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Research paper

Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility

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Abstract

The role of gastrointestinal motility and pH in determining cimetidine bioavailability as well as double peaks in plasma profiles following oral administration, in the quiescent or active phase of antral motility, to humans in the fasted state was examined. Plasma cimetidine-time curves did not show the presence of double peaks in any subject following intravenous administration. The incidence of double peaks was 73% following oral administration and was independent of antral migrating motility complex phase. Further, it was found that oral administration of cimetidine in the quiescent phase resulted in significantly higher bioavailability and in other pharmacokinetic parameters compared to that obtained following administration in the active phase. Excellent linearity in plots of motility peaks vs. plasma peaks with slopes close to unity were evident for both quiescent ($r^2 = 0.93$) and active phase ($r^2 = 0.97$) administration. A total of 14 peaks out of 22 (10 subjects, 64%) and 20 out of 27 peaks (11 subjects, 74%), were accounted for in quiescent and active phase oral administration, respectively. The proximal occurrence of plasma peaks to antral motility peaks typical of phase III contractions strongly implies that motility patterns may be responsible for secondary maxima following oral cimetidine administration in the fasted state.

Keywords: Cimetidine; Antral motility phase; Gastrointestinal motility; Gastrointestinal pH; Pharmacokinetics; Double peaks; Secondary maxima,; Human bioavailability

1. Introduction

The appearance of secondary maxima in cimetidine plasma concentration-time curves following oral administration has been studied extensively [1–9]. This phenomenon occurs only after oral administration of cimetidine in the fasted state, and double peaks are not present after intravenous administration or oral administration in the fed state. The incidence of this occurrence with cimetidine is 50–75% in humans [1]. Double peaks have also been observed with other drugs, including flurbiprofen [10], penicillamine [11], aspirin [12], furosemide [13] and acetaminophen [14]. Several hypotheses based on region-dependent variation in absorption [15], enterohepatic recirculation [4,5], variable gastric emptying and intestinal transit rates [1] and intestinal bacterial reconversion of biliary metabolite [16] have been proposed to account for these observations.

Enterohepatic recirculation effects are highly unlikely to contribute to this phenomenon based on the observations that double peaks do not occur following intravenous administration of cimetidine. Also, the extent of biliary secretion of cimetidine and metabolites were found to be insufficient to contribute to a second plasma level peak since only 1.8% of the total dose of cimetidine was recovered in bile [16]. It has also been recently demonstrated that cimetidine sulfoxide levels in rat intestinal perfusion studies were similar in antibiotic-treated and untreated rats [15].

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Thus, intestinal bacterial re-conversion effects may not be sufficient to account for secondary maxima. Cimetidine absorption has been shown to be lower in rat jejunum than in duodenum and ileum [17] and has been postulated as a possible explanation for plasma level double peaks in humans [18]. The observation of double peaks, however, in perfusion studies with jejunostomy patients by Voinchet et al. [19] appears to counter such a proposition.

The possible role of gastrointestinal motility as a major determinant of the phenomena of secondary maxima occurring only in the fasted state has been previously addressed [7,20]. Such a possibility is quite founded since gastrointestinal motility patterns are unique in the fasted state in humans and dogs and is altered drastically in the fed state in the two species. Gastrointestinal motility in the fasted state is characterized by cyclical fluctuations in contractile activity of the stomach and intestine and is composed of four phases [21]. The initial basal phase, phase I, is characterized by a complete lack of contractions. This is followed by a 'preburst' activity, also termed phase II, wherein the contractions increase in number and activity. The third phase, phase III, is characterized by large-amplitude contractions that occur at the maximum frequency observable. Phase III is followed by an intermediate stage, phase IV, before the cycle repeats itself. Phase IV is sometimes absent and is a transition period between the intense activity in phase III and the basal quiescent phase I. This cyclical pattern of contractile activity is termed the migrating motility complex (MMC) since, (a) it migrates in an aboral direction, (b) motility is a general term to describe contractile activity, and (c) the event is composed of many phases. The regulation of MMC has been reported to be under both humoral and neural control. Of the hormones, motilin is widely implicated in the initiation of phase III activity. The duration of the various phases or phase lengths have been reported to be similar in dogs and humans [21,22], and the entire cycle in humans is on average about 90 min and is highly variable [21]. In general, duration of phase III activity is fairly constant and is altered only by completely abolishing MMC. The duration of phases I and II, however, vary and are inversely related. Phase II activity is influenced by nerve activity and by intraluminal contents. Thus, cholinergic nerves enhance and adrenergic nerves suppress phase II activity. Also, increased intraluminal contents increase duration of phase II. Conversely, total parenteral nutrition was accompanied by a decrease in duration of phase II activity [21].

Woodtli and Owyang [23] reported that duodenal pH fluctuates with MMC phases. The authors observed that a duodenal pH greater than 7.0 was essential for phase III initiation. It is likely that the pharmacologic action of an H2-receptor antagonist such as cimetidine (weak base, $pK_a = 7.1$) would increase gastric pH and duodenal pH. This could directly affect cimetidine absorption via a pH-dependent absorption effect or indirectly modulate absorption by affecting phase II duration and overall MMC. Cimetidine absorption in rats was found to be pH-dependent and the absorption rate constant at pH 6 was about 1/5 of that obtained at pH 8 [24]. It is also possible that H2-receptor antagonists affect gastrointestinal motility by altering histamine action on smooth cells in the gastrointestinal tract.

In this study, we report the results of the pharmacokinetics of cimetidine following its administration in fasted subjects in various phases of antral motility along with simultaneous monitoring of gastrointestinal motility and pH in different regions of the gastrointestinal tract. The inter-relation between pharmacokinetic parameters and motility parameters were carefully examined to ascertain if the occurrence of secondary maxima in cimetidine plasma levels is directly attributable to gastrointestinal motility patterns.

2. Materials and methods

2.1. Drugs and reagents

Cimetidine (Tagamet®) was obtained from SmithKline Beecham Pharmaceuticals (Philadelphia, PA). All other chemicals for the assay were purchased from Sigma Chemical Company (St. Louis, MO), and HPLC grade solvents were used in all of the assays.

