J Clin Gastroenterol 2001;32(5):394–399.

Gastric Emptying Characteristics of a Novel ^{13}C-Octanoate–labeled Muffin Meal

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Abstract

Goals: Determine the gastric emptying characteristics of a novel, 350-kcal test meal consisting of two muffins, using scintigraphy and the ^{13}C-octanoate breath test (OBT). **Study:** Healthy volunteers underwent three studies on separate days within a 1-week period. On day 1, we measured emptying of the 350-kcal muffin test meal labeled simultaneously with ^{99m}Tc sulfur colloid and ^{13}C-octanoate. On day 2, reproducibility of the OBT using a single-labeled 350-kcal test meal was assessed. On day 3, the effect of erythromycin on the 350-kcal OBT was determined. **Results:** The mean (±SD) half-emptying time (T1/2) as measured by scintigraphy was 104 ± 24 minutes, versus 212 ± 52 minutes by OBT. There was a strong correlation between T1/2 determined by scintigraphy and the breath test (r = 0.83). Multiple linear regression analysis identified a significant relationship between T1/2 determined by scintigraphy and the 90- and 180-minute breath samples. There was a strong correlation (r = 0.830, slope = 0.732 ± 0.120 [SE], intercept = 26.4 ± 12.7) between the T1/2 obtained using the regression equation and the actual T1/2 obtained by scintigraphy. The mean T1/2 (±SD) for replicate determinations using the OBT was 209 ± 52 minutes, compared with 196 ± 42 minutes on days 1 and 2, respectively (not significant, p = 0.28, paired Student t test). Treatment with erythromycin on day 3 produced a significant decrease in T1/2 (155 ± 49 minutes, p = 0.002). **Conclusions:** The 350-kcal muffin meal OBT provides a convenient, nonscintigraphic way of measuring solid-phase gastric emptying. Multiple linear regression appears promising as a method of analyzing OBT data and may allow for an abbreviated breath test protocol.

Key Words: Gastric emptying—Scintigraphy—Octanoate—Breath tests.

The current gold standard for the identification of abnormal gastric emptying in humans is quantitative scintigraphy. This method involves the ingestion of a radiolabeled meal and subsequent measurement of gamma emission as the test meal is emptied from the stomach. A gamma camera interfaced to a computer permits region of interest analysis for the labeled test meal.[1] Evaluation of the scintigraphy data reveals the gastric emptying parameters lag time (Tlag) and half-emptying time (T1/2). Lag time is the time for the meal to be processed (grinding into less than 2-mm particles) before it exits the pylorus. Half-emptying time is the time required for one half of the test meal to empty from the stomach.

The utility of scintigraphy in routine evaluation of patients with suspected gastroparesis is hampered by several factors, including high cost, radiation exposure, and the need for specialized equipment operated by highly trained personnel. In particular, the issues of cost and radiation exposure[2] limit the ability of the clinician or researcher to conduct repeat measurements to monitor the effectiveness of prokinetic therapy.

In addition to problems with safety, cost, and availability, scintigraphy is hampered by methodologic inconsistencies. Each center that uses this technology may implement its own test meal formulation, data acquisition sequence, and data interpretation. Thus, patient results and subsequent evaluations are tied to the methods and conditions under which the data was collected. A recent publication describes an attempt to standardize a simplified protocol for the scintigraphy "gold standard" among seven different Canadian centers.[3] Until widespread adoption of a single protocol occurs, results will only be meaningful at the clinical site at which the measurement was made. Consequently, the raw number for T1/2 becomes less important than the diagnosis of either "normal" or "delayed."

Breath tests using stable isotopes offer a potential alternative to scintigraphic techniques for the measurement of gastric emptying. Following the original demonstration by Ghoos et al.,[4] several groups have applied the test under a variety of clinical conditions, ranging from investigating efficacy of prokinetic agents[5,6] to measuring motility in patients at risk for gastroapresis.[7–9] The test relies on the administration of a test meal, typically scrambled eggs with toast and butter, labeled with ^{13}C-octanoate.

The choice of test meal for the ^{13}C-octanoate breath test (OBT) has been influenced by the routine use of the egg meal for scintigraphy and the relative ease of labeling with

Submitted June 7, 2000. Accepted September 19, 2000.

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Supported by a Phase I SBIR and Metabolic Solutions Inc. Nashua, NH, U.S.A.

Part of this work was presented at Digestive Diseases Week (Orlando, FL; May 1999).

