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Cimetidine clearance and bioavailability in hepatic cirrhosis

Nine patients with compensated alcoholic and nonalcoholic cirrhosis of the liver and 11 patients with peptic ulcer received 200 mg of cimetidine orally and intravenously. No differences were observed in cimetidine clearance between the group with peptic ulcer (556 ± 44 ml/min, $\bar{x}$ ± SEM) and the group with cirrhosis (606 ± 64 ml/min). The bioavailability of cimetidine was unchanged (84 ± 4% and 97 ± 7%). In the patients with cirrhosis, cimetidine clearance did not correlate with galactose elimination capacity or antipyrine clearance. Cimetidine clearance was related to creatinine clearance only when both groups were considered. A reduction of cimetidine dose in patients with compensated cirrhosis appears unwarranted.

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Cimetidine is widely used in the treatment of peptic ulcer disease and upper gastrointestinal bleeding complicating liver disease. Its kinetic properties in man have been investigated.[4-6, 18, 19] Cimetidine is mainly excreted unchanged by glomerular filtration but a significant part is metabolized. Incomplete absorption or hepatic first-pass effect has been suggested to explain that less unchanged drug is excreted after oral than intravenous doses.[17, 19] Cimetidine side effects have been reported in patients with renal and hepatic dysfunction, and a reduction in dose has been recommended for them.[13]

Our study was designed to investigate the bioavailability and elimination kinetics of cimetidine after single oral and intravenous doses in patients with alcoholic or nonalcoholic cirrhosis in order to evaluate the need for adjustment of dose recommendation in such patients.

Materials and methods

Our subjects were nine patients with cirrhosis of the liver and 11 otherwise healthy control patients with peptic ulcer disease. Cirrhosis of the liver was confirmed by needle biopsy. None of the liver patients had ascites or encephalopathy. In one patient (K. J. C.), an end-to-side portacaval anastomosis had been performed several years prior to this study. Table I gives the clinical and laboratory data in the patients with cirrhosis and a list of concomitant medication. Liver function was evaluated quantitatively by estimation of the galactose elimination capacity[18] and the antipyrine clearance.[1]

In the controls peptic ulcer disease was confirmed by endoscopy. Three patients had

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Table I. *Clinical and laboratory data in patients with cirrhosis*

Subject	*Age/Sex*	*Body weight (kg)*	*Diagnosis*	*Plasma albumin (μmole × l⁻¹)*	*Prothrombin index*
E. C. U.	55/F	47	Alcoholic cirrhosis	500	56
J. A. M.	45/M	111	—	321	48
A. B. J.	46/M	105	—	350	61
C. C.	51/M	73	—	425	43
K. J. C.	61/M	88	—	473	65
S. G. E.	66/M	91	—	445	36
L. B. A.	51/F	45	Cryptogenic cirrhosis	378	69
S. D. T.	76/F	80	—	460	109
K. J.	60/M	57	—	587	121
$\bar{x}$ ± SEM		77 ± 8		438 ± 27	68 ± 23

Table II. *Kinetic parameters of nine patients with cirrhosis after single oral and intravenous cimetidine 200 mg: Quantitative liver function tests and galactose elimination*

	Oral		*Intravenous*			
Subject	*t½ (min)*	*AUC (mg × min × ml⁻¹)*	*t½ (min)*	*AUC (mg × min × ml⁻¹)*	*F (%)*	*Intravenous clearance (ml × min⁻¹)*
E. C. U.	103	305.0	103	341.3	89	586
J. A. M.	184	276.9	125	308.4	90	649
A. B. J.	111	272.8	98	256.1	107	781
C. C.	133	201.6	117	340.1	59	588
K. J. C.	120	192.9	117	247.2	78	809
S. G. E.	161	451.0	147	476.1	95	420
L. B. A.	77	292.4	81	226.4	129	883
S. D. T.	130	631.7	124	565.5	112	353
K. J.	139	393.6	153	515.5	76	388
x ± SEM	129 ± 11	335.3 ± 46.1	118 ± 8	364.1 ± 41.6	93 ± 7	606 ± 64

gastric and eight, duodenal ulcers. None had previously undergone biliary or gastric surgery. All results of routine laboratory tests in the controls were normal, and only one patient (J. P. K.) received daily medication (prednisone and theophylline). The mean age was 50 yr (range 21 to 71) and the mean body weight, 63 kg (range 46 to 80).

At 8 A.M. the subjects received 200 mg cimetidine orally or intravenously. Oral and intravenous doses were separated by 1 day and given in random order. The patients fasted 10 hr before cimetidine and for the following 2 hr. Heparinized blood samples were drawn before and at 20, 40, 80, 120, 240, 300, 380, 460, 540, and 620 min after the drug.

