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Research Article

Effects of Gender, Posture, and Age on Gastric Residence Time of an Indigestible Solid: Pharmaceutical Considerations[1]

Parviz Mojaverian,[2,3] Peter H. Vlasses,[2] Paul E. Kellner,[2] and Mario L. Rocci, Jr.[2]

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We have recently reported the effect of varying food composition on the gastric residence time (GRT) of an indigestible solid, the Heidelberg capsule (HC). The purpose of the present evaluation was to evaluate the reproducibility and the effect of gender, posture, and age on the GRT of the HC. The reproducibility in measurement of the GRT of the Heidelberg capsule was evaluated in two trials separated by 1 week. Mean GRT values obtained in nine healthy men on day 1 were not statistically different from those on day 8 (3.5 ± 0.6 vs 3.5 ± 0.7 hr, $P > 0.05$). To evaluate the influence of gender on the GRT of the HC, 12 healthy male volunteers and 12 age (± 3 years)- and race-matched female counterparts entered into a randomized study. Each subject was served a standardized 500-kcal breakfast 30 min prior to oral ingestion of the HC. The mean ($\pm$SD) ambulatory GRT in the males was significantly faster than in the females (3.4 ± 0.6 vs 4.6 ± 1.2 hr, $P < 0.01$). Influence of posture on the GRT of HC was examined in the same 12 men in a two-way, randomized, crossover study. The mean GRT for volunteers in the supine state was not statistically different from that in the upright, ambulatory state (3.4 ± 0.8 vs 3.5 ± 0.7 hr, $P > 0.05$). The effect of age on the GRT of the HC was evaluated in 12 healthy elderly males (>65 years) with no prior gastrointestinal complications. The mean value of the GRT 30 min after a 500-kcal breakfast was significantly prolonged compared to that of the young male volunteers (4.5 ± 1.1 vs 3.4 ± 0.6 hr, $P < 0.02$). A larger GRT is consistent with the results of gastric emptying of a digestible solid in the elderly, reported by other investigators. In summary, the data indicate that even when the hormonal changes due to the menstrual cycle are normalized, women emptied their stomach slower than men, regardless of weight, height, or body surface area. In addition, the GRT of an indigestible capsule was prolonged in the elderly, especially in subjects >70 years old.

KEY WORDS: radiotelemetry; Heidelberg capsule; gastric transit time; indigestible solid; effects of gender, posture, and age; intragastric pH measurement via radiotelemetry.

INTRODUCTION

Gender, posture, and age are factors that have been reported to affect the gastric emptying time of digestible solids and/or liquids (1–11). The half-emptying time of digestible solids and liquids measured by sequential scintigraphy is significantly shorter in males than age- and race-matched female counterparts, regardless of weight, height, or body surface area (1–3). Posture dependency of gastric emptying has been studied by Burn-Murdoch and co-workers, who showed a delay in gastric transit time of digestible test meals when subjects are placed in the left lateral decubitus position (10).

Using dual-isotope gamma-scintigraphy, a delay in the rate of gastric emptying half-time of a digestible liquid meal has also been reported in elderly subjects (12,13). The purpose of the present studies was to evaluate the influence of gender, posture, and age on the gastric residence time (GRT)[4] of an indigestible solid and to evaluate whether the effects of these factors parallel those on digestible solids and liquids. Our interest is based on the fact that certain pharmaceutical dosage forms (e.g., enteric-coated tablets, some sustained-released tablets) are indigestible in the gastric milieu and their gastric residence time could affect their drug release characteristics (8,14,15). The Heidelberg capsule (HC) is a pH-sensitive, radiotelemetric hard plastic encapsulated device that has been employed as a noninvasive tool to measure intragastric pH (16–18). With pyloric passage of the capsule (i.e., stomach to duodenum), a sharp rise in pH is observed. The nondigestible nature of the HC allows gastric residence time to be a marker of the GRT of indigestible solid dosage forms.

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[2] Division of Clinical Pharmacology, Department of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania 19107.

[3] To whom correspondence should be addressed at Schering-Plough Pharmaceutical Research Division, 60 Orange Street, Bloomfield, New Jersey 07033.

