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Cimetidine Disposition in Patients with Laennec's Cirrhosis During Multiple Dosing Therapy

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Summary. The disposition of cimetidine after oral and intravenous administration during multiple dosing was studied in 11 patients with Laennec's cirrhosis. The average metabolic clearance of cimetidine in these patients was 15 l/h, similar to values reported for normal subjects. However, in 4 subjects with plasma prothrombin times above normal, the metabolic clearance was significantly decreased and ranged between 4.3 and 13.0 l/h. The renal clearance of cimetidine was proportional to the creatinine clearance in all subjects, regardless of the severity of the liver disease. The clearance of cimetidine in patients with Laennec's cirrhosis, therefore, appears to be predictabable from creatinine clearance and prothrombin time.

Key words: cimetidine, alcoholic cirrhosis, multiple dosing, pharmacokinetics

Administration of cimetidine to patients with Laennec's cirrhosis poses several potential problems for the clinician. The assessment of overdosing and toxic reaction is rendered particularly difficult because both the disease state itself and the overdose/toxic reaction may involve the central nervous system. What might be mental confusion and hallucinations from cimetidine administration [1–4] may well be thought to be hepatic encephalopathy [5]. The frequency of cimetidine toxic reactions appears to increase when renal dysfunction and multiple organ dysfunction occur [4]. In addition, the blood-brain barrier permeability of cimetidine appears to be increased in patients with cirrhosis, resulting in an increased central nervous system plasma concentration ratio [6].

The bioavailability is reported to be higher in patients with alcoholic cirrhosis than in normal subjects after single dosing studies [7]. The total plasma clearances appear to be similar, although the nonrenal clearances are lower than in normal subjects [7]. Comparing normal subjects and patients with compensated alcoholic cirrhosis, no differences in bioavailability or elimination were found [8].

The higher bioavailability could explain why elevated cimetidine plasma levels have been reported for cirrhotic patients receiving chronic cimetidine therapy [9]. However, several other potential reasons for such increases in plasma concentration during mulitple dosing may exist. Hepatic blood flow may be decreased after cimetidine therapy [10], thereby causing a decreased hepatic elimination of cimetidine. This hypothesis, however, has recently been questioned [11, 12]. Cimetidine is also know to inhibit the metabolism of a number of drugs [13–17] and may well also inhibit its own metabolism as well as be responsible for the observed deterioration of renal function upon multiple dosing [18–20] and cause damage to the liver with resulting hepatitis [21–23].

This study was, therefore, undertaken to assess the disposition of cimetidine in patients with varying degrees of alcoholic cirrhosis receiving chronic cimetidine therapy.

Material and Methods

Subjects

Eleven stable patients with biopsy-proven Laennec's cirrhosis who were already receiving cimetidine (300 mg q. i. d.) for peptic ulcer disease were electively admitted to the General Clinical Research Center (GCRC) at San Francisco General Hospital. All pat-

ients had received cimetidine for at least one week preceding the study. To ensure compliance with the dosing schedule, the subjects were admitted to the GCRC one day prior to the study.

On the morning of the study, the subjects first received their usual 300-mg oral dose of cimetidine. A 9-ml blood sample was obtained in redtop Vacutainers[1] at 10 min before and again at 15, 30, 45, 60, 90, 120, 180, 300, and 360 min after dosing. At their next scheduled dose, their regular oral dose was substituted with a 300-mg intravenous dose of cimetidine given as an intravenous infusion over 15 min. A 9-ml blood sample was obtained at 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after the end of the infusion, at which time the regular oral cimetidine dosing therapy was resumed. The patients were fasted from 6 p.m. on the day prior to the study until 3 h into the oral study period.

The blood samples were allowed to clot and were centrifuged, the serum removed, and stored frozen at −20 °C until assayed.

Urine was collected every 2 h throughout the study. Urine volume and urine pH were measured and an aliquot was stored frozen at −20 °C until assayed.

The study protocol was approved by the Committee on Human Research at the University of California, San Francisco, August 1980.

