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Report

Upper Gastrointestinal (GI) pH in Young, Healthy Men and Women

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The pH in the upper gastrointestinal tract of young, healthy men and women was measured in the fasting state and after administration of a standard solid and liquid meal. Calibrated Heidelberg capsules were used to record the pH continuously over the study period of approximately 6 hr. In the fasted state, the median gastric pH was 1.7 and the median duodenal pH was 6.1. When the meal was administered the gastric pH climbed briefly to a median peak value of 6.7, then declined gradually back to the fasted state value over a period of less than 2 hr. In contrast to the pH behavior in the stomach, feeding a meal caused a reduction in the median duodenal pH to 5.4. In addition, there was considerable fluctuation in the postprandial duodenal pH on an intrasubject basis. The pH in the duodenum did not return to fasted state values within the 4-hr postprandial observation period. There was no tendency for the duodenal pH to be related to the gastric pH in either the fed or fasted phases of the study. Furthermore, pH in the upper GI tract of young, healthy subjects appears to be independent of gender. The differences in upper GI pH between the fasted and the fed state are discussed in terms of dosage form performance and absorption for orally administered drugs.

KEY WORDS: gastric pH; duodenal pH; fasted state pH; fed state pH; young adults; gender effects; carryover pH; food effects.

INTRODUCTION

Since small changes in the GI pH profile can affect dosage form performance, drug dissolution, and drug absorption (1–5), it is important for the formulator to know the range of usual values for GI pH and how it varies under normal physiological conditions. There have been numerous previous studies specifically designed to examine pH in the upper GI tract (6–23). However, the experimental protocol (meals, method of measurement, duration of monitoring period, frequency of sampling, etc.) varied widely among these studies, making it difficult to compare the results obtained and to interpret them in terms of the pH to which a dosage form would be exposed under normal dosing conditions. In addition, in some of the studies, there was a wide range of subject ages or a high mean subject age. This is an important point since other studies have indicated that increasing age is associated with changes in GI pH (24,25).

None of the previous studies have measured pH by continuous monitoring under fasting and fed conditions in the same group and at both gastric and duodenal locations. In particular, the pH in the mid to distal duodenum has received little attention. A further problem is that most of the meals studied were not designed to resemble the average North American diet. Only Malagelada *et al.* (6,7), McCloy *et al.* (8), and Savarino *et al.* (9) have attempted to study pH response to ordinary solid/liquid meals. Moreover, the number of subjects in most of the studies is relatively small, most of the studies used predominantly male subjects and there was usually little restriction on the subject age range.

In this article, we report data for fed and fasted GI pH in a total of 34 healthy, young subjects (24 subjects for the gastric phase and 22 subjects for the duodenal phase). The data were obtained using a continuous monitoring device, the Heidelberg capsule. Continuous recording of data allowed us to better characterize peaks and fluctuations in pH and to follow the functional form of the rate of return to baseline after a meal. A standard solid/liquid meal was given to assess the pH response that might be typical for the North American diet. The study design also permitted the investigation of correlation between gastric pH values and duodenal pH values within specific subjects. The information obtained from these studies is intended to help identify situations in which drug bioavailability might vary as a result of pH changes associated with normal physiological function of the upper GI tract.

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MATERIALS AND METHODS

Subject Selection

The study was conducted in the Clinical Research Center of The University of Michigan Hospitals on an outpatient basis, with approval of the Institutional Review Board for studies involving human subjects. All participants gave written informed consent. Thirty-four healthy volunteers (18 female, 16 male), with a mean age of 25 years (range, 21–35 years), participated in the study. Twelve subjects completed both phases, twelve subjects completed only the gastric phase, and ten subjects completed only the duodenal phase of the study. None of the participants had a history or any clinical or laboratory evidence of gastrointestinal disease. The health status of each subject was confirmed by a general physical examination and routine screening of blood samples for renal and hepatic function. None were taking medications on a chronic basis. Smoking, alcohol, and all medications were discontinued for 3 days prior to and throughout each study phase.

pH Measuring System

Continuous determination of pH with time was accomplished using a radiotelemetric device, the Heidelberg capsule (10–12). The device consists of a battery-operated high-frequency radio transmitter and a pH electrode housed in a nondigestible acrylic capsule 7 mm in diameter and 20 mm in length. The frequency of transmission changes with the pH of the capsule's environment and can be calibrated using standard buffer solutions. The subject wears an antenna strapped around the waist to receive the radio signal, which is then converted back to pH and recorded continuously as a function of time on an analogue recorder and digitally at 15-sec intervals on an Apple IIe computer (Apple Computer Co., Cupertino, CA).

