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Correlation of Caffeine Elimination and Child's Classification in Liver Cirrhosis*,**

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Summary. Apparent pharmacokinetic parameters of caffeine elimination from the circulation were determined in 27 patients with histologically confirmed liver cirrhosis, 8 patients with miscellaneous liver disease, and 8 patients with other than liver disease. The usefullness of this quantitative test to assess the severity of liver cirrhosis was compared to the Child-Turcotte or Child-Pugh classification score as well as to the galactose elimination capacity of these patients. Using reversed-phase high pressure liquid chromatography caffeine, paraxanthine, theophylline, and theobromine were analysed in blood plasma collected before and after an oral dose of caffeine. Compared to apparent caffeine pharmacokinetics in patients with normal livers or miscellaneous liver disease, cirrhosis was characterized by a statistically significant reduction in apparent caffeine clearance and prolongation in half-life. The reduced apparent plasma disappearance rate of caffeine in cirrhotics was related to the retarded formation of paraxanthine which was the main metabolite of caffeine in blood plasma both in the absence or presence of liver disease. The apparent caffeine clearance in cirrhosis decreased with increasing Child-Turcotte classification score: Child's class A patients differed significantly from Child's class B or Child's class C patients, whereas the difference between Child's class B and C patients did not reach statistical significance (Wilcoxon's rank test). In addition there was a strong correlation between the Child-Pugh classification score and apparent caffeine clearance ($P < 0.001$). However, no correlation existed between Child's classification and galactose elimination capacity. Our data emphasize the value of the Child-Turcotte or Child-Pugh classification in assessing the severity of liver cirrhosis in a simpler and less time-consuming way than using quantitative liver function tests.

Key words: Child's classification – Caffeine elimination – Liver disease

Caffeine, widely consumed in beverages, is of very low toxicity [1] in usually ingested doses of coffee or tea [21]. In patients with alcoholic hepatic disease [37] and cirrhosis [13] prolonged serum half-lives of caffeine have been observed. Recently, caffeine has been introduced as a model compound for measuring the metabolic capacity of the liver [19, 35, 44, 45]. After its almost complete absorption from the intestinal lumen [5] caffeine is degraded by *N*-demethylation to theophylline, paraxanthine, and theobromine [11, 39], accounting for 96% of caffeine metabolism in humans [19, 23]. Minor pathways include formation of 1,3,7-trimethyluric acid and the ring-opened derivative 6-amino-5-[*N*-formylmethylamino]-1,3-dimethyluracil [17]. The dimethylxanthines are metabolized further to form a range of xanthines, urates, and uracils. Hepatocellular cytochrome P-448 catalyses the rate-determining first steps in oxidative demethylation of caffeine [44]. Exposure of patients to defined doses of caffeine and the subsequent analysis of the compound in blood plasma [34, 43, 45], saliva [16], or labeled CO_2 in the exhalation air [34, 44] allowed a quantitative measure of hepatic microsomal activity [31]. Moreover, fasting

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Abbreviations: AUC = Area under curve; Cl = apparent caffeine clearance; GEC = galactose elimination capacity; V_0 = distribution volume

plasma caffeine concentrations have been suggested to be a simple guide to the severity of chronic liver disease [35, 42].

Quantitative liver function tests require xenobiotics [31] which often carry the risk of side effects. Moreover, some of these tests are time-consuming and involve the need for special analytical equipments. A simpler attempt to assess severity and thus prognosis of chronic liver disease is based on clinical and laboratory observations, first made by Child and Turcotte, including serum bilirubin and albumin, ascites, neurological disorder, and nutrition [9]. These authors developed a severity score to select patients for portocaval shunt surgery which has been used in several studies, also when shunt surgery was not the issue [10]. Although this classification has many problems, which have been reviewed recently [12], the empirical value of the different scoring systems concerning prognosis and severity of liver cirrhosis is now well established [10, 11, 14, 27].

Recently, in patients with liver cirrhosis, the prognostic value and the capacity to assess hepatic function impairment have been evaluated for two different quantitative liver function tests [2, 41] and compared to the information obtained by the Child-Turcotte classification. One of these studies indicated that the aminopyrine breath test did not add further information to the ability to predict the outcome of cirrhotic patients once the Child-Turcotte classification score has been used [41]. In addition a significant correlation was found between the individual values of the aminopyrine breath test and the corresponding Child-Turcotte score [27], modified according to Pugh [32]. However, scoring only provided gross information about severity of cirrhosis when compared to the hepatic clearance of indocyanine green [2].