[4] Abbreviations used: GRT, gastric residence time; HC, Heidelberg capsule; IMMC, interdigestive migrating myoelectric complex.

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MATERIALS AND METHODS

Heidelberg Capsule

The Heidelberg capsule consists of a pH-sensitive, radiofrequency transmitter encased in an inert, indigestible shell approximately the size of a No. 1 gelatin capsule (7 mm in diameter, 20 mm in length) and with a density of 1.50 g/cm^3. Before use, each capsule must be activated by immersion in 0.9% saline solution for 2 min and then calibrated with pH 1.0 and 7.0 buffer solutions. After oral ingestion, the capsule transmits signals from the gastrointestinal tract to an antenna embedded in a wide belt worn by the subject. These signals are passed to a receiver, decoded, and displayed as a pH value. On average, the capsule functions for 20 hr after activation. The accurate measuring range of the Heidelberg capsule is pH 1 to 8, with a measuring error of ±0.5 pH units (19). In the studies described below, pH was measured after HC ingestion at frequent intervals (15 to 30 min) until a sharp sustained rise (≥3 units) was observed. The GRT was recorded as the time required for this sharp rise to occur. The Heidelberg Telefunken Instrument and the capsules were purchased from Heidelberg International, Inc., Atlanta, Georgia.

Study Design

Interday Variation in GRT. An initial two-way crossover study was undertaken to establish the reproducibility of GRT measurements with the HC in a group of subjects. The protocol was approved by the Thomas Jefferson Institutional Review Board and all volunteers signed an informed consent form prior to their participation in these studies. Nine healthy male volunteers between 28 and 39 years of age (mean, 34 years) and weighing 66–82 kg (mean, 75 kg) reported to the Clinical Research Unit at 8:00 AM following an overnight fast. Each subject was served a standardized 500-kcal breakfast 30 min before oral ingestion of the HC. Breakfast, which was completely consumed over 30 min, included the following: skim milk, 150 ml; orange juice, 100 ml; black coffee or tea, 100 ml; two fried eggs; two pieces of toast; margarine, 5 g; cheese, 20 g; and sugar, 1 teaspoon. The gross weight of the ingested breakfast was 350 g. All of the following studies were performed after standardized feeding to allow for inhibition of the gastric interdigestive migrating myoelectric complex (IMMC) cycle and establishment of a baseline condition in all subjects (20). No other food or beverage intake was permitted until pyloric passage of the HC had occurred. Following a 1-week drug-free washout period, each subject was restudied in an identical manner.

Gender and GRT. The HC was evaluated in 12 healthy males and 12 race- and age-matched females in a randomized study. Males (20 to 34 years; mean, 26 years) and females (21 to 33 years; mean, 26 years) were judged to be in good health on the basis of medical history, physical examination, and the results of routine laboratory tests. The females had no history of oral contraceptive use for the previous 2 months, and all were studied during the first week following the end of their last menstrual period. Following a 1-week drug-free period, subjects reported to the Clinical Research Unit, having fasted from the previous midnight. Each subject was served the same standardized 500-kcal breakfast described above 30 min prior to oral ingestion of the Heidelberg capsule. Subjects were ambulatory throughout the study and received no other food or drink until the time of pyloric passage of the capsule.

Posture and GRT. Twelve healthy male volunteers who previously participated in the gender study participated in a randomized two-way crossover study. Following an overnight fast, all subjects received a 500-kcal standardized breakfast, 0.5 hr prior to ingestion of the HC and assumed either supine (flat on back) or standing (ambulatory) positions for the duration of the experiment. The ambulating subjects were restricted to an upright posture, with limited walking and no physical exercise. Subjects were allowed no other food or drink until the passage of the HC from the stomach to the small intestine was recorded.

Age and GRT. The influence of age on gastric retention of an indigestible capsule was studied in a group of 12 healthy elderly male (>65-year) subjects. Elderly subjects were race-matched against the younger subjects and the evaluations were conducted in a randomized manner. Each volunteer was screened for gastritis, gastrointestinal ulcer, diabetes, history of drug abuse, or use of any other drug that was known to affect gastrointestinal motility. The subjects' age ranged from 65 to 79 years (mean, 69 years). Following an overnight fast, each volunteer received a standardized 500-kcal breakfast 30 min before oral administration of the Heidelberg capsule. Data obtained in the elderly group were compared with the GRT values measured in the group of young males.

