Gastric pH Influences the Appearance of Double Peaks in the Plasma Concentration-Time Profiles of Cimetidine After Oral Administration in Dogs

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The plasma concentration-time profiles of cimetidine often exhibit two peaks following oral administration of a single dose in the fasted state, while the concurrent administration of some antacids results in a lower extent as well as rate of absorption. In the present work, absorption of cimetidine after a single dose in the fasted state was studied as a function of gastric pH in male beagle dogs to determine whether gastric pH plays a role in the double peak phenomenon and/or can account for the decrease in bioavailability when antacids are coadministered. The extent of absorption of cimetidine was not influenced significantly by gastric pH, indicating that elevation of gastric pH is not the cause of decreases in the bioavailability of cimietidine when it is administered with antacids. Distinct double peaks or plateaux were noted in 8 of 10 plasma profiles when the gastric pH was 3 or below. Irregular absorption behavior was observed in 2 of 6 profiles in the pH range of 3 to 5, while single peaks were observed in all 10 profiles when the gastric pH was maintained at pH $\geq$ 5. It was concluded that gastric pH is a major factor in the generation of cimetidine double peaks. Changes in gastric pH also resulted in changes in the apparent kinetics of absorption. Below pH 5, absorption mostly followed zero-order kinetics (9 of 16 profiles) or a more complex kinetic process involving at least two components to the absorption phase (5 of 16 profiles). At gastric pH $\geq$ 5, however, absorption followed first order kinetics in 7 of 10 profiles. These differences in kinetics of absorption are postulated to arise from variations in gastric emptying as a function of pH and/or carryover effects of gastric pH into the upper intestine.

KEY WORDS: cimetidine; double peaks; bioavailability; absorption rate constant; gastric pH; intestinal pH; gastric emptying.

INTRODUCTION

When cimetidine is administered orally in a tablet or in liquid form in the fasting state, the plasma concentration-time profile frequently shows two maxima, the first at about 1 hour and the second at about 3 hours after dosing (1). The double-peak effects disappears if the drug is administered intravenously or with a meal (1). Double peaks have also been observed in the plasma level curves of several other drugs such as acetaminophen (2), aspirin (3), furosemide (4), penicillamine (5) and flurbiprofen (6) following oral administration. It has been hypothesized that variations in gastrointestinal pH may be responsible, at least in part, for the occurrence of double peaks in the plasma profiles of cimetidine following oral administration in the fasted state (7,8).

Another area where gastric pH may play a role in the absorption of cimetidine is the interaction with antacids. High potency antacids cause a signifiant reduction in the extent of absorption of cimetidine when administered concurrently as a single oral dose in the fasted state to healthy volunteers or to patients suffering from duodenal ulcers (9,10). It has been suggested that this may be a result of the elevation in gastric pH induced by antacids. Since cimetidine is a weak base (pKa = 7.1), the substantial elevation of gastric pH associated with antacid administration may create conditions unfavorable to dissolution and hence result in poorer absorption.

The objectives of the present study were to determine whether gastric pH plays a role in the generation of double peaks following oral administration of cimetidine and/or the poorer and less predictable bioavailability of this compound when coadminstered with antacids.

METHODS

Animals

Four healthy male beagle dogs weighing 14–19 kg were studied. Dogs were chosen for the study since the upper gastrointestinal tract of dogs is more similar to that of man than other available species. With respect to this study, one important similarity is that the fasted state motility cycle in dog follows a pattern and periodicity similar to that in humans. Also patterns of liquid emptying are similar, though the emptying rate constant may be a little higher and the half life shorter in dog (11). As in humans, the fasting gastric pH is usually acidic, although the basal gastric acid output appears to be lower in dogs and therefore their gastric pH is occasionally indistinguishable from intestinal pH (12).