In our present study, we tried to add to the information on the metabolism of caffeine in cirrhotic liver disease and to the ongoing discussion whether to score or to measure in the evaluation of severity in liver cirrhosis [3]. Two quantitative liver function tests, caffeine clearance and galactose elimination capacity [40], were correlated to the Child-Turcotte classification.

Materials and Methods

Patients

Forty-three patients admitted to the department of internal medicine of the University of Freiburg for diagnosis or treatment of liver disease or other diseases were entered into the study. Twenty patients had alcoholic cirrhosis and seven posthepatitic cirrhosis (Table 1). The diagnosis of cirrhosis was confirmed histologically in all patients by laparoscopy or at autopsy. Eight control patients had other than liver disease and eight patients suffered from noncirrhotic liver disease (Table 2). Smokers were evenly distributed among the patients amounting to 38% in noncirrhotic liver disease, 50% in controls, and 41% in liver cirrhosis.

At inclusion, the patients with liver cirrhosis were classified according to the Child-Turcotte criteria [9] and Child-Pugh scoring system [32] (Table 3). Each of the five variables (ascites, encephalopathy, serum albumin, serum bilirubin, nutritional status, or prothrombine time (Child-Pugh classification)) was given a value of 1, 2, or 3 for increasing abnormality, and the values summed over the five variables for each patient. Thus the best possible score is 5 and the worst 15. Child's A, Child's B, and Child's C classifications ranged from 5–7, 8–10, and 11–15, respectively. Ascites was confirmed in each case by abdominal sonography and graded according to Christensen et al. [10]. Encephalopathy was assessed by the Reitan number connection test or by the inability to reproduce simple designs with matches. Patients with hepatic coma were excluded from the study. We also recorded prothrombine time, serum aspartate transaminase (AST), cholinesterase, and serum gamma-glutamyltransaminase (γ-GT). At the time of the caffeine study most of the patients were receiving various drugs: *Liver cirrhotics* (number of patients in parenthesis): benzodiazepines (3), furosemide (1), spironolactone (14), xipamide (5), lactulose (11), digoxine (6), primidone (2), isosorbide dinitrate (3), chlomethiazole (3), ranitidine (7), cimetidine (1), metoprolol (3), pirenzipine (2), allopurinol (1), nifedipine (1). *Controls:* digoxine (2), allopurinol (1), xipamide (1), isosorbide dinitrate (1), nifedipine (4), cimetidine (1), clonidine (1). *Miscellaneous liver disease:* benzodiazepine (1), furosemide (1), digoxine (2), isosorbide dinitrate (1), ranitidine (1), metoprolol (3), allopurinol (1).

Informed consent was obtained from each of the patients included into the study.

Blood Sampling

After a 24-h period without methylxanthines, caffeine monohydrate was orally administered (7 mg/kg body weight; Cascan, Wiesbaden, FRG) between 8 and 9 a.m. Before and up to 48 h after the caffeine dose, blood samples were collected for methylxanthine analysis (Fig. 1). On the 1st day

Table 1. Clinical and laboratory data of patients with liver cirrhosis classified according to the Child-Turcotte scoring system

Patient	Sex	Age (years)	Total serum bilirubin (mg/100 ml)	Albumin (g/100 ml)	AST (U/l)	ChE (U/l)	γ-GT (U/l)	Prothrombine time (%)
Child's A								
H.B.	F	35	1.1	3.4	121	3775	628	70
K.G.	M	46	0.7	4.1	16	2590	25	53
E.B.	M	55	2.6	3.6	12	5891	36	70
F.N.	M	62	0.9	4.5	8	4215	101	68
M.M.	F	65	1.4	2.8	93	2679	69	64
Z.K.	M	43	2.3	4.7	66	6646	760	80
N.W.	M	52	1.5	3.2	51	2720	116	60
Mean ± SD		51 ± 11	1.5 ± 0.7	3.8 ± 0.7	35[a]	3811[a]	119[a]	66 ± 9
Range					(12–101)	(2588–5610)	(32–446)	
Child's B								
G.H.	M	37	3.8	3.2	35	3425	124	60
G.Z.	F	55	2.8	3.0	83	2192	73	64
S.J.	M	65	1.7	2.4	25	2428	25	45
M.A.	F	54	2.0	3.3	34	2206	31	37
P.W.	M	53	2.0	3.1	28	2063	46	44
L.R.	M	42	0.8	3.9	10	1776	24	71
K.L.	M	34	2.7	3.0	30	939	69	40
H.K.	M	32	1.7	2.5	81	5809	370	47
Mean ± SD		47 ± 12	2.2 ± 0.9	3.1 ± 0.5	34[a]	2307[a]	61[a]	52 ± 13
Range					(17–66)	(1368–3890)	(24–155)	
Child's C								
K.H.	M	67	7.9	2.6	143	1271	35	40
B.H.	M	71	11.0	2.2	70	741	127	38
F.G.	M	52	5.5	2.6	83	2605	277	55
Fr.G.	M	65	2.5	2.2	21	1269	39	51
S.L.	M	47	3.6	2.8	25	753	41	77
H.W.	M	60	3.6	2.8	45	1927	200	44
J.O.	M	58	3.4	3.0	38	1282	38	41
Z.L.	F	74	2.3	2.9	20	1280	50	40
H.S.	M	58	6.0	2.3	71	777	74	54
S.H.	M	44	1.3	3.3	14	985	83	66
M.A.	M	74	6.8	4.4	27	2834	37	35
H.S.	M	57	2.2	3.1	14	1622	14	50
Mean ± SD		61 ± 10	4.7 ± 2.8	2.9 ± 0.6	36[a]	1312[a]	65[a]	46 ± 9
Range					(17–77)	(836–2061)	(29–148)	

