Mechanism of Gastric Emptying of a Nondisintegrating Radiotelemetry Capsule in Man[1]

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We studied the mechanism of gastric emptying of a pH-sensitive radiotelemetry capsule with respect to phases of the interdigestive migrating motor complex (IMMC) in fasting normal volunteers and the effect of the Heidelberg capsule (HC) on the duration or timing of the IMMC phases. A manometric catheter with eight mounted solid-state strain gauges was passed transnasally and positioned fluoroscopically in the duodenum and jejunum in four normal, fasted male volunteers, in their right lateral position. The HC was administered orally following the establishment of one complete IMMC cycle (defined by the recording time between the end of two subsequent phase III activity fronts) and during the beginning of Phase I of the next cycle. The gastric residence time (GRT) of the HC was measured as the time of a gastric pH rise of $\geq$3.0 units. In three subjects, GRT of the HC lasted to within 5 min of the onset of the next duodenal phase III of the IMMC, while in the fourth subject, the HC passed during the second phase III activity front. There were no significant differences in the duration of each phase of duodenal IMMC in the presence or absence of the HC (Phase I, 54 $\pm$ 9.3 vs 31.6 $\pm$ 10.1; Phase II, 22 $\pm$ 8.1 vs 58.9 $\pm$ 32; Phase III, 5.3 $\pm$ 0.7 vs 4.2 $\pm$ 0.7 min; mean $\pm$ SE; $P > 0.1$ in all phases). In addition, the HC had no effect on motility index or patterns of contractions. The Heidelberg radiotelemetry device (7 $\times$ 20 mm) may be used as a noninvasive, nonradioactive means of measuring the activity of the IMMC and the presence of Phase III peak IMMC activity. Further, it permits detailed evaluation of the emptying patterns of solid dosage forms (i.e., enteric-coated tablet or controlled-release matrix) in humans under fasted or fed conditions.

KEY WORDS: Heidelberg capsule; radiotelemetry technique; manometry recording; Phase III of interdigestive migrating motor complex (IMMC); indigestible solid capsule; gastric residence time; pH-sensitive device; gastric and intestinal IMMC.

INTRODUCTION

Hinder and Kelly (1) first demonstrated differences in the gastric emptying patterns of a liquid, a digestible solid, and an indigestible solid in dogs (1). Distinct mechanisms are responsible for gastric transition of liquids, solid food, and indigestible solid materials in animals and in humans (1–5). The slow, sustained contractions of the proximal stomach which determine intragastric pressure mediate the gastric emptying of liquids and small particulate material (<2–3 mm in diameter). Emptying of digestible solids >2 mm in diameter is a function of antral peristaltic contractions. Emptying of solid food particles greater in size than the pyloric opening are delayed until they are reduced in size by grinding mechanism of these antral contractions and gastric trituration. Solids >2–3 mm in diameter are retained within the stomach until the digestive process is complete.

It has been suggested that the emptying of large indigestible objects from the stomach is dependent on the contractile activity of the interdigestive migrating motor complex (IMMC) (1–5). The IMMC, which occurs in the fasted state (when the liquid and digestible solid food have cleared out of stomach completely), is characterized by the three phases of myoelectric and motor activity (3–6). Phase I is represented by a period of motor inactivity with only rare contractions, which lasts about 45 to 60 min. During Phase II, intermittent peristaltic contractions occur that increase in frequency and amplitude over a 30- to 45-min period. Phase III, represents the "activity front," the intense bursts of action potentials and contractions which continue for 5 to 10 min. This powerful electromechanical activity of Phase III sweeps slowly from the stomach to the ileum and is responsible for emptying of indigestible debris left over from a meal (the so-called housekeeper wave of the gastrointestinal tract). This cyclical pattern of electrical activity showing noticeable intra- and intersubject viarability in duration occurs on average every 120 min in fasting humans (2–6).

