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BIOAVAILABILITY OF CIMETIDINE IN MAN

SIDNEY S. WALKENSTEIN, PH.D., JEFFREY W. DUBB, M.D., WARREN C. RANDOLPH, M.S., WILFRED J. WESTLAKE, PH.D., ROBERT M. STOTE, M.D., AND ALFRED P. INTOCCIA, PH.D.

Smith Kline & French Laboratories, and Clinical Research Unit, Presbyterian University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

The bioavailability of parenteral cimetidine was tested in 12 volunteers in a balanced three-way crossover study. Blood levels and urinary excretion were compared after intramuscular and intravenous injection and oral administration of 300 mg of cimetidine. The results indicated that the intramuscular and intravenous routes are virtually interchangeable for parenteral cimetidine, and that the oral liquid, although exhibiting a reduced area under the blood level curve as compared with the parenteral doses, nevertheless demonstrated equivalence with respect to the time the blood level remained above 0.5 μg per ml. The 300-mg cimetidine tablet formulation was found in another group of 12 volunteers to be bioequivalent to a 300-mg dose of oral liquid.

Cimetidine and its forerunners, burimamide and metiamide, are specific histamine H_2-receptor antagonists.[1-3] Clinical trials have shown cimetidine to be of value in the treatment of duodenal ulcer and other conditions where gastric acid is implicated.[4-6] The degree of inhibition of gastric acid by cimetidine was found to vary with drug concentrations in blood.[3, 7-9] These observations made it of interest to examine the pharmacokinetics of cimetidine after oral, intramuscular, and intravenous administration.

Materials and Methods

Twenty-four volunteers gave their informed written consent to participate in bioavailability studies approved by the Presbyterian University of Pennsylvania Medical Center Research Committee.

Parenteral study. This was a balanced three-way crossover study in which each of the 12 volunteers received each of the following regimens at 1-week intervals: regimen A: 300-mg intravenous dose, 2 ml of cimetidine parenteral dosing solution made up to 20 ml with physiological saline and administered over a 2-min period; regimen B: 300-mg intramuscular dose of cimetidine, 2 ml of parenteral dosing solution; and regimen C: 300-mg oral dose of cimetidine, 5 ml of solution followed by 240 ml of tap water. The dosing schedule is shown in table 1.

The doses were administered after an overnight fast, 2 hr before breakfast. Heparinized blood samples were taken prior to and at 1/4, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 6, 8, and 10 hr after each dose. Total urine output was collected for the 24-hr period preceding and for 24 hr after drug administration. Whole blood and urine samples were frozen as quickly as possible after collection and kept frozen until analyzed by the method of Randolph et al.[10] using a liquid chromatograph (model 1220, Perkin-Elmer Corporation, Norwalk, Conn.) equipped with a variable wavelength detector (model LC 55, Perkin-Elmer).

Laboratory determinations done on control blood samples on each dosing day, at 24 hr after each dose, and again at 1-week post-study included: complete blood count with platelet estimate, fasting blood glucose, blood urea nitrogen, alkaline phosphatase, SGOT, creatinine, uric acid, total bilirubin, sodium, potassium, chloride, and carbon dioxide. Urinalysis was also done at the same times.

The volunteers were observed for any adverse reaction for 10 hr after dosing. Blood pressure and pulse (supine and erect) were taken as follows: intravenous dosing: 0, 1, 3, 5, 15, 30, and 45 min as well as 1, 2, 3, and 10 hr; intramuscular dosing: 0, 1/2, 1, 2, 5, and 10 hr; and oral dosing: 0, 1, 5, and 10 hr.

The oral study. On the 1st week of the study 6 volunteers were given a liquid formulation (300 mg in 5-ml solution) and 6 volunteers were given the 300-mg cimetidine tablet. One week later each group received the alternate formulation. All doses were administered with 240 ml of tap water after an overnight fast, and 2 hr were allowed to pass before breakfast. Heparinized blood samples were collected before and at 1/2, 1, 1 1/2, 2, 3, 4, 6, 8, and 12 hr after the dose and complete urine collection for the two 24-hr periods preceding and following the dose. In all other respects this study was the same as the parenteral study.