[a] Geometric mean

blood was taken for determination of the galactose elimination capacity [4, 40].

Analytical Methods

Galactose elimination capacity was determined according to Tygstrup [40] and modified as described by Bircher et al. [4]. Caffeine, paraxanthine, theobromine, and theophylline were measured in blood serum using a procedure described by Stavric and Klassen [38]. The metabolites were extracted with chloroform-isopropanol (85:15) from 100-µl serum samples after prior addition of 10 nmol 8-chlorotheophylline and 1.2 g NH_4HCO_3. The supernatant was filtered through Millex HV 0.45 µm filter units (Millipore, Eschborn, FRG) to remove undissolved NH_4HCO_3. The extraction procedure was repeated twice and the filtrates were pooled in a polypropylene test tube. The filtered extracts were evaporated to dryness at 50° C under a stream of nitrogen and the residue was dissolved in 500 µl of the HPLC buffer which was composed of distilled water/isopropanol/acetonitrile/acetic acid (91,4,4,1; v/v/v/v). The samples were injected onto a Perkin-Elmer/HS C18 column (5 µm; Perkin Elmer, Überlingen, FRG) connected in series

Table 2. Clinical and laboratory data of the control patients studied

Patient	Sex	Age (years)	Total serum bilirubin (mg/100 ml)	Albumin (g/100 ml)	GOT (U/l)	ChE (U/l)	γ-GT (U/l)	Prothrombine time (%)	Diagnosis
Patients with other than liver disease									
F.K.M.	M	54	1.1	4.8	12	6462	29	100	Hypertension
E.L.	M	60	0.9	4.3	9	5968	10	100	Esophagitis
H.G.B.	M	51	0.5	3.8	5	4565	27	81	Pneumonia
G.K.	M	72	0.7	3.4	14	4632	13	73	Urinary tract infection
A.K.	M	72	0.7	3.7	6	3100	10	74	Pulmonary embolism
S.K.	M	48	0.6	4.7	9	6848	20	90	Atrial fibrillation
H.H.	M	59	0.8	4.7	11	5594	7	98	Coronary heart disease
H.F.	M	57	1.1	4.6	6	4923	26	90	Lung tumor (limited disease)
Mean ± SD		59 ± 9	0.8 ± 0.2	4.2 ± 0.5	8	5129	16	88 ± 11	
Range					(6–12)	(3981–6607)	(9–27)		
Miscellaneous liver disease									
U.H.	M	36	4.6	3.3	30	2915	218	76	Fatty liver[a]
Z.H.	F	53	0.7	4.3	34	8539	45	91	Fatty liver[b]
A.S.	M	48	0.7	4.7	13	8037	30	82	Fatty liver[b]
K.M.	M	86	1.2	4.3	8	3623	99	100	Congestive liver
J.T.	M	34	1.0	4.3	36	6031	1936	100	Fatty liver[a]
G.L.	M	51	1.9	5.5	10	8414	38	95	Fatty liver[a]
P.W.	M	77	1.2	3.5	18	3514	158	68	Liver metastases[a]
G.K.	F	38	0.8	4.0	352	1892	252	–[c]	NANB Hepatitis
Mean ± SD		53 ± 19	1.5 ± 1.3	4.2 ± 0.7	26	4715	131	87 ± 12	
Range					(9–87)	(2673–8317)	(34–508)		