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^{13}C-octanoate.[4] Once absorbed, ^{13}C-octanoate is carried to the liver by the portal circulation where it is metabolized to $^{13}CO_2$. Breath is collected for quantification of expired $^{13}CO_2$. The OBT is an indirect measure of gastric emptying because the rate at which $^{13}CO_2$ appears in the breath reflects the sum influence of gastric emptying, digestion, absorption, and metabolism. The metabolic processing of octanoate is rapid and reproducible; thus, delays in emptying are caused by differences in gastric motility.[10] Nonetheless, the functional nature of the OBT explains the differences in T1/2 and Tlag yielded by the OBT and scintigraphy.

The OBT does not require the ingestion of radioactive isotopes and promises to be significantly less costly than scintigraphy. As such, the OBT could be potentially useful in the care of patients and for the purposes of clinical research. However, as with scintigraphy, the optimal test meal, breath sampling protocol, and means of data analysis remain unresolved.[11,12] For example, the scrambled egg test meal has to be prepared on the day of the study, is unpalatable to some patients, and suffers from a lack of uniformity because of variable egg size and cooking differences. In addition, prolonged frequency and duration of breath collection can negatively impact the cost and convenience of the test. Further, data analysis requires the application of curve-fitting procedures that are difficult to implement in the clinical setting.

In the current study, we sought to address some of the limitations of the OBT through substitution of the 250-kcal egg meal with a novel, 350-kcal muffin test meal. We determined the gastric emptying characteristics of a standardized meal consisting of two muffins with a total caloric value of 350 kcal double-labeled with ^{99m}Tc sulfur colloid and ^{13}C-octanoate. Reproducibility of gastric emptying parameters for the 350-kcal ^{13}C-octanoate muffin meal were investigated by administering the test on 2 separate days within a 1-week period. We further evaluated the effect of the prokinetic drug, erythromycin, on gastric emptying of the 350-kcal ^{13}C-octanoate muffin meal. Gastric emptying parameters were derived by the methods described by Ghoos et al.[4] and by an alternate method of data analysis based on multiple linear regression.[12]

MATERIALS AND METHODS

Human Subjects

Healthy volunteers were recruited for this study by public advertisement. Twenty healthy controls (14 women and 6 men; mean age ± SE = 30 ± 3 years; range = 19–64 years) participated in this protocol. During the study, participants did not take medications that are known to delay gastric emptying. The protocol was approved by the Institutional Review Board for human investigation at the University of Michigan Medical Center (Ann Arbor, MI, U.S.A.). All participants gave written informed consent.

The protocol included three studies conducted on separate days. The test meal was identical for each of the 3 days of the study, consisting of two muffins with a combined caloric value of 350 kcal prepared from premeasured bulk ingredients on the day the test was administered. Preparing muffins individually rather than in one batch allowed us to assess the influence of muffin preparation variability on the overall results. On day 1, we measured gastric emptying of the test meal double-labeled with ^{99m}Tc sulfur colloid and ^{13}C-octanoate. For days 2 and 3 of the study, the muffin meal was single-labeled with ^{13}C-octanoate. On day 2, we evaluated the reproducibility of gastric-emptying parameters obtained with the ^{13}C-octanoate–labeled muffin meal. On day 3, we determined the effect of the prokinetic drug, erythromycin, on gastric emptying parameters measured with the ^{13}C-octanoate–labeled muffin meal. Participants arrived at the clinical site after an 8- to 12-hour fast. All three parts of the investigation were completed within 7 days for each participant. To minimize the effects of diurnal variation in gastric motility, studies were performed at the same time of day for a given participant.

Comparison Between Scintigraphy and the ^{13}C-Octanoate Muffin Meal

On day 1, participants ingested a test meal consisting of two freshly prepared muffins (350 kcal; 49% carbohydrates, 13% protein, 38% fat) labeled with 1 mCi of ^{99m}Tc sulfur colloid and 91 mg of ^{13}C-octanoate (Cambridge Isotope Laboratories, Andover, MA, U.S.A.). The muffins were consumed along with 150 mL of water at room temperature within 15 minutes while the participant sat in front of a large field of view, single-head gamma camera. Once the meal was ingested, gastric scintigraphy was performed as 120 1-minute frames in the anterior projection (Hitachi 1024 DT/C). Signal intensity (raw counts in the gastric region of interest) was entered into a spreadsheet, and data points were corrected for the reduction in counts owing to the radioactive decay of the ^{99m}Tc (τ = 6 hours). Then, the data was normalized and fitted using a modified power exponential function.[13] Gastric emptying parameters T1/2 and Tlag were obtained using constants derived from curve-fitting of the data.[14]