Statistical Analysis. Paired or unpaired Student's t tests were used for establishing statistical difference in GRT measurement, in male vs female (unpaired t test), ambulatory vs supine (paired t test), and young vs old (unpaired t test). A regression analysis of interday variability in GRT was conducted by a perpendicular least-squares procedure, which considers the presence of experimental error in both x and y variables (21).

RESULTS

Interday Variation in GRT

The GRT of the HC exhibited remarkable reproducibility when tested in these nine healthy men on two occasions separated by 1 week. Mean (±SD) values of GRT were not statistically different between day 1 and day 8 (3.5 ± 0.6 vs 3.5 ± 0.7 hr, $P > 0.05$). A plot of the individual GRT measurements on day 1 versus day 8 is presented in Fig. 1. A strong and highly significant relationship ($r = 0.82$, $P < 0.005$) existed between the GRT measurements made on two separate occasions in the same individuals.

Gender and GRT

No significant age differences existed between the male and the female group values (26 ± 3.9 vs 26 ± 3.8 years, $P > 0.05$). Mean values of the intragastric pH versus time profile in 12 ambulatory males and females are shown in Figs. 2 and 3, respectively. The buffering capacity of the 500-kcal standardized mixed meal ingested 30 min before oral administration of the HC is shown by an increase in gastric pH at

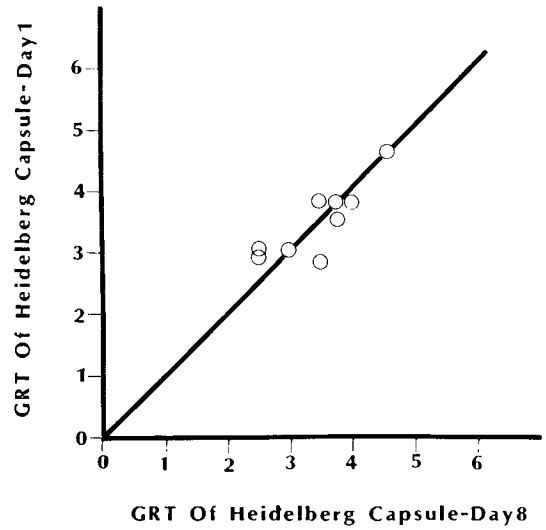

Fig. 1. A plot of GRT of the Heidelberg capsule measured in nine healthy volunteers on day 1 versus the same measurements on day 8. The capsule was administered orally 30 min after ingestion of a 500-kcal standardized mixed meal. The solid line shows the line of identity ($y = x$).

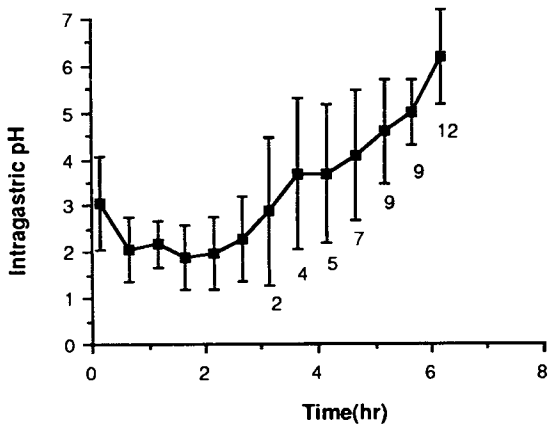

Fig. 3. A plot of the pH vs time profile in healthy, ambulatory female subjects following a 500-kcal mixed meal. pH measurements were begun 30 min after meal ingestion. Each point represents the mean (± SD) for 12 subjects. The numerical values on the error bars (i.e., 2, 4, 5, 7, 9, and 12) are representative of the number of subjects with pH > 5.5 at those time points (i.e., at 3 hr only 2 of the 12 females showed the pyloric passage of the HC, while by 4 hr GRT of HC was observed in a total of 5 subjects).

