Acta Med Scand, Suppl 624: 99–105, 1979

Paracetamol (Acetaminophen) Clearance in Patients with Cirrhosis of the Liver

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ABSTRACT. The pharmacokinetics of paracetamol were studied in 11 patients with cirrhosis of the liver and 12 controls. The average biological half-life after oral administration of 1 g paracetamol was significantly prolonged in patients with hepatic cirrhosis compared to the controls (3.7 hr vs. 2.1 hr) and, correspondingly, the average plasma clearance was significantly reduced from 337 ml × min^{-1} in the controls to 162 ml × min^{-1} in the patients with cirrhosis of the liver.

After subchronic dosing of paracetamol with 1 g paracetamol t. i. d. the plasma half-lives of paracetamol remained unchanged. Steady-state levels of paracetamol were significantly increased in the patients with cirrhosis of the liver. A significant correlation between the values of plasma clearance of paracetamol and prothrombin time ($r = +0.88$), galactose elimination capacity ($r = +0.66$), plasma albumin ($r = +0.47$) and plasma clearance of phenazone ($r = +0.85$) was found. No clinical or biochemical signs of hepatotoxicity were observed during the study.

KEY WORDS. Paracetamol, Acetaminophen, cirrhosis of the liver, pharmacokinetics, liver function, hepatotoxicity.

Paracetamol, a widely used analgesic, causes dose-dependent hepatotoxicity in animals and man (13). Although paracetamol is considered a safe drug when used in therapeutic dosage, liver damage has been observed even after intake of 5–10 grams (4, 15, 18).

Several risk-factors for developing paracetamol toxicity at lower dosages have been indicated, i. e. taken inducers such as drugs or alcohol, malnutrition and liver disease (2, 7, 20).

We have studied paracetamol metabolism in patients with cirrhosis of the liver following single and/or multiple oral administration to evaluate the need for a modified dosage regime in patients with various degrees of impaired liver function.

MATERIAL AND METHODS

We studied 11 patients with alcoholic and idiopathic cirrhosis of the liver and 12 patients without liver disease admitted to our department for investigation and treatment. Informed consent was obtained before starting the experiment. Table I gives the clinical and laboratory details of the patients studied. The diagnosis of hepatic cirrhosis was confirmed by liver biopsy. A careful drug history was recorded. Among the drugs administered, case No. 1, 3, 4, 5, 7, 10 and 12 received spironolactone (75–150 mg/day). No. 8, 10 and 19 prednisone. No. 18 sanocrysine and No. 11 azathioprine.

Design: Patients were fasted from midnight. At 8 a. m. two tablets, each containing 0.5 grams of paracetamol (Winthrop) were administered orally together with 50 ml water. Fasting was maintained until 10 a. m. Venous blood samples of 10 ml each were drawn into heparinized test tubes just before and at 30, 60, 120, 180, 240, 300 and 360 min after adminis-

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tration of paracetamol. Further samples were drawn around 480 and 720 min.

In addition, nine patients without liver disease and four patients with hepatic cirrhosis were given 1.0 gram paracetamol p. o. t. i. d. (at 8 a. m., 2 p. m. and 8 p. m.) the following five days. The next day, a repeated paracetamol elimination study was performed as described above. Venous blood samples were drawn before before dosage at 8, 10 and 12 a. m. and 2 p. m. during the second day and at 8 a. m. and 2 p. m. during the fifth day. The galactose elimination capacity and phenazone plasma clearance were studied a few days before or after the paracetamol study.

Analysis: Plasma concentration of paracetamol was estimated by gas-liquid-chromatography (14). Phenazone plasma clearance (1) and galactose elimination capacity (17) were estimated by the methods indicated.

