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Research Article

Upper Gastrointestinal pH in Seventy-Nine Healthy, Elderly, North American Men and Women

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Gastric and duodenal pH levels were measured in 79 healthy, elderly men and women (mean ± SD = 71 ± 5 years) under both fasted and fed conditions using the Heidelberg capsule technique. The pH was recorded for 1 hr in the fasted state, a standard liquid and solid meal of 1000 cal was given over 30 min, then the pH was measured for 4 hr postprandially. Results are given as medians and interquartile ranges: fasted gastric pH, 1.3 (1.1–1.6); gastric pH during the meal, 4.9 (3.9–5.5); fasted duodenal pH, 6.5 (6.2–6.7); and duodenal pH during the meal, 6.5 (6.4–6.7). Although fasted gastric pH, fasted duodenal pH, and duodenal pH during the meal differ statistically from those observed in young subjects, the differences are not expected to be clinically significant in terms of drug absorption for the majority of elderly subjects. Following a meal, gastric pH decreased from a peak pH of 6.2 (5.8–6.7) to pH 2.0 within 4 hr in most subjects. This rate of return was considerably slower than in young, healthy subjects. Nine subjects (11%) had a median fasted gastric pH >5.0, and in five of these subjects the median pH remained >5.0 postprandially. In this group, drugs and dosage forms which require an acidic environment for dissolution or release may be poorly assimilated.

KEY WORDS: gastric pH; duodenal pH; elderly; gender effects; food effects; fasted-state pH; fed-state pH; Heidelberg radiotelemetry capsule.

INTRODUCTION

A number of physiological alterations associated with aging are expected to affect drug absorption from the gastrointestinal tract (1). Reductions in the number of absorbing cells and an associated decrease in the functional absorptive capacity of the small intestine will tend to reduce the rate and, in some cases, the extent of absorption. Reduced mesenteric blood flow may also contribute to a decrease in systemic levels, resulting in therapeutic failure of some drugs and dosages forms that work quite adequately in young people. In other cases, the alterations in upper gastrointestinal (GI) physiology may serve to increase the fraction of drug absorbed. For example, a decrease in the gastric emptying rate will tend to increase the extent of absorption of compounds whose dissolution rate is the rate limiting step to absorption. Similarly, elevated gastric pH may permit greater availability of acid-labile compounds. Combined with physiological changes in other organs due to aging, such as slower liver metabolism or decreased renal excretion, a greater fraction absorbed could lead to toxicity in the elderly at doses which are normally safe for the younger population. Further investigation is needed to understand the degree to which changes in the upper GI physiology occur with aging, and to what extent they are interrelated, so that a predictive model for drug absorption in the elderly can be constructed. By investigating changes which occur in upper GI pH with aging, we hoped to move one step closer to understanding oral drug absorption in the elderly population.

Although there have been numerous studies of gastric acid secretion and gastrointestinal pH which included elderly subjects (2–11), several of these studies included patients with GI diseases along with the healthy individuals. Almost all of the studies were cross-sectional in design, with some including only small numbers of elderly subjects. Dietary and ethnic backgrounds were also diverse, including studies of Japanese, Scandinavian, Central European, and English origin. Furthermore, the definition and criteria for establishing achlorhydria (the absence of gastric acid secretion) varied widely among the studies. As a result, the picture of incidence and rate of development of pH changes in the

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elderly North American population still is not clear. Some generalizations, however, can be made by examining the studies to date. First, the majority of individuals over the age of 65 have gastric acid secretion similar to that of young people. The incidence of achlorhydria in the elderly is somewhere in the neighborhood of 10–20%, compared to <1% in those under age 40 (4,6,9,11). However, the incidence of high baseline pH recordings appears to be somewhat larger than the incidence of true achlorhydria (5,7). According to Holt *et al.* (11), it is now generally believed that approximately 20% of the population over the age of 70 has hypochlorhydria (reduced but not absent gastric acid secretion), whereas the remainder have acid production no different from that of young adults. Finally, the incidence of achlorhydria may be highly dependent on ethnic background (2,3,8,10). For example, a Japanese study reported a 60% incidence of elevated gastric pH even in the 55 to 59 age bracket (10), whereas most of the European and American studies report incidences well below 5% in a similar age range (2,3). Other aspects of upper GI pH, including issues important to the pharmaceutical scientist such as postprandial gastric response to meals, fasted-state intestinal pH, and intestinal pH response to meals, have not been studied specifically in the elderly.

The specific aims of this study were to characterize upper GI pH in healthy, elderly subjects (≥65 years) under both fasted and fed conditions and to determine the incidence of achlorhydria in the healthy, elderly, North American population.

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 the approval of the Institutional Review Board for studies involving human subjects. All participants gave written informed consent. Eighty healthy volunteers (49 female, 31 male), with a mean age of 71 (range, 65–83), participated in the study. Figure 1 gives a breakdown of subject demographics by age and gender. Seventy-five subjects were Caucasian, one was Asian, and four were Black. None of the included participants had a history or any clinical or laboratory evidence of gastrointestinal disease or was taking medications which could alter GI pH or function. The health status of each subject was confirmed by a general physical examination and routine screening of blood samples for renal and hepatic function and complete blood counts. Smoking, medications, and alcohol were discontinued for 3 days prior to and throughout each study phase.

