Linear Gastric Emptying of Hyperosmolar Glucose Solutions

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We performed a total of 12 gastric emptying studies on 6 normal subjects with a hyperosmolar (1.85 mol/l) 400-kcal glucose solution commonly used for diagnosing diabetes and a more dilute (0.62 mol/l) 200-kcal glucose solution. The gastric half-emptying time was greatly prolonged with both glucose solutions; 107 min for the (1.85 mol/l) 400-kcal glucose solution compared to 66 min for the more dilute (0.62 mol/l) 200-kcal glucose solution. Although the 200-kcal glucose solution contained one-half the amount of glucose (50 g) compared to the 400-kcal solution (100 g), the blood glucose values obtained during a 2-hr period were only slightly lower with the former solution. This study demonstrates significantly delayed gastric emptying of glucose solutions in normal subjects and a linear pattern of gastric emptying formerly associated only with solid meals.

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Hyperosmolar glucose solutions have been noted to slow gastric emptying in man (1–3). However, the extent of slowing and the pattern of gastric emptying of hyperosmolar glucose solutions have not been previously studied with scintigraphic techniques. Our study evaluated gastric emptying of two solutions containing different glucose concentrations. The 400-kcal glucose solution (100 g of glucose, 1.85 mol/l), is a standard glucose solution used for the oral glucose tolerance test (OGTT). The 200-kcal glucose solution contained one-half the glucose dose (50 g of glucose, 0.62 mol/l) and had one-third the osmolarity of the 400-kcal solution. The results of this study have important implications both for the diagnosis of diabetes and for the understanding of gastric emptying in general.

MATERIALS AND METHODS

Gastric emptying studies were performed on six normal subjects ranging in age from 27 to 42 yr using both a 400-kcal

(1.85 mol/l) and a 200-kcal (0.62 mol/l) glucose solution. All subjects had been fasting for more than 10 hr prior to beginning each test. The aim, nature, and potential risks of the investigation were explained to each subject and each gave written informed consent. The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio.

We used "Glucose Tolerance Test Beverage," lemon-lime flavor (General Scientific, Richmond, VA), for both our 200-kcal and 400-kcal glucose solutions. The 400-kcal glucose solution, an entire bottle of standard OGTT solution (100 g of glucose, 1.85 mol/l, 300 ml), was ingested within 5 min. To prepare the 200-kcal, one-half of the bottle was added to 300 ml of water (50 g of glucose, 0.62 mol/l, 450 ml). This solution also was ingested within 5 min.

Gastric emptying studies utilizing a gamma camera (Scintronix USA Inc., Woburn, MA) connected to a nuclear medicine computer (Medical Data Systems, Inc., Ann Arbor, MI) were performed with each OGTT. Approximately 740×10^7 Bq (200 µCi) ^{99m}Tc-sulfur colloid (^{99m}Tc-SC; CIS-US, Bedford, MA) was added to the glucose solution. Each subject was then placed in a semi-reclining position (45° from horizontal) and the gamma camera was positioned anteriorly. Data were collected continuously and summed at 60-sec intervals. Images were acquired for 120 min. Counts in the stomach region of interest were evaluated in each 60-sec image, and after correcting for radioactive decay, the count rate was converted to a percentage of the maximum count rate recorded. The decay-corrected count rate was converted to percent glucose solution remaining in the stomach.

Peripheral venous blood samples were obtained to measure blood glucose just prior to beginning the study then at 30, 60, 90, and 120 min post-oral administration of the glucose solutions. The blood was collected in grey-top vacutainer tubes containing potassium oxalate and sodium fluoride (Becton Dickinson Vacutainer Systems, Rutherford, NJ). Glucose analysis was performed on a Paramax instrument (Baxter Healthcare Corp., Irvine, CA).

We analyzed the shape of the emptying pattern by applying polynomial regression analysis to the emptying data for each glucose solution (4). The differences between the two glucose solutions were assessed using an analysis of variance for repeated measurements. The half-emptying time for each test was calculated by linear interpolation. The half-emptying time was greater than 120 min for one subject (53% remaining in his stomach at 2 hr), and we used this time as his value in the calculation of the group mean. The area under a curve was calculated using the trapezoid rule.

RESULTS

Although gastric emptying was significantly and consistently more delayed with the 400-kcal hyperosmolar (1.85 mol/l) glucose solution when compared to the 200-kcal (0.62 mol/l) glucose solution (Fig. 1), both solutions emptied in a linear fashion. Among the 12 OGTTs, the smallest observed R^2 for a linear relationship was 0.884 (p < 0.001). This indicates that in all twelve tests, greater than 88% of the variation in percentage of the glucose solution remaining was accounted for by a linear relationship with time. Although a linear relationship accounts for most of the variation, there were some quadratic, cubic, or quartic trends indicating small but statistically significant (p < 0.05) departures from linearity. Using regression analysis of the log of the percent solution remaining in the stomach, no consistent improvement in the fits were noted. This analysis indicates that the gastric emptying pattern is not monoexponential.

