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THE ABSORPTION OF CIMETIDINE BEFORE AND DURING MAINTENANCE TREATMENT WITH CIMETIDINE AND THE INFLUENCE OF A MEAL ON THE ABSORPTION OF CIMETIDINE — STUDIES IN PATIENTS WITH PEPTIC ULCER DISEASE

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1 The absorption of a single oral dose of cimetidine taken on a fasting stomach or together with a meal was studied in 28 patients before and during 12 weeks treatment with cimetidine.

2 No significant changes in bioavailability were seen during treatment measured as the area under the blood concentration curve (AUC).

3 AUC after a single dose of 400 mg cimetidine was 2.05 times the area after a 200 mg dose.

4 There was a good correlation between AUC and the dose of cimetidine given corrected for body weight ($r=0.89$).

5 There was no difference in bioavailability if 200 mg cimetidine was taken on a fasting stomach or together with a beef steak meal.

6 During fasting conditions there was a peak in blood concentration at about one hour followed by a second unexplained peak during the third to fifth hour after dose administration.

7 With food the initial rise in blood concentrations was slower and there was only one peak occurring about 2 h after dose administration.

Introduction

Cimetidine, the latest histamine H_2-receptor antagonist, is a potent inhibitor of gastric acid secretion and is a promising agent for treatment of peptic ulcer disease. Half-life in blood, bioavailability and absorption patterns of cimetidine have been evaluated in limited number of healthy subject (Burland, Duncan, Hesselbo, Mills, Sharpe, Haggie & Wyllie, 1975; Griffiths, Lee & Taylor, 1977).

Cimetidine has been recommended to be taken after the meal in order to achieve highest possible blood concentrations in the interdigestive period (Spence, Creak & Celestin, 1976). The aim of the present study was to investigate in patients if there is a correlation between the dose of cimetidine and the area under the blood concentration curve. We also investigated if a meal has any influence on the absorption of cimetidine, if there are any changes in bioavailability and absorption profile during treatment and if there is an accumulation of cimetidine during treatment.

Methods

Thirty-eight patients with endoscopically proven active peptic ulcers or severe gastritis were included in the trial. All patients were treated for 12 weeks with cimetidine 200 mg three times daily and 400 mg at bedtime. Several routine tests on blood and urine were taken before and during treatment with cimetidine. The level of serum creatinine was normal in all patients.

Following an overnight fast the absorption of single oral doses of cimetidine was studied in 28 patients. Venous blood samples for measurement of cimetidine concentrations were taken immediately before, every 15 min during the first 2 h, then every 30 min between 2 and 6 h and finally 8, 9 and 24 h after drug intake — altogether 20 blood samples were thus collected. The patients were served breakfast 3 h and lunch 6 h after tablet intake.

Cimetidine 200 mg and 400 mg as single doses

In a first group of ten patients (three women and seven men with mean age of 56 years — range 33–66) the absorption of single oral doses of cimetidine 200 mg and 400 mg, taken on a fasting stomach, were investigated prior to therapeutic threatment. Each of these ten patients received both doses and was thus studied twice not less than two days apart.

Cimetidine 200 mg before and during 12 weeks' maintenance treatment.

In a second group of eight male patients (mean age 50 years, range 25–71 years), the absorption of a single oral dose of 200 mg cimetidine, taken on a fasting stomach, was followed before and repeated after 8 and 12 weeks maintenance treatment with cimetidine. Continuous treatment was withdrawn for 24 h prior to the studies at 8 and 12 weeks.

Cimetidine 200 mg with or without a meal before maintenance treatment.

In a third group of ten patients (three women and seven men, mean age 55 years, range 37–67 years) the blood concentration of cimetidine was followed after a 200 mg cimetidine tablet was taken on a fasting stomach and immediately after a meal. Each patient was studied twice not less than two days apart. The meal consisted of 180 g of lean roast beef, two slices of bread with butter, vegetables and one glass of milk.

Altogether 28 patients were thus given a single oral dose of 200 mg cimetidine on a fasting stomach before treatment.

Morning blood concentration during continuous treatment with cimetidine

In a last group of ten patients (two women and eight men with mean age of 50 years — range 33–72) one blood sample for cimetidine analysis was taken every second to third week during the 12 weeks' continuous treatment. This blood sample was taken in the morning with a mean time of 10.5 h (range 8–13 h) after the evening 400 mg dose of cimetidine but before the morning dose.