time zero (see Figs. 2 and 3). There was no significant difference in postprandial baseline pH between the male and the female group (3.6 ± 1.3 vs 2.9 ± 1.0, $P > 0.05$). Wide intersubject variation in gastric pH is also exhibited by both male and female groups. Nonetheless, the mean GRT was significantly longer in the women in comparison to the men (4.6 ± 1.2 vs 3.4 ± 0.6 hr, $P < 0.01$; Fig. 4). That men exhibited a shorter gastric transit time for the HC is also reflected in Figs. 2 and 3, by the numbers of subjects who showed clear indication of pyloric passage of the HC. For example, emptying of the HC into the small intestine occurred in 12 males at 4.5 hr (Fig. 2), while only 7 females had emptied by that time (Fig. 3).

Posture and GRT

The GRT values for individual male volunteers in the supine (flat on the back) and standing positions are presented in Fig. 5. No significant differences in GRT could be detected in the supine versus standing postures (3.5 ± 0.7 vs 3.4 ± 0.8 hr, $P > 0.05$). In subjects assuming a standing posture, the GRT ranged from 2.5 to 4.0 versus 2.0 to 4.5 hr, when the GRT was measured in the supine position.

Age and GRT

The influence of age on gastric retention time of the indigestible solid capsule was evaluated in 12 elderly male (>65-year) volunteers. The mean ages of the young and old

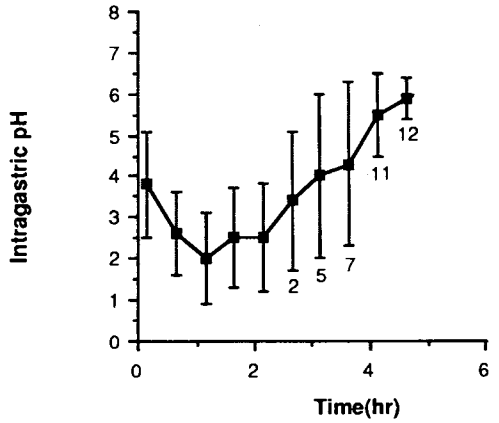

Fig. 2. A plot of intragastric pH vs time in 12 healthy, ambulatory male subjects following a 500-kcal mixed meal. pH measurements were begun 30 min after meal ingestion. Each point represents the mean (± SD) for 12 subjects. The numbers shown on the error bars (i.e., 2, 5, 7, 11, and 12) represent the number of volunteers with pH > 5.5 at the corresponding time points. For example, two subjects showed a GRT of 2.5 hr, while at 3 hr a total of five subjects showed emptying of the capsule into small intestine.

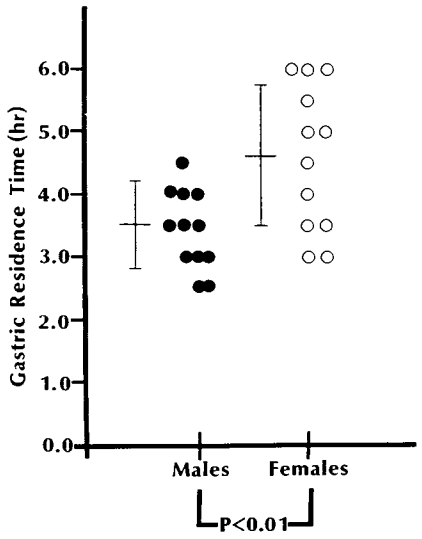

Fig. 4. Individual GRT measurement in 12 healthy male and 12 age- and race-matched female counterparts. Both groups remained ambulatory throughout the study. The mean (± SD) is shown for each group.

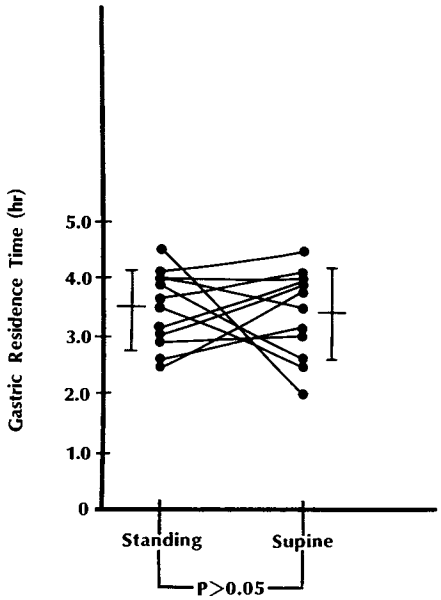

Fig. 5. GRT measurements in 12 healthy males in ambulatory (standing) and supine positions. No difference was observed between the GRT values in the two positions.