Figure 1 shows the percent glucose solution remaining in the stomach during the 2-hr period using both the 400-kcal and 200-kcal glucose solutions. The percentage of solution remaining in the stomach with the 200-kcal solution was significantly lower than the percentage remaining in the stomach with the 400-kcal solution at every time greater than or equal to 30 min postingestion (p < 0.017). After 2 hr, an average of 43 g of glucose remained in the stomach after ingestion of
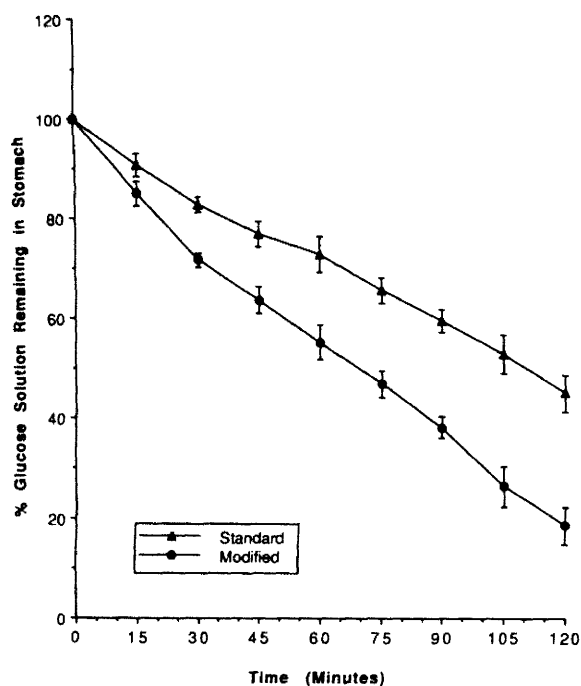
the 400-kcal glucose (100 g in 300 cc H_2O) solution compared to 10 g after ingestion of the 200-kcal glucose (50 g in 450 cc) solution. The area under the gastric emptying curve for the 200-kcal solution was 78% of the area obtained using the 400-kcal solution (p = 0.002). During the first 30 min, 84-kcal of the 200-kcal solution were emptied into the duodenum and 96 cal of the 400-kcal glucose solution. During the first 60 min, 114-kcal of the 200-kcal glucose solution were emptied into the duodenum; 136 kcal with the 400-kcal solution. After 2 hr, the amount of glucose solution remaining in the stomach ranged from 7% to 26% following ingestion of the 200-kcal glucose solution. After ingestion of the 400-kcal glucose solution, a range of 36%–53% of the solution remained in the subjects' stomachs.

Figure 2A shows the diffuse distribution within the stomach of the 200-kcal glucose solution 5 min after ingestion. After 90 min (Fig. 2B), the solution has almost completely emptied from the stomach. Figure 2C reveals a retention of the 400-kcal glucose solution in the proximal fundus of the stomach (a gastric band) 5 min after ingestion. We found this same pattern, previously described by Moore (5) using solid meals, in all our patients after ingestion of the 400-kcal glucose solution. Figure 2D, taken 90 min after ingestion of the 400-kcal solution, shows a large amount of glucose remaining in the proximal fundus of the stomach.

The half-emptying time average (Fig. 3) was approximately 60% longer with the 400-kcal glucose solution (107 min) compared to the 200-kcal glucose solution
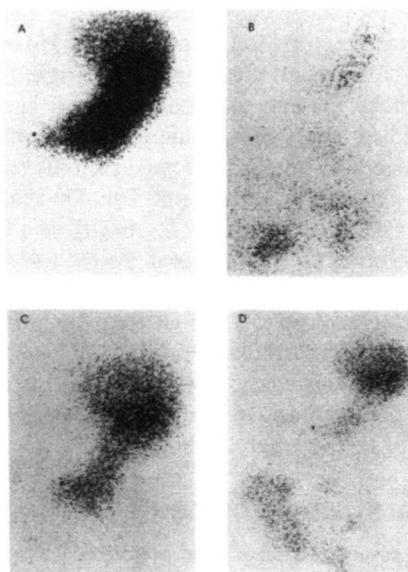