Throughout the separate studies there were no changes in the patients' diets.

Method of cimetidine analysis

The blood concentration of cimetidine has been measured by high pressure liquid chromatography using UV-detection. This method has been developed at Smith, Kline & French laboratories in England and in USA (Darkin & Bavin, personal communication; Randolph, Osborne, Walkenstein & Intoccia, 1977).

Blood (1 ml) mixed with 1 ml carbonate buffer (1 M, pH 9), containing 2 μg/ml metiamide as internal standard, was extracted with 4 ml octanol. After centrifugation the octanol layer was transferred to another tube and 2 ml 0.02 N HCl were added. Extraction and centrifugation were then repeated and the octanol layer discarded. The aqueous layer was transferred to a small centrifuge tube, 100 μl acetonitrile added and the solution was then saturated with solid K_2CO_3. After a final centrifugation 10 μl of the upper acetonitrile layer was injected into the liquid chromatograph. The column was 250 × 3 mm lichrosorb Si 60 5 μm, the eluent was a mixture of CH_3CN: conc NH_4OH:H_2O (1000:2.5:20) and the flow was 1.6 ml/min. Detection was done at a wavelength of 228 nm.

Minimal detectable blood concentrations of cimetidine in these series were about 0.05 μg/ml. All blood samples were analysed in duplicate (coefficient of variation between double blood sample analyses was 3%).

Results

In 22 of the 28 patients the blood concentration curve after an oral dose of cimetidine taken on a fasting stomach had both an initial peak appearing within the first 2 h and a second peak during the third to fifth hour after dose administration. The second peak was more marked after the 400 mg dose. Figure 1 illustrates a typical blood concentration profile in one patient. The results in Tables 1 and 3 are given both as the mean of the peak blood concentrations during the first 2 h and during the third to fifth hours after dosing.

For all the 28 patients receiving a 200 mg dose on a fasting stomach prior to maintenance treatment the peak blood concentrations (mean ± s.e. mean and range) and time of occurrence are presented in Tables 1 and 3. The individual areas under the blood concentration curves (AUC) corrected to kg body weight are presented in Tables 2 and 4.

Cimetidine 200 mg and 400 mg as single doses

The results from the ten patients, who received both a 200 mg and a 400 mg dose on a fasting stomach before treatment, are presented in Figure 2. Mean ± s.e. mean and range of the peak blood concentrations are given in Table 1 and the individual AUC corrected to kg body weight are given in Table 2. The mean ratio between AUC of the 400 mg dose and the 200 mg dose was 2.05 (range 1.66–2.34) Table 2).

There was a good correlation between AUC and dose of cimetidine given expressed as mg per kg body weight ($r = 0.89$) (Figure 3).

Cimetidine 200 mg dose before and during 12 weeks maintenance treatment

The mean ± s.e. mean and range of the peak blood concentrations of cimetidine obtained in this separate study are given in Table 1 and the individual AUC corrected to kg body weight in Table 2. The mean of blood concentrations before and during treatment with cimetidine are presented in Figure 4. Because the timing of the highest blood concentrations differed

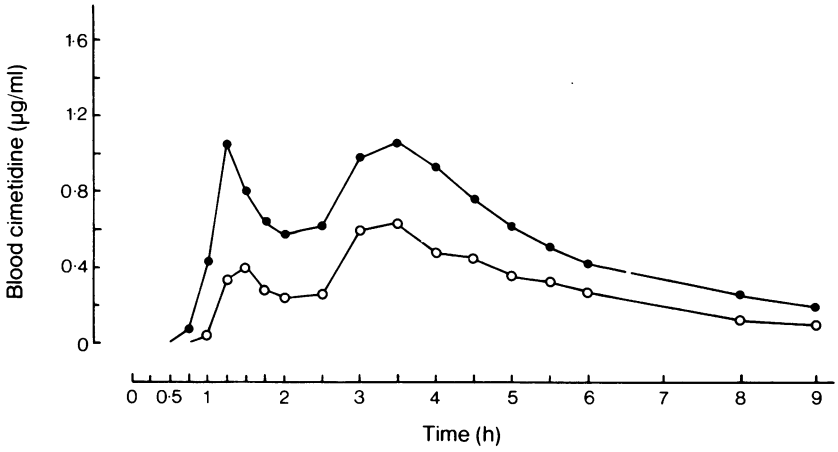

Figure 1 Blood concentration after oral intake of 200 mg (○) and 400 mg (●) cimetidine on a fasting stomach in one patient before treatment.