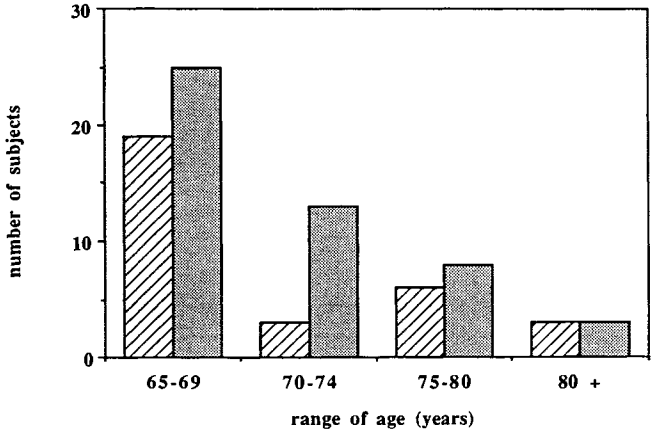

Fig. 1. Demographics of subjects who participated in the study of upper gastrointestinal pH in 80 healthy, elderly men and women. Males, hatched bars; females, shaded bars.

pH Measuring System

Continuous determination of pH with time was accomplished using a radiotelemetric device, the Heidelberg capsule (Heidelberg International, Norcross, GA), which has previously been used for measurement of upper GI pH and gastric emptying (12–17). pH was recorded continuously as a function of time on an analog recorder and as 15-sec means on an Apple IIe computer (Apple Computer Co., Cupertino, CA). In the case of computer malfunction, pH data were manually digitized using an Apollo DN4000 computer (Apollo Computer, Inc., Chelmsford, MA). An architecture digitizing program, DIGITIZE (Summa Graphics, Seymour, CT, and Architecture and Planning Research Laboratory, Ann Arbor, MI), and an original FORTRAN program (PHARMACY) were used to read pH data from the original Heidelberg pH stripchart.

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 control 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. The protocol was repeated with a new capsule in the few cases of equipment failure. *In vitro* studies had been conducted previously to confirm the pH unit accuracy to within ±0.5 pH unit over an 8-hr study period (12).

Methods

Treatment A: Gastric pH

The subject fasted (water only) for at least 12 hr before swallowing a tethered Heidelberg capsule. After the capsule had traveled approximately 55 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) when possible and was then verified by fluoroscopy. A fasting serum gastrin level was drawn in subjects with elevated gastric pH. Fasting pH in the body of the stomach was recorded for 1 hr in all 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 instructed to consume the meal over a period of fifteen

to thirty minutes. Postprandial gastric pH was monitored for 4 hr after completion of the meal, then the capsule was retrieved orally to check consistency with prestudy calibration.

Treatment B: Duodenal pH

The subject fasted (water only) 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. In subjects with an elevated gastric pH, the emptying was assessed by increasing 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 thread to the subject's cheek. Tether length at this position was 70–80 cm. The correspondence of this tethering procedure to the D3–D4 region of the duodenum was verified by fluoroscopy. Fasting pH in the duodenum was recorded for 1 hr. Then a standard meal identical to that administered in Treatment A was given. Postprandial pH in the duodenum was monitored for 4 hr after completion of the meal, then the capsule was retrieved orally.

Achlorhydria was defined for the purpose of this study as a fasted gastric pH greater than pH 5, with the pH remaining above 5 both during the meal and postprandially.

Data Analysis and Statistical Considerations

The pH measurements for the study were stored as means for each 15-sec interval 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 44 min. Data from one subject were excluded for both the gastric and the duodenal phases because fluoroscopy revealed a partial gastrectomy. Data were excluded for three additional subjects for the duodenal phase, due to lack of gastric emptying in two cases and due to the subject biting through the tether on two separate occasions in the third case.

Nonparametric statistical analysis was preferred due to the significant nonnormality of the pH data distribution as determined by a Shapiro–Wilk test.

Descriptive statistics were determined for all older subjects (including achlorhydrics) and for the five achlorhydric subjects. The median of fasted gastric pH, gastric pH during the meal, fasted duodenal pH, and duodenal pH during the meal were calculated for each subject and then for all subjects within each period of interest.

Individual and median area under the pH-versus-time curve (AUC) was calculated during the gastric and duodenal, fasted, and postprandial periods utilizing the trapezoidal rule. Four subjects were excluded from AUC calculations during the fasted gastric period and one subject was excluded during the gastric postprandial period due to missing data. One subject's data were excluded for the duodenal postprandial period due to missing data.