Results

The Parenteral Study

Clinical observations. After intramuscular injection, 5 volunteers had arm soreness lasting 10 min to 24 hr; 2 volunteers felt arm stiffness for 15 min and 5 1/2 hr, respectively; 1 volunteer had a burning sensation at the site during injection; and 1 felt "flushed" for 1 min after injection. Symptoms with the intravenous injection lasted less than 1 min: 5 volunteers noticed an odd taste or odor, 6 volunteers had a light-headed or dizzy feeling, and 1 volunteer felt flushed.

Address requests for reprints to: Dr. Sidney S. Walkenstein, SmithKline Corporation, 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101.

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Examination of the blood pressure data revealed no clinically significant change in any volunteer. Laboratory data showed a minimal decline in hematocrit and/or hemoglobin in 8 of the volunteers during the parenteral study. These deviations were ascribed to blood drawing (approximately 200 ml per week for 3 weeks). No other significant deviations in laboratory measurements were observed.

Blood levels. After intravenous injection measurable blood levels of cimetidine were observed for 10 hr (table 2). The first sample, drawn 15 min after injection, ranged from 3.50 to 7.43 μg per ml. A steady decline in blood levels was observed at all sampling times, with one exception. Volunteer 1 exhibited an unusually sharp fall from the 15-min to the 30-min sampling time and then a rise at the 45-min period. This anomalous behavior was ascribed to an inadvertent (though unverified) labeling error. The mean half-life of drug in blood of the other 11 subjects was 1.79 hr. In most subjects, levels in excess of 0.5 μg per ml were maintained for at least 4 hr.

A similar blood level pattern was found upon intramuscular injection (table 3). The concentration of the 15-min sample averaged only 12% less than that of the corresponding intravenous sample, and values for this period ranged from 3.17 to 5.95 μg per ml. At the 4th hr the blood concentration remained above 0.5 μg per ml in most subjects at levels very similar to those after intravenous injection. Measurable levels were still found at the 10th hr, and, as in the intravenous group, these averaged less than 0.1 μg per ml. The small differences observed between intramuscular and intravenous values throughout the study indicated rapid absorption from the intramuscular injection site.

After a 300-mg dose of oral liquid (table 4) all but 4 volunteers attained or exceeded the 0.5 μg per ml blood level of cimetidine within 15 min. The mean level was

TABLE 1. *Dosing schedule: parenteral study*

Volunteer	Regimen		
	Week 1	Week 2	Week 3
1, 2	A	B	C
3, 4	C	A	B
5, 6	B	C	A
7, 8	C	B	A
9, 10	B	A	C
11, 12	A	C	B

TABLE 2. *Cimetidine blood levels after a 300-mg intravenous injection*

Subject	Concentration in whole blood (μg/ml)											
	0 hr	1/4 hr	1/2	3/4 hr	1 hr	1 1/2 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	$t^{1/2}$[a]
													hr
1	0	4.10	1.86	2.75	1.53	1.19	0.88	0.54	0.39	0.21	0.14	0.06	
2	0	5.07	3.38	2.73	2.43	1.80	1.54	0.90	0.69	0.32	0.11	Trace[b]	1.61
3	0	7.43	4.20	2.89	2.29	1.92	1.89	1.21	0.85	0.46	0.22	0.15	2.24
4	0	6.34	3.75	2.43	1.98	1.45	1.04	0.73	0.51	0.22	0.10	Trace	1.69
5	0	3.50	2.32	1.73	1.34	1.00	0.72	0.52	0.33	0.12	0.06	Trace	1.65
6	0	4.92	2.70	2.11	1.89	1.25	1.04	0.73	0.46	0.26	0.12	0.08	1.54
7	0	4.50	3.13	2.51	1.92	1.59	1.21	0.82	0.62	0.25	0.13	0.06	1.82
8	0	4.87	2.87	2.11	1.83	1.39	0.96	0.79	0.61	0.30	0.22	0.11	2.10
9	0	5.33	3.14	2.60	2.20	1.59	1.29	0.97	0.68	0.61	0.23	0.14	2.24
10	0	6.23	3.76	2.55	2.23	1.63	1.31	0.87	0.58	0.33	0.15	0.10	1.78
11	0	6.03	3.68	2.74	2.54	1.66	1.38	0.79	0.56	0.31	0.15	0.08	1.41
12	0	4.43	2.74	2.10	1.89	1.34	1.22	0.73	0.49	0.27	0.10	0.06	1.65
Mean	0	5.23	3.13	2.44	2.01	1.48	1.21	0.80	0.56	0.31	0.14	0.08	1.79

[a] Calculated from compartmental analysis (by co-author W. J. Westlake).
[b] <0.05 μg per ml.