Breath samples were obtained in duplicate at 15-minute intervals concurrent with scintigraphy and, thereafter, for an additional 2 hours, for a total duration of 4 hours. Breath samples were collected in a 3-L bag (Quintron, Milwaukee, WI, U.S.A.) and immediately transferred to evacuated breath storage tubes (Exetainer, Labco Limited, Birmingham, U.K.). Samples were shipped to an off-site laboratory for analysis of $^{13}CO_2$ (Metabolic Solutions, Inc., Nashua, NH, U.S.A.). The quantity of $^{13}CO_2$ in each tube was determined by gas chromatography isotope ratio mass spectrometry using a Europa 20/20 (PDZ Europa LTD, Crewe, U.K.). The ratio of $^{13}CO_2$ to $^{12}CO_2$ was measured in each sample and compared with a reference (5% CO_2, balance 75% N_2, and 20% O_2) calibrated against international standards (IAEA-303, Vienna, Austria). Isotopic enrichment of $^{13}CO_2$ is expressed as delta (δ) per mil given by the equation:

$$\delta\ (\text{per mil}) = \left(\frac{Rspl}{Rstd} - 1\right) \times 1{,}000$$

where *Rspl* and *Rstd* are the ratios of the 45 (*m/z*) to the 44 (*m/z*) signal for the sample and standard, respectively. The standard is referenced to Pee Dee Belemnite (PDB) where *Rpdb* = 0.0112372.[15] Vendor-provided instrument control software (Automated Breath Carbon Analysis, ABCA v3.5; PD2 Europa LTD) performs delta (δ) enrichment calculations that have been independently verified off-line using a spreadsheet calculation program (Microsoft, Redmond, WA, U.S.A.). The analytical precision of the instrument is less than 0.2 per mil (±SD) for $^{13}CO_2$ determinations in breath.

Reproducibility of the ^{13}C-Octanoate Muffin Meal

Intrasubject reproducibility of the OBT was assessed from results obtained on days 1 and 2 of the study. On day 2, a muffin meal labeled with 91 mg of ^{13}C-octanoate was administered to study participants, along with 150 mL water, and was consumed within 15 minutes. No radioisotope was administered for this part of the study. Breath samples were collected at 15-minute intervals over 4 hours. Samples were analyzed by isotope ratio mass spectrometry, and gastric emptying parameters T1/2 and Tlag were calculated as described above.

The Effect of Erythromycin on Gastric Emptying as Measured by the ^{13}C-Octanoate Muffin Meal

On day 3, participants received the gastric prokinetic drug erythromycin (200 mg intravenously) 30 minutes before ingesting the ^{13}C-octanoate muffin meal. The breath collection protocol, sample analysis, and calculation of gastric emptying parameters were conducted as described previously. Gastric emptying parameters obtained after the erythromycin treatment were compared with those obtained without drug on day 2.

Statistical Analysis

The relationship between gastric emptying parameters, T1/2 and Tlag, for scintigraphy and the OBT was evaluated by determining the correlation coefficient of the least-squares regression line.[16] Data was analyzed using the regression analysis tools provided in a commercial spreadsheet (Microsoft Excel 97; Microsoft Corp., Redmond, WA, U.S.A.).

In a separate analysis using multiple linear regression, data from day 1 was analyzed to determine whether a significant relationship existed between scintigraphic gastric emptying parameters and an abbreviated breath test data set. The aim was to determine whether a select few points on the gastric emptying curve could be used exclusively to provide estimates for scintigraphic gastric emptying parameters. Multiple regression analysis was conducted using the PC version of the commercial software package Minitab v 6.1.1 (Minitab, Inc., State College, PA, U.S.A.).

Reproducibility of the OBT was investigated by comparing gastric emptying parameters obtained on days 1 and 2. A paired Student t test was used to test the hypothesis that no difference in gastric emptying parameters existed for the replicate tests. We sought to accept the hypothesis. The correlation between the two tests was also investigated.

A paired Student t test was used to compare breath test values obtained on day 2 (baseline) and day 3 (erythromycin treatment). A paired Student t test was used to test the hypothesis that no difference in gastric emptying parameters existed for the baseline and treatment tests. We sought to reject this hypothesis.