2.2. Study protocol

Twelve healthy subjects (nine males and three females) gave written informed consent to participate in the study. This investigation complied with tenets of the Declaration of Helsinki promulgated in 1964 and was approved by the University of Michigan Institutional Review Board. The subjects were 19–39 years of age (25 ± 5.1 years) and were within 20% of their ideal body weight (76.8 ± 12.6 kg). Subjects were deemed healthy based on medical history, physical examination, complete blood count and serum chemistries. Persons with a history of renal, hepatic, gastrointestinal, cardiovascular or psychiatric disease were excluded from the study, as were subjects with a history of clinical illness within 2 weeks of the start of their participation in the study. In addition, all subjects were medication free, including over-the-counter agents, for at least 3 days prior to the study.

Following a 10-h overnight fast, subjects were admitted to the clinical research center and the multilumen tube containing manometric [25,26], and pH meter catheters was introduced orally after the upper throat was locally anesthetized with benzocaine (Bentlich L.P., Waukegan, IL). The multilumen tube contained eight catheters (Synectics Medical Inc., TX) and manometric (motility) and pH (pH Meter SYN-02 System, Synectics Medical Inc., TX) recording sites were positioned, under fluoroscopic examination, in the antrum, the duodenum and the proximal jejunum. The tube was 200 cm long with an external diameter of 5 mm. Of the five available motility ports, three were used in

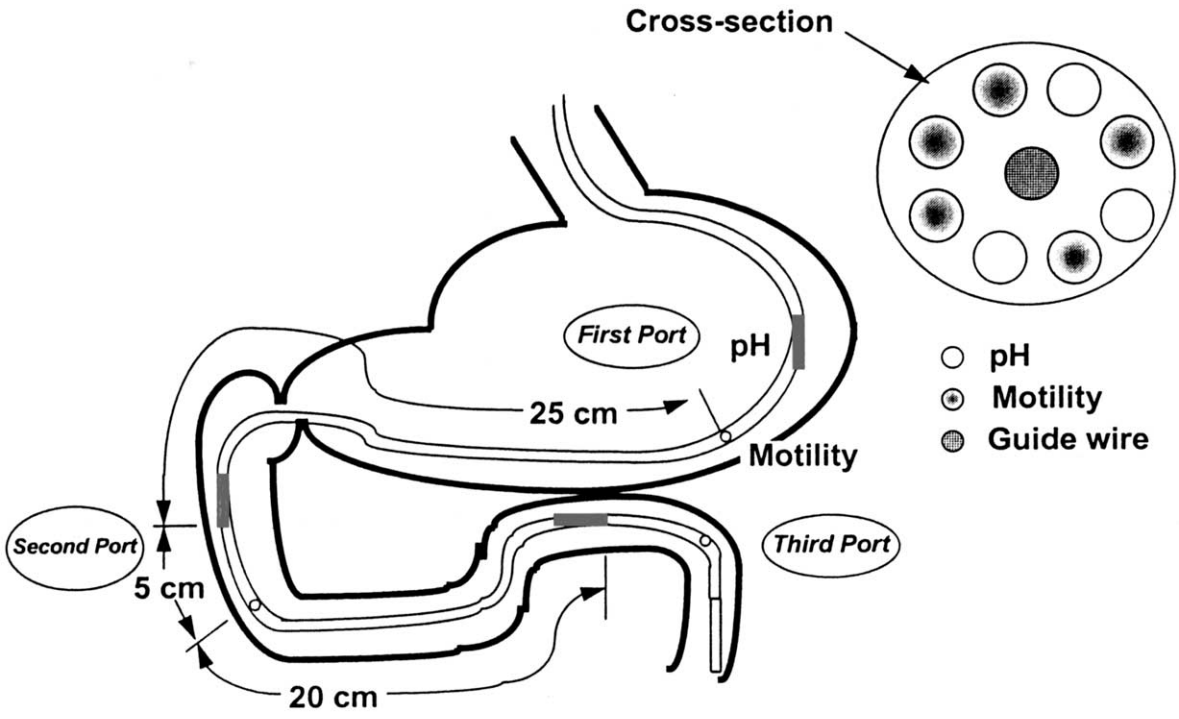

Fig. 1. Schematic of motility and pH probes in the gastrointestinal tract.

this study. A 5 cm weighted tip was located on the distal end of the tube to facilitate the passage of the tube into the jejunum. In addition, a guide wire was used during the insertion of the tube to ease the passage of the tube through the pylorus. The distance between the first motility probe and the second motility probe was 30 cm, and that between the second and third probes was 25 cm. The distance between each motility probe and the corresponding pH probe was 5 cm (Fig. 1). Once the placement was verified, the subjects remained seated upright throughout the course of the study in order to minimize movement of the tube and disruption of the pH and motility measurements. Following placement of the tube and positioning of the motility and pH probes, both motility and pH were monitored for a period approximating two MMC cycles before administration of cimetidine. Administration of cimetidine was carried out in three treatment regimens as follows:

Treatment regimen 1 (Quiescent p.o.): Cimetidine 300 mg solution (Tagamet® oral solution, 300 mg/5 ml) was administered orally during early phase I of MMC (quiescent phase) with 20 ml of water. Early phase I of MMC was defined as 15 min following the end of phase III.

Treatment regimen 2 (Active p.o.): Cimetidine 300 mg solution was administered orally at the initiation of phase II (active phase) with 20 ml of water.

Treatment regimen 3 (Active i.v.): Cimetidine 300 mg solution (Tagamet® injection, 300 mg/2 ml) was infused intravenously for 10 min with an infusion pump at the initiation of phase II (active phase). At the start of the infusion, the subject was given 25 ml of water to drink.

Each subject participated in the three treatment regimens in a randomized crossover fashion. A washout period of at least a week was allowed between each administration. However, three of the twelve subjects could not undergo intravenous administration treatment due to the inability to place indwelling catheters. The data from Subject 11 in treatment regimens 1 and 2 were excluded due to improper time of dosing. Also, the data from one subject (Subject 4) in treatment regimen 1 was excluded in the plasma-motility correlations due to artifacts in motility measurements.