In vitro studies were conducted previously to confirm the pH unit accuracy to within ±0.5 pH unit over an 8-hr study period (13). The capsule battery was activated with normal saline the morning of the study. Immediately prior to administration, the capsule unit was calibrated in pH 1 and 7 buffer solutions maintained at 37°C. The capsule was tethered using surgical thread (Supramid Extra 2-O, S. Jackson Inc., Alexandria, VA) to regulate capsule placement during the study and to facilitate oral retrieval. At the end of each study day, the capsule was recovered and its response to pH 1 and 7 buffers checked against the prestudy values. The response was required to be within 0.5 pH unit of the prestudy values for results to be included in the data analysis.

Study Protocols

Phase A. The participants fasted (with only water permitted) for at least 12 hr before swallowing a tethered Heidelberg capsule. After the capsule had traveled approximately 50 cm, its position was fixed by taping the tether thread to the subject's cheek. Position in the body of the stomach was indicated by a combination of tether length and continuous recording of normal gastric pH (approximately pH 3 or lower) and was verified by fluoroscopy in twelve of the subjects. Fasting pH in the body of the stomach was recorded for 1 hr in all 24 subjects. Then a standard meal consisting of 6 oz of hamburger, 2 slices of bread, 2 oz of hash brown potatoes, 1 tbsp each of ketchup and mayonnaise, 1 oz each of tomato and lettuce and 8 oz of milk (for a total of 1000 Kcal) was given. Subjects were required to consume the meal within 30 min. Postprandial gastric pH was monitored for 4 hr after completion of the meal, then the capsule was retrieved orally.

Phase B. The participants fasted (with only water permitted) for at least 12 hr before swallowing a tethered Heidelberg capsule. Gastric pH was monitored until the capsule emptied into the small intestine, an event marked by a rapid, unreversed elevation in pH accompanied by an increase in tether length. After the capsule emptied from the stomach, it was allowed to travel approximately 10–15 cm farther (i.e., to the mid to distal region of the duodenum). The position was fixed by taping the tether to the subject's cheek. Tether length at this position ranged from 65 to 85 cm. The correspondence of this tethering procedure to the D3–D4 region of the duodenum was verified by fluoroscopy in 12 subjects. Fasting pH in the duodenum was recorded for 1 hr in 12 subjects and 30 min in 10 subjects. Then a standard meal identical to that administered in Phase A was given. Postprandial pH in the duodenum was monitored for 4 hr after completion of the meal, then the capsule was retrieved orally.

Data Analysis and Statistical Considerations

The pH measurements for the study were stored at 15-sec intervals using a program written in BASIC for the Apple IIe computer. Data were divided into three periods (fasted, during the meal, and postprandial) for both the gastric phase and the duodenal phase of the study. Data were collected for 1 hr in the fasted state and for 4 hr in the postprandial state. Data were also collected during meal ingestion, a period which varied between 12 and 30 min.

