. Prognostische Bedeutung der Coffein-Clearance bei aethyltoxischer Lebericirrhose. Z. Gastroenterol 1987; 25:3–4.