Assay Procedure

Plasma and urine were assayed using the liquid chromatographic method described below.

Plasma. Two hundred µl of patient serum of standard (0.6–10 µg/ml cimetidine in human serum) were mixed with 150 µl 500 ng/ml RO7-1051 (Hoffman-La Roche, Nutley, New Jersey) in 50% methanol as internal standard and the serum protein precipitated with 2 ml acetonitrile. The mixture was vortexed for 30 s and centrifuged at 300 g for 10 min. The supernatant was removed and evaporated to dryness using a gentle stream of nitrogen. The residue was dissolved in 200 µl mobile phase consisting of 30% methanol in 0.013 M phosphate buffer, pH 6.8. Fifty µl of this solution was then injected onto a 150-cm, 4.6-nm bore Ultrasphere C-18 column[2] and eluted with the mobile phase at a rate of 1.5 ml/min using a Beckman Model 110 A high pressure liquid chromatographic pump[3]. The absorption of the eluent was determined at 220 nm using a Hitachi Model 100-30 spectrophotometer[2].

Urine. Urine or aqueous cimetidine standards were first extracted by mixing 25 µl urine or standard, 100 µl internal standard (250 ng/ml RO7-1051) and 50 µl 5N sodium hydroxide with 10 ml ethyl acetate. The mixture was vortexed for 30 s and centrifuged at 300 g for 10 min. The ethyl acetate layer was removed and evaporated to dryness under a gentle stream of nitrogen. The residue was then treated as described above.

Data Treatment. A two-compartment model was fitted to the plasma concentration-time data after the intravenous administration of cimetidine using the program, DRUGFUN [24], available through the PROPHET computer system [25], adjusting for the initial concentration, assuming it to be in the post-absorptive, post-distributional phase of oral administration. The area under the plasma concentration-time curves was obtained using the linear trapezoidal rule during the absorption phase and infusion phase, and the log-trapezoidal rule during the elimination phase [26].

The clearance was obtained by dividing the amount given intravenously by the area under the plasma concentration-time curve from the time the i.v. dose was given until the time the plasma concentration again reached the initial concentration. When the concentration equals the initial concentration, the amount eliminated equals the amount administered. In all 11 subjects this phenomenon occurred between 4 and 6 h after the intravenous dose was given.

The renal clearance was obtained by dividing the total amount of cimetidine recovered unchanged in the urine by the area under the plasma concentration-time curve. This value for renal clearance is the time-averaged value. The renal clearance for each individual urinary collection period was obtained by dividing the amount excreted unchanged in the urine by the area under the plasma concentration-time curve for the same period.

Metabolic clearance was calculated as the difference between the total and renal clearance.

Bioavailability was determined from the ratio of the area under the plasma concentration-time curve from the oral and i.v. curves. The areas were determined by taking the area under the plasma concentration-time curves from the time of administration of the respective doses until the time the plasma concentrations again reached a value identical to the initial concentration. At this point in time, the amount in the body is identical to the amount in the body be-

[1] Becton-Dickinson, Rutherford, New Jersey
[2] Altex, Berkeley, California
[3] Beckman, Berkeley, California

Table 1. Clinical laboratory data for the Laennec's cirrhotic patients

Subject [Nos.]	Age [years]	Weight [kg]	Creatinine clearance [ml/min]	Albumin [μM]	Total bilirubin [μM]	Direct bilirubin [μM]	Alkaline phosphatase [IU/l]	[1]LDH [IU/l]	Prothrombin time [s]	[2]Child's classification
1	28	72	146	390	70	44	644	313	11.5	C
2	47	55	97	460	55	46	248	290	11.0	C
3	57	79	64	570	60	29	111	145	13.5	C
4	28	83	90	260	65	39	246	121	12.5	C
5	32	81	110	570	48	32	317	245	11.4	B
6	27	74	108	490	9	5	163	198	10.7	A
7	39	106	56	380	140	75	342	240	12.8	C
8	52	67	100	390	275	255	570	302	11.7	C
9	51	121	50	350	50	29	191	341	13.4	C
10	44	47	69	460	17	5	178	189	9.6	B
11	44	75	83	550	17	5	193	180	10.2	A

