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Gastric Emptying of Indigestible Tablets in Relation to Composition and Time of Ingestion of Meals Studied by Metal Detector

KLAUS EWE, ANDREAS G. PRESS, SUSANNE BOLLEN, and ILSE SCHUHN

Enteric-coated tablets leave the stomach mainly during the interdigestive phase. Composition as well as time of ingestion of meals may influence their gastric emptying considerably. In 12 normal volunteers gastric emptying of a plastic tablet with a metal core was followed by a metal detector in relation to different compositions and various times of ingestion of meals. With an empty stomach and after ingestion of 250 ml water, the mean time for gastric emptying of the tablet was 38 ± 11 min (mean ± SEM) and 38 ± 8 min. Two hundred fifty milliliters of milk (652 kJ) and a formula diet (1000 kJ) delayed gastric emptying time to 128 ± 14 and 152 ± 6 min, respectively ($P < 0.05$). Breakfast (2200 kJ) further retarded gastric emptying compared with both liquids to 249 ± 24 min ($P < 0.05$). There was a close correlation between nutritive density and gastric emptying of the tablet ($r = 0.92$; $P < 0.0001$). Main meals also delayed gastric emptying of tablets when compared to empty stomach ($P < 0.05$). A snack after breakfast further delayed gastric emptying from 201 ± 10 to 278 ± 19 min ($P < 0.05$). The largest delay was observed following ingestion of breakfast, lunch, dinner, and additional snacks (509 ± 220 min). We conclude that the delay of gastric emptying of enteric-coated tablets by food is related to its nutritive density and eating habits. The gastric emptying of an enteric coated tablet that is ingested early in the morning may be delayed until late at night when several meals and snacks are ingested during the day, leading to unwanted alterations in bioavailability and to possible adverse effects.

KEY WORDS: gastric emptying; indigestible tablets; formula diet; meals; snacks; metal detector.

The pharmaceutical industry has developed a large variety of tablet formulations to protect drugs from damage by low gastric pH or from being absorbed rapidly in the upper small intestine to prevent a fast and short rise in the concentration of drug blood levels. Although it was shown two decades ago that indigestible solids are emptied from the stomach during phase III of the migrating motor complex (MMC) and that the sieving function of the antrum regulates this process (1–3), it is still often assumed that tablets and capsules are emptied from the stomach with meals or shortly thereafter. Phase III of the MMC starts approximately 100 min following the emptying of the meal (4, 5). The interdigestive

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From the I. Medizinische Klinik und Poliklinik, Johannes Gutenberg Universität, Langenbeckstrasse 1, D-6500 Mainz 1, Germany.

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Address for reprint requests: Prof. Dr. K. Ewe, I. Medizinische Klinik und Poliklinik, Johannes Gutenberg Universität, Langenbeckstrasse 1, D-6500 Mainz 1, Germany.