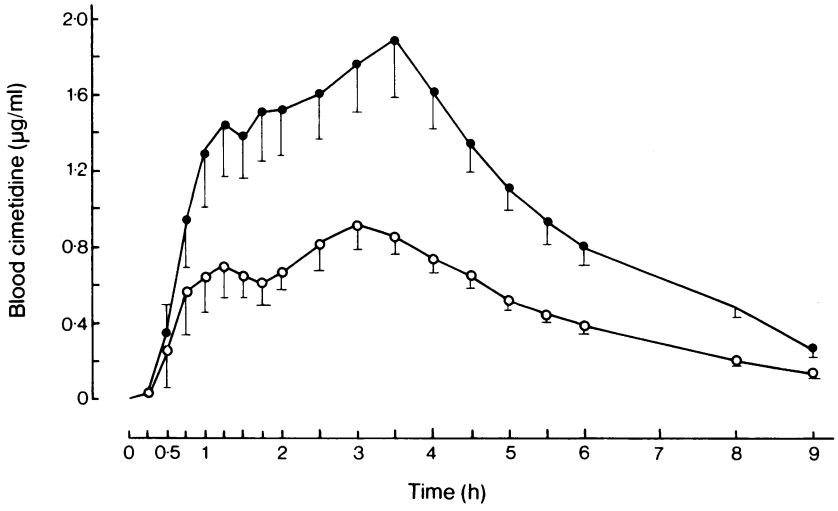

Figure 2 Blood concentration (mean ± s.e. mean) after oral intake of 200 mg (○) and 400 mg (●) cimetidine on a fasting stomach in 10 patients before treatment.

between patients, the double peak curves that occurred when cimetidine was taken on a fasting stomach are not clearly seen in Figure 4.

The pattern of the blood concentration profile following oral administration of cimetidine did not change during treatment (Figure 4). There was no statistically significant differences either in level and timing of the mean peak blood concentrations or in AUC before and during cimetidine treatment. After discontinuing the drug for 24 h the eight patients either had none or just detectable blood concentrations of cimetidine.

Cimetidine 200 mg with or without food

In eight out of these ten patients the blood concentration curve after an oral dose of 200 mg cimetidine taken on a fasting stomach had two peaks (Figure 5). The first peak occurred during the first 2 h and the second during the third to fifth hours after dose administration. The mean ± s.e. mean and range of these two peaks and times of their occurrence are given in Table 3 and the individual AUC corrected to kg body weight in Table 4.

When 200 mg cimetidine was taken with food, the

Table 1 Mean ± s.e. mean and range (μg/ml) of peak blood concentrations of cimetidine and time of its occurrence (min) after dosing on a fasting stomach. In all 18 patients received a 200 mg dose before treatment. Ten of these patients received both a 200 mg and a 400 mg dose before treatment and eight of these patients received a 200 mg dose before (week 0) and after 8 and 12 weeks treatment.

		200 mg before treatment (all patients)	*200 mg and 400 mg before treatment*		*200 mg before and during treatment*		
			200 mg	*400 mg*	*week 0*	*week 8*	*week 12*
1–120 min	Mean time of peak (min) (range)	72 (45–105)	73 (45–90)	68 (45–105)	70 (45–105)	60 (45–90)	71 45–185)
	Peak blood concentration (μg/ml) (range)	1.12 ± 0.14 (0.34–2.25)	1.03 ± 0.24 (0.34–2.25)	1.84 ± 0.31 (0.74–2.97)	1.24 ± 0.08 (0.98–1.45)	1.06 ± 0.12 (0.75–1.58)	1.20 ± 0.24 (0.88–2.65)
120–300 min	Mean time of peak (min) (range)	182 (120–270)	192 (150–270)	207 (120–270)	167 (120–210)	167 (150–180)	188 (150–210)
	Peak blood concentration (μg/ml) (range)	1.02 ± 0.08 (0.58–1.68)	1.01 ± 0.12 (0.58–1.68)	2.12 ± 0.27 (1.05–3.90)	1.03 ± 0.11 (0.65–1.42)	1.00 ± 0.08 (0.72–1.34)	0.99 ± 0.07 (0.86–1.14)

Table 2 The area under the blood concentration curve (AUC) corrected to kg body weight after oral intake of 200 mg and 400 mg cimetidine on a fasting stomach before treatment in ten patients and of 200 mg cimetidine before (week 0) and after 8 and 12 weeks treatment with cimetidine in eight patients.