For the descriptive part of the data analysis, the data are displayed as box-whisker plots (26), which list the median and interquartile range for each subject or for pooled data (see Fig. 1), or as frequency distributions. In all cases where overall median values are reported, they are calculated from the subjects' individual medians. Individual medians were calculated based on all data points of a subject in each specified phase. Interquartile ranges show the difference between the individual first and third quartiles. The frequency distribution plots show the percentage of the pooled data

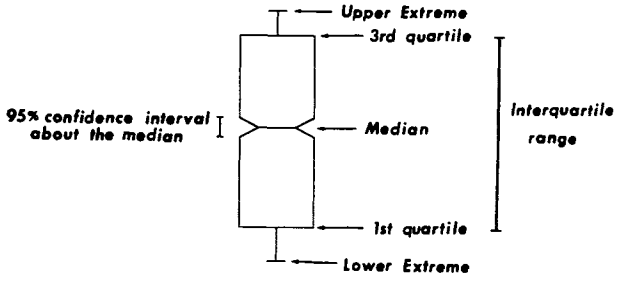

Fig. 1. Typical form of the box-whisker plot.

above or below specific pH values. The median absolute deviation (MAD) was used to describe variability. This parameter is defined as the median of the absolute deviation from the individual medians and was calculated for each subject for fasting, during the meal, and postprandial periods in both the gastric and the duodenal phases. The MAD was used because it is a robust estimate of the spread of a distribution (27).

For the construction of the 5-min interval box-whisker plots, each subject's data were divided into 5-min periods and the median of each successive period was computed. Each box in such a plot shows the between-subjects grand median for the 5-min interval. Since the meal period varied between 20 and 30 min, during the meal data were not included in the 5-min interval plots.

Time-series and spectral analyses (28) were performed on fasting and postprandial data, smoothed by condensing into 5-min medians, to determine any temporal effects. To diagnose periodicity in the time domain, time-series analysis was initially performed. Wherever the results were ambiguous, spectral analysis to look for autoregressive patterns and check for periodicity in the frequency domain followed. In no case were any periodic temporal effects detected.

The gastric postprandial phase data for each subject were then fitted to two-parameter exponential equations. The two parameters (starting pH value and first-order rate constant for the rate of return of pH to the premeal value) were tested for normality and found to be normally distributed. Subsequently, the mean value of each parameter was used in the general equation, which empirically describes the change in postprandial gastric pH with time. The time to return to a specific pH after the meal was finished, in the gastric postprandial phase, was estimated from 2-min median smoothed data by reading the first time at which the pH of interest was reached postprandially. In cases where the pH did not return to a specific value, an entry of 240 min corresponding to the whole 4-hr monitoring period was recorded and used for subsequent analysis (right data censoring). Those cases where the pH was already below the specific value of interest when the postprandial period started were omitted from the time-to-return-to-pH analysis.

Nonparametric statistical procedures were used to analyze the data since, regardless of transformation, the pH distributions deviated considerably from normality, as determined by the Kolmogorov–Smirnov normality test (29). Specifically, the data from 50% of the subjects in the fasted gastric, 64% of the subjects in the fasted duodenal, 29% of the subjects in the gastric postprandial, and 41% of the subjects in the postprandial duodenal phase were nonnormal. Postprandial, during the meal, and fasted duodenal medians were compared using Wilcoxon's signed-rank test (20).

Gender differences in the parameters of the monoexponential model were evaluated using the unpaired Student *t* test (30) since those data were found to be normally distributed. For each phase of the study, median values for male and female subjects were compared using Wilcoxon's rank-sum (Mann–Whitney *U*) test (30). Spearman's rank correlation coefficient (31) for the medians was calculated to determine whether there was a carryover effect between the gastric and the duodenal pH values in each of the phases of data collection, i.e., fasted state, during the meal and postprandial.

For all tests, a P value <0.05 was considered significant. The statistical software packages Midas, Statview, and BMDP were used for the analysis of all data.

RESULTS

Typical pH Profiles

Figure 2 shows typical gastric and duodenal pH profiles. In the fasted state, there were periods during which gastric pH remained steady, while at other times there were fluctuations during which the pH was elevated to higher values. This kind of behavior was observed to a varying degree in almost all gastric preprandial profiles, usually for a period of about 1 to 15 min (average duration, 7 ± 6 min). High pH values were attained while the meal was being ingested. Postprandially, the gastric pH decreased gradually over time and, in most cases, returned to the fasted state levels within the 4-hr period of monitoring. In the duodenum the pH re-