[a] Confirmed by histology
[b] Suspected by ultrasound
[c] Treatment with coumarin for venous thrombosis

Table 3. Child-Turcotte (Child-Pugh) criteria and their distribution in patients with liver cirrhosis

Group designations (grading)	A (1)		B (2)		C (3)	
Serum bilirubin (mg/100 ml)	< 2.0	(33%)	2.0–3.0	(34%)	> 3.0	(33%)
Serum albumin (g/100 ml)	> 3.5	(26%)	3.0–3.5	(33%)	< 3.0	(41%)
Ascites	None	(33%)	Easily controlled	(30%)	Poorly controlled[a]	(37%)
Neurological disorder	None	(52%)	Minimal	(48%)	Advanced coma[b]	
Nutrition	Good[c]	(67%)	Fair[d]	(18%)	Poor[e]	(15%)
Prothrombine time (%)[f]	> 70	(11%)	40–70	(78%)	< 40	(11%)

[a] Moderate or marked ascites
[b] Excluded from the study
[c] Normal or fat
[d] Meagre
[e] Cachectic
[f] Child-Pugh score includes prothrombine time instead of nutritional status

with a Guard-PAK precolumn module containing a C_{18}-μBondapak insert (Waters, Königstein, FRG). The flow rate was 1 ml/min at room temperature. UV absorbance was recorded at 276 nm using an isocratic HPLC apparatus from Du Pont De Nemours (Bad Nauheim, FRG). Peak areas were integrated by a Spectra-Physics (Darmstadt, FRG) printer-plotter SP 4100 and quantified using 8-chlorotheophylline as an internal standard and by referring to methylxanthine standards that had been weighted out on a Sartorius 2004 MP6 microbalance (Göttingen, FRG). No peaks interfering with caffeine in the HPLC chromatograms could be detected. Samples containing impurities with

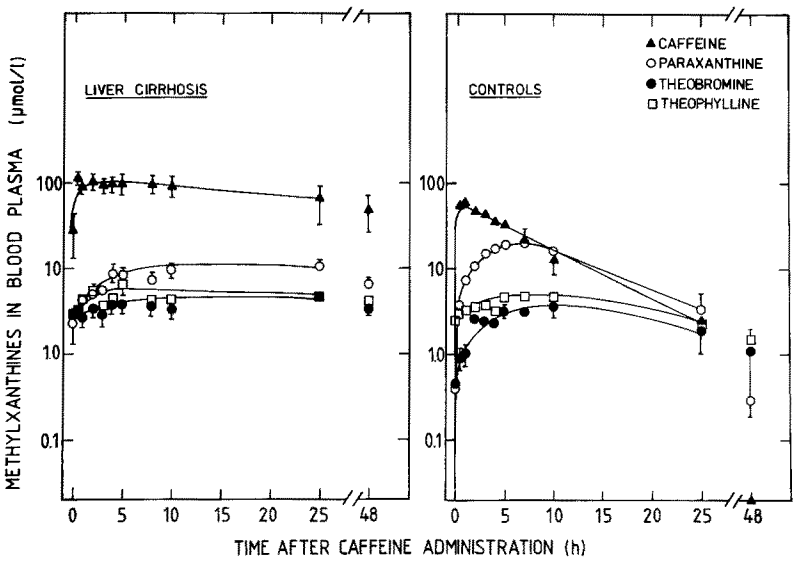

Fig. 1. Blood plasma concentration-time curves for caffeine and its major metabolites, paraxanthine, theophylline, and theobromine after an oral dose of caffeine monohydrate (7 mg/kg body weight) in ten patients with liver cirrhosis and five patients with other than liver disease. Caffeine administration was preceded by a 24-h caffeine-free period. Methylxanthines were measured as described [28]. Data are shown as mean ± standard error (SE). In some cases SE was smaller than the symbol used

similar retention times as theobromine, paraxanthine or theophylline were not used for the time course studies of caffeine metabolites. Reproducibility and limits of detection were identical to published data [38].

Standard procedures were used for the determination of prothrombine time (% of normal values), serum aspartate aminotransferase, cholinesterase, bilirubin, serum albumin, and serum gamma-glutamyltransaminase (γ-GT).