Oral Absorption Studies

Oral absorption of cimetidine was studied after administration of a 300 mg tablet (as the free base, Tagamet®, Lot #979T13, Smith Kline and French Labs, Philadelphia PA). After a 20-hour fast (water available), a calibrated Heidelberg® capsule tethered to a string was administered to the dog with 20 ml water (more if necessary to facilitate swallowing). The dog then received one of the following treatments:

Treatment A: Famotidine (0.3–0.6 mg/kg, i.v., Pepcid®, Lot #0617S, Merck & Co., West Point PA) to raise intragastric pH above 5.0, followed after 30 minutes by cimetidine (300 mg) with 120 ml water,

Treatment B: Glutamic acid oral suspension (six or seven 500 mg tablets, Lot #9202, Solgar Co., Lynbrook NY, crushed and suspended in 60 ml water) to maintain pH be-

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tween 3.0 to 5.0, followed after 10 minutes by cimetidine (300 mg) with 60 ml water, or

Treatment C: Hydrochloric acid (100 ml, 0.1 N prepared from concentrate, JT Baker, Inc., Phillipsburg NJ) by gastric intubation to attain pH values below 3.0, followed after 10 minutes by cimetidine (300 mg) with 20 ml water.

At appropriate intervals, up to 6 hours after administration of cimetidine, approximately 1.5 ml of blood was collected into a 3 ml plastic syringe through an indwelling heparinized catheter placed in the foreleg vein of the dog. Samples were transferred to plastic tubes containing no preservatives (Curtin Matheson Scientific, Inc., Houston TX) and immediately centrifuged for 1 minutes at 12,000 rpm in a microcentrifuge (Model 59A microcentrifuge, Fisher Scientific, Philadelphia PA). Supernatant plasma was removed and stored in the freezer at −8°C until time of analysis. The treatments were non-randomized, with a washout period of at least 5 days between treatments. Each dog received each of the treatments at least two times.

During oral absorption studies, the pH of the stomach was monitored continuously by radiotelemetry, using the Heidelberg® capsule technique (Heidelberg International, Norcross GA). Youngberg *et al.* have investigated this radiotelemetric technique as an alternative to other methods of monitoring gastrointestinal pH in beagle dogs (13). On the morning of the study day, the Heidelberg® capsule was activated in 0.9% saline solution and calibrated in pH 1.0 and 7.0 reference buffers (VWR Scientific, Los Angeles CA) maintained at 37°C. Calibration was considered complete when it was no longer necessary to adjusts the reading of each reference solution upon switching solutions. The calibrated capsule was tied to a string (Stren® fishing line, Dupont, Wilmington DE), marked at 10 cm intervals, and administered to the dog. The string was taped to a rubber bite bar placed in the dog's mouth to prevent it from chewing the string and to keep the capsule suspended in position in the stomach (about 50 cm from the mouth) for the duration of the study. Gastric pH was read directly from the dial display every ten minutes during the first hour after cimetidine administration and at all sampling times. At the end of the study, the Heidelberg® capsule was retrieved orally and the calibration rechecked in pH 1.0 and 7.0 reference buffers at 37°C. If the calibration was off by more than 0.5 pH units, the capsule was considered faulty and the data discarded (1 of 35 experiments).

Gastric pH values read in the first hour after cimetidine administration ($n = 7$) were used to calculate the mean gastric pH for each study. The pH behavior was then categorized into low pH ($pH \leq 3$), medium pH ($3 < pH < 5$) and high pH ($pH \geq 5$) groups. These groupings corresponded exactly to the three types of pretreatment.

Intravenous Studies

The distribution/elimination kinetics of cimetidine were determined for each dog from the plasma concentration-time data obtained after an i.v. bolus dose of 150 mg (as the HCl salt equivalent to 300 mg free base/2 mL, Tagamet® Injection, Smith Kline and French Labs, Philadelphia PA). For three of the four dogs, the i.v. profiles were obtained from previous studies (11).

Plasma Sample Analysis

Chemicals. Cimetidine, codeine and famotidine were purchased from Sigma Chemical Co., St. Louis MO. All other chemicals/solvents were of reagent/HPLC grade and were obtained commercially.