To date, the mechanism of the gastric emptying of large indigestible solids has not been extensively studied in humans. The Heidelberg capsule (HC), an orally administered, pH-sensitive, nondigestible, radiotelemetric device, approximately the size of a No. 1 gelatin capsule, has been used as a noninvasive tool to measure gastric pH under various conditions (7–9). A sharp rise in pH is interpreted as pyloric passage of the capsule and allows an estimation of its gastric residence time (GRT). We have used the HC to evaluate the gastric and small bowel transition of a large indigestible solid dosage form (10–14) and reported that gastric emptying of the HC is delayed by food (10–12). Because of its size and nondigestible nature, the gastric emptying of the HC is believed to occur during Phase III of the IMMC, although direct evidence for this is lacking in man. The present study demonstrates the phase of the IMMC during which the HC empties from the fasted stomach in healthy male subjects and whether the presence of this capsule would alter the duration of activity or frequency of the IMMC phases.

MATERIALS AND METHODS

Radiotelemetry

The Heidelberg capsule is a pH-sensitive radiofrequency (1.98-MHz) transmitter encased in an inert, indigestible shell, with a 7-mm diameter, a 20-mm length, and a density of 1.5 g/cm^3. Readings from the Heidelberg capsule were continuously recorded after its ingestion. The capsule

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was considered to have entered the duodenum when the pH reading was observed to increase 3 units or greater and remain elevated for at least 30 min. This avoided small or anomalous fluctuations in the readings being interpreted as the time of gastric emptying. The gastric residence time (GRT) of the HC was defined as the length of time that the capsule remained in the stomach. After oral ingestion, the capsule transmits signals from the gastrointestinal tract to a receiving antenna incorporated in a wide belt worn by a subject. These signals are passed to a receiver, decoded, and displayed as a pH reading. Because pH values change with location within the gut, alterations in pH should be indicative of the movement of the capsule through the different segments. Generally, the capsule functions for 22 hr after activation and provides readings with ±0.5 pH unit accuracy and excellent *in vivo* reproducibility in the pH range of 1 to 8 (15). The Heidelberg radiotelemetry instrument and the Heidelberg capsule were purchased from the Heidelberg International Incorporation (Atlanta, Georgia).

Study Protocol and Manometry

The protocol was approved by the University of Pennsylvania Institutional Review Board. Four healthy male subjects between 21 and 28 years of age, with no prior signs or symptoms of ulcer or gastrointestinal dysfunction, volunteered to participate in this study. Following satisfactory completion of the physical examination and signing of the informed consent form, each subject reported to the gastrointestinal motility laboratory of the University of Pennsylvania, at 7:00 AM following an overnight fast (from 10:00 PM the previous night). The manometric catheter was passed intranasally after local application of a cocaine-based anesthetic. Pressures were recorded from an 8 French Catheter which contained eight solid-state pressure transducers, each 4 cm apart (Mikrotip catheter pressure transducer, Millar Instruments, Inc., Houston, TX). The catheter was advanced through the stomach into the duodenum and fluoroscopically manipulated so that the two most distal transducers were beyond the ligament of Trietz (in the jejunum). The catheters were connected via voltage control units, (Model TC-500, Millar Instruments) to a rectilinear chart recorder (Beckman R711, Beckman Instruments, Inc., Fullerton, CA). The output was simultaneously recorded on FM tape using a Hewlett-Packard FM tape recorder (3968A) for later analysis by computer (HP9826). Recordings were initiated and continued with the subject in the right lateral position, until two phase III patterns were recorded.

Following the passage of the second phase II IMMC, the HC was given orally along with 60 ml of water. Intraluminal (gastric) pH was then recorded continuously by the radiotelemetry technique until the pyloric passage of the HC was observed (a sustained rise of ⩾3 pH units). Only one subject was tested in each study day.

Interpretation of Manometric Recordings

The patterns of contractile activity were examined visually and the data were analyzed from tracings from six to eight transducers in each subject. Three phases were recognized in the fasting tracing. Phase I was defined as a period in which no contractions were seen. Phase II was defined as containing contractile activity and occurred between Phase I and Phase III. Phase III was characterized by a burst of rhythmic activity lasting at least 2 min and migrating down the intestine over all leads distal to the lead in which it originated. The inter-MMC duration was defined as the duration between the end of Phase III of one cycle and the end of Phase III of the subsequent cycle. The termination of Phase III was chosen rather than the beginning, as the quiescent Phase I was more easily defined than the transition from the intermittent activity of Phase II to the rhythmic activity of Phase III. The motility index (mm Hg × sec) was calculated as sum of the amplitude of all the contractile peaks multipled by the duration occupied by these contractions. The durations of the phases of fasted pattern in the presence and absence of the Heidelberg capsule were compared using an analysis of variance.