Pharmacokinetics

Apparent disappearance rate constants (k) for caffeine were determined by linear regression analysis after logarithmic transformation of its concentrations in blood serum. Plasma half-life ($t_{1/2}$) was defined as $t_{1/2} = \ln 2/k$. Areas under curves (AUC) were calculated by the trapezoidal rule in the absorptive phase and by the evaluation of integrals resulting from the exponential decrease of caffeine in blood plasma in the elimination phase. Corrections were made for zero-time caffeine concentrations ($t=0$, c_0) assuming the same time-dependent exponential decrease as calculated above for the caffeine test dose. Apparent caffeine clearance (Cl) was defined as the ratio of the oral caffeine test dose (D) and AUC. The distribution volume (V_0) was determined as the ratio of D and the extrapolated serum concentration at time zero (c_i) corrected by c_0, i.e. $V_0 = D/(c_i - c_0)$.

Statistics

Pharmacokinetic parameters and plasma enzyme activities were log-normally distributed. To prevent undue weight on a few very high values, the logarithm of each individual value was taken. The mean and standard deviations (SD) were calculated by the usual procedure. Then the antilog of the mean and the antilog of the mean minus 1 SD and antilog mean plus 1 SD are given to show how the values were distributed [25]. The arithmetic mean ± SD or standard error of the mean (SE) is given in all other cases. Wilcoxon's rank test was used to test for differences of apparent caffeine pharmacokinetics between the groups. The correlations between caffeine clearance and Child-Pugh score, serum albumin, prothrombin time, serum bilirubin, galactose elimination capacity, and serum aspartate aminotransferase were assessed using Spearman's rank-order test.

Chemicals

The methylxanthines and NH_4HCO_3 were from Sigma Chemical (St. Louis, MO). 8-Chlorotheophylline was purchased from ICN Pharmaceuticals (Plainview, NY). All other chemicals were of the highest purity available from Merck (Darmstadt, FRG). Enzymes were from Boehringer (Mannheim, FRG).

Results

Biochemical Liver Function Tests

As shown in Table 1, in patients with cirrhosis of the liver the plasma albumin level, prothrombine time, and cholinesterase were decreased, and the plasma levels of total bilirubin, the enzyme activities of aspartate aminotransferase, and of gamma-

Table 4. Apparent caffeine pharmacokinetics and galactose elimination capacity in patients with liver cirrhosis (Child-Turcotte classification), in noncirrhotics and in controls

	$t_{1/2}$[a] (h)	Cl (ml/min)	V_0 (% BW)		GEC ($mg \times min^{-1} \times kg^{-1}$)	
Controls	5.0[b] (3.1–8.1)	88.9[b] (60.9–129.7)	49.1 ± 7.3[c]	(8)[d]	6.69 ± 0.52[c]	(8)[d]
Miscellaneous	5.4 (3.0–9.7)	66.4 (37.7–116.9)	48.8 ± 9.0	(8)	6.59 ± 1.11	(8)
Liver cirrhosis						
Total	29.8 (9.5–93.4)	13.1 (3.6–46.8)	49.1 ± 13.5	(26)[e]	5.03 ± 1.20	(23)
Child's A[f]	11.8 (8.9–15.9)	41.5 (33.5–51.3)	58.3 ± 10.3	(7)	5.11 ± 1.73	(5)
Child's B[f]	32.1 (11.2–91.4)	13.5 (4.5–40.3)	44.7 ± 11.0	(7)	4.78 ± 0.91	(7)
Child's C[f]	48.8 (14.2–168.1)	6.5 (1.8–23.6)	45.4 ± 7.3	(12)	5.14 ± 1.19	(11)

[a] Abbreviations are: $t_{1/2}$, apparent half-life; Cl, apparent clearance; V_0, distribution volume; GEC, galactose elimination capacity; BW, body weight
[b] Geometric mean and range
[c] Arithmetic mean ± SD
[d] In parenthesis, number of patients
[e] One of the liver cirrhotics, classified as Child B, demonstrated no decrease in caffeine concentration over the observation period allowing no calculation of the pharmacokinetic data
[f] Child-Turcotte classification

glutamyltransaminase were increased. Patients with noncirrhotic liver disease showed elevated activities for aspartate aminotransferase and gamma-glutamyltransaminase and an increased bilirubin level (Table 2). All the values for control patients with other than liver disease were in the normal range (Table 2).