A repeated-measures analysis of variance was per-

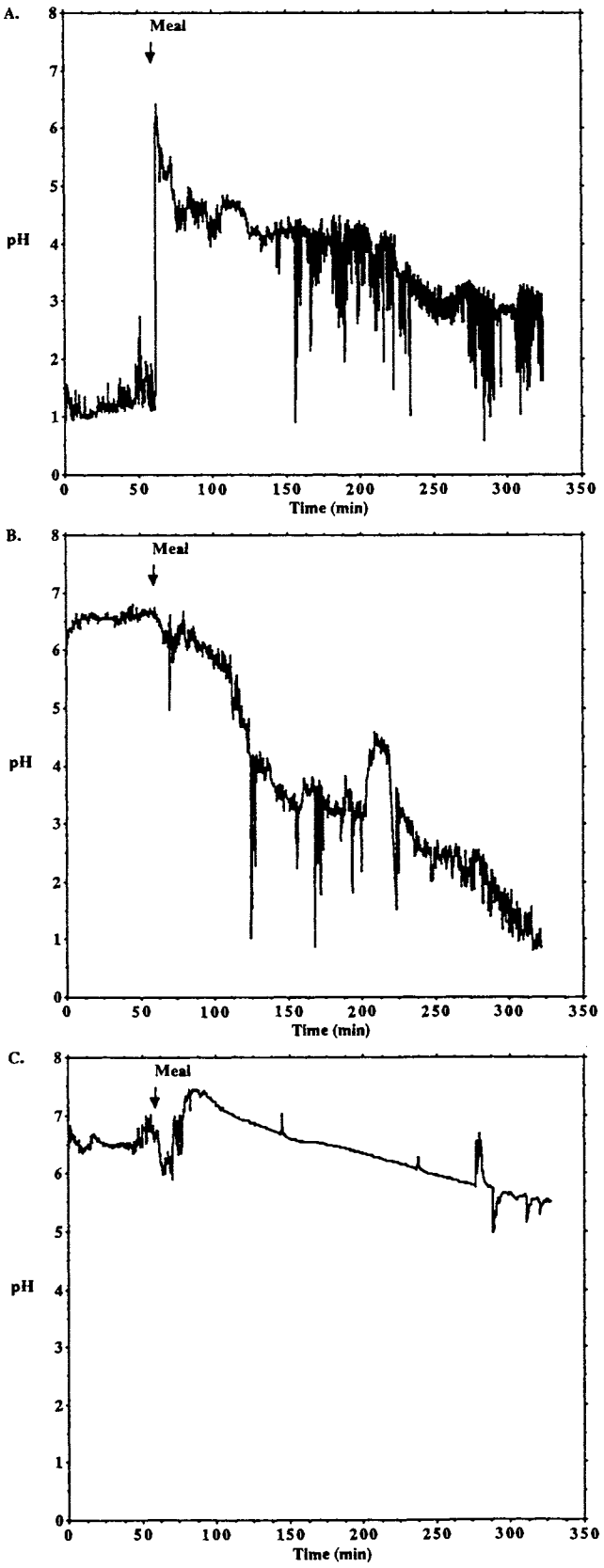

Fig. 2. Typical gastric pH profiles in the elderly: (A) low fasted pH with decrease in pH postprandially; (B) elevated fasted pH with decrease in pH postprandially; (C) elevated fasted pH and elevated postprandial pH. Arrow indicates administration of the meal.

formed on the gastric postprandial data and the duodenal postprandial data to examine changes in the postprandial pH over time. An orthogonal decomposition was subsequently used to determine whether or not changes in the postprandial pH followed a linear function.

For each subject, both the gastric postprandial period and the duodenal postprandial period were divided into 5-min intervals. A median was calculated for each 5-min period for each subject. An overall median for each 5-min interval was then calculated from all subjects' individual medians and these medians are represented graphically as box-whisker plots.

Values for time to return to a specific pH were determined by finding the first time a subject's pH dropped to the pH of interest during the gastric postprandial period. The gastric postprandial period data were first smoothed as medians for every five data points, then the first time to return to pH 5, 4, 3, and 2 was determined by inspection of each subject's smoothed data. The time to return values were right-censored to 240 min if a subject did not return to a specific pH within the observation period. Subjects with pH values at the start of the postprandial period below the pH of interest were assigned a missing datum point for the time to return.

The median duodenal pH levels at 60, 120, 180, and 240 min postprandially were calculated from the same data used for the repeated-measures analysis of variance test.

Statistical comparisons between young subjects and elderly subjects were determined using the Mann–Whitney *U* nonparametric test for unpaired data. Data for 24 young subjects with a mean age of 25 (range, 21–35) were studied previously using a protocol identical to that used in the older subjects (15). All comparisons were tested using individual subjects' median pH values except for peak pH and area under the curve comparisons.

Gender comparisons within the elderly subjects for gastric fasted, during the meal, and peak pH and duodenal fasted and during the meal pH were examined using a Mann–Whitney *U* test. All comparisons were tested using individual subjects' median pH except for peak pH. A repeated-measures analysis of variance was used to determine gender differences during the gastric and duodenal postprandial periods.

The statistical software packages BMDP (©1985, University of California at Los Angeles), Midas (©1976, 3rd ed., D. Fox and K. Guire, eds., Statistical Research Laboratories, The University of Michigan, Ann Arbor, MI), SAS (v5.16, ©1986, SAS Institute, Inc., Cary, NC), Statview