TABLE 3. *Cimetidine blood levels after a 300-mg intramuscular injection*

Subject	Concentration in whole blood (μg/ml)											
	0 hr	1/4 hr	1/2 hr	3/4 hr	1 hr	1 1/2 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr
1	0	4.02	3.52	2.71	2.26	1.59	1.16	0.71	0.60	0.23	0.15	0.07
2	0	5.07	4.69	3.22	2.70	1.90	1.71	0.86	0.70	0.31	0.18	0.07
3	0	4.38	3.72	3.07	2.37	1.86	1.29	0.95	0.67	0.34	0.21	0.14
4	0	4.18	3.44	2.59	1.88	1.32	1.01	0.62	0.44	0.23	0.07	Trace[a]
5	0	4.74	3.37	2.55	1.89	1.26	0.99	0.78	0.40	0.18	0.07	Trace
6	0	3.99	3.54	2.55	2.35	1.78	1.48	0.81	0.62	0.32	0.15	0.08
7	0	4.41	3.98	3.17	2.44	2.27	1.88	1.07	0.77	0.39	0.18	0.11
8	0	3.17	2.82	2.09	1.87	1.53	1.43	0.82	0.55	0.27	0.13	0.07
9	0	5.95	3.93	2.98	2.16	1.58	1.46	0.92	0.67	0.35	0.21	0.11
10	0	4.92	3.86	3.18	2.37	1.43	1.25	0.83	0.58	0.31	0.16	0.07
11	0	5.11	3.92	3.35	2.46	1.77	1.56	1.00	0.69	0.31	0.14	0.07
12	0	4.84	2.92	2.05	1.72	1.27	1.14	0.67	0.44	0.20	0.09	Trace
Mean	0	4.57	3.64	2.79	2.21	1.63	1.36	0.84	0.59	0.29	0.15	0.07

[a] <0.05 μg per ml.

TABLE 4. *Cimetidine blood levels after a 300-mg dose of oral liquid*

Subject	Concentration in whole blood (μg/ml)											
	0 hr	1/4 hr	1/2 hr	3/4 hr	1 hr	1 1/2 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr
1	0	0.08	0.87	1.21	1.43	0.89	0.65	0.62	0.48	0.21	0.10	Trace[a]
2	0	0.50	1.30	1.55	1.40	1.20	1.55	0.73	0.54	0.29	0.10	Trace
3	0	1.39	2.22	1.77	1.14	0.95	0.94	1.13	0.58	0.26	0.16	0.09
4	0	1.33	2.15	2.29	1.65	1.32	1.00	0.58	0.39	0.13	0.08	0
5	0	1.11	1.39	0.97	0.78	0.65	0.97	0.73	0.43	0.17	0.05	Trace
6	0	1.66	1.71	1.28	1.09	1.03	0.88	0.75	0.46	0.22	0.12	0.07
7	0	0.52	1.58	1.71	1.43	1.87	1.99	0.96	0.78	0.32	0.18	0.06
8	0	0.34	1.32	1.58	1.44	0.98	0.93	0.87	0.95	0.30	0.14	Trace
9	0	0.61	1.09	1.13	1.03	0.97	0.87	0.59	0.69	0.28	0.15	0.08
10	0	0.59	1.03	1.33	1.02	0.93	1.21	1.01	0.58	0.29	0.15	0.11
11	0	0.45	1.49	1.67	1.47	1.20	1.19	0.63	0.39	0.17	0.07	Trace
12	0	0.46	0.71	0.67	0.60	0.56	0.64	0.82	0.81	0.35	0.14	0.08
Mean	0	0.75	1.41	1.43	1.21	1.05	1.07	0.79	0.59	0.25	0.12	0.05

[a] <0.05 μg per ml.

0.75 μg per ml; range, 0.08 to 1.66 μg per ml. Drug concentrations continued above the 0.5-μg per ml value for 4 hr, at which time the mean level was almost identical to the intravenous and intramuscular means. Peak blood levels occurred anywhere from 1/2 to 3 hr after dosing. Eight of the subjects exhibited double peaks within this period; in two instances, the second peak was higher than the first. This phenomenon is being further investigated. At 10 hr, residual drug levels were comparable to those of the parenteral groups. Mean blood level curves for all three routes of administration are shown in figure 1.