Assay Method. Plasma samples were analyzed for cimetidine content using codeine as an internal standard. The HPLC system was equipped with a microcomputer-operated sampler (Model 728 Autosampler, Micromeritics, Norcross GA), an automatic switching valve fitted with an external loop injector (Valco Instruments Co., Inc., Houston TX), a dual piston pump (Spectroflow 400 Solvent Delivery system, Kratos, Ramsay NJ) and a variable wavelength UV detector (Spectroflow 773 Absorbance Detector, Kratos, Ramsay NJ) operated at 0.01 a.u.f.s. and 228 nm. A reversed-phase silica column (Partisil 10 ODS-3, Whatman Inc., Clifton NJ), 25 cm long and 0.46 mm in diameter, was used. The mobile phase consisted of 15% methanol and 85% monobasic potassium phosphate solution (0.05 M), adjusted to pH 2.7, filtered and deaerated prior to use. The flow rate was maintained at 2 ml/minute and all chromatography was performed at ambient temperature. After an injection of 100 µl, the retention time was 6–8 minutes for cimetidine and 10–12 minutes for codeine. Chromatograms were collected and peak heights determined using an automatic integrator (D-2000 Chromato-Integrator, Hitachi, Tokyo Japan). Standard curves were prepared by adding known amounts of cimetidine and codeine to plasma and treating these samples the same way as those collected during the studies. The ratios of peak heights of cimetidine to codeine were used to determine the drug content in test samples.

Data Analysis

Erratic Absorption Behavior. Erratic absorption behavior was identified according to the following criteria:

Case I: Plasma profiles were considered to exhibit double peaks when a) there were two or more plasma levels between the peaks that were lower than the two peak maxima and b) the trough plasma level was at least 10% lower than the smaller peak maximum.

Case II: Plasma profiles were considered to exhibit plateaux when a) plasma levels were within 25% of the peak maximum for at least an hour[4] and/or b) plasma levels were within 25% of the peak maximum for at least two time intervals that were thirty minutes or more away from the peak maximum.

Pharmacokinetic Parameters. Maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were recorded directly from experimental observations. The area under the cimetidine plasma concentration-time profile from 0 to 360 minutes (AUC_{0-360}) was determined by a combination of linear and log trapezoidal methods. Area under the concentration-time curve from 0 to ∞ ($AUC_{0-\infty}$) was calculated by adding the area obtained by dividing the last plasma concentration by the terminal rate constant ($k_{terminal}$) to the AUC_{0-360}. The bioavailability after an oral dose was estimated from the ratio of area under the plasma concentration-

[4] One hour corresponds to approximately one half of one elimination half life.

time profiles after an oral dose of 300 mg ($AUC_{p.o.}$) and an intravenous bolus dose of 150 ($AUC_{i.v.}$) of cimetidine, after normalizing for dose administered. The fraction absorbed (FA) in the central compartment at each sampling time was determined using the exact Loo-Riegelman Equation (14) with Proost modification (15). To determine the apparent kinetic order of absorption for individual studies, percent drug unabsorbed {(1-FA)100} was plotted as a function of time. To determine the kinetic order and absorption rate for each pH range, the means of the {(1-FA)100} values were first calculated for each sampling time, then the slope of either the rectilinear or semilogarithmic plot of mean {(1-FA)100} versus time was determined by linear regression analysis to obtain the zero order rate constant (k_0) or the first order rate constant (k_1) as appropriate. The lag time (t_0) and the time for 50% of the drug to be absorbed (t_{50}) for each pH range were then calculated from the equations of best fit for the kinetics of absorption.

Statistical Comparisons. The correlation between the mean gastric pH and each of the following variables, $k_{terminal}$, C_{max}, t_{max}, C_{max}/t_{max} and $AUC_{0-\infty}$, following oral administration was determined by least squares regression analysis (Statview™ SE + Graphics version 1.03, Abacus Concepts Inc., Berkely CA). Confidence intervals and the significance of the slopes were also determined for each correlation. The mean pharmacokinetic parameters at the three pH levels were compared by one way analysis of variance ($\alpha = 0.05$). In cases where it was necessary to stabilize the variances, the parameter values were transformed logarithmically before applying statistical tests.