Plasma was separated immediately and kept frozen at −18° until subsequent analysis. Cimetidine in plasma was assayed by liquid chromatography.[10] The elimination half-life (t½) after oral and intravenous doses of cimetidine was estimated from the terminal part of the

Bilirubin (*μmole* × l^{-1})	*Concomitant medication*
4	Metoprolol Diazepam Levoprometazin
33	Spironolactone Bumetanide
35	Bumetanide Spironolactone Bendroflumethiazide
29	Bumetanide Diazepam
12	—
142	Propanolol Allopurinol
8	Prednisone Bendroflumethiazide
13	Prednisone
11	Nitrazepam Bendroflumethiazide
32 ± 14	

Creatinine clearance (*ml* × min^{-1})	*Antipyrine clearance* (*ml* × min^{-1})	*Galactose elimination capacity* (*mmole* × min^{-1})
67	41.5	1.87
65	24.0	1.81
86	19.2	1.41
107	9.1	1.06
120	25.3	1.79
60	11.7	1.23
56	40.0	1.63
55	13.2	1.42
44	47.5	1.42
73 ± 8	25.7 ± 4.7	1.52 ± 0.09

plasma concentration:time curve using regression analysis. The terminal part of the curve was defined to begin 2 hr after intravenous doses and at the second sample point following the peak plasma concentration after oral doses. In case of a second peak this was used. The lower limit for safe quantitation was 0.15 μg/ml and all concentrations below it were rejected.

The area under the plasma concentration:time curve (AUC) was calculated according to the trapezoidal rule. Residual area up to infinite time was estimated assuming first-order kinetics. Further calculations were made from the following formulas:

$$\text{Bioavailability (F)} = \frac{AUC_{oral} \cdot 100}{AUC_{iv}} \quad (1)$$

$$\text{Plasma clearance (Cl)} = \frac{Dose_{iv}}{AUC_{iv}} \quad (2)$$

All statistical calculations were performed as indicated by Armitage[2]; p values under 0.05 were taken to indicate statistical significance.

Results

Mean plasma concentration:time curves in cirrhotics and controls after oral and intravenous doses of cimetidine are shown in Figs. 1 and 2. Five subjects among the liver patients and four in the control group exhibited two peaks in their curves after oral doses. The second peak appeared either at the 120- or the 180-min sample point.

The kinetic parameters, quantitative liver function tests, and creatinine clearance of the cirrhotic patients are shown in Table II. Results of the control patients are given in Table III. There was no difference between the control group and the group of cirrhotics with regard to cimetidine clearance (556 ± 44 ml/min and 606 ± 64, $\bar{x}$ ± SEM), cimetidine bioavailability (84 ± 4% and 93 ± 7%), or creatinine clearance (95 ± 10 and 73 ± 8 ml/min). Neither the intravenous nor the oral elimination t½s differed (138 ± 7 and 118 ± 8 min; 157 ± 10 and 129 ± 11 min) (Student's t tests). In three patients with cirrhosis and two with peptic ulcer, bioavailability (F) exceeded 100% (range 105% to 129%). The residual area up to infinite time slightly exceeded 10% of the total AUC in two of the liver patients and in one of the controls.

The correlation coefficients between the prothrombin index and the cimetidine clearance (r = 0.40), between galactose elimination and cimetidine clearance (r = 0.42), and between antipyrine clearance and cimetidine clearance (r = 0.12) did not differ significantly from zero. The linear regressions of cimetidine clearance on creatinine clearance in the control group and the cirrhotic group (Fig. 3) were indistinguishable with regard to slope (regression