FIGURE 1
Average percentage glucose solution remaining in stomach after ingestion of the 400-kcal and 200-kcal oral glucose solutions (n = 6). Note delay in gastric emptying with the 400-kcal glucose solution. Bars represent standard errors.
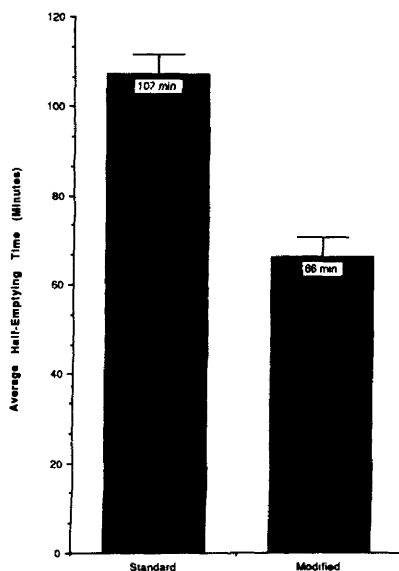

FIGURE 2
Gastric emptying scans at (A) 5 min after ingestion of the 200-kcal glucose solution; (B) 90 min after ingestion of the 200-kcal solution; (C) 5 min after ingestion of the 400-kcal glucose solution; and (D) 90 min after ingestion of the 400-kcal solution.
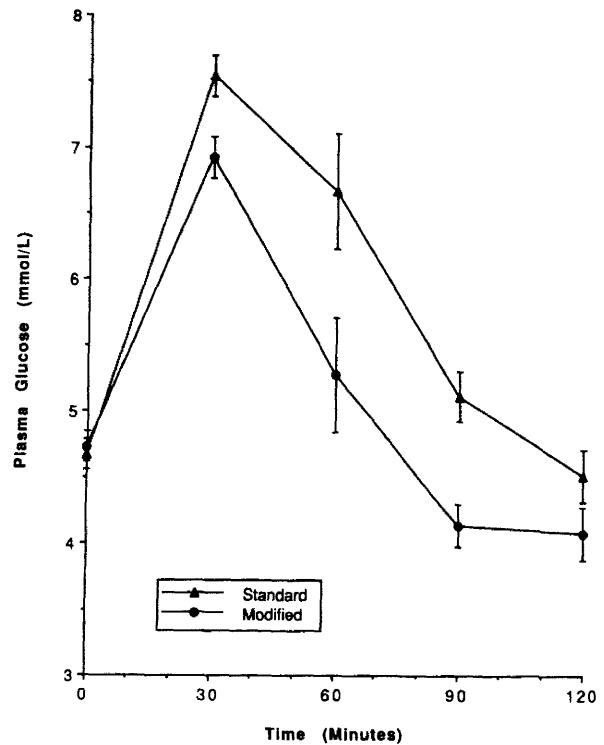
(66 min) (p = 0.001). The 200-kcal glucose solution actually emptied 2.5 times faster per volume during the first hour of the test and presented slightly less glucose to the duodenum. Although less glucose (50 g) was in the 200-kcal glucose solution compared to the 400-kcal (100 g) solution, the average blood glucose values during the 2-hr period after ingestion were only slightly less using the 200-kcal solution (Fig. 4). At 30 min post-ingestion, the 200-kcal solution resulted in a slightly lower blood glucose concentration (p = 0.042). At 60, 90, and 120 min postingestion, the glucose concentrations were lower with the 200-kcal solution but were not significantly different (p > 0.05). The area under the curve using the 200-kcal solution was 88% of the area obtained using the 400-kcal solution (p = 0.014).

DISCUSSION

The gastric emptying rates and the linear patterns of emptying of both glucose solutions were similar to those recorded by other investigators for solid meals. Liquids have been previously thought to empty monoexponentially with time, and solids have always been considered to empty slower than liquids (6,7). The gastric emptying rate of both the 200-kcal glucose solution (half-emptying time, 66 min) and the 400-kcal glucose solution (half-emptying time, 107 min) were extremely prolonged and much greater than the reported gastric emptying rates for saline (half-emptying time, 8–12 min in human subjects) (8,9). This extremely prolonged gastric emptying time and linear gastric half-emptying rate of the 400-kcal standard glucose solution used in the diagnosis of diabetes has not been previously reported. The prolonged retention of the 400-kcal glucose solu-

FIGURE 4
Average blood glucose values (n = 6) after ingestion of the 200-kcal (50 g) and 400-kcal (100 g) glucose solutions. Bars represent standard errors.

tion observed in our study may be responsible for the frequent nausea and vomiting encountered with this test (10–12).

Although a larger volume of liquid (450 ml) was administered with the 200-kcal glucose solution, the pattern of gastric emptying still remained linear and did not change to an exponential pattern. The 450-ml volume would be expected to slightly increase the emptying rate (13) compared to a 200-kcal glucose solution in a smaller volume of liquid. Research by Malmud et al. (13) indicates that gastric emptying of liquids is dependent upon the gastroduodenal pressure gradient. The increase in volume presumably would increase the gastroduodenal pressure gradient and should mildly increase the gastric emptying rate. Because the fundus of the stomach is able to relax in response to an increased volume, however, there is not a direct linear relationship between increased gastric volume and the rate of gastric emptying (13).