Calculation. The elimination half-lives of paracetamol was estimated from regression analysis using the concentrations from 120 min on after the administration and the apparent plasma clearance of paracetamol estimated assuming an absorption fraction of 1 from the formula:

$$\text{Clearance} = \frac{D}{AUC} \qquad (1)$$

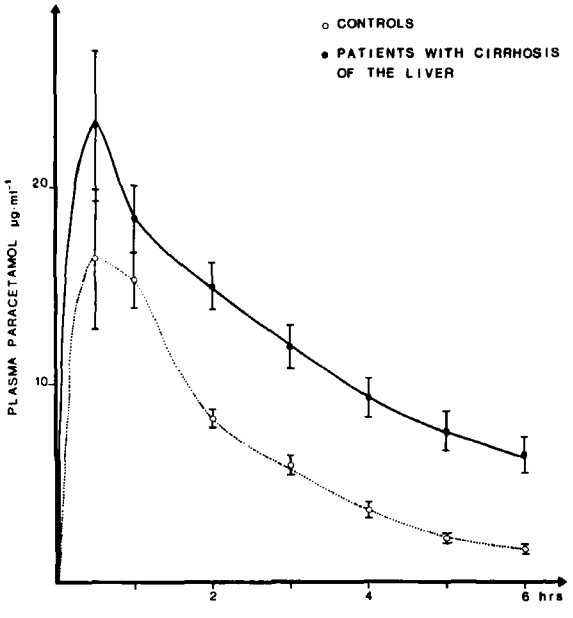

Fig. 1. Plasma concentrations of paracetamol (mean ± S.E.M.) after the oral administration of 1.0 g to 11 patients with cirrhosis of the liver and 12 controls. Sampling points after six hours are not depicted as they were not taken at fixed hours.

Table 1. *Clinical and laboratory details of 11 patients with cirrhosis of the liver and 12 controls.*

Case no.	Age/sex	Diagnosis
1.	44/F	alcoholic cirrhosis
2.	52/F	–
3.	37/M	–
4.	44/M	–
5.	50/M	–
6.	56/M	–
7.	66/M	–
8.	32/F	cryptogenic cirrhosis
9.	55/F	–
10.	62/F	–
11.	69/F	–
Mean ± SD		
12.	41/F	diabetes mellitus
13.	47/F	peripheral neuropathy
14.	49/F	intervertebral degeneration of lumbar spine
15.	50/F	multiple myeloma
16.	52/F	rheumatoid arthritis
17.	61/F	–
18.	65/F	–
19.	66/F	–
20.	67/F	atherosclerosis
21.	69/F	collagenosis
22.	53/M	chronic pancreatitis
23.	56/M	rheumatoid arthritis
Mean ± SD		

Normal values. Prothrombin 85–115 %, plasma album in 532–813 μmol · l^{-1}, galactose elimination capacity 1.38–3.50 mmol · min^{-1}, phenazone clearance 21.7–80. 1 ml · min^{-1}.

RESULTS

Fig. 1 shows the average plasma curves of paracetamol among the group of patients with hepatic cirrhosis and the group without hepatic disease. Statistically significant higher plasma concentrations of paracetamol are found at all sampling points in the group of patients with hepatic cirrhosis up to 6 hrs. ($P < 0.05$). Later

Body weight	Ascites	Prothrombin	Plasma albumin (μmol · 1-1)	Galactose elimination capacity (mmol · min-1)	Phenazone plasma clearance (ml · min-1)	Paracetamol	
						T/2 (hour)	Plasma clearance (ml · min-1)
71	+	49	542	1.17	11.9	3.2	182
57	–	75	412	1.04	–	2.2	293
76	+	25	301	1.17	–	5.1	135
49	+	23	369	0.95	7.2	3.8	111
66	+	50	441	1.55	22.1	3.8	168
70	+	38	258	–	–	4.9	140
63	+	58	307	–	22.1	3.8	176
54	+	63	372	–	–	3.8	151
54	–	56	384	0.88	–	3.9	128
51	–	57	446	0.64	–	3.7	110
51	–	54	271	1.04	19.5	2.9	186
60±9		50±16	373±86	1.06±0.26	16.6± 6.7	3.7±0.8	162±51
75	–	157	645	3.35	–	1.8	435
59	–	87	–	1.82	–	2.4	306
60	–	85	*658*	1.89	–	3.6	207
68	–	98	480	–	–	2.4	363
74	–	124	–	–	–	2.4	349
70	–	96	–	–	33.0	2.2	326
53	–	136	438	2.19	64.0	1.6	373
56	–	132	400	1.04	–	1.9	388
47	–	113	535	1.32	–	1.8	288
47	–	108	–	–	37.4	2.2	356
50	–	136	471	1.72	–	1.4	406
59	–	92	–	1.83	–	1.4	461
60±10		114±23	518±100	1.90±0.69	44.7±16.8	2.1±0.6	355±68

values are not given since fixed sampling times were not employed thereafter.