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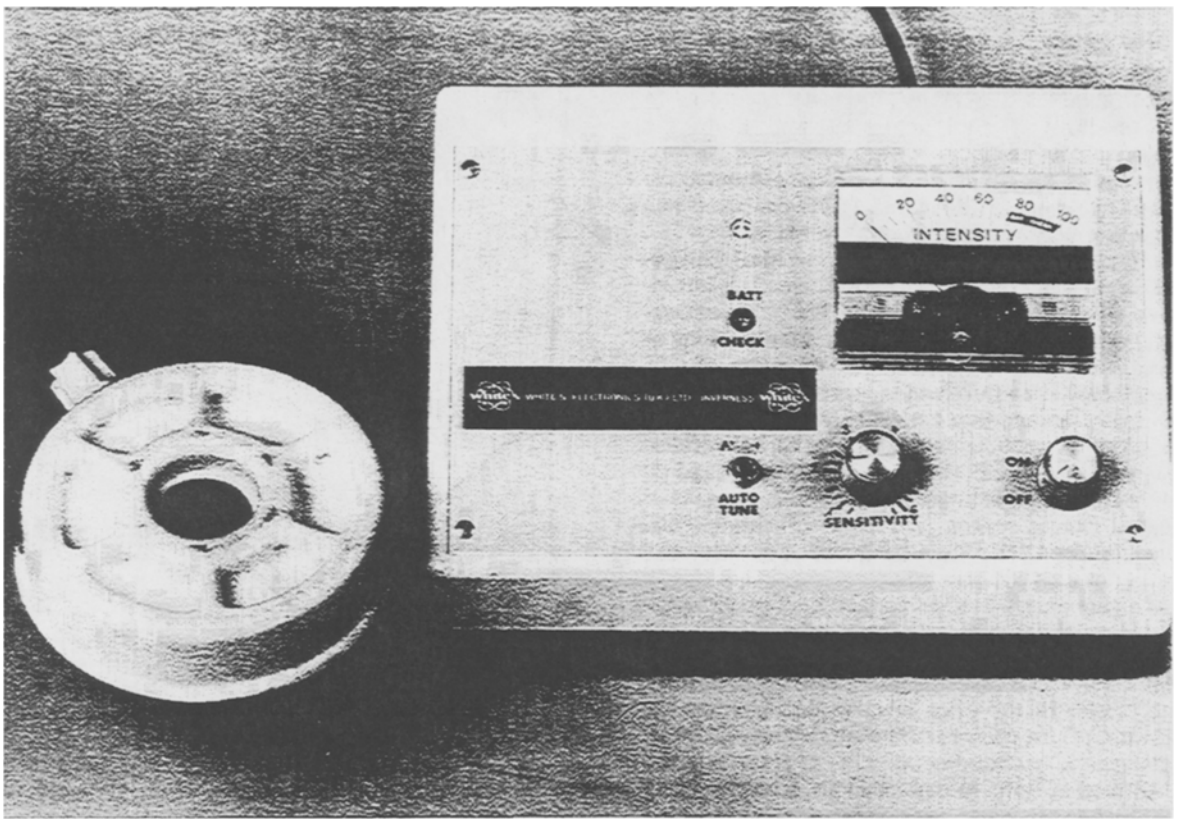

Fig 1. Metal detector EAS II with plate-shaped probe. A tuner allows for compensation of the metal content of the surroundings. The sensitivity adjustment modifies the intensity of the signal. It permits measurements in the optimal range of the scale and to calculate the distance of the metal particle to the probe.

phase of gastric motility maybe interrupted by the frequent ingestion of snacks and meals. In such a situation, phase III of the MMC may rarely occur, leading to a significant delay in the emptying of indigestible solids from the stomach (6). In addition to the frequency of meal intake, the composition of the meal determines the rate of gastric emptying and will also determine the rate at which a MMC occurs and thus influence the emptying of indigestible solids (6–10).

Gastric emptying of indigestible solids is usually measured by means of radioactive isotopes or radiological techniques (11–13). Such studies can only be performed in a laboratory environment and, therefore, do not allow conclusions regarding gastrointestinal motor function under conditions of everyday life. Moreover, since such investigations involve radiation exposure, it may become an ethical issue whether they can be performed in healthy volunteers.

We have developed a method that overcomes these obstacles. It uses a metal detector that can localize and follow the position of tablets containing a metal core throughout the abdominal cavity (14). With this method gastric emptying can be defined by the extent and direction of movements of the metal particle and the intensity of the signal. Since the equipment weighs only 1.5 kg, is battery driven, and can be handled easily, measurements can be performed at home under every day circumstances (Figure 1).

The aim of the present investigation was to investigate the effect of varying food compositions and the application of frequent snacks on gastric emptying of tablets with the use of a metal detector.

MATERIALS AND METHODS

Study Design. Twelve healthy volunteers (four males and eight females) with a mean age of 31 years (range 22–59 years) participated in this investigation. In six subjects the effect of different meal compositions on gastric emptying was studied, while the effect of frequent feedings was studied in the six remaining volunteers. After being instructed on the use of the metal detector

(14), they were supplied with an instrument and several "metal core tablets." All investigations were performed in the home environment. Measurements included the localization of tablet, sensitivity, intensity according to the time schedule of meal intake as well as to the composition of the meals.

The study was approved by the ethical committee of the Landesärztekammer Rheinland-Pfalz. Informed and written consent was obtained from all subjects.