2.3. Collection of blood samples and drug analysis

Blood samples were obtained through a forearm venous catheter for multiple blood draws and placed in heparinized Vacutainer® vials (Becton Dickinson, Rutherford, NJ). The sampling time points were at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 7, and 8 h for treatment regimens 1 and 2. For treatment regimen 3, blood samples were withdrawn at 0.16, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8 h. The blood samples were centrifuged and the plasma immediately stored at −20°C until being assayed.

The concentration of cimetidine in plasma samples was determined with a high performance liquid chromatography (HPLC) method. The HPLC system consisted of an HPLC pump (Waters 501, Waters Corporation, Milford, MA), an autoinjector (Waters 712, Waters Corporation, Milford, MA) and an UV detector (KRATOS Spectroflow 773, Applied Biosystems, Ramsey, NJ). The mobile phase consisted of a mixture of 0.067 M potassium–sodium phosphate buffer containing potassium chloride 10 g/liter, and

acetonitrile (60:40%, v/v) [27]. The separation was performed on a Nucleosil 100SA ion exchange column (10 μm, 250 × 4.6 mm, Alltech). The UV absorption was recorded at 228 nm and ranitidine was used as an internal standard. 20 μl of the internal standard solution (200 mg/ml), 250 μl of Na_2SO_4 solution (40 mg/ml) and 9 ml of ethyl acetate were added to 0.5 ml of the sample. After vortexing for 2 min the mixture was centrifuged at 2500 rpm for 10 min. The ethyl acetate layer was transferred to a fresh tube and evaporated to dryness under nitrogen. The residue was reconstituted in 200 μl of the mobile phase, vortex-mixed, and filtered (0.45 μm, Acrodisc®, Gelman Sciences). 20 μl of the filtered reconstituted solution was then injected immediately onto the column. The retention times of cimetidine and ranitidine were 7.3 and 14.3 min, respectively. Standard calibration curves were constructed with cimetidine solutions in the concentration range of 0.2 μg/ml to 10 μg/ml. The intra-day coefficient of variation (CV) of the assay was 5.25 and 3.62% at a cimetidine concentration of 0.2 and 10 μg/ml, respectively. The corresponding inter-day CV at the two cimetidine concentrations was found to be 26.68 and 8.23%. The limit of quantitation (LOQ) was set at the lowest concentration of cimetidine in the calibration curve. The detection limit (LOD) of the assay was 0.02 μg/ml.

2.4. Monitoring of motility and pH

Degassed deionized distilled water was perfused at a constant rate of 0.1–0.2 ml/min through the motility ports (Fig. 1) with the aid of a pneumohydraulic system. The pressure was measured with a capillary infusion pump system with pressure transducers connected to a meter, a transducer amplifier and a Model 4600 Data acquisition signal analysis system (DASA), (Gould Inc., Valley View, OH). Intraluminal pressure was transformed into electrical signals via the strain gauge transducers and recorded on a thermal chart recorder (TA2000) as well as converted to text file on the computer using DASA VIEW II computer software (Gould Inc., Valley View, OH) at a data sampling rate of 10 per second. The voltage output from the pH meters were also converted to text file by DASA VIEW II software and stored in the computer for further analysis.

2.5. Data analysis

2.5.1. Pharmacokinetic parameters

Maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained from experimental observations. The number of peaks in plasma concentration- time curves was calculated based on the intra-day CV (5.25%) of the cimetidine assay. Thus, an increase in plasma cimetidine concentration of twice the intra-day CV, 10.5% compared to the concentration at the previous sampling time-point was judged to be a peak. The area under the cimetidine plasma concentration–time curve (AUC), and the mean residence time (MRT) were determined by a trapezoidal method with extrapolation. The bioavailability after oral administration (regimens 1 and 2) was estimated from the ratio of AUC obtained for the oral dose to that obtained following intravenous administration of cimetidine (regimen 3). Pair-wise two-tailed Student's *t*-tests were performed to ascertain differences in pharmacokinetic parameters obtained with the two oral administration regimens.

2.5.2. Motility and pH data

The converted data for each motility and pH channel was analyzed using software designed in our laboratories. Briefly, this program allows the data files to be analyzed using filtering variables that include sampling rate, minimum slope, minimum peak height and minimum width. After the noise was filtered and smoothed by Satovitzky–Golray method [28], peak detection was carried out. Contractile activity was summarized according to peak timing, frequency and area under peak. The total peak area obtained over a period of every 0.04 h or 2.4 min were pooled and represented activity at that time point. A normalization procedure was then carried out to obtain a normalized motility index, M, that is defined by the following equation:

$$M_i = P_i / \sum_{i=1}^{n} P_i$$

where M_i = motility index at i^{th} time point (dimensionless); P_i = pooled peak area at i^{th} time point (mm^2 per 2.4 min); n = number of time points (multiples of 2.4 min).

The normalization procedure was included such that comparisons between different subjects with widely differing magnitudes of motility could be undertaken. Plots of motility index as a function of time would provide the classic patterns of low, medium and rapid spiking activity encountered in literature. A cumulative normalized motility index was then obtained wherein the total cumulative motility index is unity at the end of the monitoring period. The cumulative normalized motility index from the time of administration (time zero) to 5 h following administration was used in the analyses of phase III contractile activity. Two separate sets of criteria were applied in order to evaluate the ability to match plasma peaks in a realistic and consistent manner. Thus, in the first set a phase III contraction or 'regular spiking activity' was judged to have occurred if the total increase in cumulative normalized motility index was greater than 7.5% or 0.075 units over a period of 14.4 min. In the second set, a phase II contraction was judged to have occurred if the total increase in cumulative normalized motility index was greater than 10% or 0.10 units over a period of 14.4 min.

