Reproducible Lactulose Hydrogen Breath Test as a Measure of Mouth-to-Cecum Transit Time

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Breath hydrogen monitoring after oral lactulose syrup is a conventional measure of mouth-to-cecum transit time (MCTT), but its reproducibility has been questioned. We compared the reproducibility of five measurements of MCTT after a conventional breakfast (380 kcal) taken with tea containing 20 g lactulose to five measurements of MCTT after 20 g lactulose in water in eight normal volunteers. Individual mean breakfast transit time was not significantly different from lactulose transit time in each of the seven subjects, but one had a breakfast transit time of 151 ± 15 min and a lactulose transit time of 86 ± 22 minutes (X ± SD, P < 0.001). The coefficient of variation of breakfast transit time (11.6 ± 5.3%, range: 6.9–24.2%) was less than that of lactulose transit time (30.7 ± 7.8%, range: 22.1–50.0%, P < 0.001). In a second set of experiments, the liquid phase marker (99mTechnetium-diethylene triamine pentaacetic acid) emptied from the stomach more rapidly after the lactulose solution (T1/2 16.3 ± 5.4) than after the breakfast (33.9 ± 10.9 min, P < 0.01) and MCTT was shorter after lactulose (77 ± 32 vs 104 ± 40 min, respectively, P < 0.05). There was no correlation between MCTT of lactulose and breakfast and between half-time gastric emptying and MCTT of either lactulose or breakfast. We conclude that the ingestion of inert lactulose induces an abnormally rapid MCTT and that breakfast MCTT is a much more reproducible investigation and should be employed in studies requiring serial measurements.

KEY WORDS: mouth-to-cecum transit time; breath hydrogen; lactulose; gastric emptying.

Mouth-to-cecum transit time (MCTT) is an important indicator of small bowel function. Identification of abnormally rapid movement of nutrients through the small intestine may be important in clinical medicine in detecting the cause of diarrhea or obscure abdominal pain. For example, an acceleration in small bowel transit time after gastric surgery could lead to a reduction in contact time between food and absorptive epithelium, which may induce malabsorption (1), abdominal cramps, and diarrhea. Small intestinal diseases such as celiac disease, giardiasis, and Crohn’s disease, as well as lactase deficiency induce malabsorption, which may lead to an acceleration of small bowel transit. Bond and Levitt were the first to show that pulmonary excretion of hydrogen (H2) occurred within 10 min after introduction of carbohydrate into the cecum (2). Since then, breath H2 measurement has been used extensively to study carbohydrate malabsorption (3) and MCTT (4–6). The lact-
tulose drink H\textsubscript{2} breath test is the most popular technique to study MCTT (4, 7–10), but lacks reproducibility (10–12), and some subjects may not produce an identifiable H\textsubscript{2} peak (3). The use of lactulose may also be criticized because it is a nonabsorbable carbohydrate that has a laxative action and might itself induce an acceleration of MCTT. Recently, more normal solid meals containing the nonabsorbable carbohydrates stachyose and raffinose, naturally present in beans, have been used and have been suggested as a second test (5, 6). However, these meals have very long MCTT (6–10 h), which renders the test tedious, because of the prolonged fasting, and even dangerous for dehydrated or diabetic patients. These defects of the liquid lactulose MCTT and bean meal MCTT led us to examine the reproducibility of a test incorporating both a conventional breakfast and liquid lactulose with that of the standard liquid lactulose MCTT. Finally, by simultaneous gastric emptying and MCTT studies, we investigated the hypothesis that gastric emptying may affect in some way variations of MCTT (5, 10).

**MATERIALS AND METHODS**

Sixteen normal volunteers (11 males, five females age 35.8 ± 11.0 years, mean ± 1 SD) were studied. All were of normal body weight were taking a normal diet and had a normal bowel habit. None had symptoms or history of gastrointestinal disease or surgery or had received antibiotics in the two months prior to the study. Menstruating women were studied during the follicular phase (days 6–12) (8). Verbal informed consent was obtained from all individuals tested. The protocol of the study was approved by the Greek Ethical Committee on human studies (December 2, 1983).