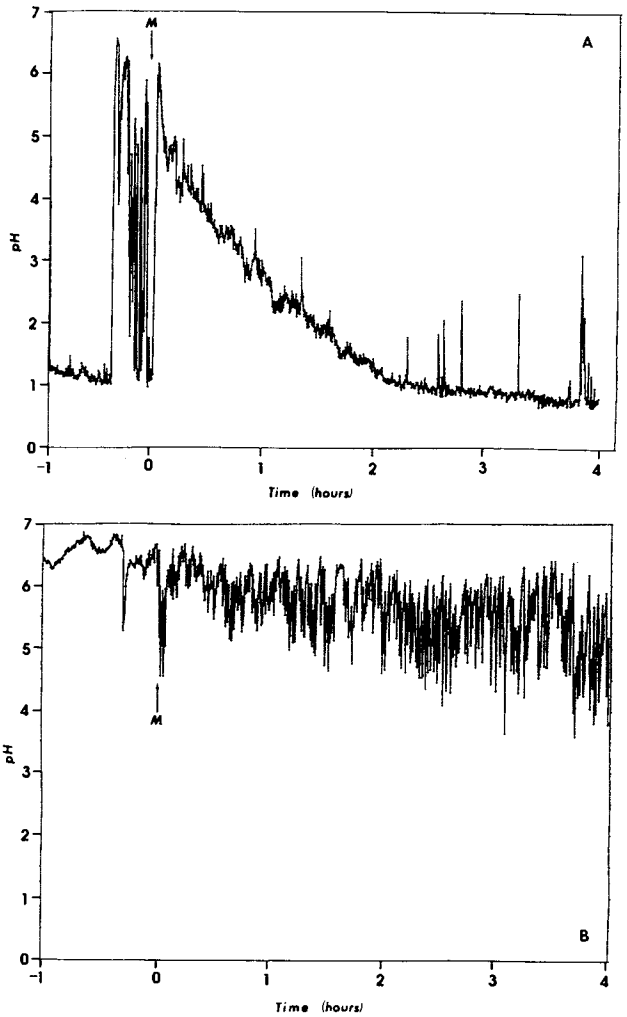

Fig. 2. Typical pH profiles in gastric (upper panel) and duodenal (lower panel) phases of the study for subject J. L. Meal administration is marked by M.

mained relatively constant in the fasted state. In contrast, wide fluctuations in duodenal pH were observed during the postprandial period. The usual duodenal pH appeared to be lower in the postprandial than in the fasting state, and in most cases there was no return to the fasted state pattern within the 4-hr postprandial observation period.

Gastric Data

The overall median fasting pH was 1.7, with an interquartile range of pH 1.4–2.1. During the meal, the pH increased to a median value of 5.0 with an interquartile range of pH 4.3–5.4. The peak value was 6.7 (6.4–7.0). Figure 3 shows the pH frequency distribution in the fasted state and during the ingestion of the meal. Figure 4 shows the box-whisker plot for the postprandial period in 5-min intervals using data pooled from all subjects, beginning at the end of the meal. The first three boxes correspond to the 15-, 30-, and 45-min intervals in the fasted state. Values of pH recorded during the meal were not included, as the period of ingestion varied from 12 to 30 min. The general trend of the gastric postprandial pH data was to decline gradually from a near-neutral peak pH. The postprandial pH data were subsequently fitted to a two-parameter exponential equation,

$$\text{pH} = 4.13 \cdot e^{-0.005t} \quad (1)$$

Table I presents the time taken to return to pH 5, 4, 3, and 2 postprandially. The means, standard deviations, medians, and ranges are shown.