The peaks in cumulative normalized motility index obtained with the above two sets of criteria were evaluated for each subject in the two oral administration groups and compared with plasma cimetidine peaks for the corresponding subject and administration mode. The time period of

14.4 min was chosen because it was the closest integral multiple of the periodicity in motility readings (integrated every 0.02 h or 2.4 min) to the plasma sampling time of every 15 min over the first 2.5 h (slightly over average T_{max}) of the study.

The output voltage from the pH meters, following conversion to text file, were used to obtain the pH value using the following equation:

$$pH = (voltage) \times 3 + 1.0$$

The conversion of voltage to pH values was achieved using software developed in our laboratories.

3. Results and discussion

For clarity purposes the three treatment regimes will henceforth be designated as follows:

- Treatment regimen 1 – Quiescent phase oral administration (Q-phase).
- Treatment regimen 2 – Active phase oral administration (A-phase).
- Treatment regimen 3 – Active phase intravenous administration (IV).

3.1. Duration of MMC cycles

Fig. 2 shows the mean duration of phase I, II and III of MMC cycles obtained for the three administration groups along with baseline values that were calculated using MMC cycles obtained before cimetidine administration. The baseline MMC cycles ranged from 67 to 218 min in this study. The mean duration of the MMC cycles in Q-phase (Quiescent p.o.), A-phase (Active p.o.), IV (Active i.v.), and the baseline, was 91.6 ± 26.5, 103.9 ± 30.6, 111.2 ± 50.9, and 143.8 ± 46.4 min (mean ± SD), respectively. It is clear that

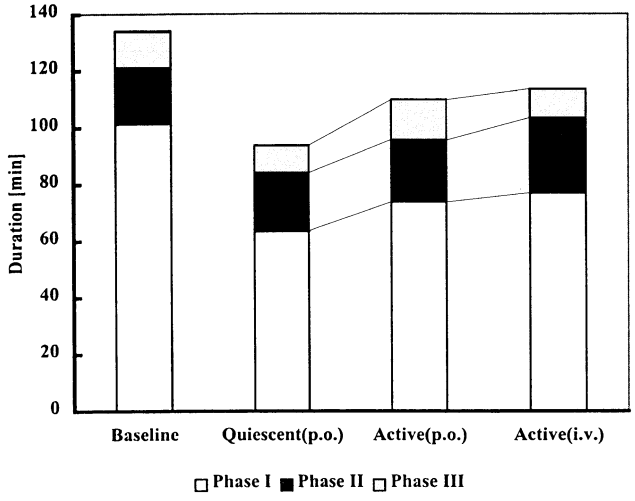

Fig. 2. Mean duration of various phases of MMC cycles for various treatment regimes.

MMC cycle appears to be shortened quite significantly upon administration of cimetidine in all three groups. However, an examination of Fig. 2 suggests that this is almost totally due to a significant shortening of mean duration of phase I upon cimetidine administration. Thus, it was found that the mean duration of phase I following cimetidine administration in all three groups was shorter than that observed in baseline MMC, with the effect being most pronounced for group Q. Fig. 2 also indicates that mean duration of phase II or phase III in the cimetidine treated groups are not significantly different from baseline values.

3.2. Plasma profiles of cimetidine

The total number of plasma peaks (0–5 h) obtained from 11 subjects (excluding subject 11) in Q-phase and A-phase using the criteria described earlier was 24 and 27, providing peak number values of 2.2 ± 0.9 and 2.5 ± 1.3, respectively. In both oral administration groups, multiple plasma peaks were observed in eight out of the eleven subjects for an incidence rate of ~73%. Thus, the effect of phase of administration on the incidence of the double peak phenomena was not significant. On the other hand, the plasma concentration after the intravenous administration did not show the double peak phenomenon in any subject. The mean bioavailability in the two oral modes of administration was calculated using the mean values of AUC from the same nine subjects as in the intravenous group.

3.3. Comparison of pharmacokinetic parameters

The mean pharmacokinetic parameters following oral and intravenous administration of cimetidine are shown in Table 1. The values represent the mean obtained from 11 subjects for Q-phase and A-phase, and from nine subjects for IV administration. Table 2 shows the values of the pharamacokinetic parameters $AUC_{0-\infty}$, C_{max}, C_{max1}, T_{max}, and T_{max1} obtained with each individual subject following oral administration of cimetidine in the quiescent phase or active phase of antral motilty. Table 2 also lists *P*-values obtained by pair-wise comparison in two-tailed Student's *t*-tests. It is evident from an examination of Table 2 that $AUC_{0-\infty}$,

Table 1
Mean pharmacokinetic parameters of cimetidine following oral or intravenous administration

Parameter	Q-phase	A-phase	IV
$AUC_{0-\infty}$ (μg.h/ml)	5.69 ± 1.62	4.54 ± 1.89	9.03 ± 1.94
Number of peaks	2.18 ± 0.87	2.45 ± 1.29	–
C_{max1} (μg/ml)	1.37 ± 0.88	0.96 ± 0.58	–
C_{max} (μg/ml)	1.68 ± 0.72	1.33 ± 0.59	12.24 ± 3.53
T_{max1} (h)	1.18 ± 0.34	0.89 ± 0.36	NA
T_{max} (h)	2.02 ± 0.83	1.84 ± 0.72	NA
MRT (h)	4.47 ± 1.33	4.58 ± 1.79	2.89 ± 1.44
Number of subjects	11	11	9
Bioavailability[a] (%)	60.53 ± 17.38	50.02 ± 20.13	100

[a] Bioavailability estimates were obtained using nine subjects.