RESULTS

The plasma concentration vs. time profiles exhibited double peaks or pleateaux in eight out of ten studies at gastric pH $\leq$ 3. Two out of six cases in the pH 3–5 range demonstrated erratic absorption while single peaks were noted in all ten studies at pH $\geq$ 5. Figures 1A to 1D are representative plasma concentration-time profiles after oral doses of cimetidine administered under low, medium and high gastric pH conditions. Figure 2 shows the mean of cimetidine concentration (±SE) for the three pH categories plotted against time for the four dogs. Table I summarizes the effect of gastric pH on pharmacokinetic parameters of cimetidine following a single oral dose.

Regression analysis showed no significant correlation ($R^2 = 0.11$) between $k_{terminal}$ and gastric pH. Neither was there a significant difference between the elimination rate constants following oral ($x = 0.0065 \pm 0.001\ min^{-1}$) or intravenous ($x = 0.006 \pm 0.0006\ min^{-1}$) administration of cimetidine. In a separate set of experiments (16), the uptake of cimetidine by rings cut from the rat small intestine did not change significantly in the presence of glutamic acid ($p = 0.04$).

For all dogs, high gastric pH resulted in higher C_{max} values. The positive correlation between C_{max} and mean gastric pH is shown in Figure 3A ($R^2 = 0.54$, $p = 0.0001$). There was a commensurate decrease in the t_{max} of cimetidine with increasing gastric pH, as illustrated in Figure 3B ($R^2 = 0.57$, $p = 0.0001$). Accordingly, the C_{max}/t_{max} ratio increased significantly ($R^2 = 0.69$, $p = 0.0001$) suggesting an increase in

