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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

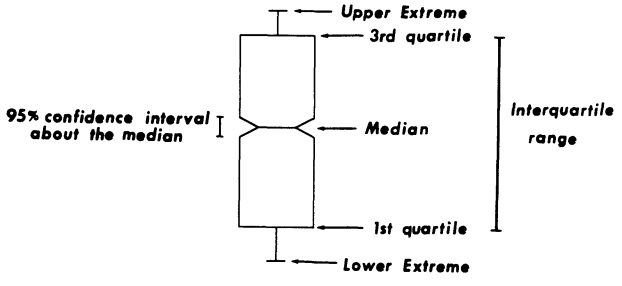

Fig. 1. Typical form of the box-whisker plot.