Duodenal Data

The overall median fasting pH was determined to be 6.1,

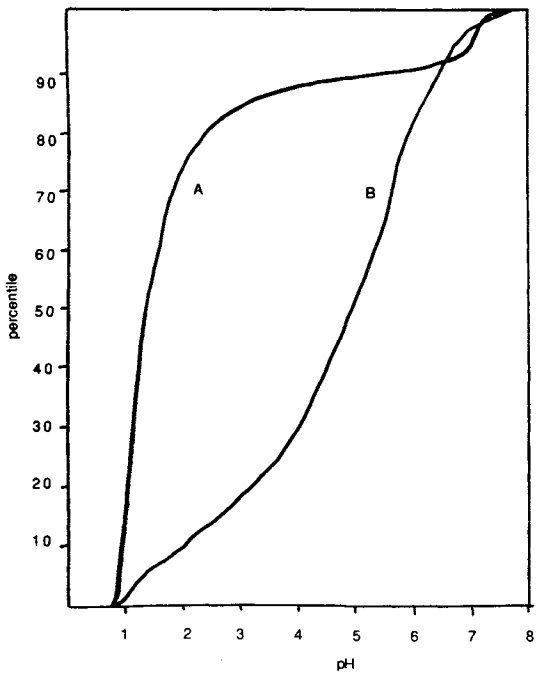

Fig. 3. Frequency distribution plots for pooled gastric pH in the fasted state (A) and during ingestion of the meal (B). The percentage of data falling below a given pH value can be obtained by reading the percentile corresponding to the pH of interest.

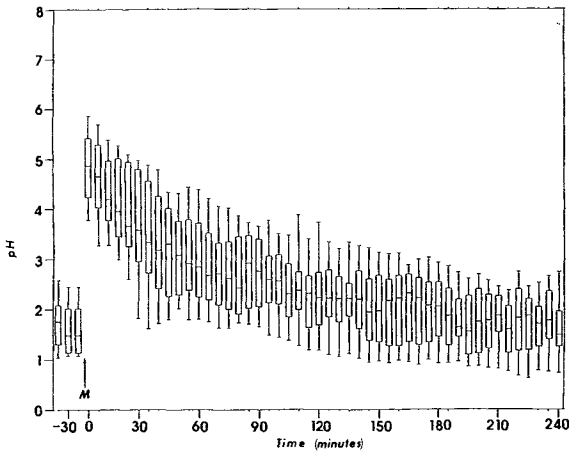

Fig. 4. Box-whisker plots for pooled data from three 15-min intervals prior to meal administration and at 5-min intervals postprandially for the gastric phase of the study.

with an interquartile range of pH 5.8–6.5. During the meal the overall median pH was 6.3 (interquartile range of 6.0–6.7). Time-series analysis showed that duodenal postprandial data did not exhibit any periodicity or other temporal effects but, rather, that pH fluctuated randomly around a grand median value of 5.4. Individual medians varied from pH 4.9 to pH 6.0. The pH values fluctuated from a minimum of pH 3.1 to a maximum of pH 6.7 (overall median values). Comparison of duodenal pH in the three phases showed that pH was highest during ingestion of the meal and lowest in the postprandial period. Differences between phases reached significance in each case.

Correlation Between Gastric and Duodenal pH

Correlation coefficients were below the critical value for significance between fasted gastric and duodenal pH and between postprandial gastric and duodenal pH.

Variability

The ratio of highest to lowest median absolute deviation (MAD) was 17:1 for the gastric fasted state pH, indicating considerable differences in pH variability between subjects. Variability in gastric and duodenal pH during the meal also showed large differences between subjects, with the ratio of largest to smallest being 12:1 for the gastric and 11:1 for the duodenal study. In contrast, the range of variability for the postprandial phases was relatively small, with ratios of 5:1 and 7:2 for the gastric and duodenal studies, respectively. Likewise, little intersubject variability was observed for the fasting phase of the duodenal study, where the MAD ratio

Table I. Time to Return to Specific pH Values, After Completion of the Standard Meal (Minutes)

	Mean ± SD	Median	Range
pH 5	11 ± 10	8	2–34
pH 4	28 ± 24	14	4–74
pH 3	56 ± 41	45	2–158
pH 2	107 ± 70	96	8–240

was 4:1. With regard to intrasubject variability, there was a higher variation in the gastric phase during the meal and in the duodenal postprandial phase, relative to the other phases.

Gender Effects

With regard to gender effects, data were not significantly different between men and women in any of the phases of the study.