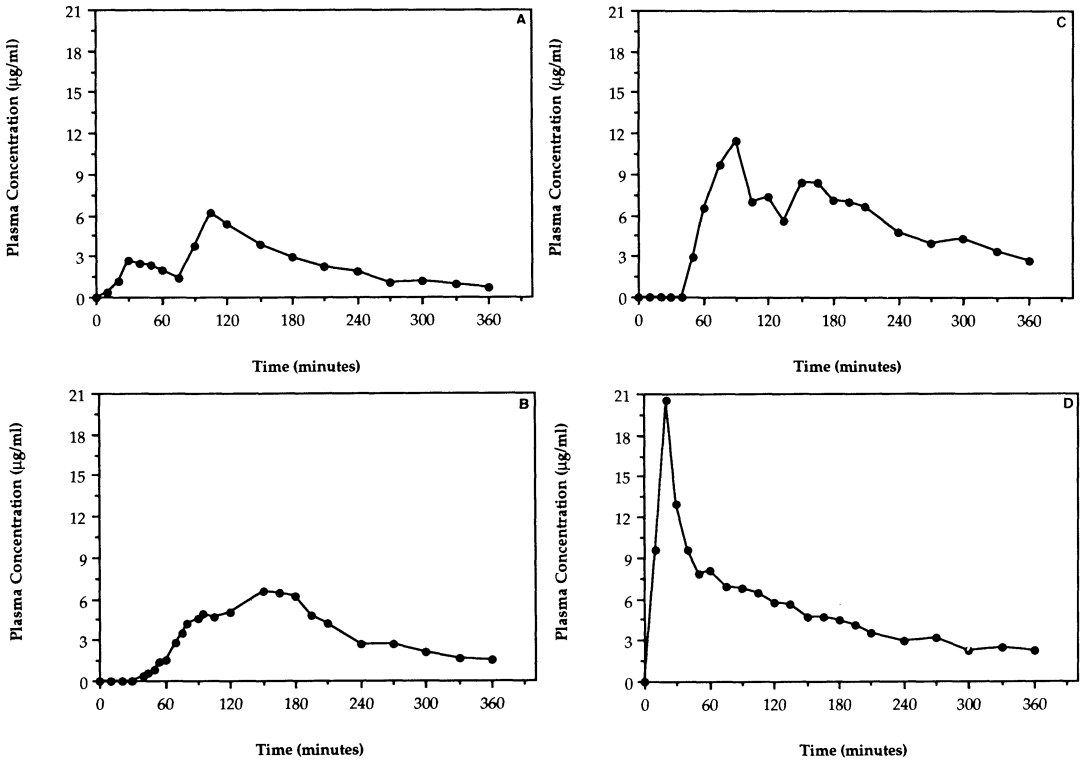

Fig. 1. Individual plasma concentration-time profiles after oral administration of 300 mg of cimetidine to male beagles. (A) Dog #1, mean gastric pH 0.9. (B) Dog #3, mean gastric pH 1.0 (C) Dog #4, mean gastric pH 3.6. (D) Dog #4, mean gastric pH 6.9.

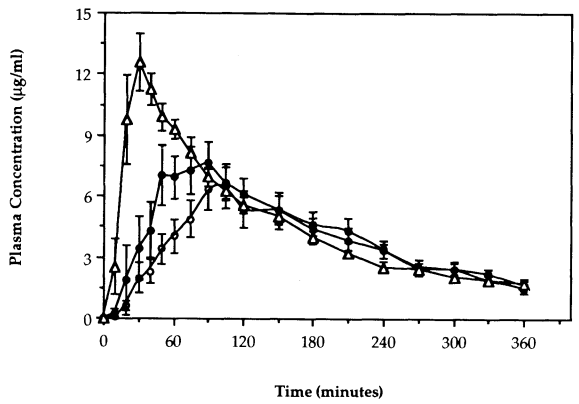

Fig. 2. Mean plasma concentration-time profiles after a single oral dose (300 mg) of cimetidine. (○) indicate gastric pH ≤ 3, (●) indicate gastric pH 3 < pH < 5 and (△) indicate gastric pH ≥ 5. Each point represents the mean percent unabsorbed (±SE) from six to ten studies for four dogs.

the rate of absorption of cimetidine with gastric pH elevation (Figure 3C).

The $AUC_{0-\infty}$ tended to increase with an increase in the pH of the gastric contents, though the effect was clear only in dogs #1 and 3. Dog #2 did not exhibit a marked increase between pH 1.3 to 6.1 but $AUC_{0-\infty}$ was significantly higher at pH 7.1. In dog #4, the absorption was more than 85% complete even at low pH. As a result, no significant trend ($p = 0.1$) in $AUC_{0-\infty}$ with gastric pH was observed for the pooled data.

At pH ≤ 3, seven out of ten profiles exhibited apparent zero order absorption kinetics while at pH ≥ 5, seven out of ten cases showed first order absorption. Three out of ten studies at pH ≤ 3 and two out of six studies between pH 3 and pH 5 exhibited a mixed order absorption process which corresponded to double peaks in the plasma profiles. When data were pooled according to the three gastric pH ranges and the mean percent unabsorbed plotted as a function of time (Figure 4), the profiles were linear with time when pH was below 5, suggesting that absorption was apparent zero order in this pH range. At pH ≥ 5, linearity was observed when log (mean percent unabsorbed) was plotted against time, indicating that in this pH range absorption was mostly first order. At pH ≥5, t_{50} was only 24 minutes, while at pH ≤ 3, t_{50} was 78 minutes. The lag time for onset of absorption, t_0, did not appear to vary with the change in gastric pH.

DISCUSSION

The data show that the incidence of double peaks decreased when cimetidine was administered under high gastric pH conditions and that the differences in cimetidine absorption between treatments can be attributed to pH related changes rather than alteration in renal clearance or enhancement of intestinal permeability by glutamic acid.

Several theories have been proposed in the literature regarding the appearance of two peaks in the plasma profiles of cimetidine. Veng Pederson and Miller developed a pharmacokinetic model for cimetidine absorption which included enterohepatic cycling to explain the double peak behavior (17). Subsequent studies showed that less than 2% of the dose of cimetidine is recovered in bile following either intravenous or oral administration in humans and rats (18–20). Grahnen *et al.* suggested that the major metabolite of cimetidine, the sulfoxide, could be reduced back to the parent drug by human fecal bacteria with subsequent reabsorption in the colon thus resulting in enterohepatic recycling (21). This does not seem likely given the gastrointestinal transit time, the temporal spacing of the second peak and the fact that at least 10% of the dose would need to be metabolized and reabsorbed to account for the size of the second peak (22).