Caffeine Disposition in Liver Cirrhotics

The time-concentration curves of caffeine and of its primary degradation products in blood plasma of ten patients with liver cirrhosis and of five control patients without liver disease are shown in Fig. 1. Plasma peak levels of caffeine were reached within 1 h after administration of the oral test dose. Abstinence from caffeine containing beverages for 24 h was not long enough for 16 of 27 patients with liver cirrhosis to eliminate preexisting methylxanthine levels in blood plasma resulting in high concentrations of all methylxanthines at zero time (Fig. 1). In control patients caffeine was not present in blood plasma taken before the onset of the caffeine test [35, 42, 45]. In controls the fall in caffeine levels was rapid and followed by an inverse increase in paraxanthine formation. A much slower decline in blood plasma concentrations of caffeine was observed in liver cirrhotics. In both groups paraxanthine was the quantitatively most important metabolite of caffeine and reached or exceeded the concentration of caffeine after approximately 12 h. The concentration of theobromine was always lower than that of theophylline. Caffeine was no longer detectable in blood plasma of controls and of patients with miscellaneous liver disease 48 h after the test dose (7 mg/kg body weight), which differed considerably from the findings in patients with liver cirrhosis (Fig. 1). Only 6% of the patients in both control groups ($n=16$) revealed detectable caffeine concentrations at 48 h in contrast to 93% of the patients with cirrhosis of the liver ($n=26$). At this time point control patients, too, still had measurable amounts of paraxanthine, theophylline, and theobromine in blood plasma (Fig. 1).

Apparent Pharmacokinetic Parameters of Caffeine

The different apparent pharmacokinetic parameters of caffeine elimination were calculated from the time-concentration curves obtained after oral administration of the test dose. These data are

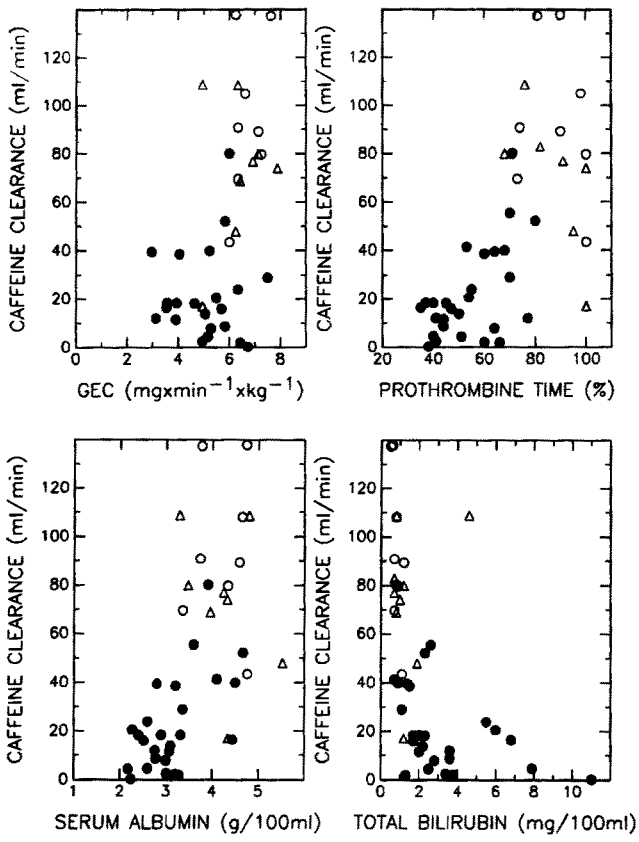

Fig. 2. Correlation between apparent caffeine clearance and galactose elimination capacity (GEC), prothrombine time, serum albumin, and total serum bilirubin. Data are given for patients with liver cirrhosis (*closed circles*), miscellaneous liver disease (*open triangles*), and other than liver disease (*open circles*)

summarized in Table 4. The values of controls and patients with miscellaneous liver disease significantly differed from those of patients with liver cirrhosis ($P<0.001$, Wilcoxon's rank test). No difference was found between non-cirrhotics and patients with other than liver disease. The apparent caffeine clearance ($P<0.002$), half-life ($P<0.01$), and area under curve ($P<0.01$) of the latter were statistically different from Child's class A patients (Child-Turcotte classification). The apparent volume of distribution (V_0) did not differ between controls, patients with miscellaneous liver disease, or cirrhotics (Table 4). However, Child's class A patients with cirrhosis of the liver had a larger mean distribution volume (% body weight) as compared with Child's class B or Child's class C patients ($P<0.05$).

The apparent clearance of paraxanthine assuming an 80% conversion of caffeine into paraxanthine [19, 23] amounted to 110.5 ml/min and 55 ml/min and the apparent half-life was 6.6 h and 34.4 h for patients with other than liver disease and cirrhotics, respectively.