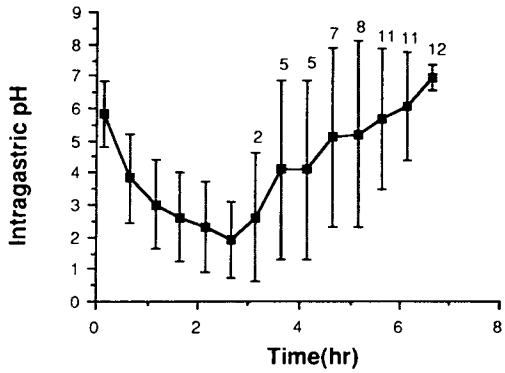

Fig. 6. A plot of intragastric pH versus time in 12 healthy male elderly subjects in ambulatory positions measured via radiotelemetry method. Data are presented as mean (± SD). Numerical values on each error bar represent the total number of individuals who showed the pyloric passage of the Heidelberg capsule at those time points.

male subjects were 26.0 ± 0.4 and 69 ± 4 years, respectively. The individual GRT values along with other physical data are shown in Table I. The GRT of the HC in these elderly volunteers ranged from 3.0 to 6.5 hr. Figure 6 demonstrates a plot of the mean (± SD) intragastric pH versus time in the 12 elderly volunteers. In general, the mean pH values were higher in the elderly group compared to the young ambulating male counterparts (i.e., 30 min after ingestion of a mixed meal the mean gastric pH was 5.6 ± 1.0 in the elderly group vs 3.6 ± 1.3 in the young group, $P < 0.001$, as shown in Figs. 2 and 6). Mean GRT values obtained in the ambulating elderly subjects were significantly prolonged compared to the corresponding values measured in the ambulating young individuals (4.5 ± 1.1 vs 3.4 ± 6.0 hr, $P < 0.02$; Fig. 7). There was no strong linear relationship between the GRT and age, when data from young and old subjects were combined. This may be due to the lack of GRT data in the 30- to 65-year age range.

DISCUSSION

Most drugs are given in solid dosage form. Often formulations are given orally in the form of enteric-coated or pH-dependent controlled-release matrices which are nondisintegrating in the acidic environment of the stomach and release their active ingredient only in the higher-pH medium of the small intestine (pH > 5.8). There is enough evidence from both animal and human studies to confirm that the small intestine is the major site of drug absorption for most orally administered drugs due to the combination of longer transit time (compared to the stomach) and larger surface area for absorption (8,9,14,15). Therefore, evaluation of the GRT of a solid nondisintegrating dosage form will provide important information on the oral absorption and bioavailability of such formulations (22,23).

We have previously shown that both solid and liquid

Table I. Physical Parameters and Gastric Residence Time of the Heidelberg Capsule in 12 Healthy Elderly Volunteers (>65 years) 30 min After Ingestion of a 500-kcal Standard Mixed Meal[a]

Subject	Age (years)	Race	Weight (kg)	Height (cm)	BSA (m^2)	GRT (hr)
H.W.	73	B	80	175	1.95	6.5
W.W.	66	C	91	178	2.08	5.0
S.W.	79	C	67	175	1.81	5.5
D.S.	66	C	101	183	2.23	3.0
D.M.	66	C	91	180	2.10	3.0
A.F.	69	C	77	170	1.88	3.5
R.B.	67	C	80	183	2.02	3.5
T.D.	67	C	94	170	2.24	3.5
L.C.	66	B	98	183	2.20	4.5
E.D.	69	B	95	185	2.18	5.5
W.W.	65	B	102	180	2.21	4.5
W.H.	71	C	82	173	1.96	5.5
Mean ± SD	69 ± 4		88 ± 11	178 ± 5	2.07 ± 0.15	4.5 ± 1.1

[a] B, Black; C, Caucasian; BSA, body surface area; GRT, gastric residence time.