Table 2
Individual pharmacokinetic parameters obtained following oral cimetidine administration in the quiescent (Q) or active phase (A) of antral motility ($n = 11$)[a]

Subject	AUC $_{0-\infty}$ (μg.h/ml)		C_{max} (μg/ml)		C_{max1} (μg/ml)		T_{max} (h)		T_{max1} (h)	
	Q	A	Q	A	Q	A	Q	A	Q	A
1	5.68	3.15	1.69	1.73	1.22	0.88	2.00	1.50	1.00	0.50
2	6.11	4.36	1.59	1.05	1.55	0.87	1.00	2.50	1.00	0.75
3	2.41	1.78	0.45	0.38	0.24	0.38	1.50	1.00	0.75	1.00
4	7.15	4.07	2.13	0.88	1.56	0.50	3.00	3.50	1.75	0.50
5	5.52	4.12	1.41	1.13	1.04	0.43	2.25	2.00	1.50	0.50
6	5.52	5.49	1.43	1.50	0.34	0.82	3.50	2.00	1.00	0.75
7	6.17	7.79	2.87	2.18	2.87	2.18	1.00	1.75	1.00	1.75
8	6.86	6.83	2.77	1.83	2.77	1.83	1.75	1.00	1.75	1.00
9	5.52	4.52	1.49	1.64	1.11	1.07	3.00	1.75	1.25	0.75
10	8.20	5.96	1.87	1.79	1.83	1.79	1.75	1.25	1.00	1.25
12	3.43	1.89	0.85	0.46	0.53	0.42	1.50	2.00	1.00	1.00
Mean	5.69	4.54	1.68	1.33	1.37	0.96	2.02	1.84	1.18	0.89
SD	1.62	1.89	0.72	0.59	0.88	0.58	0.83	0.72	0.34	0.38
P-value[b]	0.020		0.025		0.036		0.518		0.128	
Q > A[c]	10/11		8/11		9/11		7/11		7/11	

[a] Q, quiescent phase administration; A, active phase administration.
[b] Pair-wise two-tailed Student's t-test.
[c] Number of subjects exhibiting higher value in Q-phase than in A-phase.

C_{max} and C_{max1} values following oral administration in the quiescent phase were significantly higher than the corresponding values obtained following oral administration in the active phase ($P < 0.05$, pair-wise two-tailed Student's t-tests). No significant differences were found for T_{max}, T_{max1} (and MRT, not shown) between the two modes of oral administration ($P > 0.1$). However, in seven out of eleven subjects both T_{max1} and T_{max} were significantly shorter ($P = 0.004$), following administration in the active phase of antral motility. Also, excluding only one individual out of eleven (Subject 7, who exhibited much lower T_{max1} in the quiescent phase), revealed that T_{max1} was significantly higher in the quiescent phase compared to that observed in the active phase of oral administration ($P = 0.033$). Fig. 3 shows comparison plots of AUC, C_{max1} and T_{max1} obtained for each subject in the two modes of oral administration. A comparison of oral bioavailability of cimetidine in individual subjects following oral administration in the quiescent or active phase of antral motility is shown in Table 3. The bioavailabilities were calculated using $AUC_{0-\infty}$ values obtained following intravenous administration in the corresponding individual. It is seen that six of the nine subjects exhibited substantially higher bioavailability in the quiescent phase of administration ($P = 0.006$, pair-wise two-tailed Student's t-tests). Comparison of the values for eight of the nine subjects also reveals a highly significant difference ($P = 0.013$); for all nine subjects bioavailability following administration in the quiescent phase still appears to be significant at a 90% confidence level ($P = 0.063$). It is apparent from the comparison of various pharmacokinetic parameters that the oral administration of cimetidine in the quiescent phase of antral motility results in significantly higher absorption compared to that obtained with its oral administration in the active phase of antral motility. Together with the shorter T_{max1} values following oral administration in the active phase of antral motility, the overall pharmacokinetic behavior of cimetidine absorption may be compatible with the following scenario:

(a) That oral administration in the quiescent phase of antral motility results in a greater extent of absorption (higher bioavailability (AUC), C_{max}, C_{max1}), because emptying is gradual and allows for a greater residence time of cimetidine in the duodenum wherein cimetidine permeability has been shown to be much higher than in the jejunum or ileum [17,29];
(b) Conversely, oral administration in the active phase of antral motility results in lower absorption because cimetidine solution is emptied into the duodenum at a faster rate (lower T_{max1}, C_{max1}), thus shortening the residence time in the duodenum. It is also possible that rapid emptying of gastric contents could lower duodenal pH to an extent whereby cimetidine permeability is lowered [24].

The pH profiles monitored in the present study did not exhibit unusual or distinct patterns that could be correlated with differences in the pharmacokinetic parameters in the two oral modes of administration. The mean of average pH of all subjects over the time period 0–3.5 h following oral administration were as follows: gastric pH in Q-phase and A-phase was 4.1 ± 1.1 and 4.4 ± 1.4, respectively. Thus, oral administration of cimetidine appears to elevate gastric pH and is consistent with that expected for a weak base. The corresponding mean pH values in the duodenum was