Correlation Between Apparent Caffeine Clearance and Biochemical Parameters of the Child Classifications

The apparent caffeine clearance of controls, patients with miscellaneous liver disease, and liver cirrhosis was found to correlate with serum albumin ($R_S=0.685$, $P<0.001$), prothrombine time ($R_S=0.692$, $P<0.001$), and serum bilirubin ($R_S=-0.701$, $P<0.001$; Fig. 2). No correlation was found between caffeine clearance and serum aspartate aminotransferase activity. Exclusive statistical evaluation of the data of patients with liver cirrhosis gave somewhat lower values for the correlation between caffeine clearance and serum albumin 0.524 ($P<0.01$), prothrombine time 0.469 ($P<0.01$), and serum bilirubin -0.512 ($P<0.01$), respectively.

Comparison of Caffeine Clearance, Galactose Elimination Capacity, and Child-Turcotte or Child-Pugh Classification

Assessment of 27 patients with liver cirrhosis using Child's criteria is given in Table 3. The severity of liver disease as assessed by these scoring systems was associated with a progressive impairment of the elimination of caffeine from the circulation (Table 4, Fig. 3). Accordingly, the mean apparent caffeine clearance dropped from its highest value in Child's class A patients to its lowest value in Child's class C patients (Table 4). Using the Child-Pugh classification, which includes the prothrombine time instead of the nutritional status [32], the correlation coefficient between apparent caffeine clearance and Pugh points was $R_S=-0.635$ ($P<0.001$; Fig. 3). Similarly, the mean caffeine half-life increased with rising Child-Turcotte scores (Table 4). The apparent pharmacokinetic parameters of Child's class A patients showed a statistically significant difference from Child's class B or C patients ($P<0.001$, Wilcoxon's rank test). However, the difference between Child's class B and C patients did not reach statistical significance.

The mean galactose elimination capacity (GEC) did not differ between patients with different Child-Turcotte (Table 3) or Child-Pugh (Fig. 3) classifications. The GEC of 22 patients with liver cirrhosis was plotted against their individual apparent caffeine clearance values (Fig. 2). No correlation could be detected between galactose elimination capacity and apparent caffeine clearance in these patients ($R_S=0.049$).

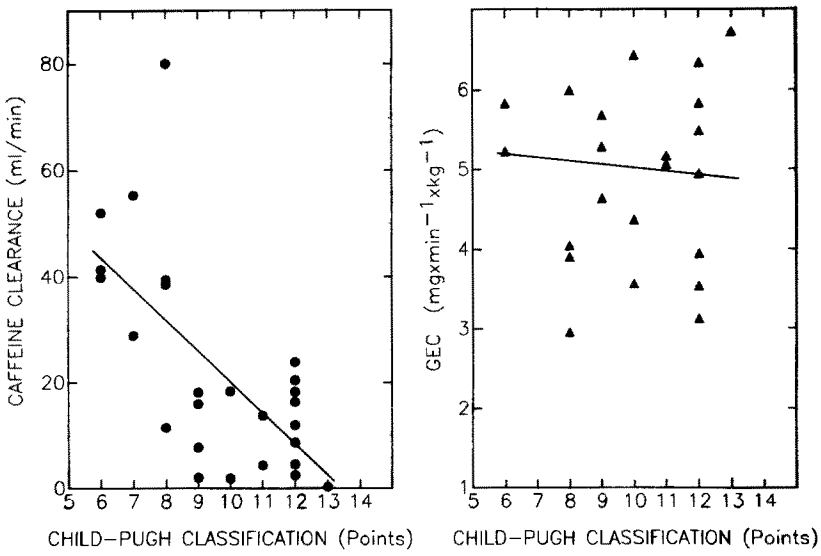

Fig. 3. Correlation between Child-Pugh classification and apparent caffeine clearance or Child-Pugh classification and galactose elimination capacity (GEC) in patients with liver cirrhosis. The Pugh points are calculated as indicated in Table 3. The regression lines calculated from the data shown are included in both figures