[1] Lactate dehydrogenase; [2] reference [38]

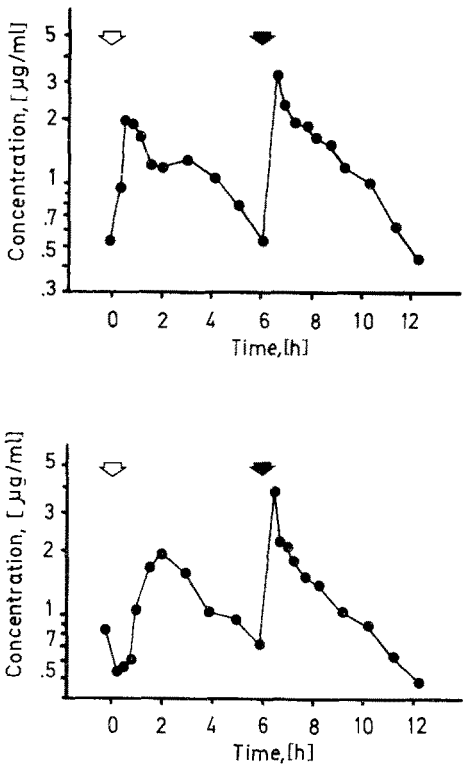

Fig. 1. Plasma concentration time data from two representative subjects. Open arrows represent administration of 300-mg oral maintenance dose: closed arrows, the start of 15-min, 300-mg intravenous infusion. *Upper panel.* Typical profile from a Subject (No. 11) having a double peak during oral dosing. *Lower panel.* Typical profile from a Subject (No. 6) having a delay in absorption. No double peak is apparent

fore the oral dose administration, and the amount lost must, therefore, be equal to the amount of drug delivered to the general circulation.

In 7 of 11 subjects, the oral concentration-time curve had to be extrapolated to reach a concentration equal to the starting concentration. This was achieved by using the last concentration from the oral administration and the terminal rate constant obtained from the i. v. bolus dose.

The volume of distribution of the central compartment and the steady-state apparent volume of distribution were obtained from two-compartment model parameters according to Gibaldi and Perrier [27].

Correlation between the various pharmacokinetic parameters and the laboratory data was carried out using the mulitple correlation program, MULTIPLE [28], which is also available through the PROPHET computer system [25].

Results

Clinical and routine laboratory data for the 11 subjects studied are presented in Table 1. No patient was obtunded or had asterixis during the study period.

Typical plasma concentration-time plots of cimetidine during the study period are given in Fig. 1 for two representative subjects. Eight of the 11 subjects showed two concentration peaks during the oral administration (Fig. 1, upper panel). The second peak coincided with the first meal during the study period as is consistent with enterohepatic recycling of cimetidine [29]. Similar peaks after the later meals during the study period were discernible as small peaks in only four patients. Four of the subjects, including all three who did not show double peaks after the oral administration, demonstrated delay in the absorption of cimetidine (Fig. 1, lower panel).

The concentration-time data after intravenous administration of cimetidine were consistent with two-compartment disposition characteristics and the

Table 2. Pharmacokinetic[1] parameters of cimetidine in Laennec's cirrhotic patients