RESULTS

Comparison Between Scintigraphy and the ^{13}C-Octanoate Muffin Meal

Data from 19 of 20 participants was available for analysis of the scintigraphy results. An error in scintigraphic data sampling prevented implementation of the data-processing algorithm in one case. The participant did complete the entire study, so the OBT data was available for analysis.

Figure 1 presents a comparison between data derived from scintigraphy and the OBT in one study participant. The curve derived from scintigraphy reflects the decrease from maximum ^{99m}Tc signal at $t = 0$ as the test meal empties from the stomach. The OBT curve starts at low signal, increases to a maximum, and then decreases as the ^{13}C-octanoate–labeled test meal passes through the stomach to the small intestine.

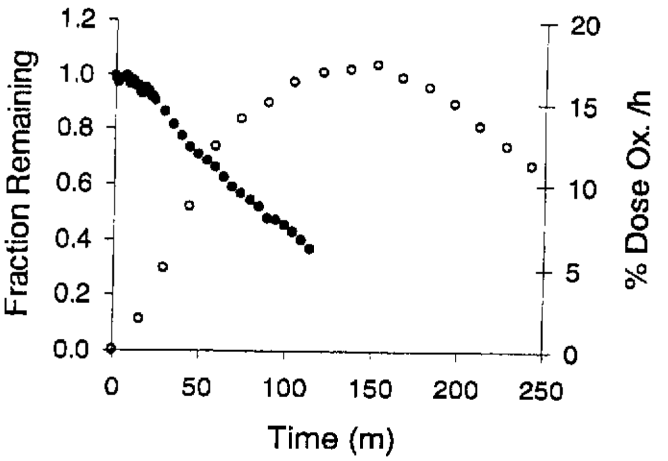

FIG. 1. A comparison of data derived from scintigraphy and the OBT. The scintigraphy data is presented as filled circles plotted against the y-axis as fraction remaining. The OBT data is presented as open circles plotted against the secondary y-axis as percent dose oxidized per hour.

The overall mean T1/2 as measured by scintigraphy was 104 ± 24 minutes (mean ± SD). In contrast, the mean T1/2 by OBT was 212 ± 52 minutes. Individual T1/2 results obtained from scintigraphy and the OBT have been plotted in Figure 2A. The equation of the regression line for this data is $y = 1.7972(x) + 25.593$ ($r = 0.83$).

The mean Tlag measured by scintigraphy was 42 ± 19 minutes, whereas the mean Tlag obtained using the OBT was 121 ± 25 minutes. The equation of the fitted line for Tlag was $y = 0.8608(x) + 85.683$ ($r = 0.63$). Individual Tlag results obtained from scintigraphy and the OBT have been plotted in Figure 2B.

When we evaluated the data using multiple linear regression analysis, we found a strong relationship between scintigraphy T1/2 and the OBT data collected at 90 and 180 minutes. Multiple linear regression analysis yielded a significant relationship for the equation T1/2 = 97.1 − 10.2 (90 minutes) + 9.40 (180 minutes) ($p < 0.000$). This equation describes a relationship between scintigraphy and the breath test enrichment expressed as delta per mil at 90 and 180 minutes. There was a strong correlation ($r = 0.830$, slope = 0.732 ± 0.120 [SE], intercept = 26.4 ± 12.7 [SE]) between the T1/2 values calculated using the regression equation and the actual T1/2 values obtained using scintigraphy.