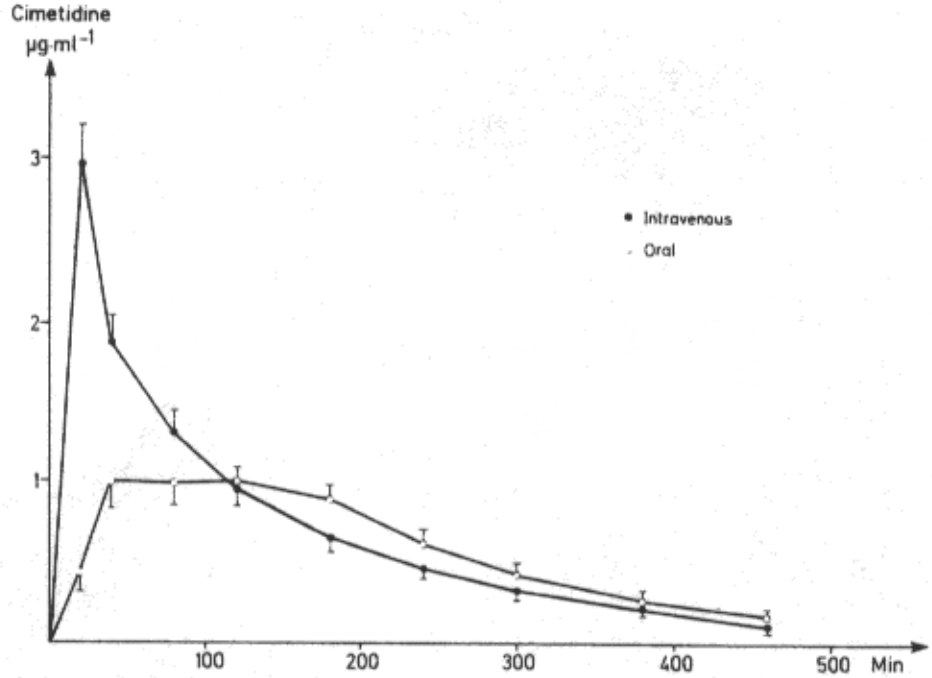

Fig. 1. Mean plasma concentration curves in nine patients with cirrhosis after single oral and intravenous doses of cimetidine 200 mg.

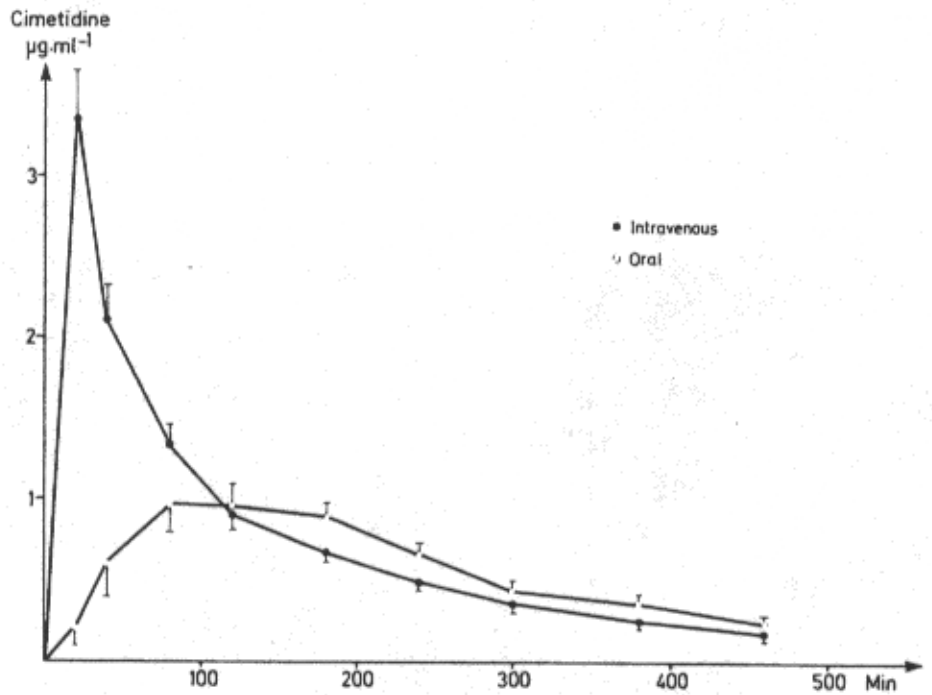

Fig. 2. Mean plasma concentration curves in 11 patients with peptic ulcer disease after single oral and intravenous doses of cimetidine 200 mg.

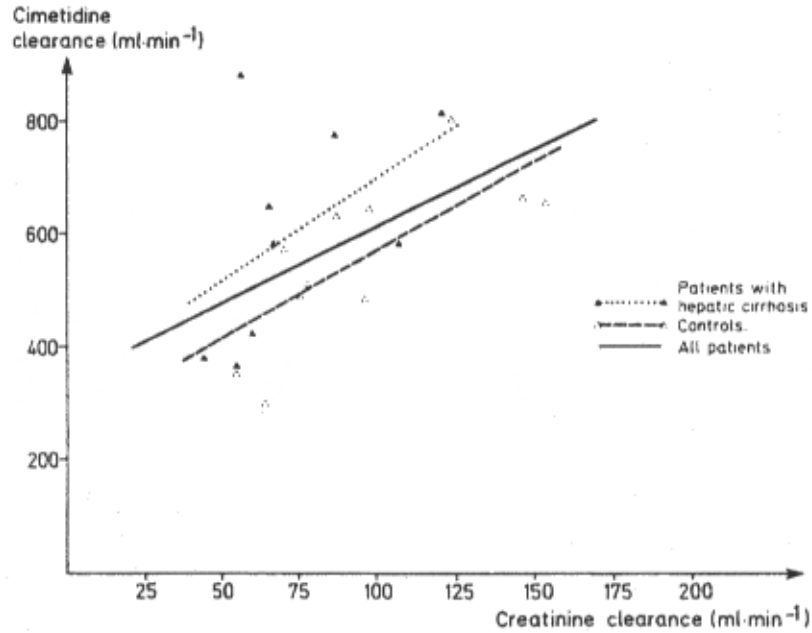

Fig. 3. Linear regressions of cimetidine clearance on creatinine clearance in nine patients with cirrhosis and 11 with peptic ulcer after cimetidine 200 mg intravenously.