Subject [Nos.]	λ_1 [h^{-1}]	λ_2 [h^{-1}]	Cl [l/h]	Cl_R [l/h]	Cl_M [l/h]	V_c [l/kg]	V_{ss} [l/kg]	F	fe
1	1.8	0.474	61.6	37.3	24.3	0.68	1.00	0.97	0.61
2	2.3	0.281	37.4	17.9	19.5	0.60	1.49	0.97	0.48
3	5.0	0.160	15.5	11.2	4.3	0.44	1.03	0.59	0.72
4	6.1	0.294	29.1	19.2	9.9	0.10	0.54	0.48	0.66
5	1.6	0.208	45.7	20.3	25.4	0.58	1.41	1.00	0.44
6	3.8	0.271	41.6	22.0	19.4	0.49	1.55	0.98	0.53
7	3.1	0.188	23.3	10.3	13.0	0.26	0.84	0.90	0.43
8	1.5	0.154	35.4	20.9	14.5	0.69	1.97	1.07	0.59
9	1.6	0.142	16.8	10.6	6.2	0.49	0.95	0.95	0.63
10	2.6	0.210	33.1	13.7	19.4	0.68	2.70	1.10	0.41
11	5.4	0.273	40.3	17.1	23.2	0.40	1.48	0.96	0.42
Mean	3.2	0.241	34.5	18.2	16.3	0.49	1.36	0.91	0.54
±SEM	0.5	0.029	4.0	2.3	2.2	0.06	0.60	0.06	0.033

[1] λ_1 and λ_2 are the fast and slow rate constants in the concentration versus time curve; Cl – total clearance; Cl_R – metabolic clearance; V_c – apparent volume of distribution of the central compartment; V_{ss} – steady-state apparent volume of distribution; F – bioavailability; fe – fraction excreted unchanged in the urine

various pharmacokinetic parameters obtained by fitting a 2-compartment model to the data are given in Table 2.

The metabolic clearance was found to be highly correlated with the observed prothrombin time ($r^2 = 0.643$, $p = 0.0024$; Fig. 2). A large part of the residual sums of square of the metabolic clearance could be removed by incorporating creatinine clearance ($r^2 = 0.813$, $p = 0.0012$). Inclusion of age, total serum bilirubin concentration, serum albumin concentration, alkaline phosphatase, or lactase dehydrogenase values only marginally decreased the residual sums of square (increased the p-value).

Variability in renal clearance could, on the other hand, be primarily explained as a variability in creatinine clearance ($r^2 = 0.923$, $p = 0.0001$; Fig. 3). By including albumin concentration in the correlation, the residual sums of squares could be reduced by approximately 1.3 ($r^2 = 0.947$, $p = 0.0001$). Inclusion of age, weight, bilirubin concentration, prothrombin time, uric acid concentration, urine flow, and urine pH only marginally reduced the residual sums of square.

The renal clearance was determined throughout the study period every 2 h. Renal clearance usually varied throughout the study, but no correlation between urine flow and urine pH could be established (data not reported). Furthermore, no statistically significant differences in renal clearance between the oral and i.v. doses could be ascertained.

Bioavailability of cimetidine upon multiple dosing averaged 91% in these patients (Table 2) and ranged from a low value of 48% to a high value of 110%.

Discussion

A substantial variation in both renal and metabolic clearances was observed among the patients. The renal clearances varied approximately four-fold and the metabolic clearances approximately six-fold. The variation is, however, similar to that previously reported in normal subjects [30–32], as well as in alcoholic cirrhosis subjects [7]. The total clearance is, on the average, not different from values reported in single-dose experiments in alcoholic cirrhosis subjects, both compensated and non-compensated, and in normal subjects (33–52 l/h [7, 8, 30, 31, 33]). Interesting to note, however, is that the fraction of drug excreted unchanged in the urine is 0.54, which suggests that hepatic and renal elimination contribute approximately equally to the overall elimination in these subjects. In other studies, the fraction excreted unchanged has been reported to vary between 0.60 and 0.77 on the average, both in normal and alcoholic cirrhosis patients, after single intravenous dosing [7, 30, 34, 35]. With constant attendance of nursing staff during the relatively short study period (6 h for each dose interval), the recovery of urine is likely to be complete for these subjects. To verify further the completeness of urine collection, the amount of cimetidine sulfoxide excreted in the urine was determined. The fraction of the dose excreted as cimetidine sulfoxide varied fram a low of 0.06 in Subject No. 9 to a high of 0.20 in Subject No. 4 with an average value of 0.13. This is similar to the fraction of 0.11–0.13 of intravenously administered cimetidine that was recovered as cimetidine sulfoxide in normal subjects [7, 34], but higher than what was found in al-