RESULTS

A typical pH vs time profile obtained in a fasting volunteer by continuous monitoring of intragastric pH after oral ingestion of the Heidelberg capsule is shown in Fig. 1. Duodenal entry of the capsule occurred at t = 30 min as shown by a sharp rise in pH (Fig. 1). In four male volunteers, the GRT of the HC ranged from 0.67 hr (in subject G.S., who emptied the capsule along with the first Phase III IMMC) to 3.5 hr (in subject P.T., who emptied the capsule during second phase III IMMC). The mean (±SD) GRT observed in the present study was 1.9 ± 1.1 hr. In all four subjects in the right lateral position, the sharp rise in pH (shown in Fig. 1) occurred during phase III duodenal IMMC, and never prior to a phase III IMMC (Fig. 2).

Gastric IMMC was recorded in two subjects (P.T. and A.G.). In each case, the capsule emptied during phase III complex.

The Effect of the Heidelberg Capsule on Duodenal IMMC

A typical manometric recording in a fasted subject is shown in Fig. 2. As illustrated in the figure, three phases of the motor complex are clearly recorded from the pressure 2 transducer located in the proximal duodenum. Duodenal pressure 2 recording shows the intermittent peristaltic contractions of Phase II leading into a burst of continuous con-

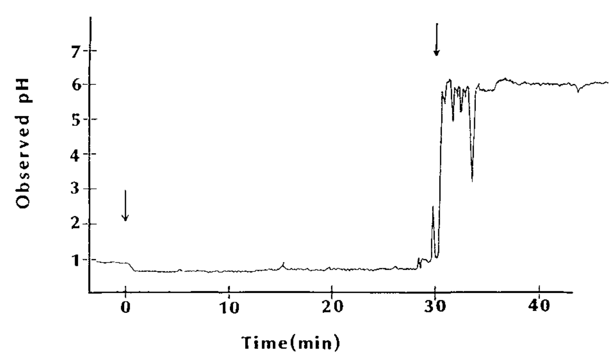

Fig. 1. pH vs time profile obtained by continuous monitoring of the Heidelberg capsule after its oral ingestion at t = 0 in a normal volunteer after an overnight fast. Gastric emptying time coincided with a sharp increase in pH (arrow), which occurred 30 min after the oral intake of the capsule.

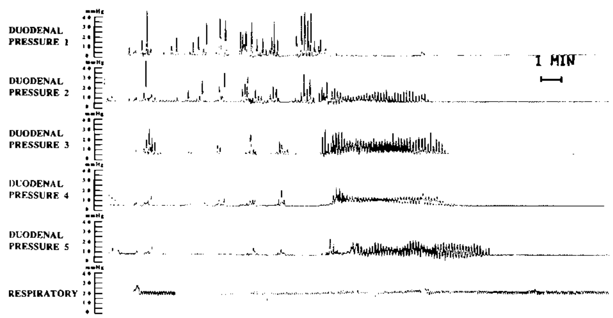

Fig. 2. The passage of the activity front of Phase III of a migrating motor complex can be seen to progress from duodenum pressure lead 1 to lead 5 in an orderly fashion in a fasted subject after oral administration of the Heidelberg capsule. As shown by the pressure transducer at location 2, intermittent contractions of Phase II leads into a burst of "activity front" of Phase III (which lasts about 4 to 6 min) and, finally, ends with the period of inactivity of Phase I of the migrating motor complex. This pattern, which is propagated distally along the duodenum (positions 2 to 5), is independent of the subject's respiration rate (bottom panel). The 1-min scale is shown by the horizontal bar.

tractions of Phase III (lasts about 4 to 6 min) and ending with the quiescent period of Phase I of IMMC. This contraction pattern is propagated through pressure transducers positioned at locations 3, 4, and 5 along the mid to distal duodenum. The uniform respiration rate shown in the bottom panel implies that the phasic changes of IMMC contractions recorded at positions 1 through 5 are independent of the subject's respiration rate.