A second explanation offered for the double peak behavior of cimetidine is that there are two distinct absorption sites in the gut, separated by a region of poor absorption (20,23). According to the discontinuous absorption model proposed by Funaki *et al.*, most of the cimetidine is absorbed from the duodenum after administration in a solid form, but the fraction that is not dissolved in the duodenum dissolves during its transit through the jejunum and is then absorbed from the ileum (20). However, the high aqueous solubility of cimetidine (6 mg/ml at 25°C) suggests that dissolution would not be rate limiting to absorption. The observation by Voinchet *et al.* that double peaks occurred after administration of cimetidine in two jejunostomy patients is also inconsistent with the theory of site specific absorption (24).

A physiological flow model was proposed to demonstrate that variability in gastric emptying with interdigestive migrating motor complex (IMMC) phase could cause plasma level double peaks (25). Since the IMMC is disrupted when nutrients are introduced into the gut, this theory is supported by the absence of two peaks when cimetidine is administered in the fed state. However, subsequent studies in healthy subjects showed that phase dependent variability in gastric emptying cannot completely explain the double peak phenomenon (7). The frequency appears to be related to gastric events since double peaks have been observed more often following oral dosing than duodenal dosing in dogs (8).

In the current study, double peaks were observed more frequently when gastric pH was low. The percent unabsorbed versus time profiles below gastric pH of 5 appeared to be either a biphasic combination of zero and first order absorption processes or a monophasic zero order absorption with a time lag. Mean percent unabsorbed profiles suggested that zero order absorption is predominant below pH 5. Conversely, the mean percent unabsorbed profile at pH ≥ 5 indicated that absorption is monoexponential under these dosing conditions. These results suggest an important role of gastric pH, either directly or indirectly, in the generation of double peaks. Since cimetidine is not absorbed directly from the stomach (23), it is hypothesized that these differences in kinetics of absorption may be associated with differences in gastric emptying as a function of pH. Hunt *et al.* (26) reported slowing of gastric emptying by both weak (*e.g.* lactic, tartaric and ascorbic acids) and strong acids (*e.g.* hydrochloric and nitric acids) while sodium bicarbonate or disodium phosphate solutions were found to increase the rate of emptying in healthy subjects (27). More recently, the gastric emptying of a standard meal was determined to be faster when alkaline bicarbonated water was coadministered versus tap water in the first 30 min in ten healthy subjects (28). Slower gastric emptying of cimetidine at low gastric pH

Table I. Pharmacokinetic Parameters After an Oral Dose of Cimetidine (300 mg) in Four Dogs at Various Gastric pH Levels

Pharmacokinetic Parameter	Low pH (≤3)	Medium pH (3 < pH < 5)	High pH (≥5)
% Cases with Erratic Absorption	80	33	0
C_{max} (μg/ml)	8.22 ± 0.97	10.35 ± 0.57	14.51 ± 0.96
t_{max} (minutes)	111 ± 14	81 ± 9	35 ± 5
C_{max}/t_{max} (μg/ml/minute)	0.083 ± 0.012	0.137 ± 0.019	0.501 ± 0.077
k_0 (%/minute)	0.75	1.03	—
k_1 (minute^{-1})	—	—	0.065
t_{50} (minutes)	78	67	24
t_0 (minutes)	12	18	13
$AUC_{0-\infty}$ (μg/ml/minute)	1503 ± 162	1730 ± 194	1864 ± 108
Bioavailability (%)	60 ± 7	70 ± 8	75 ± 4

Data either represent the mean or mean ± SE for six to ten studies.

would result in a slow rise in plasma concentration, plateau-like behavior and a longer t_{max}. In addition, if only a small portion of cimetidine is emptied with the first IMMC following the dose, then a second peak in the plasma profile may appear due to the emptying of the rest of the drug with the next IMMC. Peaks are typically separated by one to three hours, consistent with the motility cycle length in dogs (11). Elevation of gastric pH may increase the gastric emptying rate, with a substantial amount of the drug emptying into the duodenum soon after administration. This would explain the very rapid increase in plasma concentration and also the appearance of a single peak in the plasma cimetidine profiles when mean gastric pH is above 5.