	Patient receiving fasting before treatment				*Patients receiving cimetidine 200 mg fasting*		
Patient	*cimetidine 200 mg*	*cimetidine 400 mg*	*Ratio* $\frac{AUC\ 400\ mg}{AUC\ 200\ mg}$	*Patient*	*Week 0*	*Week 8*	*Week 12*
	(μg h kg ml^{-1})				*(μg h kg ml^{-1})*		
B.J.	336.7	651.5	1.94	S.B.	364.0	426.1	441.9
O.B.	458.4	998.8	2.18	P.-O.L.	226.4	255.9	289.4
M.G.	320.0	550.3	1.72	S.D.	421.8	404.2	—
H.B.	350.6	749.3	2.14	T.J.	426.0	449.2	446.2
J.G.	417.2	821.0	1.97	A.S.	285.0	319.7	301.7
G.M.	324.3	759.2	2.34	J.H.	357.8	3.53.3	354.2
Y.K.	445.6	910.8	2.04	H.M.	403.0	—	324.4
K.-E.G.	415.6	690.3	1.66	K.-E.G.	372.5	384.6	468.5
H.L.	269.3	596.5	2.22				
K.W.	397.0	914.6	2.30				
Mean	373.5	764.2	2.05	Mean	357.1	370.3	375.2
± s.e. mean	± 19.3	± 8.7		± s.e. mean	± 24.5	± 25.2	± 28.4

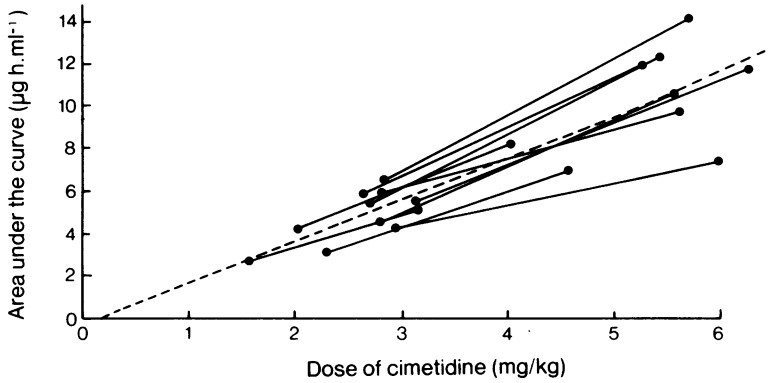

Figure 3 Individual data and linear regression line of area under the blood concentration curve (µg h ml^{-1}) related to given dose of cimetidine per kg body weight after 200 mg and 400 mg cimetidine in ten patients. (The areas are not corrected to kg body weight).

Table 3 Mean ± s.e. mean and range of peak blood concentrations during the first 2 h (0–120 min) and during the third to fifth hours (120–300 min) after an oral dose of 200 mg cimetidine taken on a fasting stomach and of the peak blood concentration after 200 mg taken with a meal in ten patients. The mean and range of time (min) for the peaks to occur are also given.

	Fasting				*Food*	
	0–120 min		*120–300 min*			
	Cimetidine (µg/ml)	*Time (min)*	*Cimetidine (µg/ml)*	*Time (min)*	*Cimetidine (µg/ml)*	*Time (min)*
Mean	1.18	55	0.97	197	1.09	128
± s.e. mean	0.14	7.5	0.07	7,3	0.1	18.5
range	0.47–2.01	30–105	0.64–1.32	180–240	0.66–1.70	60–210

Table 4 The area under the blood concentration curves (AUC) corrected to kg body weight after an oral dose of 200 mg cimetidine taken on a fasting stomach or with food in ten patients. The ratio between AUC with and without food is presented to the right.