When we performed the multiple regression analysis for

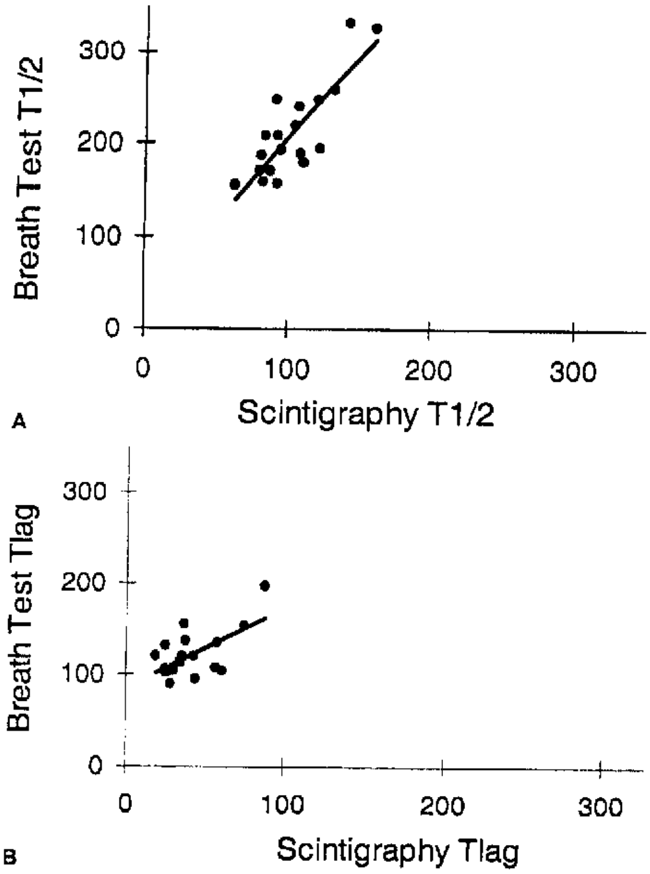

FIG. 2. A: Half-emptying times in minutes determined by scintigraphy and the OBT using a muffin test meal labeled with ^{99m}Tc and 1-^{13}C-octanoate. The regression equation for this data is $y = 1.7972(x) + 25.593$ ($r = 0.83$). **B:** Lag times in minutes determined by scintigraphy and the OBT using a muffin test meal labeled with ^{99m}Tc and 1-^{13}C-octanoate. The regression equation for this data is $y = 0.8608(x) + 85.683$ ($r = 0.63$)

Tlag, we found a strong relationship between the 60- and 90-minute breath samples. The regression equation yielded Tlag = 57.4 + 13.2 (60 minutes) − 13.5 (90 minutes) ($p = 0.001$). Similarly, there was a good correlation ($r = 0.755$, slope = 0.570 ± 0.120 [SE], intercept = 18.1 ± 5.44 [SE]) between the Tlag values calculated using the regression equation and the Tlag values obtained using scintigraphy.

Intrasubject Reproducibility of the ^{13}C-Octanoate Muffin Meal

The mean T1/2 (±SD) for the OBT on day 1 was 209 ± 52 minutes, compared with 196 ± 42 minutes on day 2 (not significant, $p = 0.28$, paired t test). Figure 3A presents the replicate T1/2 data obtained by OBT on both days of the study. When data for all 20 participants were included in the analysis, the least-squares regression equation for this plot was $y = 0.345(x) + 124.29$ ($r = 0.42$). When two participants with the largest deviation in test results were excluded from the analysis, the equation for the fitted line was $y = 0.584(x) + 82.33$ ($r = 0.62$).

The mean Tlag (±SD) for the OBT was 120 ± 25 minutes on day 1 and 121 ± 25 minutes on day 2 of the protocol (not significant, $p = 0.96$). Replicate Tlag data have been plotted in Figure 3B. The equation for the fitted line of this plot was $y = 0.753(x) + 29.922$ ($r = 0.75$).

The Effect of Erythromycin on Gastric Emptying as Measured by the ^{13}C-Octanoate Muffin Meal

The mean (±SD) T1/2 without treatment with erythromycin was 196 ± 42 minutes. In comparison, the mean (±SD) T1/2 after treatment with erythromycin was significantly shorter at 155 ± 49 minutes ($p = 0.005$, paired Student t test). A plot of replicate T1/2 data is presented in Figure 4A. The mean (±SD) Tlag was also significantly decreased after the administration of erythromycin from 121