The mean (±SE) duration of each phase of IMMC measured prior to administration of the HC (baseline recording) or after ingestion of the radiotelemetry capsule were not statistically different: Phase I, 31.6 ± 10.1 vs 54 ± 9.3; Phase II, 58.9 ± 32.5 vs 22.0 ± 8.1; and Phase III, 4.2 ± 0.7 vs 5.3 ± 0.7 min ($n = 5$; $P > 0.1$ in all phases). The individual baseline inter-MMC intervals ranged from 31 to 223 min (mean ± SE, 94.4 ± 30.5 min) and were not significantly affected by the administration of the HC (81.1 ± 17.2 min, $n = 5$, $P > 0.1$). There were marked intra- and intersubject variabilities in duration of the inter-MMCs (Fig. 3).

Further, the motility index during each of the three phases of IMMC was not influenced by the presence of the

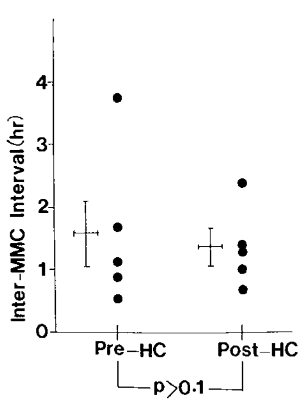

Fig. 3. The individual inter-MMC intervals shown in male volunteers prior to and post administration of the Heidelberg capsule. The mean ± SE are shown by the solid bars.

capsule (data not shown). Visual inspection of the manometric recordings also indicated that the HC had no significant effect on the patterns of the IMMC contractions.

DISCUSSION

In the present study, manometric recording of IMMC in healthy subjects revealed that an indigestible radiotelemetry capsule (the HC) empties from the fasted stomach along with the Phase III of duodenal IMMC. The present work is the first evidence demonstrating the mechanism of the gastric emptying of an indigestible capsule in man. Evaluation of the literature indicated that gastric emptying (measured by serial X rays) of radiopague dosage form (16) or large nondigestible solids may be dependent on the activity of IMMC wave in beagle dogs (17) and in humans (16,18).

In the present study, there were considerable inter- and intrasubject variabilities in duration of each phase of the IMMC and the inter-MMC interval as demonstrated by the mean manometric data in the presence or absence of the radiotelemetry capsule. This finding is consistent with the recent report by Ouyang *et al.* (6) and the previous reports by other investigators (19–21). Although the presence of the HC had no effect on the duration or pattern of the IMMCs, the posture played an important role in the gastric emptying of this telemetry capsule by the sweeping Phase III IMMC. The HC passed into the small bowel during the first Phase III only when the subjects were in the right lateral position. In a previous study with subjects in supine or left lateral positions, emptying of the HC occurred along with the first Phase III IMMC in only two of the eight experiments (data not shown). The posture dependency observed with the HC in the present study is in general agreement with the already accepted phenomenon that in man, gastric emptying of both liquids and digestible solids is accelerated when the right lateral posture is assumed (22–24).

Based on the results of this study, the HC may be used as a noninvasive device to examine the presence and the time of occurrence of Phase III IMMC, which coincides with the gastric residence time of the capsule.

In addition, the recent work by our group (10–15, 25–27) and others (28–31), utilizing the Heidelberg radiotelemetry method in man, has contributed to the present understanding of oral absorption of solid dosage forms under various pH conditions, intersubject variability in absorption lag time of enteric-coated formulations in the fasted and fed conditions, gastric and intestinal transit time of the solid nondisintegrating matrices, and variability in the gastrointestinal motility. A number of other techniques have also been used to characterize the gastrointestinal transit time and *in vivo* performance of controlled release formulation. These include the use of X ray (18), external gamma scintigraphy (14, 32–34), neutron activation (35,36), and stable isotopes. Each method provides some advantages and few drawbacks (i.e., radiation hazard and expensive equipment).

The HC offers the advantage of simple and inexpensive instrumentation which avoids the repeated exposure to radiation and the need for nasogastric intubation. This radiotelemetry device has been used alone as a reliable *in vivo* pH meter (37,38) and, in combination with several solid formulations, to evaluate the gastrointestinal transit time of various nondisintegrating solid dosage forms in man (11,12,25–31). Furthermore, the HC has been instrumental in recent clinical studies evaluating the effect of physical/biological parameters such as various feeding regimens (10), posture, gender, and age (13,39), and disease state (40) on the gastric residence time of a large solid matrix.

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