Patient	*Cimetidine 200 mg Fasting (µg h kg ml^{-1})*	*Cimetidine 200 mg Food (µg h kg ml^{-1})*	*Ratio AUC with food / AUC fasting*
E.R.	543.1	529.5	0.98
A.W.	322.9	307.2	0.95
M.-L.F.	354.8	440.1	1.24
K.-A.L.	417.6	418.5	1.00
M.-L.A.	606.4	438.7	0.72
S.K.	238.3	264.7	1.11
S.K.	413.7	343.9	0.83
M.E.	345.7	231.7	0.67
S.W.	448.7	413.7	0.92
G.E.	374.7	328.7	0.88
Mean	406.6	371.7	0.93
± s.e. mean	±33.87	±29.03	

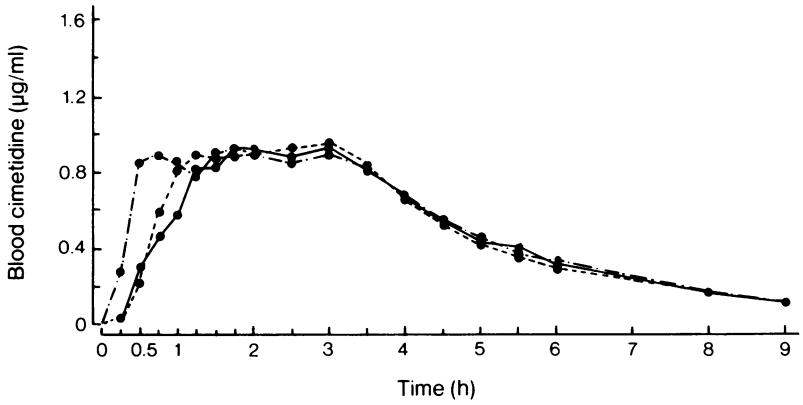

Figure 4 Mean blood concentration after oral intake of 200 mg cimetidine on a fasting stomach before (week 0) and during (week 8 and 12) treatment with cimetidine in eight patients.———— week 0, ----- week 8, -.-.-.-.-. week 12.

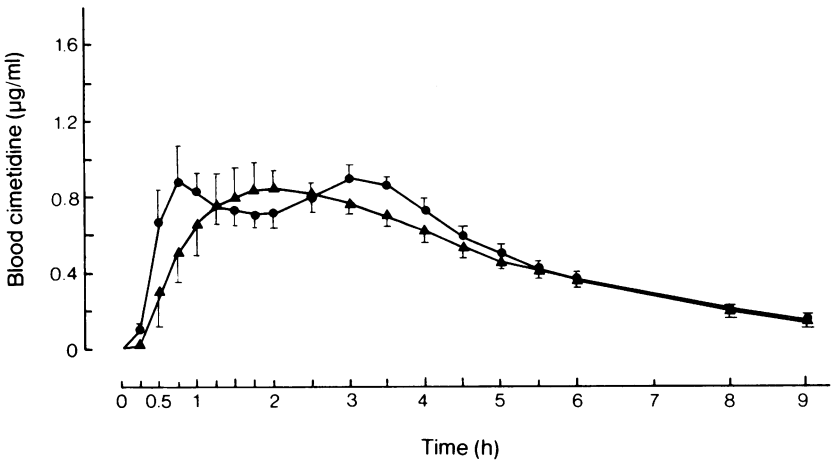

Figure 5 Blood concentration (mean ± s.e. mean) after 200 mg cimetidine taken with (▲) or without (●) food in ten patients.

absorption curve had only one absorption maximum in all ten patients. This appeared during the second and the third hours after dosing i.e. between the first and second peaks that were observed when the drug was taken on a fasting stomach (Figure 5). The blood concentrations of cimetidine were very similar from the fifth hour and onwards after the drug intake regardless if the drug was taken with or without food (Figure 5). Mean ± s.e. mean and range of the maxima and the individual AUC corrected to kg bodyweight after the drug was taken together with food are given in Tables 3 and 4. The mean ration between the AUC of a 200 mg dose cimetidine taken immediately after food and of a 200 mg dose taken on a fasting stomach was 0.93 (range 0.67–1.24) (NS) (Table 4).

Morning blood concentration during maintenance treatment with cimetidine.

These ten patients were on continuous treatment with cimetidine 1 000 mg daily. The morning blood concentration (mean ± s.e. mean) after 2 weeks' treatment was 0.29 ± 0.05 µg/ml (range 0.06–0.54) compared to 0.23 ± 0.08 µg/ml (range 0–0.72), when the patients ended the 12 weeks' treatment (NS). None of the patients showed any tendency to accumulate cimetidine during treatment. The morning blood concentrations were roughly on the same level in the individual patients all through treatment.