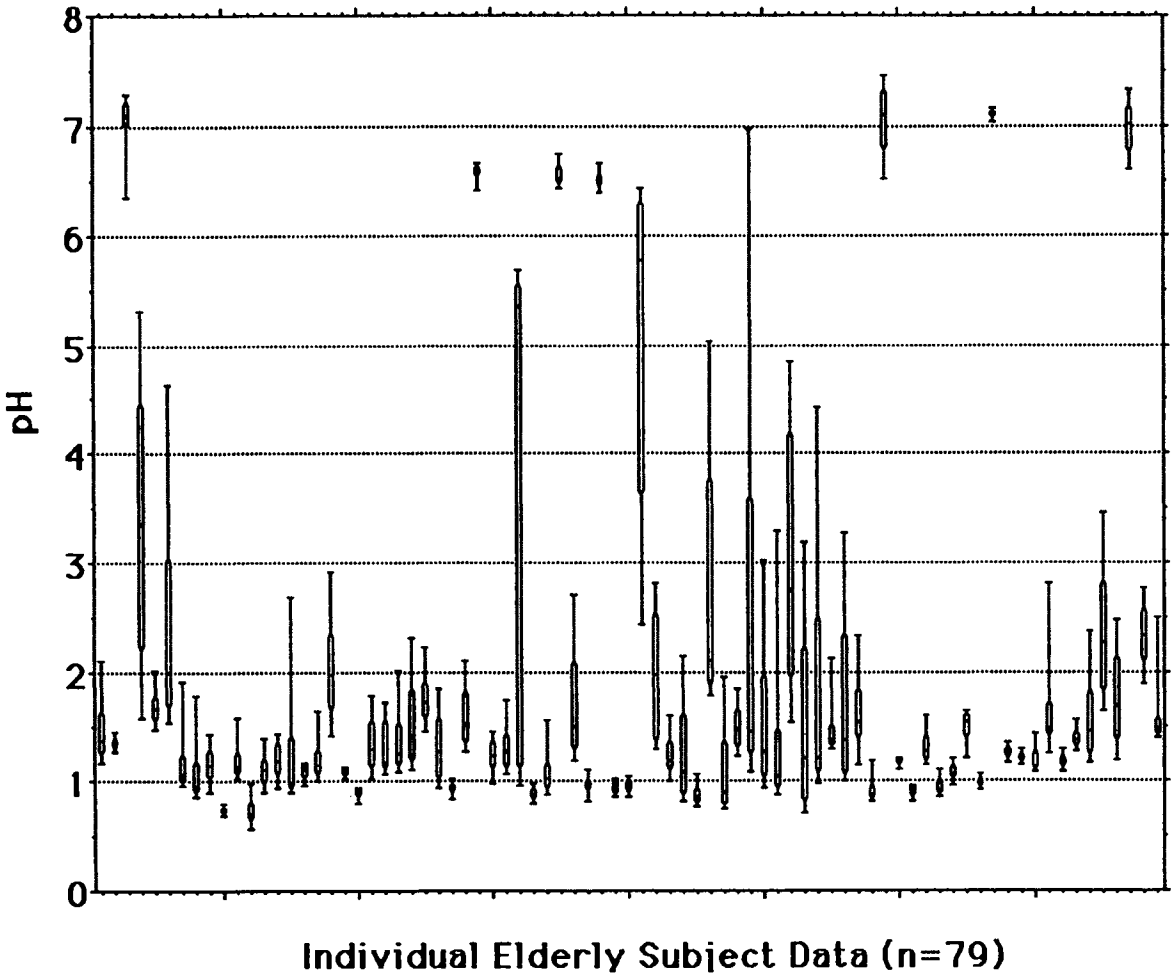

Fig. 3. Box-whisker plots of the distribution for fasted gastric pH within each of the 79 subjects. Each box represents the distribution of pH values over the entire 1-hr fasted pH recording period (n = 240).

SE + Graphics (v1.03, ©1988, Abacus Concepts, Inc.), and SYSTAT (v4.1, ©1989, Systat, Inc., Evanston, IL) were used for the transfer and analysis of data.

RESULTS

Individual Gastric pH Profiles

Three individual subject profiles are shown in Fig. 2 to illustrate the range of behavior seen in elderly gastric pH profiles.

Seventy of the 79 subjects studied had a low gastric pH, fluctuating around pH 1–3 in the fasted state, with postprandial pH profiles ranging in behavior from profiles similar to that found in young subjects to profiles in which the gastric pH following the meal decreased more slowly than is typical in a young, healthy subject (Fig. 2A). Four subjects of the 79 exhibited a gastric pH elevated above pH 5 in the fasted state, but the pH dropped in response to the meal stimulation (Fig. 2B). Five of the 79 subjects had gastric and duodenal pH profiles typical of an achlorhydric subject (Fig. 2C).

Gastric pH

The distribution of pH values during the 1-hr fasted period for each subject is represented as an individual box-whisker plot in Fig. 3. Each box-whisker represents the distribution of the 240 pH values recorded for one subject during the fasted gastric pH recording period. A total of nine subjects had a median fasted gastric pH above pH 5 (11.4%). Seven of these subjects had median pH values above pH 6 with narrow interquartile ranges. The two other subjects had fasted median pH values above pH 5 but exhibited 25th percentiles of 1.2 and 3.7, respectively.

Table I compares the descriptive statistical parameters for both young and elderly subjects during the gastric pH studies. The median fasted gastric pH for the elderly subjects was 1.3 (interquartile range, 1.1–1.6). This was significantly lower than the pooled young fasted gastric pH of 1.7 (interquartile range, 1.4–2.0), with $P = 0.014$. The area under the pH time curve also differed significantly ($P = 0.006$), with the median for elderly subjects 1.4 (interquartile range, 1.2–1.9) and that for young subjects 2.0 (interquartile range, 1.6–2.4).

Median pH did not differ significantly during the meal between young and elderly subjects ($P = 0.74$). The pooled median pH during the meal for elderly subjects was 4.9 (interquartile range, 3.9–5.5) and that for young subjects was 5.0 (interquartile range, 4.4–5.6). However, the median peak pH was significantly lower ($P = 0.020$) in the elderly subjects, with a median of 6.2 (interquartile range, 5.8–6.7), than in the young, with a median peak pH of 6.6 (interquartile range, 6.3–7.0).

Repeated-measures analysis of variance confirmed that the gastric pH significantly decreased over time following completion of the meal ($P < 0.0001$ based on the Greenhouse–Geisser correction). The median gastric pH at the start of the postprandial period was 5.2 (interquartile range, 4.5–5.8) and the median had dropped to 1.5 (interquartile range, 1.0–2.3) by 240 min following the meal. Ninety-eight and one-half percent of the variance in pH could be explained by a significant linear trend over time ($P < 0.0001$), and 1.2% by a significant quadratic trend ($P = 0.012$).