Gastric emptying has already been reported to play an important role in determining the blood level profiles for drugs such as acetaminophen (2) and flurbiprofen (6). Comparison of cimetidine absorption patterns with those of acetaminophen (2) further suggests that the gastric pH effect may be mediated via the variations in gastric emptying. The observation that the cimetidine absorption rate constants (0.024 min^{-1} to 0.10 min^{-1}) are on the same order of magnitude as the liquid gastric emptying rate constants in humans (0.02 min^{-1} to 0.24 min^{-1}) after ingestion of a 50 ml or a 200 ml volume (7) and a little lower than in dogs (0.18 min^{-1} to 0.30 min^{-1}) after administration of a 40 ml or 200 ml volume (11) is also compatible with the hypothesis that gastric pH effects on cimetidine absorption could be mediated via effects on gastric emptying.

Marked changes in gastric pH have been reported to result in a change in the pH of the upper small intestine in

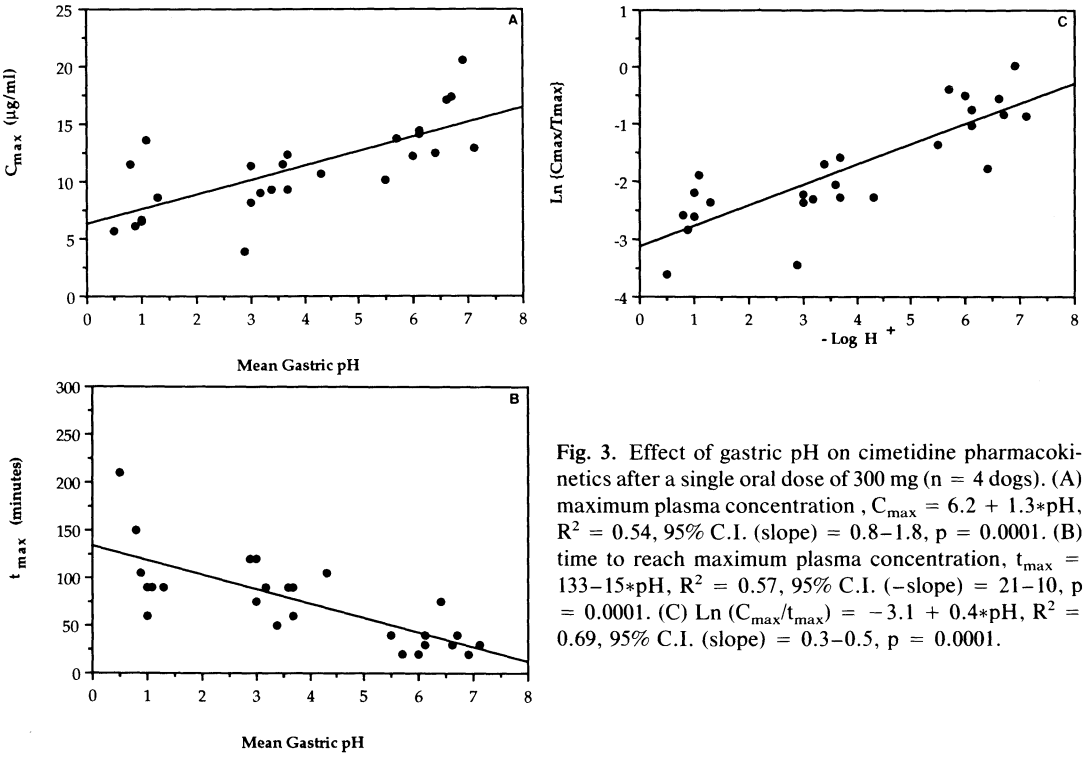

Fig. 3. Effect of gastric pH on cimetidine pharmacokinetics after a single oral dose of 300 mg (n = 4 dogs). (A) maximum plasma concentration, C_{max} = 6.2 + 1.3*pH, R^2 = 0.54, 95% C.I. (slope) = 0.8–1.8, p = 0.0001. (B) time to reach maximum plasma concentration, t_{max} = 133–15*pH, R^2 = 0.57, 95% C.I. (-slope) = 21–10, p = 0.0001. (C) Ln (C_{max}/t_{max}) = −3.1 + 0.4*pH, R^2 = 0.69, 95% C.I. (slope) = 0.3–0.5, p = 0.0001.

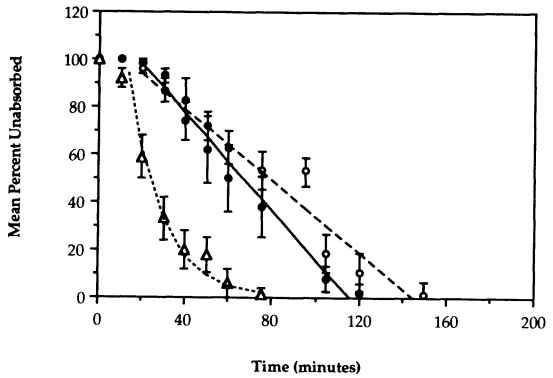

Fig. 4. Mean percent unabsorbed-time profiles after a single oral dose of cimetidine (300 mg). (○) indicate gastric pH ≤ 3, (●) indicate gastric pH 3 < pH < 5 and (△) indicate gastric pH ≥ 5. Each point represents the mean percent unabsorbed (±SE) from six to ten studies for four dogs.

humans due to carryover effects (29). Similar effects can be expected in dogs, since the upper gastrointestinal tract of dogs is similar to that of humans. According to pH-partition theory, a change in the pH of the upper small intestine in the region of pH 5.5 to 7 would significantly alter the fraction of nonionized form of a weakly acidic or basic drug. Cimetidine is a weak base with a pKa of 7.1 and an