DISCUSSION

Fasting gastric pH has been well studied (6,7,9,14–19), with little variation among the results obtained. The generally accepted value for fasting gastric pH is approximately pH 2. We observed a median fasted gastric pH of pH 1.7, with a considerable degree of intersubject variation. The frequency distribution in Fig. 3 indicates that the fasted-state gastric pH is below pH 2 68% of the time and below pH 3 90% of the time. In young healthy volunteers, pH above 4 is evident about 6% of the time, while pH above 6 is very rare in the fasted state.

During the 1-hr observation period in the fasted state, episodes of elevated pH were recorded in the majority of subjects. It is postulated that this may be due to contact of the measuring device with the stomach wall. Alternatively, there may be a genuine elevation of the lumenal pH. The latter would explain why some "tubeless gastric pH analysis" and single-point aspiration studies (20) reported a higher incidence of raised gastric pH than multipoint aspiration or continuous monitoring study designs.

Postprandial gastric pH (6,7,9,17–19) is not as well characterized as fasted-state data. The only groups in this series which studied pH changes after a normal solid meal were Savarino *et al.* (9) and Malagelada *et al.* (6,7). The pH response during and immediately after the meal is ingested is particularly poorly characterized because data were either collected by pooling aspirates or reported only at certain intervals. These methods tend to obscure important data such as peak pH value and time of peak pH. Return to fasting pH in the studies listed generally occurred within 60 min after the meal. In our study, ingestion of the meal resulted in a substantial elevation of the gastric pH. The median peak pH following ingestion of the hamburger, hashed brown potatoes, and milk meal was 6.7, with an interquartile range of 6.4 to 7.0. This can most likely be attributed to the buffering effect of the fluid (in this case, milk) and food ingested. When the meal was homogenized, its pH was 5.72. Other meals with lower-pH fluids such as coffee, cola drinks, fruit juices, etc., may not buffer the gastric pH to as high a peak pH. Malagelada and co-workers' (6,7) studies used water as the fluid portion of the meal, while Savarino *et al.* did not describe the meal contents. Some of the fluid-only meals consisted of chocolate milk, which contains alkaloids such as caffeine. These alkaloids may augment the normal nutrient stimulation of gastric acid secretion.

During meal ingestion, the pH was above pH 4 73% of the time (Fig. 3), above pH 5 45% of the time and above pH 6 20% of the time. The time taken to ingest the meal was between 12 and 30 min for all subjects. The peak pH usually occurred within the first 5 min of eating. These results suggest that it would be unwise to recommend administration with meals for formulations/drugs which require acidic pH for rapid release. Further, enteric-coated preparations may partially release drug in the stomach if ingested during meal intake. Depending on their composition, other meals may result in a lower peak pH, but the prescriber must guard against worst-case pH conditions.

After the meal was completed, the pH gradually declined until fasted-state pH was reestablished. Decline in pH is most likely a function of both the ability of the meal to stimulate gastric acid secretion and the rate at which the meal is emptied from the stomach. The information in Table I indicates that after meal ingestion is complete, the pH quickly falls back below pH 5 and then gradually declines back to fasted state values over a period of less than 2 hr. The fact that we observed a somewhat longer time for restoration of the fasting state pH (~120 min, versus 60 min in most reported studies) is probably due partly to the large meal size (long emptying time) and partly to the high buffer capacity of the meal. There was considerable subject-to-subject variation in the rate of return to premeal values. In most people, though, medications administered 2 hr or more after meals should encounter gastric pH conditions similar to the fasted state. Enteric-coated dosage forms with a dissolution pH of 5 or greater could be safely administered 20 min after meal intake is complete. These probably represent maximum times as most other meals would be smaller and/or have lower buffer capacity.

Fasting duodenal pH has been most extensively measured in the duodenal bulb (6,8,15,17–19,21). The wide variation in mean pH values reported may be due to wide temporal and positional fluctuation in pH in this area of the duodenum, which makes it difficult to determine an accurate mean value (22).