Medians with interquartile ranges for first time to return to pH 5, 4, 3, and 2 after the meal are given in Table I for both young and elderly subjects. For all pH values of interest, the first time to return to a specific pH was significantly longer in elderly subjects than in young subjects. For example, the median time to return to pH 3 in the older subjects was almost double that in the young, with a median of 89 min for older subjects and 42 min for young subjects. Likewise, the area under the pH-versus-time curve over the 4-hr postprandial period was significantly lower ($P = 0.0001$) in the

Table I. Comparison of Gastric pH Between Young and Elderly Subjects

Treatment phase	Young ($N = 24$)[a]	Elderly ($N = 79$)[b]	P value[c]
Fasted			
Median pH[d]	1.7 (1.4–2.0)	1.3 (1.1–1.6)	0.014
AUC (pH * hr)	2.0 (1.6–2.4) ($N = 24$)	1.4 (1.2–1.9) ($N = 75$)	0.006
During the meal			
Median pH	5.0 (4.4–5.6)	4.9 (3.9–5.5)	0.74
Peak pH	6.6 (6.3–7.0)	6.2 (5.8–6.7)	0.02
Postprandial			
Time to return to pH 5 (min)	8 (2–17)	23 (6–46)	0.015
Time to return to pH 4 (min)	14 (8–40)	52 (27–115)	0.0002
Time to return to pH 3 (min)	42 (26–83)	89 (44–167)	0.0026
Time to return to pH 2 (min)	100 (44–143)	154 (82–210)	0.026
AUC (pH * 4 hr)	10.8 (8.1–12.2) ($N = 24$)	12.3 (8.6–15.3) ($N = 78$)	0.0001

[a] From Ref. 15.
[b] Pooled elderly values include the achlorhydric older subjects.
[c] Given for the Mann–Whitney U-test statistic from comparisons between young and elderly.
[d] Values are given as medians, with interquartile ranges in parentheses.

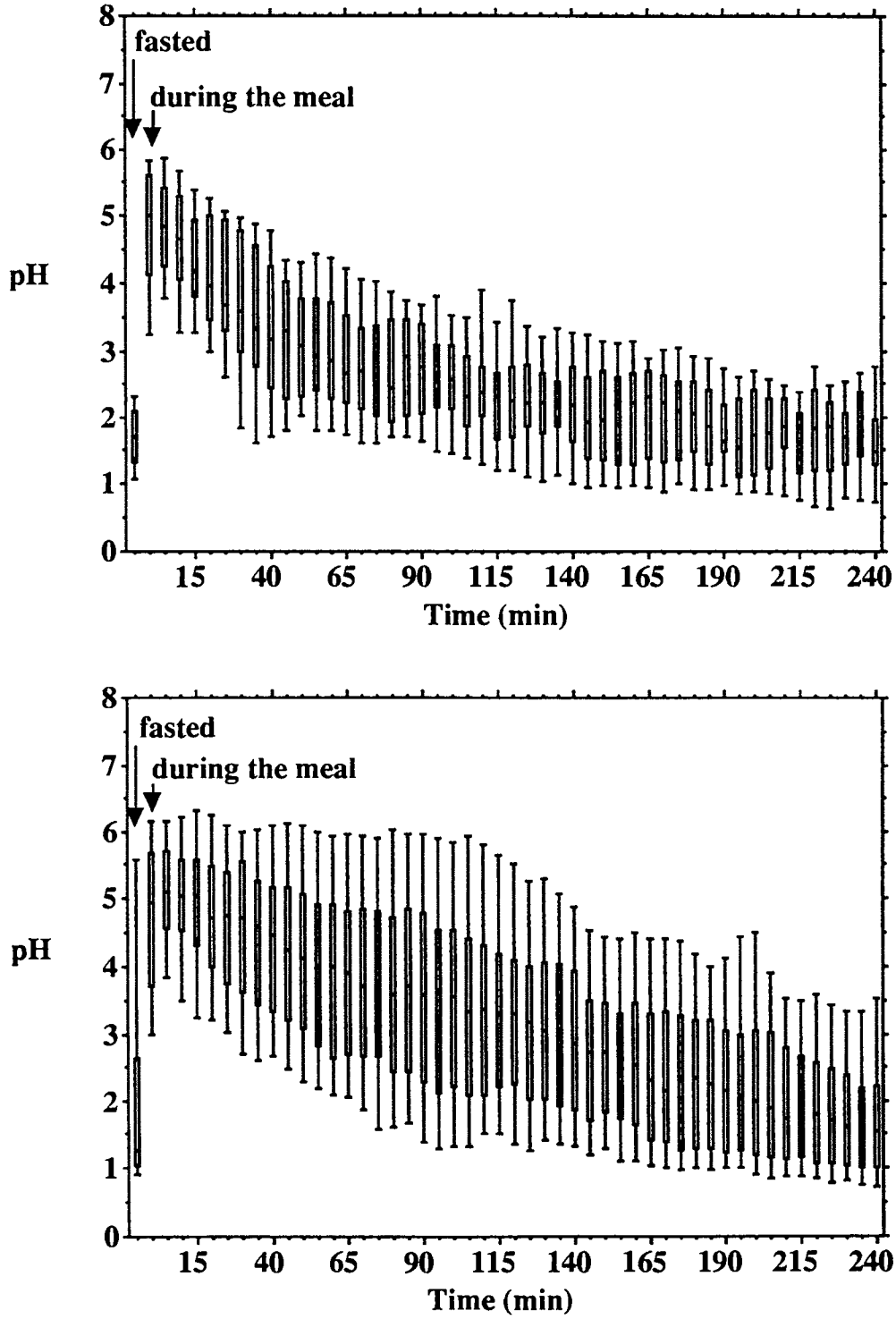

Fig. 4. Box-whisker plots representing the distribution of median gastric pH data from all young subjects (N = 24; top) (15) and from all elderly subjects (N = 79; bottom) for each 5-min interval following the meal. Time is given as minutes after completion of the meal. The first and second box-whiskers represent the distribution of median pH for all subjects in the fasted state and during the meal, respectively.

young (median, 10.8; interquartile range, 8.1–12.2), than in the elderly (median, 12.3; interquartile range, 8.6–15.3).