Gastric Emptying in Relation to Different Meal Compositions. After an overnight fast, the subjects were instructed to swallow the tablets under five different conditions: (1) with an empty stomach, (2) after drinking of 0.25 liters of tap water, (3) following ingestion of 0.25 liters of milk (652 kJ), (4) following ingestion of 0.25 liters of a chemically defined liquid meal (Fresubin) (this meal contains 3.8 g protein, 3.4 g fat, and 13.8 g carbohydrates/100 ml, which equals a calorie content of 1000 kJ), and (5) ingestion of a continental breakfast and two cups of tea or coffee with a calorie content of 2200 kJ (the continental breakfast consists of 2 rolls with butter, one also with jam, and the other with cheese).

To investigate intraindividual variability of gastric emptying of tablets, the first measurement was repeated five times, the remaining measurements three times at different days. Repeated investigations were all performed when the tablets of the prior investigation had already been excreted. Thus, each person went through a total of 17 investigations. Measurements with a metal detector were performed at 5- to 10-min intervals when either no nutrients or when tap water were ingested; measurements after milk and meal ingestions were performed at 10- to 15-min intervals.

Gastric Emptying in Relation to Meals and Frequent Snacks. During this part of the investigation, measurements of the emptying of tablets were performed under seven different experimental conditions: (1) with an empty stomach, (2) after a continental breakfast, as outlined above; (3) after breakfast and an additional snack given 2.5 hr later and consists of an apple or yogurt; (4) with lunch that has an approximate calorie content of 4000 kJ; (5) with lunch followed by a snack consisting of a piece of cake or a cookie and a cup of coffee or tea; (6) with supper containing a calorie content of approximately 2400 kJ; and (7) with a breakfast followed by a snack, lunch, snack, and supper at 2.5-hr intervals.

The main meals were roughly standardized in terms of calories. The intake and the composition of the meals was adjusted to the individual eating habits of the volunteers. As in the experiments with different meal compositions, the first investigation (with an empty stomach) was repeated five times and each of the remaining studies was repeated three times. Thus, each subject performed a total of 23 tests. Following meals, measurements were performed at 30-min intervals for the first 2 hr and at 15-min intervals for the remaining test period until the tablets had left the stomach. If emptying did not occur within this time period, the next meal was given after 2.5 hr in experiments 3, 5, and 7.

Metal Detector. The newly developed metal detector EAS II (AS Metal Detector System, Kühlwetterstr. 28, Box 140 106, D-4000 Düsseldorf, Germany) consists of a small box (22 × 15 × 10 cm, weight 1.5 kg) containing the electronic equipment, the battery, and a plate shaped probe (10 × 3 cm) (Figure 1). It works by emission of electromagnetic pulsed waves, which cause eddy currents in metal objects (14). The resolution power of the detector to localize a tablet is 0.5–1 cm, depending on the distance to the probe.

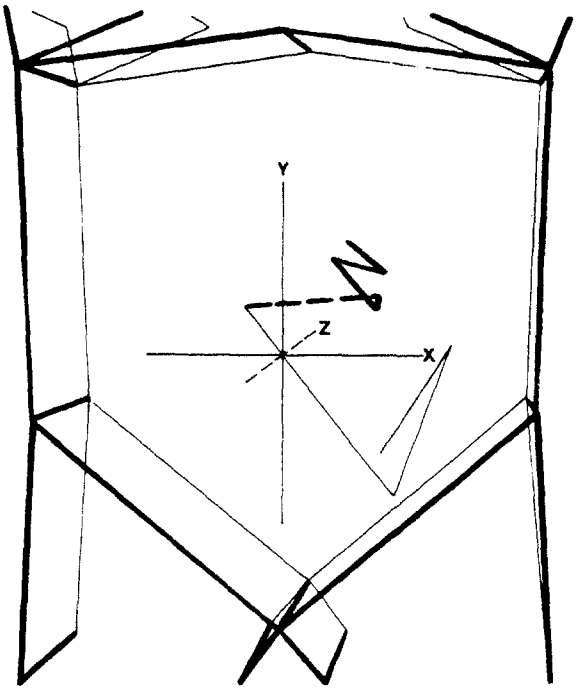

Fig 2. Graphic presentation of movement of the metal particle in the human body. X, horizontal; Y, vertical, Z, sagittal axis. The fat line represents the movement of the tablet in the stomach, the interrupted line gastric emptying with decrease of intensity because of the retroperitoneal localization in the duodenum, the thin line the movement in the small bowel.