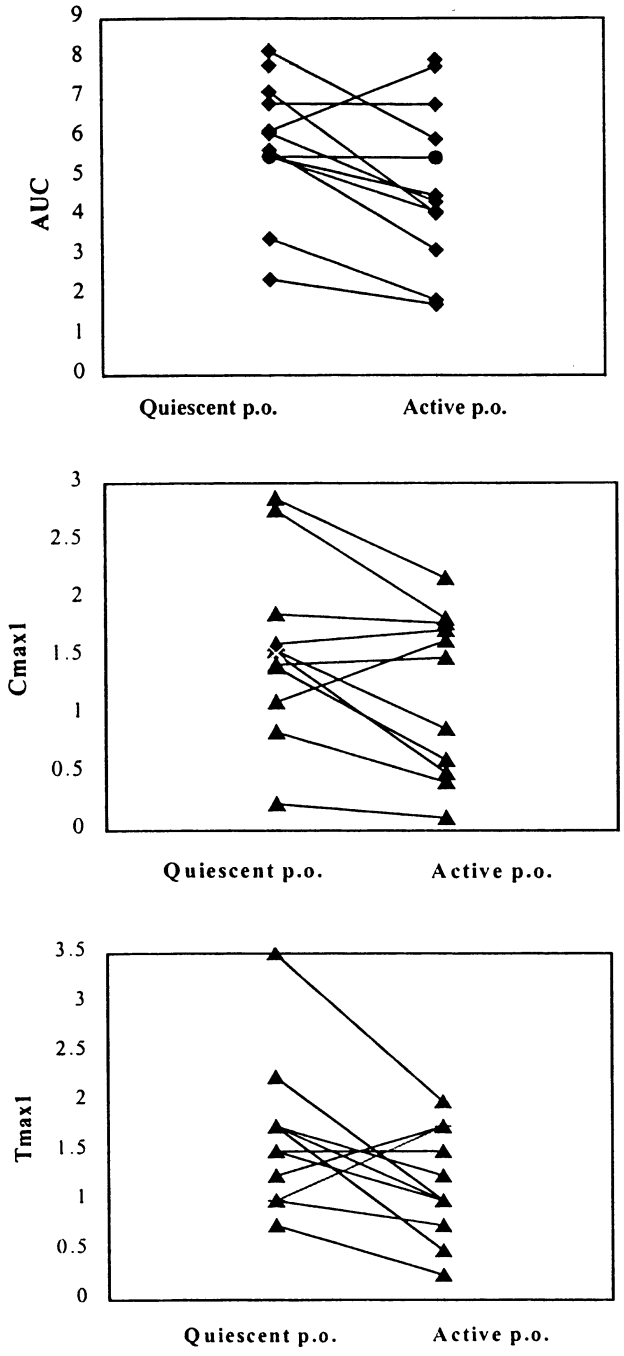

Fig. 3. Comparison plots of AUC, C_{max1}, and T_{max1} obtained with each subject following oral cimetidine administration in quiescent phase or active phase of antral motility.

5.4 ± 1.2 (range 2.3–6.2) in the Q-phase and 5.7 ± 0.3 (range 5.0–6.0) in the A-phase. It was also observed that neither gastric nor duodenal pH exceeded the pK_a of cimetidine over the entire 5 h monitoring period. Mummaneni et al. [9] reported that gastric pH influenced the appearance of double peaks following oral cimetidine administration in dogs. The authors showed that oral administration at low gastric pH (≤1.0) led to double peaks whereas that administered at gastric pH ≥ 5 always resulted in single peaks. Erratic absorption patterns were observed following oral administration of cimetidine at gastric pH ranging from 3 to 5. The authors also demonstrated a fairly linear correlation between gastric pH and pharmacokinetic parameters such as C_{max} and T_{max}. It was argued that gastric pH influenced gastric emptying and thus controlled pharmacokinetic behavior. In our present study, differences in gastric pH and/or duodenal pH in the two modes of oral administration cannot explain the differences in pharmacokinetic parameters or the multiple peaks in plasma cimetidine observed. The lack of distinct correlations of pH variations with plasma profiles indicates that motility patterns may be directly responsible for not only the differences in pharmacokinetic parameters but also the phenomenon of secondary maxima with cimetidine.

3.4. Correlation of plasma profiles with motility patterns

Figs. 4A and B show typical overlay plots of plasma profiles and antral motility for Subject 9 following oral administration in the quiescent and active phases of antral motility, respectively. Figs. 4A and B also show overlay plots of cumulative normalized motility index and motility peaks identified using an increase of 7.5% in the index over 14.4 min for the two phases of administration. Fig. 4C shows an overlay plot of plasma profile and antral motility following intravenous administration in the active phase of antral motility. The lower part of Fig. 4C shows a profile of the corresponding duodenal motility for Subject 9. The cumulative normalized motility index data for each subject obtained following oral administration of cimetidine in the quiescent phase or active phase of antral motility was analyzed according to the criteria described above. The motility peaks so identified were then compared with

Table 3
Comparison of bioavailability following oral administration of cimetidine in the quiescent or active phase of antral motility (n =9)

Subject	$AUC_{0-\infty}$, (μg.h/ml)			Bioavailability (%)	
	Q-phase	A-phase	IV	Q-phase	A-phase
2	6.11	4.36	8.86	68.98	49.23
3	2.41	1.78	6.96	34.62	25.50
4	7.15	4.07	8.46	84.58	48.12
5	5.52	4.12	11.03	50.02	37.33
6	5.52	5.49	6.44	85.67	85.14
7	6.17	7.79	10.73	57.48	72.62
8	6.86	6.83	12.26	55.93	55.73
9	5.52	4.52	8.56	64.49	52.78
12	3.43	1.89	7.97	42.99	23.71
Mean	5.41	4.54	9.03	60.53	50.02
SD	1.55	1.99	1.94	17.38	20.13
P-value[a]				0.063	

[a] Pair-wise two-tailed Student's t-test.

plasma cimetidine peaks. A motility peak was considered to correspond to a plasma peak provided (a) the motility peak occurred prior to the plasma peak and/or (b) that the time of occurrence of the two peaks were within 15 min of each other. The second provision was included due to the observation that motility peaks exhibited a classical S-shape in