Table I gives in addition to the individual clinical data also results of liver function tests and the half-life and clearance values of paracetamol. The mean half-life of paracetamol in the group of patients with hepatic cirrhosis was nearly twice as high compared to the controls (3.7 hr ± 0.8 vs. 2.1 hr ± 0.6, mean ± SD, $P < 0.01$). Correspondingly, the plasma clearance of paracetamol was reduced from 337 ml x min^{-1} ± 69 in the controls to 162 ml x min^{-1} ± 52 in the patients with hepatic cirrhosis ($P < 0.001$).

Subchronic dosing of paracetamol with 1 g paracetamol t. i. d. during five days to patients with hepatic disease (N = 4) and patients without liver disease (N = 9) did not influence the plasma half-lives of paracetamol (paired t-test). The individual values are depicted in Fig. 2.

Fig. 3 shows the individual plasma paracetamol concentrations among the above mentioned patients estimated at 2 p. m. just before administration of the next dose during the second and fifth day of paracetamol treatment. No intra-individual differences in plasma concentration of paracetamol were found at day 2 and day 5

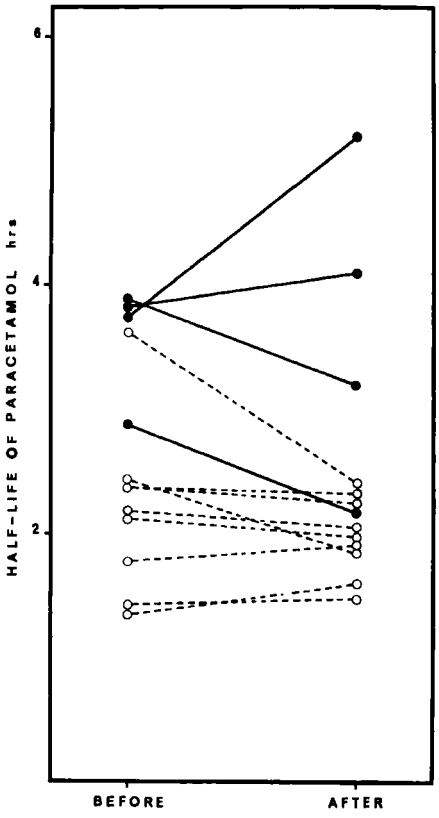

Fig. 2. The plasma half-lives of paracetamol before and after continuous dosage of 1 g paracetamol t. i. d. orally for five days in 4 patients with (—●—) and 9 patients without liver disease (—o—).

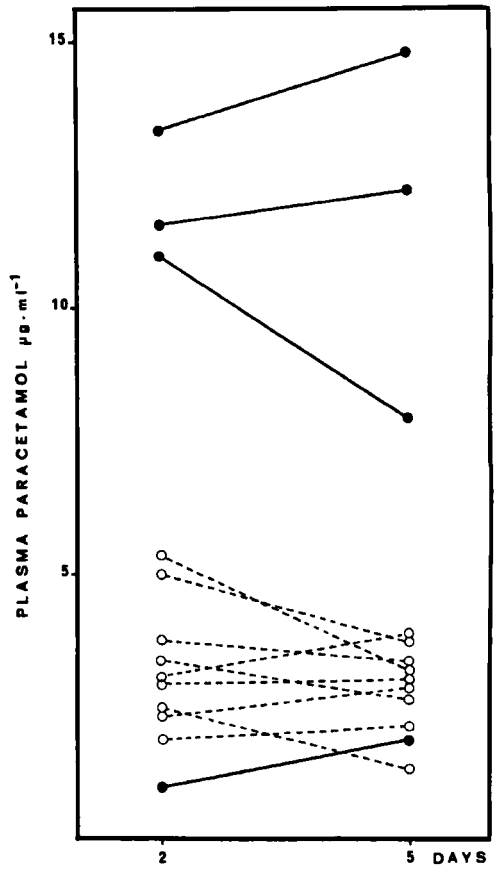

Fig. 3. Plasma concentrations of paracetamol in 4 patients with hepatic cirrhosis (—●—) and 9 controls (—o—) each receiving 1.0 g of paracetamol orally t. i. d. The plasma concentrations were measured just before the second daily dose at 2 p. m.