Tablets used for the current experiments consisted of an iron and aluminum disk that was coated with plastic foam in a mold. The tablets measured 11 × 6 mm, similar to the average commercially available tablets. The density was kept at 1.4 g/ml, which also corresponds to the average tablet.

Measurement Characteristics of Gastric Emptying. The position of the tablet was documented in a system of coordination with the navel as the central point (Figure 2). All measurements were performed in the upright position. The most important characteristics for gastric emptying of the tablet were a rapid movement within a few seconds over a distance of 6–10 cm from the left of midline to the right as well as a decrease in intensity because of the retroperitoneal localization and the changing location in the lower abdomen.

Although this method does not always allow an exact attribution of the signal to a specific anatomical structure, it is nearly always possible to determine the time when the tablet has left the stomach. Such determinations are facilitated by the fact that a decrease in signal intensity occurs when the tablet moves into the retroperitoneal

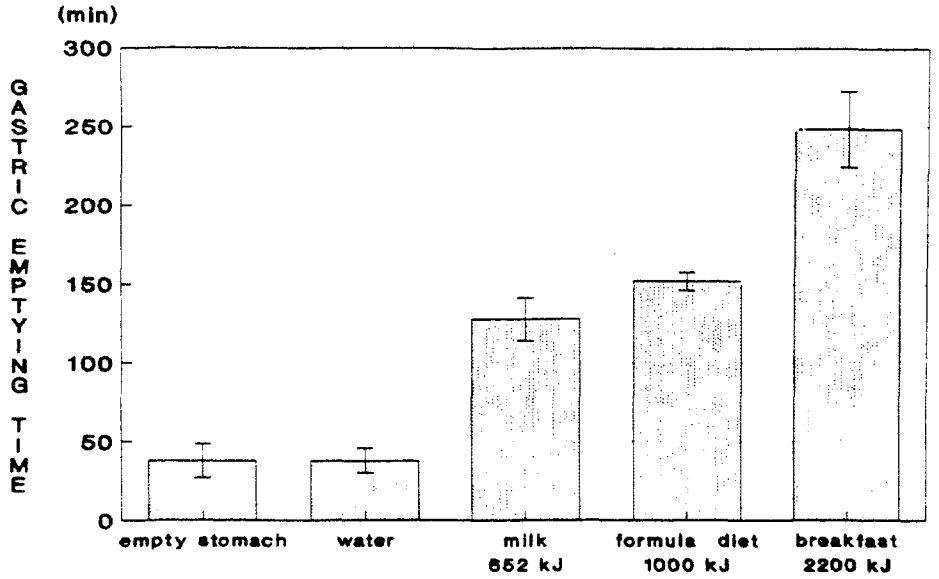

Fig 3. Gastric emptying in relation to various defined diets. Each diet was taken three times by each of six volunteers. Results are given as mean ± SEM. Each diet delayed gastric emptying time ($P < 0.05$), compared to an empty stomach and water only. Breakfast further delayed gastric emptying time in the relation to both liquid diets ($P < 0.05$).

part of the duodenum and that differences in the movement pattern between the stomach and small intestine occur. The accuracy of these measurements has been documented previously by comparative measurements using the current method and a pH sensitive radioelemetric capsule ($r = 0.99$) (6, 14).

Evaluation of gastric emptying was performed independently by two investigators. In case of differences in interpretation (six of 120 measurements), the mean of two discrepant values were taken for calculation. The results for each different experiment of a single volunteer are expressed as the mean of the five or three single measurements, respectively.

The Wilcoxon test for tied samples was used for statistical analysis. A P value of less than 0.05 was considered significant. Data are expressed as a mean ± 1 SEM.

RESULTS

Gastric emptying was influenced significantly by the composition of the meals and by the time intervals between them.