Discussion

The apparent pharmacokinetic parameters of caffeine elimination from the circulation shown in Table 4 are in agreement with data from other investigators obtained from healthy subjects and from patients with liver cirrhosis [6, 13, 22, 37, 39, 43–45]. We extended these studies by measuring not only caffeine but also its primary degradation products, paraxanthine, theobromine, and theophylline in liver cirrhosis (Fig. 1). Paraxanthine formation from caffeine was much slower in liver cirrhosis as compared to patients with other than liver disease (Fig. 1) or healthy subjects [10, 11]. This points to the importance of demethylation at position 3 of caffeine, i.e., the paraxanthine pathway, which accounts for 80% of caffeine demethylation [19, 23]. In our patients with liver cirrhosis this pathway was severely impaired (Fig. 1). Theobromine and theophylline account for 12% and 4%, respectively, of the caffeine demethylation in normal subjects [23], reflected by low concentrations of these dimethylxanthines in controls and liver cirrhotics. Forty-eight hours after caffeine administration the paraxanthine level was much lower than that of the other two methylxanthines in control subjects, which is in accordance with a significantly shorter half-life of paraxanthine (3.1 h) as compared to theophylline (6.2 h) or theobromine (7.2 h) [22]. In liver cirrhosis a similar fall in paraxanthine ($t_{1/2} = 34$ h) concentration was not observed at this late time due to its continuous formation in the presence of high caffeine concentrations. Further degradation of the dimethylxanthines presumably is also impaired in liver cirrhosis, as has been observed for theophylline elimination in cirrhotic liver disease [24].

The apparent pharmacokinetics of caffeine were not significantly different in patients with noncirrhotic liver disease as compared to control subjects (Table 4). One patient with congestive liver disease exhibited a slow elimination of caffeine with a measurable caffeine concentration 48 h after the oral dose. A similar suppressive effect of congestive heart failure on methylxanthine clearance has been described for the elimination of theophylline [15, 30]. The caffeine liver test can be used only to assess liver metabolic function and not to discriminate between patients with noncirrhotic liver disease and healthy controls (Table 4) [8, 24, 35]. In cirrhotics, a comparison of the caffeine test with the Child-Turcotte or Child-Pugh classification indicated that the scoring systems correlated with the apparent caffeine clearance in assessing severity of liver disease (Table 3, Fig. 3). Fasting plasma concentrations [35, 42, 45] or the caffeine concentration determined at 48 h after our test dosage allowed rapid information about the severity of liver disease.

The Child-Turcotte classification has been shown to provide valuable and easily obtainable prognostic information in cirrhosis [10, 14], as well as information about severity of cirrhotic liver disease [41]. Total serum bilirubin and albumin are strongly correlated to the degree of hepatic functional impairment [2, 10, 11, 27]. In addition, Child's criteria include either three or two clinical parameters, portal-systemic encephalopathy, ascites, and nutrition, which are more susceptible to being unduly influenced by nonspecific effects of

treatment and which are more open to observer variation than are the other biochemical parameters [12]. However, marked ascites, poor nutritional status, and encephalopathy were shown to have independent prognostic significance in hepatic disease associated with poor prognosis [11, 27].

Failure of the aminopyrine breath test to contribute further to the evaluation of prognosis in cirrhosis has been viewed as being due to the excellent validity of Child's criteria and to the good correlation between the aminopyrine breath test and the scoring system [41]. The results of our study demonstrate a similar correlation between impairment of caffeine elimination and the assessment of severity by the Child classifications (Table 4, Fig. 3). In contrast, another quantitative liver function test, the galactose elimination capacity (GEC) [40], did not allow any discrimination between Child's class A, Child's class B or Child's class C patients. Referring exclusively to values obtained from patients with liver cirrhosis, statistical evaluation of the data revealed no correlation between GEC and apparent caffeine clearance (Fig. 2). As compared to the caffeine clearance, the lack of correlation of the GEC to severity in liver cirrhosis as assessed by Child's criteria may be explained at least in part by their different metabolic sites [31] within the hepatocyte or presumably within the liver lobule.

The hepatic elimination of caffeine from the circulation may be influenced by a variety of factors. Some of these factors are age [16, 20], oral contraceptive steroids [29], smoking [28], cimetidine [7], obesity, and exercise [18]. Indirect effects may be exerted on caffeine clearance by drugs influencing the microvascular exchange in cirrhotic liver like verapamil [33] or by methylxanthines themselves [26, 46]. These factors have to be considered if liver function is assessed from caffeine pharmacokinetics and minor effects on caffeine clearance cannot be excluded in patients receiving multidrug treatment. Smokers were evenly distributed among our patients and the mean age was similar in the different groups. Exclusion of patients with cimetidine did not modify our results. Ranitidine, which was frequently prescribed in this study, presumably does not interfere with the elimination of methylxanthines for the circulation [36].

According to our study rapid assessment of functional impairment in liver cirrhosis can be simply accomplished using Child's scoring systems. However, it remains to be demonstrated whether repeated clearance measurements in one patient will provide better information on individual prognosis or disease progression.

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