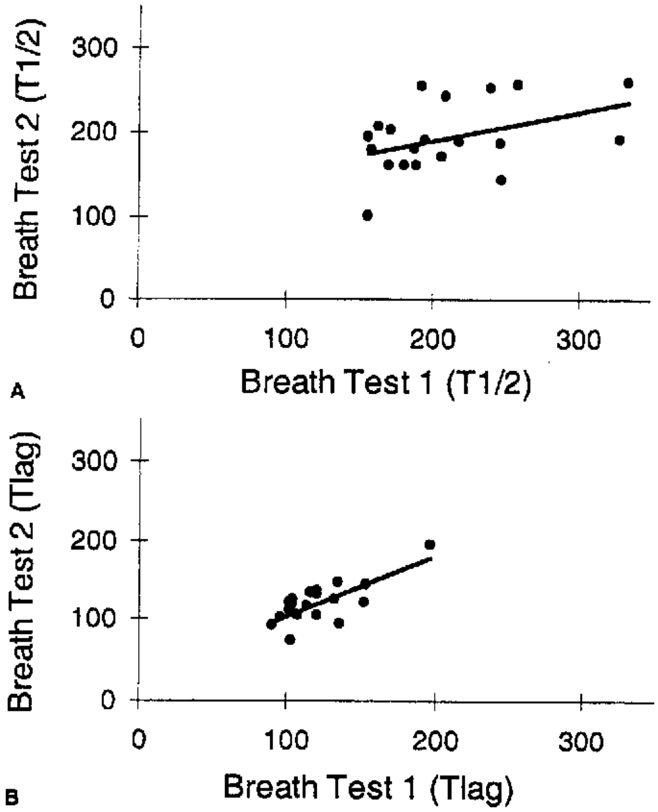

FIG. 3. A: A plot of T1/2 values (minutes) determined on 2 separate days using a ^{13}C-octanoate–labeled muffin test meal. The least-squares regression equation for this plot is $y = 0.345(x) + 124.29$ ($r = 0.42$). When the two subjects with the largest deviation are excluded, the equation for the fitted line is $y = 0.584(x) + 82.33$ ($r = 0.62$) (data not shown). **B:** A plot of Tlag values (minutes) determined on 2 separate days using the ^{13}C-octanoate–labeled muffin test meal. The least-squares regression equation for this plot is $y = 0.753(x) + 29.922$ ($r = 0.75$).

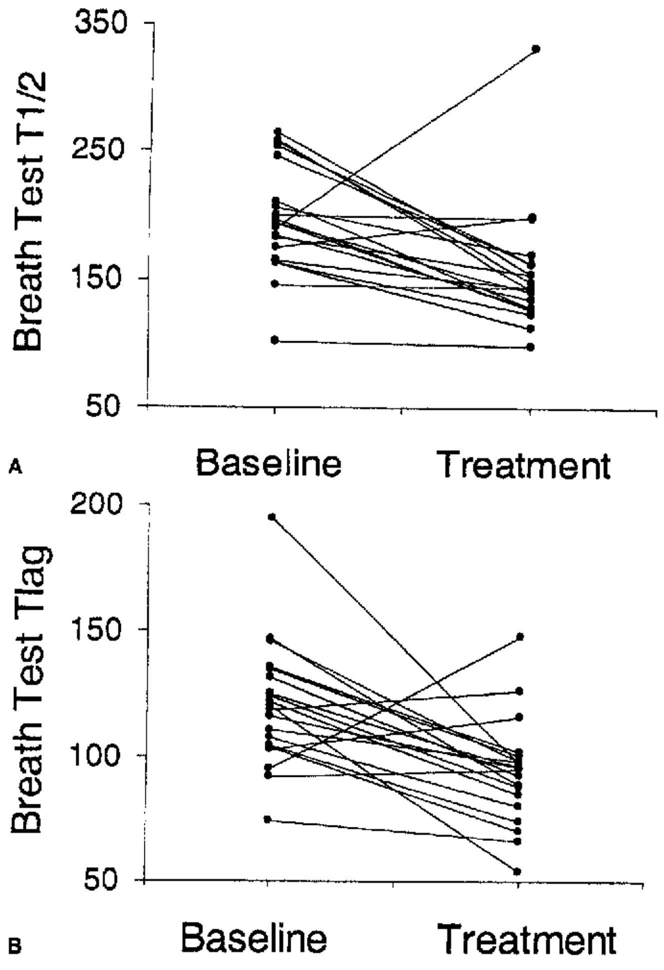

FIG. 4. A: Half-emptying time (minutes) determined with the ^{13}C-octanoate muffin meal before and after treatment with erythromycin. A paired Student *t* test confirmed a statistically significant difference between the baseline and treatment values (baseline = 196 ± 42 and treatment = 155 ± 49 minutes (mean ± SD), $p = 0.005$). **B:** Lag time (minutes) determined with the ^{13}C-octanoate muffin meal before and after treatment with erythromycin. A paired Student *t* test confirmed a statistically significant difference between the baseline and treatment values (121 ± 25 minutes vs. 94 ± 21 minutes, $p = 0.001$)

± 25 minutes to 94 ± 21 minutes ($p = 0.001$, paired Student *t* test). A plot of replicate Tlag data is presented in Figure 4B.