Gastric Emptying in Relation to Different Meal Compositions (Figure 3). With an empty stomach, the mean gastric emptying time for the tablets was 38 ± 11 min. This was identical with the values obtained following ingestion of 250 ml water (38 ± 8 min). Milk (250 ml) led to a threefold delay in the emptying of tablets from the stomach (128 ± 14 min; $P < 0.05$). A further delay was observed when tablets were given with a liquid meal (152 ± 6 min). However, the difference in gastric emptying time of tablets between the studies with milk and liquid meals did not reach statistical significance ($P = 0.06$). The greatest delay in the emptying of tablets occurred when tablets were given with a continental breakfast (249 ± 24 min) ($P < 0.05$). There was a close correlation between nutritive density and the gastric emptying time of the tablet ($r = 0.92$; $P < 0.0001$).

Gastric Emptying in Relation to Main Meals and Snacks (Figure 4). Evacuation of tablets from the empty stomach was similar as in the above experiments. The delayed emptying of the tablet after breakfast (201 ± 10 min) was further delayed for 1.5 hr (278 ± 19 min) if a cup of yogurt or an apple were ingested 2½ hr later ($P < 0.05$). Following lunch, the tablet remained in the stomach for approximately 4 hr (241 ± 38 min). Again, a further delay of approximately 1.5 hr occurred when the lunch was followed by a snack (333 ± 26 min). However, because of the large scatter of values in the test period after lunch, this difference was not statistically significant ($P = 0.15$). Supper caused a similar delay in gastric emptying of the tablet (262 ± 25 min) as lunch ($P = 0.56$).

If the tablet was given with a breakfast that was followed by meals and snacks at 2.5-hr intervals, it remained in the stomach for almost 10 hr (569 ± 120 min). Compared to the application of the tablet with breakfast or with breakfast plus snack and with

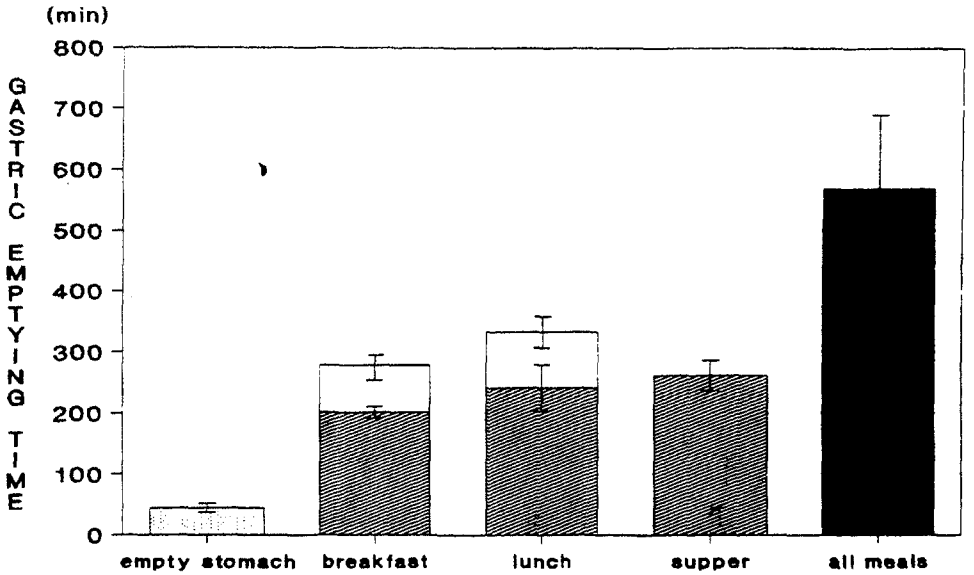

Fig 4. Gastric emptying time of main meals and snacks. Results are given as mean ± SEM. Open columns represent an additional time lag of gastric emptying due to the snacks. Each meal retarded gastric emptying time compared to an empty stomach ($P < 0.05$). A snack after breakfast further retarded gastric emptying ($P < 0.05$; no significant delay after lunch due to a large scatter of values). All meals and snacks taken consecutively delayed gastric emptying time compared to breakfast and lunch ($P < 0.05$), not to supper ($P = 0.06$).

lunch, the delay in the emptying of tablets that were followed by frequent meals was significant ($P < 0.05$). However, there were large interindividual variations in the emptying of tablets when frequent meals were applied. In two subjects they were not emptied from the stomach when measurements were terminated late at night; in three subjects they remained in the stomach for the entire day; in two others emptying occurred after lunch and before the second snack, and in one immediately prior to lunch. In one individual the tablet was detected in the stomach at the beginning of lunch but had left the stomach when the next measurement was performed. This person showed early emptying of the tablet on other occasions: in one instance it was emptied 95 min after breakfast and prior to giving a snack, and on a different day it was emptied 75 min after lunch.