Urinary excretion. There were only small differences in the amounts of cimetidine recovered in urine after intravenous (77%) or intramuscular (73%) injection of drug (table 5). However, after an oral dose only 48% was recovered in the urine. It should be noted that these values represent only metabolically unaltered cimetidine. Other metabolites, notably the sulfoxide which can account for 10% of the dose, were not determined. The range of values were 66 to 85% (intravenous), 67 to 81% (intramuscular), and 40 to 60% (oral).

Analysis of results. Three major characteristics of the blood level sequence and urinary recoveries of cimetidine were analyzed. They were: (1) area under the blood level curve from 0 to 10 hr, as a measure of drug availability (the usual logarithmic transformation was made before analysis: the 0-hr value for the intravenous and intramuscular routes was taken to be equal to the 15-min value, and levels recorded as <0.05 μg per ml were taken to be 0.025 μg per ml); (2) time for which the blood level remains above 0.5 μg per ml (the time above 0.5 μg per ml was estimated by interpolation in the sequence of blood levels); and (3) percentage of cimetidine recovered in the urine in 0 to 24 hr. These values are presented in table 6. The analyses show that: (1) there are no statistically significant differences among the three regimens with respect to the time for which blood levels remain above 0.05 μg per ml; (2) with respect to area under the curve, there are statistically significant differences between the intravenous and oral liquid and between the intramuscular and oral liquid but not between the intravenous and intramuscular; and (3) there are statistically significant differences between each pair of regimens with respect to urinary recovery of cimetidine in 0 to 24 hr. However, in the case of intravenous (77.11%) and intramuscular (73.12%) the difference is very small and it is more

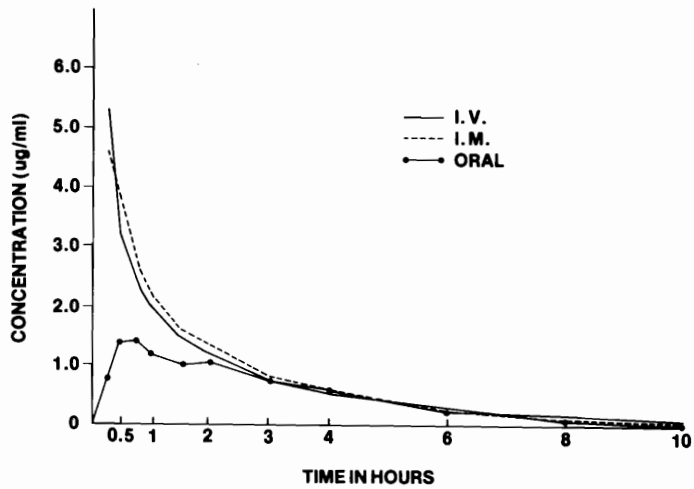

FIG. 1. Mean blood levels after dosing of 300 mg of cimetidine by various routes.

TABLE 5. *Urinary excretion (24-hr) of cimetidine*

Subject	300-mg doses		
	Intravenous	Intramuscular	Oral
	% dose		
1	71.4	69.9	42.7
2	66.7	69.6	42.7
3	83.3	81.5	50.3
4	79.6	73.3	49.2
5	85.4	74.1	54.6
6	74.4	71.5	45.3
7	75.5	72.3	48.1
8	83.3	77.3	47.1
9	69.1	71.2	40.2
10	81.5	67.4	44.2
11	76.9	73.6	51.9
12	78.2	75.8	60.6
Mean	77.1	73.1	48.1

realistic to express the results in terms of confidence intervals. If μ_v and μ_m represent the true mean amounts recovered with the intravenous and intramuscular regimens respectively, then the conventional 95% confidence interval for the difference between μ_v and μ_m is

$$1.28 < (\mu_v - \mu_m) < 6.69$$

A rough interpretation of this result is that μ_m is probably within about 9% of μ_v.

The Oral Study

Clinical observations. No symptoms were associated with administration of either oral preparation of cimetidine, tablet or liquid.

Blood levels. Mean blood levels of drug above 0.5 μg per ml were reached within 1/2 hr of a 300-mg oral dose of cimetidine liquid or tablet formulation (tables 7 and 8). The concentration in blood remained above this amount through the 4th hr. Peak blood levels of cimetidine ranged up to 2.08 μg per ml after the liquid formulation and up to 2.17 μg per ml on the tablet. The time of peak was as early as 1/2 hr on both formulations.