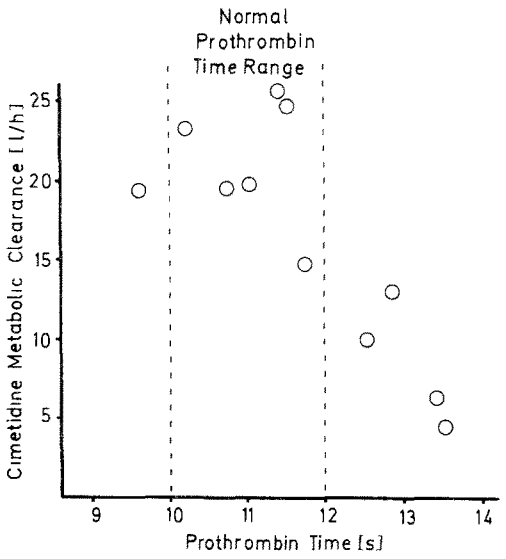

Fig. 2. Plot of cimetidine metabolic clearance as a function of prothrombin time. Stippled lines indicate the normal range for San Francisco General Hospital Laboratory

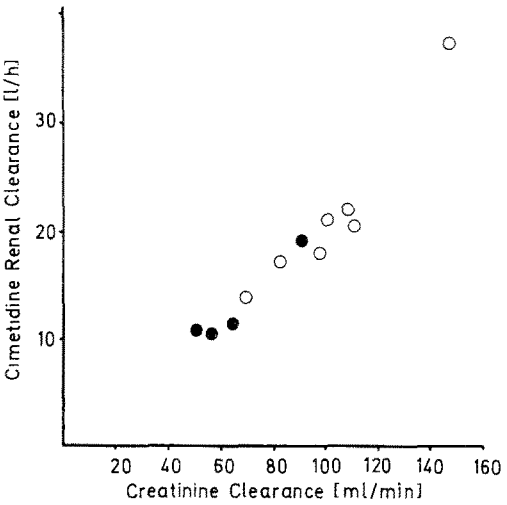

Fig. 3. Plot of cimetidine renal clearance as a function of creatinine clearance. (●) Patients with lower-than-normal creatinine clearance for age and weight. (○) Patients with normal creatinine clearance for age and weight

coholic cirrhosis patients after single dose (0.10 [7]). Because the amount of metabolite recovered was at least as high as expected, the urinary recovery during the study period is assumed to be complete.

Renal clearance of cimetidine was found to be dependent mainly upon overall renal function as estimated by creatinine clearance (Fig. 3). This result is similar to that found in patients having reduced renal function [36, 37]. The renal clearance of cimetidine in the present work also correlated inversely with the albumin concentration; however, albumin concentration was found to be only a marginal determinant in explaining the change in renal clearance. As the binding of cimetidine to plasma proteins was < 0.05 in these subjects (data not reported), the correlation with albumin concentration is unlikely to be due to binding differences. Instead, it may act as an indicator of potential concomitant deterioration of renal function. However, other determinants of liver function as prothrombin time and serum bilirubin concentration did not correlate with renal clearance values. Creatinine clearance was substantially decreased from expected values based upon age and weight [38] in only a few cases (Subjects No. 3, 4, 7, and 9). However, the decrease was not sufficient to label these subjects as renal failure patients (see Table 1). In these four subjects (all Child's Class C [39] with ascites), the reduced creatinine clearance is conceivably secondary to the severe hepatic cirrhosis. It appears, therefore, that renal elimination of cimetidine will be reduced in patients with cirrhosis only in those with compromised renal function.