DISCUSSION

Enteric-coated tablets are designed to resist disintegration in the acid environment of the stomach. They release their contents after the pH-sensitive coating is exposed to the neutral pH of the small intestine. However, little information exists regarding the time interval needed for a tablet to pass from the acid into the alkaline environment. Pharmacokinetic studies of drugs are often performed in the fasting state, and the influence of nutrition on drug absorption is ignored. Food intake clearly influences the time as well as the rate and extent of drug absorption from enteric-coated tablets (15–22). A meal-induced delay of the emptying of enteric-coated tablets may be especially detrimental when synchronization of the emptying of meals and drugs are required, as for example in the treatment of pancreatic insufficiency. For this reason, some preparations of pancreatic enzymes are now delivered as enteric-coated granules of about 1 mm in diameter, small enough to leave the stomach with the food in the digestive phase (23).

The magnitude of this pharmacokinetic problem is reflected by the large number of commercially available acid-resistant tablets. In West Germany, the pharmacopeia contains more than 40 different brands of such preparations. They mainly consist of nonsteroidal antiinflammatory drugs, enzyme preparations, laxatives, and 5-aminosalicyclic acid compounds.

Studies investigating gastric emptying of indigestible solids of different sizes have been performed in men and dogs (3, 5, 10, 23–25) and have shown that the pylorus exerts a sieving function for solid particles during the digestive phase. Such a discrimi-

nation depends on several physical factors, such as size, density, and consistency of the particles, as well as viscosity of gastric contents. There is a size-response curve between particles that have a diameter of 1–5 mm. In the dog, indigestible spheres of 1 mm are emptied at the same rate as solid food, but with increasing sizes emptying of such particles is progressively delayed (25). In men, gastric emptying of nondisintegrating tablets that are given with meals becomes increasingly unpredictable when the size of tablets increases from 2 to 7 mm in diameter (10). In addition, the emptying of spheres of identical size depends on their density and reaches its highest rate when the density approaches 1 (25). Finally, soft compressible particles are emptied faster from the stomach than more solid ones (26). Thus, the tablets used in our study, which had a firm consistency, a density of 1.4, and a diameter of 11 mm should not easily escape the discriminating action of the pylorus. Although this was confirmed by our investigations, occasional tablets escape the sieving effect of the pylorus in the digestive phase.

A similar observation was made by Davies et al (27), who had shown that one of two indigestible tablets that were given with a breakfast left the stomach with the meal in half of the volunteers. The authors designated this phenomenon as "fortuitous emptying." In addition, they could demonstrate that gastric emptying of tablets was delayed when the caloric contents of the meals were raised. Furthermore, since gastric emptying is not only influenced by the caloric content of a meal (5, 9, 10, 27) but also by its constituents (7, 8), its osmolarity (28), and its viscosity (29), the beginning of the interdigestive phase and the emptying of indigestible solids will depend largely on the composition of the meal. The current investigation, administering meals with different calorie contents, confirms that there is a highly significant correlation between the gastric emptying of tablets ($P < 0.0001$) and the calorie content of the meal. These differences are most likely due to differences in the initiation of phase III of MMC. Since 250 ml of water did not influence gastric emptying of indigestible solids, it appears unlikely that such alterations were caused by gastric distension rather than the composition of the meal.

The results of our investigation should alert physicians and pharmacologists that the emptying of enteric-coated tablets from the stomach may be unpredictable and may largely depend on the eating habits of the subject. These findings should have important implications for therapy with enteric-coated medication in that bioavailability and side effects can be improved or minimized by ingesting this drug form with an empty stomach or 1 hr before meals and by avoiding frequent food intake.

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