Figure 4 illustrates gastric pH behavior in the postprandial period for young and elderly subjects. Box-whiskers representing the distribution of individual median pH within each 5-min interval during the postprandial phase are graphed in temporal order. In comparison to the similar plot for the young subjects (15), the distributions for the older subjects during each 5-min interval are broader with an elevated 75th percentile.

Table II. Comparison of Duodenal pH Between Young and Older Subjects

Treatment phase	Young (N = 24)[a]	Elderly (N = 76)[b]	P value[c]
Fasted			
Median pH[d]	6.1 (5.9–6.4)	6.5 (6.2–6.7)	0.0009
AUC (pH * hr)	6.0 (5.8–6.4) (N = 12)	6.4 (6.1–6.5) (N = 76)	0.056
During the meal			
Median	6.3 (6.2–6.6)	6.5 (6.4–6.7)	0.030
Postprandial AUC (pH * 4 hr)	21.1 (18.8–23.3) (N = 21)	21.7 (20.7–22.8) (N = 75)	0.14

[a] From Ref. 15.
[b] Pooled elderly values include the achlorhydric older subjects.
[c] Given for the Mann–Whitney U-test statistic from comparisons between young and elderly.
[d] Values are given as medians, with interquartile ranges in parentheses.

No significant differences were found in gastric fasted pH (P = 0.22), gastric pH during the mean (P = 0.44), and peak gastric pH during the meal (P = 0.86) between males and females. A repeated-measures analysis of variance also failed to show significant gender differences in postprandial gastric pH (P = 0.95).

Duodenal pH

Table II compares the descriptive statistics for young (15) and elderly subjects during the duodenal phase. The median fasted duodenal pH in the elderly was 6.5 (interquartile range, 6.1–6.8), which was significantly greater (P = 0.001) than the young fasted duodenal pH of 6.1 (interquartile range, 5.9–6.4). The AUC for the pH-versus-time curve was not statistically different (P = 0.056) between the elderly (median, 6.4; interquartile range, 6.1–6.5) and the young (median, 6.0; interquartile range, 5.8–6.4) subjects. However, the trend in AUC was similar to the median duodenal fasted pH, with a greater AUC value in the elderly.

The pH during the meal was also significantly greater (P = 0.030) in the elderly than in the young. The median pH during the meal was 6.5 (interquartile range, 6.4–6.7) for the elderly and 6.3 (interquartile range, 6.2–6.6) for the young subjects.

A repeated-measures analysis of variance test indicated that the duodenal pH decreased significantly over time following completion of the meal (P value < 0.0001 based on the Greenhouse–Geisser correction). Eighty-one and two-tenths percent of the variance in pH could be explained by a significant linear trend over time (P < 0.0001), and 13.4% by a significant quadratic trend (P = 0.0053). The median pH (with interquartile range) at the start of the postprandial period and at 60, 120, 180, and 240 min following the meal was calculated and the results are as follows: (i) start of postprandial period, 6.4 (5.9–6.6); (ii) 60 min, 6.1 (5.5–6.5); (iii) 120 min, 5.6 (5.1–6.2); (iv) 180 min, 5.6 (5.1–6.0); and (v) 240 min, 5.6 (4.9–6.1). The decrease in duodenal pH postprandially was not as dramatic as the decline in gastric pH seen following the meal.

Figure 5 illustrates duodenal pH behavior in the postprandial period for young and elderly subjects. Box-whiskers representing the distribution of individual median pH within each 5-min interval during the postprandial phase are graphed in temporal order. The area under the pH-versus-time curve for the 4-hr postprandial period was 21.7 (interquartile range, 20.7–22.8) in the elderly. This median did not differ significantly (P = 0.14) from the median AUC for the young subjects, which was 21.1 (interquartile range, 18.8–23.3).

Gender comparisons based on individual median duodenal pH values revealed no significant differences in duodenal fasted pH (P = 0.91). Duodenal pH during the meal, however, was on the border of significance (P = 0.05) and tended to be slightly higher in the male subjects. A repeated-measures analysis of variance showed no significant differences in postprandial duodenal pH due to gender (P = 0.87).

Achlorhydric Subjects

Achlorhydric subjects were defined as subjects exhibiting both a fasted and a fed gastric pH greater than pH 5. Achlorhydria was further supported by a fasting serum gastrin test, which was elevated in all achlorhydric subjects (see Table III) but not elevated in those subjects with a low gastric pH that were tested. Demographically, the achlorhydrics consisted of two men and one woman aged 65–69, one man aged 75–79 years, and one man over the age of 80.

Table IV shows the overall medians for the achlorhydric subjects (n = 5) during all phases. No time to return was calculated for the gastric postprandial period because none of the achlorhydric subjects exhibited the typical decline in pH following the meal. The achlorhydrics' median fasted gastric pH was 7.1 (interquartile range, 6.5–7.1), and during the meal the median pH was 6.8 (interquartile range, 6.5–7.0). The fasted area under the pH-versus-time curve was 6.7 (interquartile range, 6.4–6.9) during the fasted state and 24.6 (interquartile range, 24.4–25.6) over the 4-hr period following the meal.

The median duodenal pH for the achlorhydrics was 6.8 (interquartile range, 6.5–6.9) for the fasted period and 7.0 (interquartile range, 6.8–7.2) during the meal. The area under the pH-versus-time curve was 6.8 (interquartile range, 6.4–7.0) during the fasted period and 26.3 (interquartile range, 25.2–27.1) over the 4-hr postprandial period.