The gastric emptying of liquids has commonly been thought to be a monoexponential function (8,14). Most investigators have believed that although duodenal feedback enhances or inhibits the rate of gastric emptying, it did not change the fundamental exponential emptying of liquid solutions (8). In the last 10 years, several investigators have challenged the idea that all liquids emptied in a monoexponential fashion.

FIGURE 3
Average gastric half-emptying time for the 200-kcal (50 g) glucose solution and the 400-kcal (100 g) glucose solution (n = 6). Bars represent standard errors.

Studying rhesus monkeys, McHugh et al. (15) noted that solutions of glucose assumed a linear and calorie-constant emptying pattern. McHugh et al. demonstrated that, although physiologic saline emptied exponentially, glucose, casein hydrolysate and medium-chain triglycerides solutions followed a more linear than exponential course when emptying from the stomach. McHugh et al. also noted that the stomach slowed its emptying rate as its nutrient content increased in caloric concentration with the result that calories were delivered to the duodenum at a constant rate of 0.4 kcal/min in rhesus monkeys, regardless, within limits, of the concentrations, osmolarity, or volume of the intragastric meal. In 1983, Brener et al. (8) also described linear emptying of glucose in humans. He found that human subjects emptied glucose solutions of different concentrations from their stomachs at a linear rate of approximately 2.13 kcal/min. Both McHugh (16) and Brenner (8) hypothesized that the linear gastric emptying rate depended upon an inhibitory control arising from the duodenum, by which glucose in the duodenum delayed gastric emptying. A specific mechanism by which the duodenum inhibited gastric emptying, however, was not described.

In a recent article, Velchik et al. (7) studied the effect of calories on gastric emptying. They studied three solid meals of 150 kcal, 300 kcal, or 600 kcal composed of 40% carbohydrate, 40% protein, and 20% fat. They found a significant inverse relationship between the number of calories in a meal and the rate of gastric emptying. It is interesting to note that the *liquid* 400-kcal glucose solution used in our studies had a longer gastric half-emptying time than the 600-kcal *solid* meal in the Velchik et al. study (107 min with a 400-kcal glucose solution versus 95 min with 600-kcal solid meal). This approximately equal delay in gastric emptying of the 400-kcal liquid solution compared to the 600-kcal solid meal may be related to the high elevation of blood glucose with the oral glucose solution. It is well known that a mixed solid meal does not increase the blood glucose as much as an oral glucose solution (17).

Several previous investigators (18,19) provide evidence that elevated blood glucose values are associated with delayed gastric emptying. Groop et al. (18) found evidence of delayed gastric emptying in normal volunteers given intravenous glucose solutions. Aylett (19) observed delayed gastric emptying associated with elevated blood glucose levels. Much of the prolongation in gastric emptying reported for solid foods may be related to the number of calories in the solid food or to the elevation of blood glucose secondary to the ingestion of this solid food. It is interesting to know that the retention of the 400-kcal glucose solution in the fundus of the stomach in our study is similar to the finding of a gastric band and fundal retention reported by Moore

(5) with solid foods. This finding has not been previously reported with liquids.

The 200-kcal solution is currently being studied for use in the diagnosis of diabetes (20). The 200-kcal solution results in nearly equivalent 30-min elevations of blood glucose as the 400-kcal standard OGTT solution and it delivers a tighter "bolus" of glucose to the patient. With the 200-kcal solution, only 10 g of glucose remain in the stomach at 2 hr compared to 43 g of glucose at 2 hr with the 400-kcal standard OGTT solution. Preliminary studies indicate that this bolus effect of the 200-kcal glucose solution may make it possible to detect early type II diabetes mellitus. While normal subjects have a peak blood glucose concentration at 30 min with the 200-kcal solution, type II diabetics have a peak blood glucose concentration at 1 hr or later (20). The delayed blood glucose peak in early type II diabetes is thought to be due to delayed insulin secretion and insulin resistance which are early manifestations of the disease. Ongoing investigations of this 200-kcal solution show great promise for increasing the sensitivity and specificity of oral glucose tolerance testing. An additional benefit of the 200-kcal glucose solution is the complete elimination of nausea and vomiting commonly associated with the standard 400-kcal (100 g) oral glucose solution.

In summary, this study demonstrates the significant delay and linear pattern of gastric emptying associated with the hyperosmolar glucose solutions commonly used in the diagnosis of diabetes.

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