Urinary recovery. The amount of unchanged cimetidine recovered in urine ranged from about 40% to about 60% of the dose after oral liquid administration and from about 44% to about 70% after the tablet (tablet 9).

Analysis of results. Five characteristics of the blood level sequence were analyzed. They are: (1) area under the blood level curve from 0 to 12 hr, as a measure of amount of drug absorbed (the usual logarithmic transformation was made before analysis); (2) peak blood level; (3) time at which peak blood level was attained; (4) time at which a blood level of 0.5 μg per ml was first attained; and (5) time for which blood level remained above 0.5 μg per ml. This time was estimated by interpolation in the sequence of blood levels over time.

In addition, the percentage of cimetidine recovered in the urine in 0 to 24 hr was also analyzed. Note that data from volunteers 21 and 22 were omitted from this analysis owing to a mishap in urine collection on the day when the liquid formulation was dosed. There were two differences between the liquid and the tablet formulations that were statistically significant, namely, for the time of peak ($P < 0.05$) and for time at which blood level first reaches 0.5 μg per ml ($P < 0.01$). In both cases, the liquid formulation is associated with the earlier time. These differences may be ascribed to the finite time required for dissolution of the tablet. Mean values for the various characteristics that were analyzed are given in table 10. Mean blood levels for the liquid and tablet formulation are displayed in figure 2.

These data show a striking consistency in blood levels with the results of the parenteral study reported above, although a different group of volunteers was used. The area under the curve and the time above 0.5 μg per ml differed by less than 5% in the two groups after a dose of oral liquid.

TABLE 6. *Bioavailability parameters: parenteral study*

Characteristics	Mean values		
	Intravenous	Intramuscular	Oral liquid
Area under the curve (μg/ml/hr)	8.21[a]	8.57[a]	5.07
Time for which blood level remains above 0.5 μg/ml (hr)	4.51	4.58	4.18
% cimetidine recovered in urine	77.11[b]	73.12[b,c]	48.08

[a] Difference from oral statistically significant at 0.01 level.
[b] Difference from oral statistically significant at 0.001 level.
[c] Difference from intravenous significant at 0.01 level.

Discussion

The similarity of the blood level curves for the intravenous and intramuscular routes of administration indicates that these two routes may be used interchangeably. The transient symptoms observed on injection would probably not preclude clinical use of either route, although intravenous may be preferable from the patient's standpoint.

The lower initial blood levels, smaller area under the blood level curve, and reduced recovery of drug in the

TABLE 7. *Cimetidine blood levels after administration of a single 300-mg dose of cimetidine oral liquid*

Subject	Concentration of cimetidine in whole blood (μg/ml)									
	0 hr	1/2 hr	1 hr	1 1/2 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr
13	0	1.80	1.18	0.85	1.00	0.98	0.83	0.37	0.19	Trace[a]
14	0	0.12	1.11	1.55	1.06	0.88	0.70	0.28	0.14	Trace
15	0	1.36	0.86	0.90	1.02	0.78	0.40	0.14	0.08	Trace
16	0	0.36	0.59	0.35	0.38	0.73	0.50	0.17	0.09	Trace
17	0	1.21	1.83	1.17	0.92	0.88	0.67	0.30	0.17	Trace
18	0	0.25	0.79	1.93	1.31	1.20	0.69	0.28	0.15	Trace
19	0	1.46	1.49	1.36	0.86	0.58	0.47	0.20	0.11	Trace
20	0	0.73	1.45	1.27	1.12	0.85	0.65	0.30	0.18	Trace
21	0	1.97	1.32	1.27	1.10	0.76	0.57	0.35	0.18	Trace
22	0	1.07	0.99	0.95	0.99	1.06	0.76	0.31	0.15	0.06
23	0	0.77	0.98	0.98	1.09	0.99	0.70	0.29	0.14	Trace
24	0	2.08	1.45	1.13	1.06	0.86	0.60	0.28	0.14	Trace
Mean	0	1.10	1.17	1.14	0.99	0.88	0.63	0.27	0.14	0.03

[a] <0.05 μg per ml.