DISCUSSION

Fasted Gastric pH

The majority of older subjects exhibited gastric pH profiles similar to those of the young during the fasted period. Although the median gastric pH in the fasted state was statistically different between young and older subjects (median, 1.3 vs 1.7), the value differed by only 0.4 pH unit. This small difference, with medians well in the acid range, is unlikely to be of any clinical importance.

Nine of 79 subjects (11%) had a median fasted gastric pH greater than 5. This extreme elevation in median fasted gastric pH suggests clinically significant differences in stom-

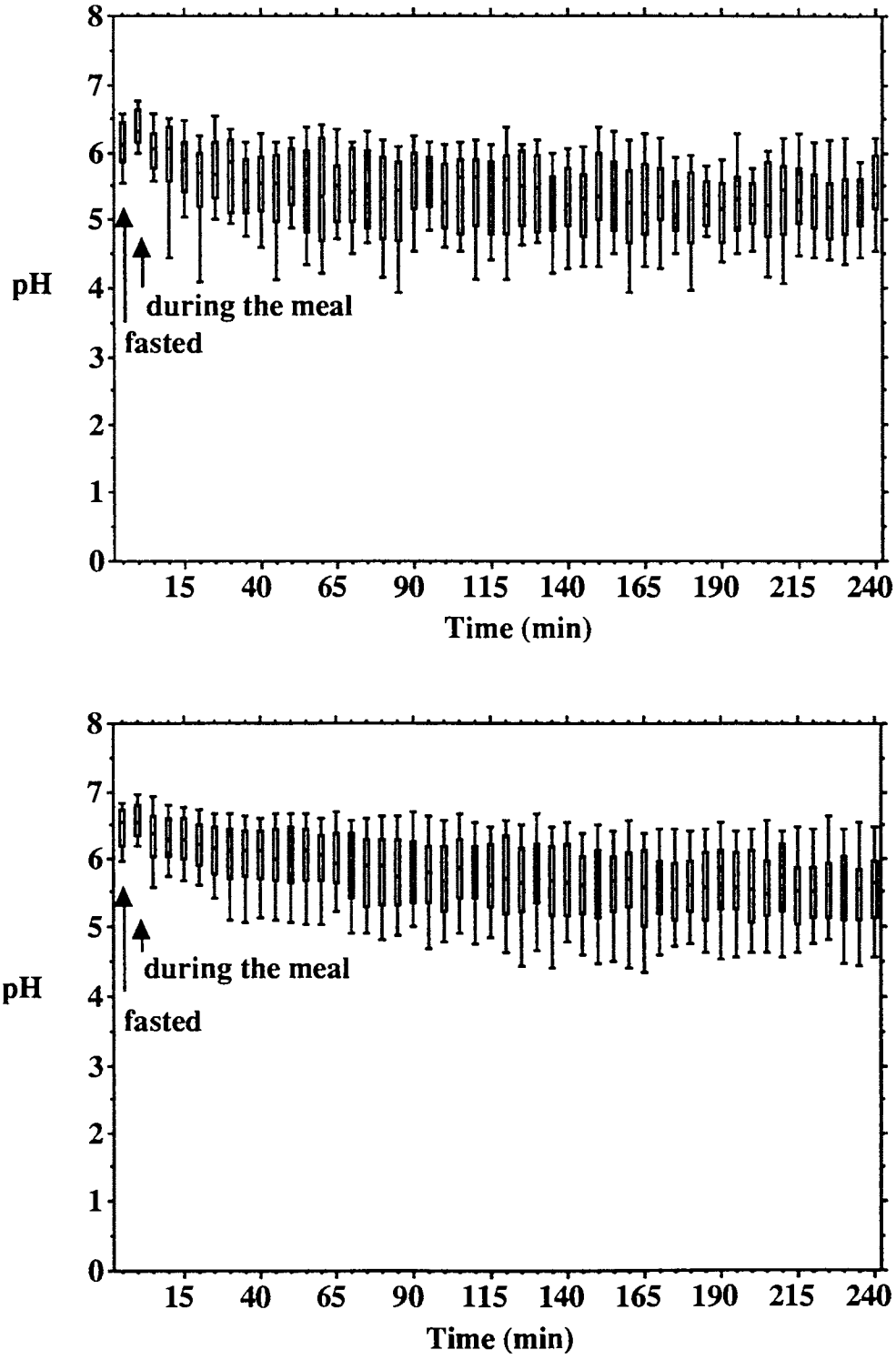

Fig. 5. Box-whisker plots representing the distribution of median duodenal pH data from all young subjects (N = 24; top) (15) and from all elderly subjects (N = 76; bottom) for each 5-min interval following the meal. Time is given as minutes after completion of the meal. The first and second box-whiskers represent the distribution of median pH for all subjects in the fasted state and during the meal, respectively.

ach function. For instance, the lack of an adequate acid barrier may result in bacterial overgrowth in the upper gastrointestinal tract. Elevated gastric pH may also result in poor absorption of minerals such as zinc, iron, and calcium. In the case of calcium carbonate supplements, which are often used to prevent osteoporosis in elderly women, elevated gastric pH may result in inadequate dissolution and subsequent lack of therapeutic effect. Some drugs, for example, keta-

Table III. Serum Gastrin Levels Collected During the Fasted Gastric pH Monitoring Period for Seven Subjects Who Exhibited a Gastric pH >6 in the Fasted State