octanol/water partition coefficient of 2.5. With this partition coefficient, it is expected to be transported, at least in part, via the transcellular route. At higher intestinal pH, there would be a higher fraction of cimetidine present in the nonionized, more readily absorbed form. Therefore, another explanation for faster cimetidine absorption at higher pH may be the higher concentration gradient of cimetidine in its nonionized form. Intestinal pH-dependent absorption of cimetidine, partly explained by pH-partition hypothesis, has been observed in rats (23) and in dogs (8). However, other studies suggest that cimetidine is absorbed to a significant extent through the paracellular route (30,31), in which case changes in permeability with pH are expected to be minor. Therefore, carryover effects on intestinal pH may be less important than slowing of gastric emptying in the generation of double peaks in plasma profiles when cimetidine is dosed under low gastric pH conditions.

Several hypotheses that have been proposed to explain the significant reduction in cimetidine bioavailability upon concurrent administration of antacids include intraluminal adsorption of cimetidine to antacid components, retardation of gastric motility by antacids and/or elevation in gastric pH by the antacids (10,32). The data from the present study clearly dispel the hypothesis that elevation in gastric pH is responsible for the decrease in absorption of cimetidine when antacids are coadministered. Other mechanisms such as the physical interaction between cimetidine and antacids appear to be a more likely explanation. Though Ganjian *et al.* (33) found no significant adsorption of cimetidine to either aluminum or magnesium hydroxide *in vitro,* the adsorption of cimetidine to insoluble complexes formed by antacid components with hydrochloric acid *in vivo* cannot be discounted.

Overall, this study identifies gastric pH as a major factor influencing the rate of absorption of cimetidine, most likely due to pH related variations in gastric emptying. Carryover effects of gastric pH into the upper intestine may also influence the absorption behavior.

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