TABLE 8. *Cimetidine blood levels after administration of a single 300-mg cimetidine tablet*

Subject	Concentration of cimetidine in whole blood (μg/ml)									
	0 hr	½ hr	1 hr	1½ hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr
13	0	0.11	0.99	1.52	1.03	1.13	0.82	0.36	0.20	Trace
14	0	Trace[a]	0.39	1.02	1.06	0.97	0.86	0.41	0.22	Trace
15	0	0.96	1.33	1.77	1.43	0.76	0.47	0.22	0.12	Trace
16	0	0.28	0.53	0.45	0.51	0.73	0.59	0.18	0.08	Trace
17	0	0.94	1.23	0.73	0.81	1.26	0.88	0.39	0.22	Trace
18	0	Trace	0.42	1.04	1.47	1.16	0.80	0.30	0.13	Trace
19	0	0.08	1.44	0.80	0.68	0.85	0.47	0.23	0.11	Trace
20	0	1.20	1.69	1.09	1.21	1.07	0.77	0.33	0.17	Trace
21	0	2.17	1.98	1.35	1.44	0.80	0.59	0.35	0.20	0.08
22	0	0.39	1.51	1.21	1.18	1.32	0.94	0.40	0.16	Trace
23	0	0.17	0.76	0.50	0.65	1.23	0.97	0.38	0.13	Trace
24	0	Trace	0.31	0.80	1.18	1.47	0.96	0.39	0.19	Trace
Mean	0	0.53	1.05	1.02	1.05	1.06	0.76	0.33	0.16	0.03

[a] <0.05 μg per ml.

TABLE 9. *Urinary excretion (24-hr) of cimetidine*

Subject	300 mg liquid	300-mg tablet
	% dose	
13	52.35	57.12
14	58.72	55.42
15	51.69	58.81
16	45.36	44.29
17	60.04	70.42
18	54.57	55.38
19	61.18	50.03
20	49.11	56.78
21		55.18
22		52.82
23	61.36	55.16
24	52.36	57.15

TABLE 10. *Bioavailability parameters: oral study*[a]

Characteristics	Formulations	
	Liquid	Tablet
Area under the curve (μg/ml/hr)	5.22	5.39
Peak blood level (μg/ml)	1.53	1.44
Time of peak blood level (hr)	1.13	1.88[b]
Time at which 0.5 μg/ml is first attained (hr)	0.34	0.65[c]
Time for which blood level remains above 0.5 μg/ml (hr)	4.23	4.35
% cimetidine recovered in urine	54.9	55.8

[a] Values adjusted for imbalance resulting from omission of data from volunteers 21 and 22.

[b] Difference is statistically significant at 0.05 level.

[c] Difference is statistically significant at 0.01 level.

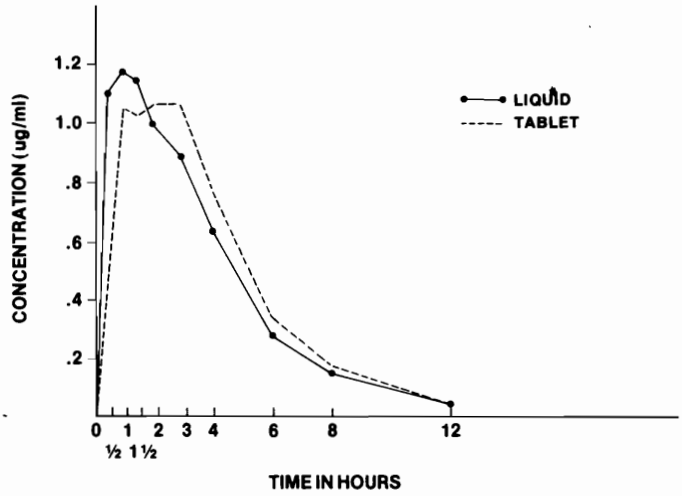

FIG. 2. Mean blood levels of cimetidine.

urine after oral dosing could indicate either impaired absorption of cimetidine from the gut or metabolic alteration. Both the area under the blood level curve and the urinary recovery of the oral dose averaged only 62% of the intravenous values. However, comparison with results of an earlier study in which radioactive cimetidine was used suggests that the reduced recovery in urine after oral administration is the likely result of a "first pass" effect, i.e., metabolic alteration of the drug in the liver after absorption. In that study[3] 70% of the orally administered radioactivity was recovered in the urine, as compared with only 48 to 55% of unaltered drug in the present study after oral dosing. Of the total amount of radioactivity found in urine by the previous authors only 70% was unchanged cimetidine. Furthermore, the authors recovered 80 to 96% of the intravenously administered radioactivity in urine. In the present study we accounted for 77% of an intravenous dose as unchanged drug. Thus, as one would expect, a greater proportion of an oral than of a parenteral dose is metabolized.