According to the data above, the blood concentration curve after the evening dose of 400 mg cimetidine

would have a second peak around 02.00 h. If the decrease in blood concentration of cimetidine after this second peak is calculated according to the reported blood half-life of 2 h, the expected morning blood concentration would be about the same as the levels we have found in our ten patients.

Discussion

In four healthy subjects, Griffiths, Lee & Taylor (1977) have found that the bioavailability after an oral dose of cimetidine is about 70%.

The present studies in patients show that there is no great interindividual variation in absorption of cimetidine and that there is no change in bioavailability during treatment. Treatment with cimetidine 1.0 g daily did not alter the level or the timing of the peak blood concentrations. The profile of the concentration curve was also unchanged during treatment. No accumulation of cimetidine was observed.

Results obtained by Griffiths *et al.* (1977) indicated a good relation between the area under the curve (AUC) and the dose of cimetidine when blood concentration was measured for 3 h. In our patients the blood concentration was measured for 9 h. The ratio between the mean AUC extrapolated to infinity after a 400 mg and a 200 mg dose was 2.05. The profiles of the blood concentration curves after a 200 mg and a 400 mg dose were the same, which indicate that the absorption and elimination of cimetidine was similar for these two dose levels. There was also a good correlation between AUC and the cimetidine dose given ($r=0.89$).

The blood concentration of cimetidine required to produce a 50% reduction of maximal acid output (IC_{50}) has been reported to be 0.5–1.0 μg/ml (Burland *et al.*, 1975; Bodemar, Norlander & Walan, 1977). The mean of the highest blood concentration after a 200 mg dose in the present series of patients was slightly above the IC_{50} of 1 μg/ml previously reported from this laboratory. Up to 4 h after a 200 mg tablet the mean blood concentration was around 0.8 μg/ml. After a 400 mg dose the mean peak blood concentration was at least twice the reported IC_{50} and the concentration is sustained above this IC_{50}–level for about 5 h.

From the studies by Henn, Isenberg, Maxwell & Sturdevant (1975) and by Pounder, Williams, Russel, Milton-Thomson & Misiewicz (1977) it can be stated, that cimetidine is highly effective in inhibiting food stimulated gastric acid secretion regardless if the tablets are taken before, during or just after a meal. Spence *et al.* (1976) have in healthy man shown that if cimetidine is administered with a meal it should be taken just after instead of just before the meal in order to best cover the time periods between meals.

We have in patients with peptic ulcer disease found that there is no difference in bioavailability if a 200 mg cimetidine tablet is taken with or without a beef steak meal. The absorption curve following tablet intake without food had in most patients an initial peak at about 1 h followed by a second peak appearing during the third to fifth hour after drug intake. With food the initial rise in blood concentration was slower and there was in all patients only one peak occurring after about 2 h (Figure 5). Spence *et al.* (1976) suggested that the drug should be taken with a meal to achieve optimal acid inhibition in the interdigestive period. Because of a second peak in blood concentration in the fasting state in our patients the blood concentration of cimetidine was not sustained on a higher level for longer periods during the first 5 h after dose administration, when the drug was taken with food compared to the fasting state. Likewise, the blood concentration of cimetidine was sustained at the same level from the fifth hour onwards after drug intake, regardless if cimetidine was taken with or without food.

The half-life of cimetidine in blood has been reported to be 2 h. We have not been able to calculate the half-life after oral administration of cimetidine to fasting patients. This is because most of our patients had a second peak of their blood concentration curve occurring about 2 h after the first initial absorption peak, when the drug was taken without food. This is clearly exemplified in one patient in Figure 1. There are a number of possible explanations for this observation. A second absorption peak could be explained by enterohepatic circulation of cimetidine, although a preliminary report by Spence, Celestin, de la Guardia, MacMullen & McCormick (1977) seems almost to exclude this possibility.

Another explanation could be that the absorption of some of orally given cimetidine is delayed in most patients. Griffiths *et al.* (1977) have shown that cimetidine is absorbed at varying rates from different isolated segments of the gut in the rat.

Calculations from the present results indicate that the contribution from a hypothetical delay absorption is as much as 50% of total AUC in some patients. Delayed absorption of this magnitude, however, is unlikely and this second peak following oral administration of cimetidine remains to be explained.

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