DISCUSSION

In 1993, Ghoos et al.[4] described the OBT for the measurement of gastric emptying in humans. After the administration of a scrambled egg meal double-labeled with either ^{13}C or ^{14}C-octanoate and ^{99m}Tc-albumin, scintigraphic images were acquired for 2 hours and breath samples were collected for 4 hours. They found an excellent correlation between the results of scintigraphy and breath testing for T1/2 ($r = 0.89$) and lag phase ($r = 0.92$). Widespread adoption of the OBT supports the effectiveness of this technique as a noninvasive, easy to perform, nonradioactive means of assessing solid-phase gastric emptying in humans. The OBT has successfully been used to quantify gastric emptying in patients with dyspepsia[6,17] and diabetes.[7,9] Studies are necessary to be sure that the accuracy of the OBT is not adversely affected by underlying pancreatic exocrine dysfunction or diseases involving the small bowel, liver, or pulmonary system.

We report the gastric emptying characteristics of a novel muffin meal in healthy volunteers. The muffin meal represents a convenient alternative to current test meals for motility studies. The muffin meal offers benefits in terms of palatability, consistency, large-scale preparation for clinical studies, and storage. We found a strong correlation between scintigraphy and the ^{13}C-octanoate muffin meal for T1/2 ($r = 0.83$) using a 4-hour breath collection period. There was a weaker correlation between the two testing methods for the lag phase ($r = 0.63$). Several authors have commented on the difficulty of quantifying Tlag obtained by scintigraphy,[18–21] even when two gamma cameras are used and geometric mean correction of the signal is used.[22] This may partly explain the poorer correlation for the lag phase between the two techniques. This point is supported by our data in which the coefficient of variation for Tlag derived from scintigraphy (coefficient of variation = 44.6%) was almost a factor of two greater than for T1/2 (coefficient of variation = 23%). The coefficient of variation for the OBT data was 20.8% and 24.8% for Tlag and T1/2, respectively.

The correlation between two replicate T1/2 measurements measured with the OBT was relatively weak ($r = 0.42$). However, when data from two individuals with the largest deviation were omitted, the correlation improved ($r = 0.62$), approaching values reported by other researchers.[4,11] Lag time data proved more reproducible, yielding a strong correlation ($r = 0.75$) for the replicate measurements. Several studies have suggested that the gastric emptying of solids in an individual can vary up to 30% on different days.[23–25] Although improved reproducibility has been achieved with the OBT,[4,11] it is possible that the true variability may go undetected if the test meal does not challenge motility. Recent electrogastrography studies revealed that the postprandial/fasting power ratio for a 350-kcal meal was significantly higher than for a 250-kcal meal.[26] Further, OBT gastric emptying parameters obtained using a 350-kcal test meal significantly correlated with 2-hour postprandial/fasting power ratios measured by electrogastrography. No correlation was found for the 250-kcal test meal by electrogastrography. For this reason, we used a larger test meal (350 kcal) compared with the typical 250- to 280-kcal meals used for OBT studies.

Investigators from the Mayo Clinic[7,12] recently described a means of simplifying the OBT protocol. We conducted a similar analysis for our data, and were able to further reduce the number of required breath samples while maintaining a significant correlation to the scintigraphy data. A study protocol designed to use our experimentally derived multiple regression equations requires breath only to be collected at 60, 90, and 180 minutes. Raw data reported as delta per mil without baseline correction are entered into the regression equations to obtain estimates for T1/2 and Tlag derived by scintigraphy. Compared to previous studies,[4,6,7,12,17,27] our method provides a significant reduction in the required number of samples (3 vs. 18–26) and the duration of breath collection (3 hours vs. 4–6 hours). Given the limited number of participants investigated for this study, our multiple regression association does not necessarily represent a generalized case. However, it does suggest that the analysis of motility curves may be approximated by a few samples obtained at critical junctures during the gastric emptying process.

In conclusion, we found a strong correlation in the evaluation of gastric emptying between the OBT and scintigraphy using a novel muffin meal. Given the limitations of a small data set, intrasubject reproducibility of the octanoate muffin meal was satisfactory for T1/2 and quite good for Tlag. The ^{13}C-octanoate muffin meal was sensitive enough to detect an increase in the rate of gastric emptying after the administration of erythromycin in healthy controls. Multiple linear regression appears to be a promising means of analyzing data derived from breath test data. This method of analysis may allow a more practical breath test protocol and deserves further evaluation.

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