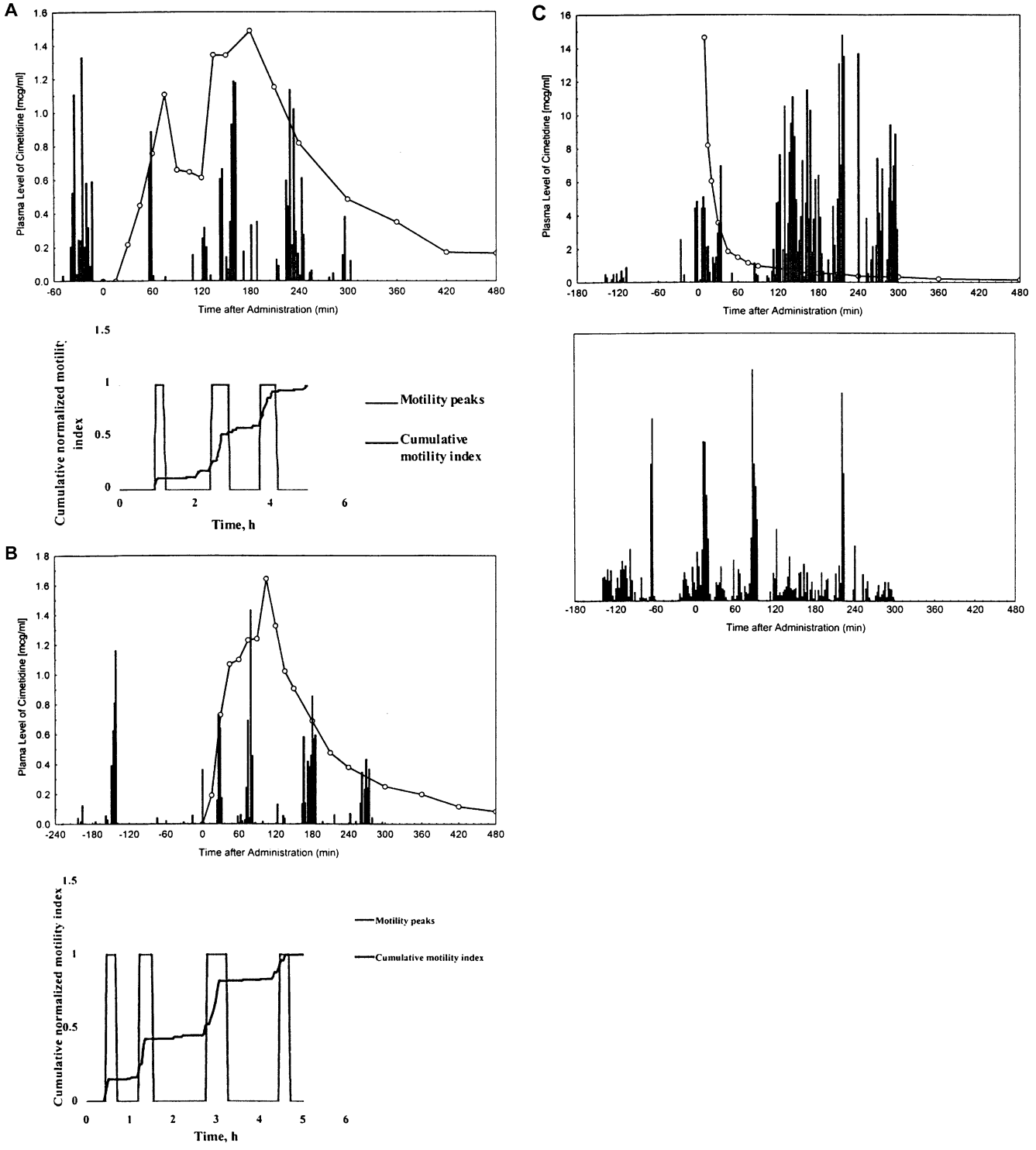

Fig. 4. (A) Overlay plot of plasma concentration of cimetidine and antral motility (upper figure) and overlay plot of cumulative normalized index and motility peaks (lower figure) as a function of time for oral administration in the quiescent phase (Subject #9). (B) Overlay plot of plasma concentration of cimetidine and antral motility (upper figure) and overlay plot of cumulative normalized index and motility peaks (lower figure) as a function of time for oral administration in the active phase (Subject #9). (C) Overlay of plasma concentration of cimetidine and antral motility (upper figure) and duodenal motility (lower figure) as a function of time for intravenous administration in active phase (Subject #9).

most cases. Thus, contractile activity showed an onset followed by a plateau spanning about 10–15 min (Figs. 4A and B). Correlation plots of motility peaks with plasma peaks were constructed using both onset time as well as plateau time for each motility peak. Figs. 5 and 6 show the correlation between motility peaks and plasma peaks obtained following oral administration of cimetidine in the quiescent and active phase, respectively. Excellent linear correlations between motility and plasma peaks were obtained for both phases of oral administration using either the onset or plateau values for motility peaks; $r^2 = 0.963$ and 0.959 for active phase (onset and plateau) and 0.928 and 0.896 for quiescent phase (onset and plateau). It is evident that the comparison is better and more appropriate if onset values are used. Thus, only correlations using onset values will be discussed. More importantly, the slopes of these correlation plots are close to unity indicating that the motility peaks and the corresponding plasma peaks occur at about the same time period. The slopes were 1.079 and 0.923, for the active and quiescent phase correlations, respectively. It was also found that 20/27 plasma peaks or 74.1% in the active phase and 14/22 plasma peaks or 63.6% in the quiescent phase were associated with motility spikes. These comparisons are shown in Figs. 7 and 8. Similar linear correlations between motility and plasma peaks were also obtained using a 10% increase in motility index over a 14.4-min span (not shown). Thus for the active phase administration 20/27 plasma peaks were accounted for with a linear correlation slope of 1.069 and a r^2 value of 0.969. However, for quiescent phase administration evaluation of motility spikes at a 10% level could account for only 10/22 peaks (45.5%) with a linear slope of 0.904 and a r^2 of 0.939.

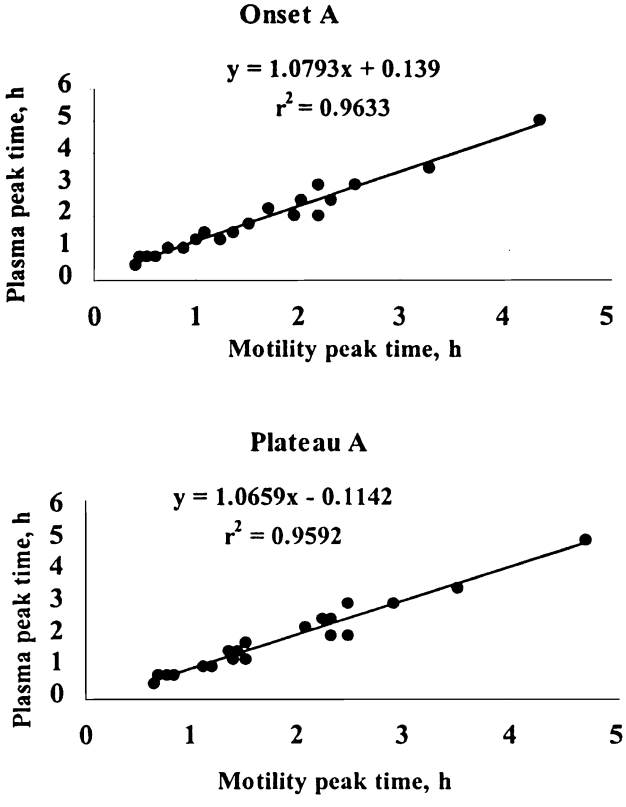

Fig. 5. Correlation between antral motility peak time and plasma peak time following oral administration of cimetidine in the active phase of antral motility. Onset of motility peak (upper figure) and plateau of motility peak (lower figure). Motility peak identification basis: 7.5% in 14.4 min, $n = 11$.