(paired t-test). However, the values among the patients with hepatic cirrhosis are significantly increased compared to those of the controls (9.2 $\mu g \times ml^{-1}$ vs. 3.2 $\mu g \times ml^{-1}$, $P < 0.01$). The corresponding values estimated at 8 a. m. on the same days were 3.7 $\mu g \times ml^{-1}$ vs. 1.1 $\mu g \times ml^{-1}$ ($P < 0.01$).

Table II gives the correlation coefficients between the plasma clearance of paracetamol and indices of liver function. Prothrombin time appears to be closely related to the plasma clearance of paracetamol both when the two groups are considered separately or together (Fig. 4). In five patients with hepatic cirrhosis and three controls a significant relationship between the plasma clearance of phenazone and paracetamol was found ($r = +0.85$, $P < 0.01$).

Signs of clinical hepatotoxicity or significant changes in the values of alanine aminotransfera-

Table II. *Correlations between the plasma clearance of paracetamol and indices of hepatic function in patients with cirrhosis of the liver and controls.*

	Paracetamol plasma clearance vs.			
	Prothrombin time	Galactose elimination capacity	Plasma albumin	Plasma clearance of phenazone
All patients				
	N = 23	N = 16	N = 18	N = 8
	r = +0.88	r = +0.66	r = +0.47	r = +0.85
	p < 0.001	p < 0.01	p < 0.05	p < 0.001
Patients with cirrhosis of the liver				
	N = 11	N = 8	N = 11	
	r = +0.63	r = +0.29	r = +0.14	–
	p < 0.05	p > 0.1	p > 0.1	

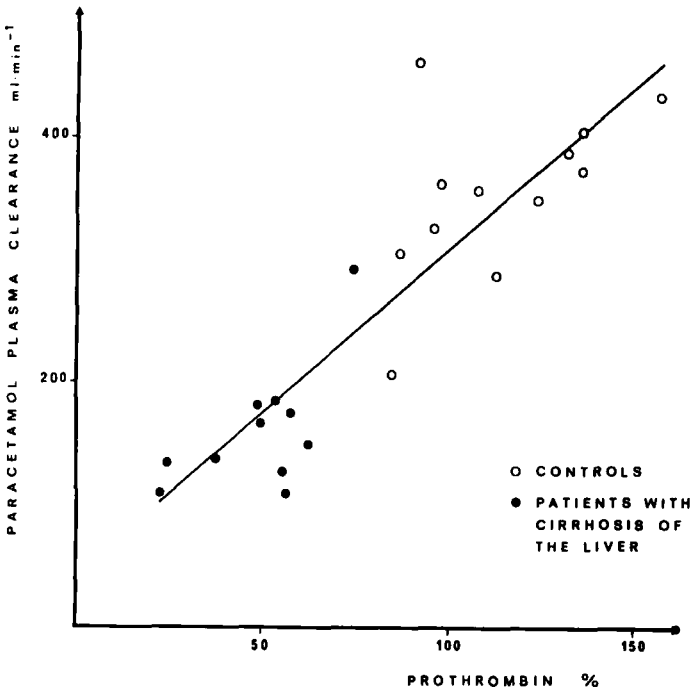

Fig. 4. The relationship between the plasma clearances of paracetamol and prothrombin levels in 11 patients with hepatic cirrhosis and 12 controls.

ses, alkaline phosphatases, prothrombin time or serum bilirubin were not observed during the study.

DISCUSSION

Paracetamol is widely used as an over-the-counter analgesic either as a single entity or in fixed combinations. Accordingly, patients with liver disease will receive the drug even if doctors are reluctant to prescribe paracetamol to this category of patients (10).

In spite of the well-known hepatotoxicity of paracetamol taken in overdosage, the acute or chronic risk of using paracetamol as analgesic treatment in patients with liver disease has not been studied systematically.