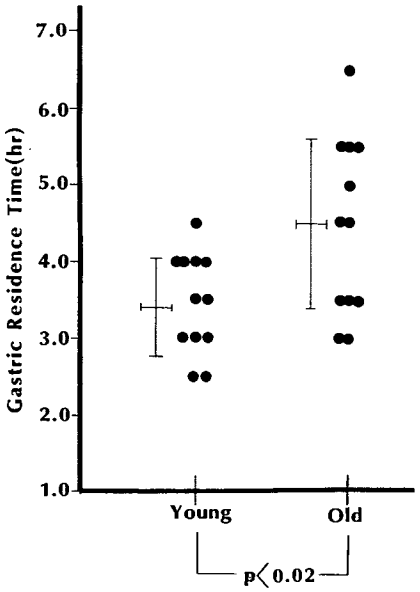

Fig. 7. Individual GRT values measured in healthy young and old subjects (N = 12 per group). Both groups remained ambulatory throughout the study. The mean (±SD) is shown for each group. Elderly subjects showed a significant delay in GRT of the Heidelberg capsule compared to the young group.

meals will prolong the GRT of the HC (20). Subsequently, we have demonstrated a faster GRT (24,25) and a shorter absorption lag time for enteric-coated aspirin (26) in healthy males compared to female subjects in the fed state. This difference in absorption lag time was linearly correlated with the corresponding GRT values. Based on animal (27–29) and human data (30) it is known that pyloric passage of a large (>2 mm in diameter) nondigestible solid is dependent on the activity of phase III of the IMMC cycle. In the present study, the effects of the additional physical and biological parameters such as posture, gender, and age are evaluated on passage of the HC into the small intestine as an indirect measure of the gastric IMMC activity. The results of the between-sexes evaluation of the GRT of the HC revealed a delay in gastric retention time in healthy young women compared to men. This observation is consistent with the findings of other investigators who reported a faster half-emptying time for liquid and digestible solids in males compared to age- and race-matched female volunteers (1–3). Notivol *et al.* reported great variability in half-emptying of digestible solids in women in relation to their menstrual cycle (2). This variable was controlled in our study. Changes in posture (standing vs flat on back) exhibited no significant effect on the GRT of the HC.

The mean GRT data in the elderly group revealed a 1-hr delay, compared to the younger group. This prolongation of the GRT was especially pronounced in >70-year-old subjects (mean GRT = 5.8 hr; N = 3). However, it should be emphasized that our study was conducted only in healthy elderly subjects who consumed no medication which would have altered the gastric motility so that the effects of aging are separated out from diseased state. The age-related changes in the gastric pH as well as the postprandial pH of the stomach in the elderly have not been studied in detail. Our data clearly indicated that postprandial gastric pH values were higher and the mean duration in time to achieve a gastric pH of ≥4.0 was significantly longer in the elderly compared to the younger population (1.3 ± 0.9 vs 0.53 ± 0.4 hr in young, $P < 0.05$). This may be due to a reduced rate of acid secretion in the older subjects. The higher gastric pH in the elderly group indicates that the oral absorption of drugs that are readily soluble in the low acidic pH of the stomach may be compromised in these subjects. Overall, our finding that gastric retention of an indigestible capsule is prolonged in the elderly (31) is in agreement with the work of Horowitz *et al.* (32) and others who have reported significantly slower emptying of digestible solids (32,12) and liquid (13) in older subjects in comparison to younger individuals.

Finally, evaluation of these physical/biological parameters has important implications in the design of various sustained-release dosage forms. It is known that the performance of any controlled-release drug delivery system is clearly dependent on the transit time through various segments of the gastrointestinal tract. Therefore, precise evaluation of these parameters (i.e., menstrual cycle, posture, age, etc.) has a direct bearing on the status of both peristaltic contractions and electromechanical activities of the stomach and small intestine. This, in turn, influences the rate and extent of oral drug absorption. The mechanism(s) responsible for the apparent gender difference and the possible changes in gastric retention time induced by the menstrual cycle requires further investigation.

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