Metabolic clearance of cimetidine was strongly correlated with the plasma prothrombin time. Including creatinine clearance of the subjects in the correlation between clinical parameters and metabolic clearance of cimetidine, the predictability of metabolic clearance increased. All subjects admitted to the hospital with an abnormally high prothombin time (> 12 s) were treated with 10 mg vitamin K daily, for three days prior to the study, as part of their routine medical care. The reported prothombin time, therefore, does not represent a dietary effect, but rather the intrinsic ability to form clotting factors in the patients. Only four of the Subjects (No. 3, 4, 7, and 9) had elevated prothombin times during the study. These four subjects also had the lowest metabolic clearance (see Fig. 2) and the results suggest that an elevated prothrombin time in cirrhotic patients is a strong indicator of a reduced metabilic clearance of cimetidine.

Why creatinine clearance also appears to explain some of the variability in metabolic clearance may not seem quite as obvious. However, upon scrutinizing the data, one can see that the four Subjects with lower creatinine clearance for age and weight (Nos. 3, 4, 7, and 9) are the same subjects who had the lowest metabolic clearances of cimetidine and highest prothrombin times (Tables 1 and 2). This suggests that in these particular patients, the reduced creatinine clearance may not be an indicator of primary renal dysfunction, but rather indicative of the severity of the underlying liver disease (i.e., early hepatorenal syndrome).

The bioavailability of cimetidine in this patient population is 0.91. These values are similar to values found in compensated alcoholic cirrhosis patients

(0.93) after single doses [8], but higher than has been reported for normal subjects (0.60–0.84 [7, 33, 35]), and for cirrhotic patients given single dose (0.77 [7]). However, we would like to point out that because of the study design the bioavailability may have been overestimated and the data, therefore, need to be interpreted cautiously. The subjects studied had been fasting 12–14 h prior to the start of the oral study, but not before the intravenous study. This could lead to an accumulation of biliary-stored cimetidine [29], from perhaps more than two doses, that subsequently was released after the first oral dose was given, consistent with the double peak seen in the majority of the patients after the first meal of the day. The pharmacokinetic parameters obtained for cimetidine in this study are, in general, in good agreement with the values obtained by Gugler et al. [7] after single doses of cimetidine were administered to 14 cirrhotic patients (some, however, nonalcoholic). The only major discrepancy is a much higher metabolic clearance found in our study (16.3 versus 7.4 l/h; Student $t=3.35$; $p<0.005$). Our values (0.25 l/h/kg) are more in line with values found in normal subjects after single doses of cimetidine (0.19 l/h/kg [12]). The reason for the higher values in our study in comparison to the results of Gugler et al. [7] is unclear. The patients in our study appear to be at least as ill as those in the study by Gugler et al. All were recently admitted to our acute care medical facility for complications of alcoholic cirrhosis (intractable ascites, variceal hemorrhage or hepatic encephalopathy). They were stabilized and later transferred to the General Clinical Research Center where the disposition of cimetidine was investigated. Five of 11 had ascites in this study, versus 5 of 15 in the study by Gugler et al. The plasma bilirubin levels were higher in our patients (73 μM versus 31 μM); the albumin levels were similar (443 μM versus 463 mM), as were the alkaline phosphatase levels (291 versus 205 U/l) and the creatinine clearance (88 vs. 95 ml/min). Moreover, our results do not appear to be due to incomplete urine collection, which would result in an underestimation of renal clearance and an overestimation of metabolic clearance (see Discussion above). That multiple dosing may stimulate cimetidine metabolism is possible; however, cimetidine is a known enzyme-inhibitor [13–17] and is more likely to inhibit, rather than stimulate, its own metabolism. The only discernible difference between this study and that of Gugler et al. is our younger subject population (41 vs. 50 years). However, no statistically significant correlation was found in this study between age and metabolic clearance of cimetidine ($t=1.82$; $0.05<-p<0.10$), although such a correlation cannot be ruled out.

Based upon the limited number of subjects in this study, it appears that it may be possible to predict the renal and metabolic clearances of cimetidine in patients with Laennec's cirrhosis from information on creatinine clearance and prothombin time. However, more studies are warranted to verify this suggestion.

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