in groups, $p = 0.61$) and intercept (analysis of covariance, $p = 0.17$) but the correlation coefficient of the two groups ($r = 0.54$) taken together is significant ($p = 0.002$).

Multiple linear regression of cimetidine clearance on creatinine clearance and galactose elimination capacity in the cirrhotic patients did not improve the fit as judged by the residual variance.

Discussion

In our study no apparent differences in bioavailability and plasma clearance of cimetidine were demonstrated in patients with compensated cirrhosis of the liver and otherwise healthy subjects with peptic ulcer disease, nor did a portacaval anastomosis appear to influence the kinetics of cimetidine.

The elimination t½ and the plasma clearance values of cimetidine after intravenous doses are compatible with other reports.[1–6, 16, 19] The presence of double peaks of the plasma concentration: time curves after oral doses has been reported.[3, 5, 6, 19] In one paper this finding was attributed to food[16] but our results do not support this hypothesis because the second peak appeared mostly at the 120-min sample point before food was eaten.

The bioavailability of cimetidine has been reported to be about 70%.[6, 15] Our results show slightly higher values. In five subjects percentages were above 100, an observation in agreement with a recent study.[5] An enterohepatic circulation of cimetidine has been suggested to account for these findings. The occurrence of double plasma concentration peaks is compatible with this explanation or with a delayed gastrointestinal absorption. Another explanation may be extrapolation of the initial part of the intravenous plasma concentration curve, by which the AUC_{iv} may be underestimated because the earliest plasma samples were drawn at 20 min.

Two studies in the rat have indicated an interaction of cimetidine with drugs that undergo hepatic microsomal drug metabolism.[11, 12] Cimetidine has been shown to inhibit the metabolism of oral anticoagulants[7, 14, 15] and diazepam in man[9] by this mechanism. Our patients were in a stable condition but received medication

Table III. *Kinetic, cimetidine, and creatinine clearance parameters in 11 patients with peptic ulcer after single oral and intravenous cimetidine 200 mg*

	Oral		*Intravenous*		
Subject	*t½ (min)*	*AUC (mg × min × ml⁻¹)*	*t½ (min)*	*AUC (mg × min × ml⁻¹)*	*F (%)*
R. P.	139	289.0	115	411.9	70
H. K.	131	327.6	162	391.8	84
P. J.	119	328.6	138	344.8	97
M. L. L.	140	594.9	144	569.4	105
L. S.	174	311.8	119	404.0	77
K. H. L.	171	290.7	159	313.6	93
O. P.	208	201.9	164	299.8	67
C. B.	137	198.2	96	249.5	79
K. M.	177	243.8	149	318.6	77
E. N.	210	490.5	158	660.3	74
J. P. K.	124	332.3	117	303.0	109
$\bar{x}$ ± SEM	157 ± 10	328.1 ± 35.8	138 ± 7	381.9 ± 37.4	84 ± 4

that might interfere with the hepatic metabolism of cimetidine, e.g., diazepam, prednisone, and spironolactone.

A decrease in antipyrine clearance after cimetidine has been reported[9, 14] but the simultaneous use of cimetidine and antipyrine might alter the elimination of cimetidine in a competitive way. We found no difference in cimetidine t½ and AUC when cimetidine was taken with antipyrine.

Our patients had a variable but moderate reduction in hepatocellular function. No consistent relationship between the degree of reduction of quantitative liver function and the clearance of cimetidine was established.

A reduction of cimetidine dose in patients with compensated hepatic cirrhosis, accordingly, appears unwarranted. Our study does not permit any conclusion about the use of cimetidine in patients with hepatic encephalopathy because we studied only patients with stable and accordingly compensated cirrhosis. We did not observe any side effects after single doses of cimetidine but our study does not exclude the possibility that increased sensitivity to cimetidine in patients with liver disease might play a role after a series of doses.[8]

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Intravenous clearance ($ml \times min^{-1}$)	*Creatinine clearance* ($ml \times min^{-1}$)
486	96
511	78
580	70
351	55
495	75
638	97
667	146
802	123
628	87
303	64
660	153
556 ± 44	95 ± 10

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