Subject	FSG (pg/ml)[a]	Age	Gender
RS	100	65	Male
AM	1791	75	Male
SB	190	65	Female
CN	101	81	Male
FS	158	65	Male
HK[b]	53	75	Female
FW[b]	65	80	Male

[a] Normal range, 0–100 pg/ml at The University of Michigan Hospitals. All subjects with a low fasted gastric pH tested had fasting serum gastrin levels of <65 pg/ml.
[b] Subjects with an elevated fasted gastric pH but who exhibited a decrease in gastric pH after ingestion of the meal.

conazole (18) and cinnarazine (19), also require acidic conditions for dissolution, and for these compounds it has been shown that administration during elevated gastric pH conditions leads to compromised absorption. Other drugs which are weak bases and which have poor intrinsic solubilities are expected to behave similarly. Dosage forms which exhibit pH-dependent disintegration and/or release properties due to their excipient composition are also likely to be assimilated differently in elderly subjects who have elevated gastric pH.

Five of the nine subjects with an elevated fasted gastric pH (approximately 6% of older subjects studied) exhibited a gastric pH above pH 5 for both fasted and fed states. These subjects exhibited an elevated fasting serum gastrin, further supporting their achlorhydric status. The percentage of achlorhydrics discovered in our characterization study is slightly less than previously reported (10–20%). A possible explanation for this difference is that several of the previous studies did not exclude subjects with gastrointestinal and other major diseases, whereas the current study was conducted in healthy individuals with no history of gastrointestinal disease.

The other four subjects with elevated fasted gastric pH medians produced acid in response to the meal stimulation. Two of these subjects had narrow interquartile ranges with a median fasted gastric pH above pH 6. The other two subjects had medians above pH 5 but exhibited quite a fluctuation in pH, particularly on the low end, with 25th percentiles as low as 1.2 and 3.7. It would be difficult to predict dosage form performance in individuals with such variable gastric pH behavior.

Table IV. Descriptive Statistics for Achlorhydric Subjects, Gastric and Duodenal Treatments

Treatment phase	Achlorhydric (N = 5)[a]
Gastric	
Fasted	7.1 (6.5–7.1)
Fasted AUC (pH * hr)	6.7 (6.4–6.9)
During the meal	6.8 (6.5–7.0)
Postprandial AUC (pH * 4 hr)	24.6 (24.4–25.6)
Duodenal	
Fasted	6.8 (6.5–6.9)
Fasted AUC (pH * hr)	6.8 (6.4–7.0)
During the meal	7.0 (6.8–7.2)
Postprandial AUC (pH * 4 hr)	26.3 (25.2–27.1)

[a] Values are medians, with interquartile ranges in parentheses.

Gastric pH During the Meal

Gastric pH did not differ significantly during the meal between young and elderly subjects. The median peak pH levels in response to the meal for young and elderly were similar, at 6.7 and 6.2, respectively. Based on this finding, it appears that the ability of a standard meal to buffer the stomach acid does not differ between young subjects and elderly subjects.

Postprandial Gastric pH

The median time to return for all pH values examined was significantly slower in the elderly subject population compared to the young subjects. The elderly subjects showed a large variation in the rate of return to fasted gastric pH following the meal, with most elderly subjects decreasing more slowly than is typically seen in young subjects. Thirteen subjects of the 79 (16.4%) tested did not return to pH 2 within 4 hr of finishing the meal, whereas most young subjects in the earlier study returned to pH within 2 hr. This could be the result of slower acid production and/or slower emptying of the meal from the stomach. In a previous study investigating postprandial gastric emptying time of the Heidelberg capsule, Mojaverian *et al.* (20) found an elevated pH in 12 elderly males 30 min after the meal compared to 12 young males (mean pH of 5.6 and 3.6, respectively). A potential ramification of the postprandial differences with respect to drug absorption is that dosage forms typically given 1 to 2 hr following a meal are likely to encounter a higher gastric pH in an older subject than in a young subject. In addition, an older person with a slow decrease in pH who routinely eats every 4 to 6 hr during the day may exhibit a low gastric pH only before eating breakfast. Finally, drugs which exhibit different pH-related absorption properties in the fed state versus the fasted state in young subjects might exhibit greater changes in fed versus fasted-state absorption behavior in the elderly.

Duodenal pH, All Phases

The differences in duodenal pH between young and elderly were statistically different for all measurement periods. The duodenal pH medians differed by 0.4 pH unit or less, which suggests that they are unlikely to be of great clinical significance. Some dosage forms with release properties in the range of pH 6–7 might exhibit different release in young subjects than in older subjects during the fasted state. The same would be true for dosage forms releasing in the range of pH 5–6 during the fed state. Enteric-coated dosage forms provide an example of those which have release properties which may change markedly within these pH ranges. Likewise, a few drugs which have strongly pH-dependent absorption properties within this pH range may exhibit altered absorption. Possible examples include methyldopa (21) and cimetidine (22).

CONCLUSIONS

In general, both gastric and duodenal pH behavior is very similar between young and the majority of healthy, elderly subjects. However, the incidence of subjects with an elevated gastric pH in both the fasted state and the fed state is greater in the elderly. In about 10% of the elderly, gastric pH is markedly elevated in the fasted state. Additionally, in roughly one-half of the elderly subjects, gastric pH decreases more slowly than in young subjects after administration of a large meal. Drugs which rely on acidic conditions in the stomach for complete assimilation are therefore likely to be absorbed to different extents in young versus elderly subjects, especially when given after meals. Differences in duodenal pH between young and older subjects, while statistically significant, are unlikely to result in altered drug absorption except for a few specific drug examples. Finally, there does not appear to be any significant difference in upper gastrointestinal pH behavior between men and women.

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