The time for which the blood level remained above 0.5 μg per ml was identical for all three routes of administration. At this concentration, basal secretion was suppressed by more than 80% and food or gastrin-stimulated secretion by more than 50%.[3, 9] This degree of suppression is probably adequate in most but not all patients.

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DISCUSSION OF PAPER PRESENTED BY DRS. WALKENSTEIN ET AL.

DR. I. T. BECK (Kingston, Ontario): Blood levels have meaning only if one assumes that cimetidine acts through the blood route. Does cimetidine have any local action on histamine receptors when applied to the stomach; and, if that were the case, is the tablet dissolved in the stomach and is the action of cimetidine faster when it is taken orally?

DR. DUBB: There is abundant evidence showing that the inhibitory effect of cimetidine on acid secretion bears a direct relationship to the blood level of the drug.

We have no evidence to indicate that cimetidine acts locally in the stomach and we would expect that the action of cimetidine would be more rapid by the parenteral than by the oral route.

DR. J. J. MISIEWICZ (London): Two other points, which perhaps might be mentioned in this context of bioavailability of cimetidine as measured by blood levels, are the effects of food and other drugs. In the studies that we have made, we found a very marked influence of varying the ingestion of the drug in relation to meals on the blood levels of cimetidine. Taken on the empty stomach, you get much more rapid absorption. If taken with or after meals, you get a much slower and perhaps a more sustained absorption. I do not think that this makes very much difference in the therapeutic efficacy because the inhibitory level is maintained whatever way you take it. But I think it may become important if a patient misses a next dose of the drug for one reason or another. If he does, then I think that it is to his advantage to have taken the medicine with or after food because he will cover himself for the missed dose.

Just one quick point on the effect of other drugs. We have also looked at the effects of concurrent administration of atropine by mouth on the blood levels and urinary excretion of cimetidine, and at the dose of 0.8 mg of atropine four times a day, given with cimetidine, the urinary excretion or the blood concentration of the H_2-receptor blocker was not affected.

DR. N. KAPLOWITZ (Los Angeles): Based on the difference that you see in intravenous and oral administration of the drug, are you, therefore, telling us that there is a significant first pass effect with regard to cimetidine? And do you have any information about a potential enterohepatic circulation for cimetidine?

DR. DUBB: By "first pass effect" you mean that a significant percentage of an oral dose is metabolized on its first pass through the liver from the gastrointestinal tract.

Metabolic studies performed with isotopically labeled cimetidine indicate that there is some first pass effect, in that less unchanged drug is recovered after oral than after intravenous administration and that a slightly higher percentage of metabolized drug such as the sulfoxide or the hydroxymethyl metabolite is found.

In answer to your second question, we do not have specific data on the enterohepatic circulation. The appearance of cimetidine in the feces has been demonstrated after intravenous administration of the drug and there is a paper in the recent Second Symposium which documents the secretion into the bile.

DR. P. SHARPE (Welwyn Garden City, England): We have data on the excretion of cimetidine in the bile after oral dosing in patients postcholecystectomies who had T-tubes in situ. We found that less than 2% of an oral dose came out in the bile.

DR. C. F. CODE (Los Angeles): There was significant difference in the amount of unchanged drug that appeared in the urine between the oral dose and the intravenous or intramuscular injections. Is this due to alteration of the drug within the gut lumen, or how do you account for it? Do bacteria affect it?

DR. DUBB: I would account for the difference in urinary recovery in two ways. First, studies with isotopically labeled cimetidine have shown that only about two-thirds of cimetidine recovered in the urine after oral administration is unchanged parent compound. Our liquid chromatographic method for measuring cimetidine is very specific for the unchanged compound and would not have detected any of the metabolites of cimetidine. Second, isotopic studies have shown that a small amount of labeled material can be recovered in the feces, probably as a result of the enterohepatic circulation. I do not know of any data concerning the effect of gut bacteria on cimetidine.