Our study shows that the plasma half-life of paracetamol is prolonged from in average 2.1 hours in control patients to 3.7 hours in patients with hepatic cirrhosis in agreement with the recent work of Forrest et al. (5). The more severe the degree of impairment of hepatic function as estimated by the prothrombin level in the blood, the galactose elimination capacity or the plasma clearance of phenazon, the more reduced the plasma clearance of paracetamol. However, the plasma clearance of the drug can not be considered to be identical to the hepatic clearance, although the present knowledge about the pharmacokinetics of paracetamol makes it probable that its plasma clearance is largely an expression of its rate of hepatic metabolism. An error in the calculation of the plasma clearance of paracetamol may be introduced if the drug is incompletely absorbed. Previous studies have found that around 90 % of a single dose of 1.0 gram reaches the systemic circulation in normals (16).

The hepatic extraction ratio may be estimated to around 0.2–0.3 in normal persons and therefore, a certain flow-dependency of hepatic elimination should be expected. The possibility for dose-dependent "first-pass" elimination of paracetamol has been propagated by some authors (16).

Another factor, that is not taken into account is the possible contribution of extrahepatic metabolism, e. g. glucuronidation or sulfation for the rate of clearance of paracetamol. Moreover, in normals around 2 % of the drug is excreted unchanged in the urine during the first 24 hours (11).

Paracetamol is less than 50 % bound to plasma proteins and changes in degree of protein-binding as a consequence of the liver-disease would

not be expected to interfere with the estimated plasma clearance of paracetamol (19).

The decreased plasma clearance of paracetamol in the patients with cirrhosis of the liver may partly be due to ineffective hepatic perfusion in our patients. Seven of 11 patients had ascites and in these patients intrahepatic or extrahepatic shunting may be expected to occur. However, the principal factor accounting for the decreased rate of clearance of paracetamol should be explained by a reduced rate of hepatic metabolism.

We observed no accumulation of paracetamol in the blood during five days of oral administration. However, the plasma levels were 2–3 times higher in the patients with cirrhosis of the liver indicating that a corresponding reduction may be recommended in patients with cirrhosis of the liver. It should be stressed that a study of the relationship between plasma levels of paracetamol and analgesic effect has not been performed and even in patients with normal liver function has the optimal therapeutic level of the drug not yet been established (10).

The intraindividual reproducibility of the estimation of paracetamol half-lives before and after subchronic dosage of paracetamol indicates the reliability of the half-life determination and furthermore that auto-induction does not occur.

A recent report indicates that some patients with liver disease may be susceptible to develop liver damage following therapeutic dosages of paracetamol (2). The possible role of concomitant protein deficiency or alcoholism may be difficult to discriminate from the effect of the liver disease itself.

Preliminary results of analysis of the urinary excretion of paracetamol and its conjugated metabolites show a decreased excretion of the glucuronide conjugate in patients with hepatic cirrhosis (P. B. Andreasen, L. Hutters, E. Dybing and S. D Nelson, unpublished).

In a recent study in patients with liver damage induced by paracetamol overdosage, a decrease in the sulfate conjugate was found, whereas the glucuronide conjugate excretion was unchanged (8).

However, the renal excretion of the cysteine and mercapturic acid conjugate is of special toxicological interest. Conjugation of a highly reactive metabolite of paracetamol with glutathione and cysteine is believed to be decisive for protecting the human liver against nucleophilic attack of macromolecules at lower doses of paracetamol (11).

The rate of cytochrome P-450 mediated hydroxylation of drugs has been reported to be decreased in patients with hepatic cirrhosis reflecting the severity of the metabolic derangement of the liver (1, 3, 6, 9). Thus, the rate of formation of the toxic metabolite may actually be reduced in patients with cirrhosis of the lever. On the other hand, no data have been published about the glutathione content or the glutathione synthetizing capacity of the diseased liver. At the moment, therefore, neither clinical evidence nor biochemical studies allow any definite conclusion concerning an enhanced risk of patients with liver disease to develop paracetamol hepatotoxicity.

Further studies should be designed to establish genetic or environmental factors affecting paracetamol metabolism to identify possible risk groups. Furthermore, a long-term study of patients with liver disease receiving paracetamol for conditions demanding analgesic therapy is needed.

ACKNOWLEDGEMENT

The expert technical assistance of Mrs. B. Korsholm is very much appreciated.

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