**Preliminary Study.** In a double-blind comparison, 10 normal volunteers ingested 10, 20, and 30 g of lactulose in 250 ml of water in random order on three consecutive occasions one week apart. Breath hydrogen was monitored every 10 min. The corresponding MCTTs were 83 ± 32, 81 ± 39, and 84 ± 20 min ($F_{2,24} = 0.02$, $P = NS$). Following the ingestion of 10 g of lactulose, three of the volunteers produced less than 10 ppm of breath hydrogen, while all produced more than 10 ppm when a 20-g dose of lactulose was used. The ingestion of a 30-g dose induced abdominal pain and/or diarrhea in five of the volunteers tested. It was then decided to use 20 g of lactulose as a probe marker to study MCTT.

**Test Meals.** The lactulose drink consisted of 20 g of lactulose (30 ml of Duphalac, Duphar, Southampton, U.K.) in 250 ml of tap water at room temperature. The breakfast consisted of two slices of toast (17 g), butter (15 g), marmalade (20 g), one hard boiled egg, and 200 ml of weak tea containing 20 g of lactulose and 10 g of sugar. The complete meal contained 280 kcal, 42% of the calories were derived from carbohydrate, 10% from protein, and 48% from fat. Milk was not included in the breakfast since it has been shown that the prevalence of lactose malabsorption in Greece is 75% (13). However, because 30 ml of Duphalac contains about 2.4 g of lactose, all volunteers were tested with 5 g of lactose in isotonic solution. There was no postprandial increase of breath H\textsubscript{2} over the basal values for 4 hr, and none of the volunteers reported symptoms of lactose intolerance during the test period. Formal lactose tolerance test with a 50-g lactose load was not performed.

**Mouth-to-Cecum Transit Time (MCTT) Studies.** The reproducibility of MCTT after lactulose or breakfast was investigated in eight normal persons. Each volunteer was studied five times with lactulose or breakfast; they were ingested in random order at one-week intervals. After an overnight fast (10–12 hr), the volunteer drank the lactulose drink or consumed the breakfast within 10 min. Breath hydrogen concentration was determined at −30 and 0 min and at 10-min interval thereafter for 4 hr. End-expiratory breath samples were collected in 50-ml polyethylene syringes while the volunteer exhaled through a modified Haldane-Priestley tube (14) and the H\textsubscript{2} concentration measured by a research chromatograph (Hewlett-Packard 5750 G) equipped with a thermal conductivity detector. The operating conditions have been published elsewhere (13). The minimum hydrogen concentration detectable was 3 ppm, which gave a recorder deflection of 2 mm. MCTT was taken as the interval between finishing the meal and the beginning of sustained rise of breath hydrogen in three consecutive samples, where at least a 10-ppm incremental increase existed between any two of the samples appeared (10). During the test period, subjects were not restricted to a chair or bed, and they were allowed to walk or sit. They were instructed not to smoke (15), drink, or eat (6) until the end of the study. The occurrence of abdominal symptoms and frequency and consistency of bowel motions were recorded during the test period and for 3 hr thereafter (total 7 hr).

**Simultaneous Gastric Emptying and MCTT Studies.** The effect of the TV\textsubscript{2} gastric emptying of the lactulose solution or the liquid phase of the breakfast on MCTT was studied in eight normal volunteers in a single blind crossover study. After an overnight fast, the volunteer either drank the lactulose solution or consumed the breakfast with tea containing lactulose, to which 1 mCi of $^{99m}$Tc-DTPA has been added. After finishing the meal the subject was immediately placed standing in front of a $\gamma$-camera (S-400, Ohio Nuclear) positioned at the stomach area and 30-sec image was taken and repeated at 5-min intervals for at least 45 min. Between isotopic scans, volunteers were allowed to sit. One observer reviewed the images without knowledge of the meal type and drew a gastric region of interest (ROI) on each frame.

All the results were corrected for decay of the isotope and plotted against time. Gastric emptying was expressed as $TV_{2}$, i.e., the time in minutes taken for the maximal count to be reduced by half. The radiation dose received by the volunteer was highest to the colon. When the dose is expressed in millirads per 500 µCi of $^{99m}$Tc-DTPA the...