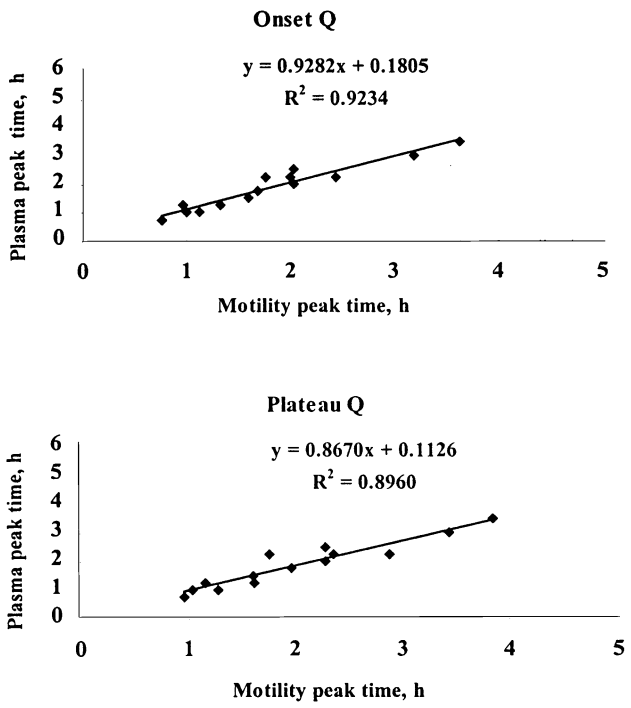

Fig. 6. Correlation between antral motility peak time and plasma peak time following oral administration of cimetidine in the quiescent phase of antral motility. Onset of motility peak (upper figure) and plateau of motility peak (lower figure). Motility peak identification basis: 7.5% in 14.4 min, $n = 10$.

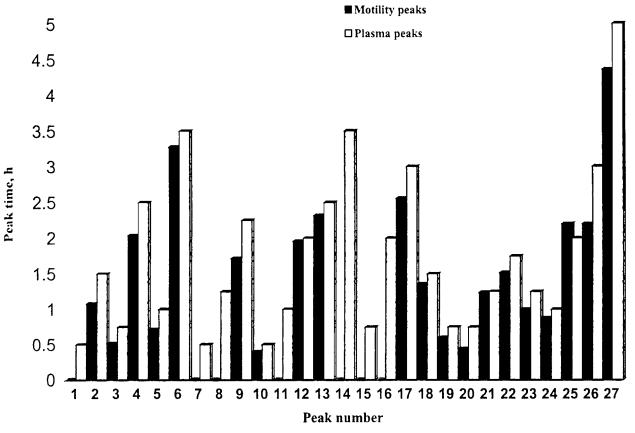

Fig. 7. Comparison plot of plasma peaks with corresponding motility peaks following oral cimetidine administration in the active phase of antral motility. $n = 11$, 20/27 plasma peaks accounted for (74.1%).

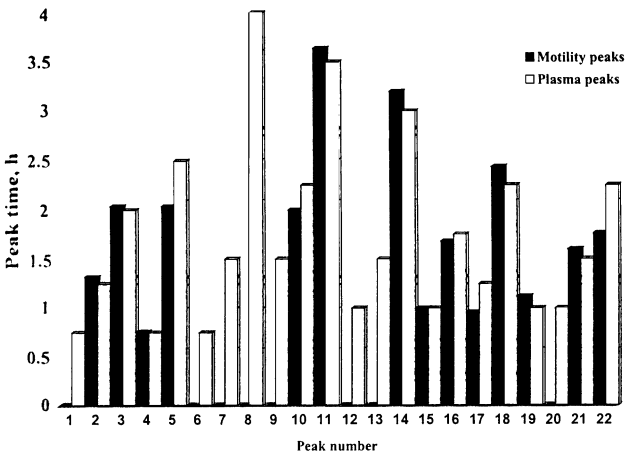

Fig. 8. Comparison plot of plasma peaks with corresponding motility peaks following oral cimetidine administration in the quiescent phase of antral motility. $n = 10$. 14/22 plasma peaks accounted for (63.6%).

4. Conclusions

The oral administration of cimetidine in the fasted state to humans during the quiescent or active phase of antral motility resulted in multiple plasma peaks. The incidence of multiple peaks was ~73% in both cases. Neither secondary nor multiple peaks were observed with intravenous administration in any of the subjects. A significant increase in bioavailability (AUC), C_{max} and T_{max} was evident for oral administration in the quiescent phase of antral motility compared to that obtained with administration in the active phase of antral motility. There were no discernible patterns in gastric pH or duodenal pH that could account for the differences in pharmacokinetic behavior or the occurrence of multiple peaks in the two modes of oral administration. Analyses of cumulative normalized motility indices in terms of an enhancement of 7.5% over roughly 15 min resulted in the identification of phase III contractile activity. Excellent correlations of such motility spikes with plasma peaks were observed for both phases of oral cimetidine administration (linear regression coefficients, $r^2 \geq 0.93$). The numbers of plasma peaks so accounted were 74.1% in the active phase and 63.6% in the quiescent phase. The overall results suggest strongly that antral motility is the primary factor responsible for variation in bioavailability and for the occurrence of secondary phenomenon when cimetidine is orally administered in the fasted state.

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