There have been only three studies which investigated pH in the mid to distal region of the duodenum. Of these three, two (6,15) used older subjects, with ages ranging up to 63 and 67, respectively. Unlike the stomach, the fasted mid to distal duodenum appears to be very stable with respect to pH. This was illustrated by the low MAD values in this phase of the study. The median pH of 6.1 (interquartile range of 5.8 to 6.5) was similar to previously reported results for the distal duodenum. Figure 5 indicates that the pH in the fasted state is above pH 5 more than 90% of the time but rarely exceeds pH 7.

There are only two studies which have reported values for postprandial pH in the mid to distal duodenum. Of these two, Ovesen *et al.*'s (18) used a liquid meal rather than a standard solid meal. The other (6) included older subjects and reported pH of pooled intestinal aspirates rather than using a continuous monitoring device. Pooling samples over collection intervals of several minutes makes it difficult to observe the fluctuations in duodenal pH which occur in the fed state (22). In contrast to the gastric results, the pH at mid to distal duodenum was observed to be lower postprandially than in the fasting state. Furthermore, in contrast to the duodenal bulb region, the low pH appears to be maintained throughout an extended observation period.

Upon ingestion of the meal, a brief period of elevated duodenal pH was often observed. This can be attributed to the cephalic phase of pancreatic bicarbonate secretion (13).

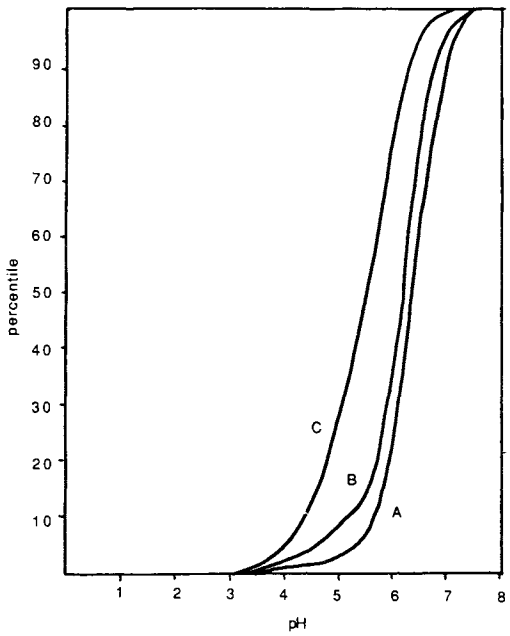

Fig. 5. Frequency distribution plots for pooled duodenal pH during ingestion of the meal (A), in the fasted state (B), and in the postprandial state (C).

The pH in the postprandial phase in the duodenum is considerably lower than in the fasted state. The pH is below 5 28% of the time in the fed state, compared with 8% in the fasted state. The equivalent numbers for time spent below pH 6 are 80 and 38%, respectively. Drugs for which the pH of half-maximal absorption lies in the pH 5 to 7 range may therefore be absorbed at different rates if given in the fed state as opposed to the fasted state. Formulations with pH-sensitive release profiles may also be expected to perform differently under fasted- versus fed-state conditions.

During and following the meal, there were randomly spaced fluctuations in duodenal pH. These can be explained by the periodic emptying of chyme from the stomach, followed by reneutralization with pancreatic bicarbonate. Overall, the pH in the postprandial phase of the duodenal study appears to be somewhat lower and much more variable than the pH observed in the fasting state. The fluctuations in pH have been observed previously in the distal duodenum when continuous monitoring was employed (18).

There was no trend for those with higher gastric pH to have high duodenal pH, or vice versa, among the young, healthy adults enrolled in this study. It should be noted, though, that in certain disease states where lumenal pH values are far from the normal range of values, carryover pH effects have been observed (e.g., Ref. 23).

A trend toward differences in gastric pH due to gender was reported by Dotevall (14), with the pH for males slightly lower than the pH for females. Other studies either report no significant difference in gastric pH due to gender (24) or make no reference to gender-related differences. Often, the number of female subjects was too small for statistically meaningful comparison. In our study, no gender differences in gastric or duodenal pH or in the intersubject or intrasubject variability in pH were observed.

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