Stepped assessment of gastric emptying of a solid meal using the $^{13}$C-octanoic acid breath test

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Abstract

The $^{13}$C-octanoic acid breath test is widely used for evaluating gastric emptying of solids. Since the results of this test are influenced by multiple factors such as the time required to grind the solid meal into smaller particles, the gastroduodenal transport time of the ground meal, and the time required for bowel drug absorption and drug dispersion, the administration of a test meal by the oral route alone cannot result in an accurate measurement of the complicated process of emptying the stomach of solids. The aim of the present study was to evaluate each phase of gastric emptying of solids by varying the administration route of the test meal. Six healthy male volunteers (mean age: 33.2 yr) participated in the study. The test meal consisted of a bowl of rice topped with a mixture of boiled chicken and eggs admixed with 100 mg of $^{13}$C-octanoic acid (total: 273 kcal). All subjects were given the test meal by each of the following three methods: 1. Normal oral intake of the test meal, 2. Feeding of the ground test meal through a nasogastric tube, 3. Feeding of the ground test meal through a duodenal tube. For each set of examinations, the mean residence time (MRT), half-emptying time ($T_{1/2}$), gastric emptying coefficient (GEC), lag phase (L-breathe), and measured maximum $^{13}$C excretion time ($T_{\text{max}}$-measured) were calculated. The data was analyzed to determine the time for each phase of gastric emptying as follows: mean grinding time (MGT) = MRT$^{\text{oral}}$ - MRT$^{\text{nasogastric}}$, mean gastroduodenal transport time (MGDTT) = MRT$^{\text{nasogastric}}$ - MRT$^{\text{nasoduodenal}}$. Data was expressed as the mean ± SE. The values of the parameters of MGT were 0.82 ± 0.50 hr (MRT), 0.64 ± 0.18 hr ($T_{1/2}$), 0.51 ± 0.24 hr (L-breathe), -0.45 ± 0.30 hr (GEC), and 49.2 ± 8.0 min ($T_{\text{max}}$-measured). The values of the parameters of MGDTT were 0.87 ± 0.38 hr (MRT), 0.26 ± 0.29 hr ($T_{1/2}$), 0.92 ± 0.36 hr (L-breathe), 0.55 ± 0.23 hr (GEC), and 63.33 ± 8.16 min ($T_{\text{max}}$-measured). The times required for the drug absorption and disposition were 1.60 ± 0.20 hr (MRT), 1.03 ± 0.24 hr ($T_{1/2}$), 0.10 ± 0.08 hr (L-breathe), 3.72 ± 0.46 hr (GEC), and 19.67 ± 2.11 min ($T_{\text{max}}$-measured). By varying the administration route of a test meal containing $^{13}$C-octanoic acid, we may be able to assess each phase of the emptying of gastric solids in detail, thus leading to a better understanding of gastroduodenal motility.

Key words: gastric emptying, breath test, stepped assessment
Introduction

Gastric emptying is currently assessed by various examination techniques, including radioscintigraphy (Heading et al., 1976; Collins et al., 1983), MRI (Schwizer et al., 1992) and radionuclide marker (Feldman et al., 1984) techniques. However, such examination procedures expose the subject to a substantial amount of radiation. The acetaminophen emptying test (Heading et al., 1973) has the disadvantage of requiring blood collection and ultrasonographic methods require complicated, special techniques (Bateman and Whittingham, 1982; Holt et al., 1986; Okamoto et al., 1997; Kusunoki et al., 2000). The $^{13}$C-octanoic acid breath test (OBT) is a new technique that measures the $^{13}$C-$CO_2$ concentration in expired air after ingestion of $^{13}$C-substrate labeled with non-radioactive carbon ($^{13}$C: a stable isotope), and it can be used to assess gastric emptying with various test meals, i.e., liquid, semisolid, and solid meals. Furthermore, it has earned a high reputation as an extremely simple, non-invasive technique (Ghoos et al., 1993; Maes et al., 1994; Braden et al., 1995; Ziegler et al., 1996; Choi et al., 1997a; Choi et al., 1997b; Duan et al., 1997; Maes et al., 1997; Maes et al., 1998; Perri et al., 1998; Lee et al., 2000).

Conventional gastric emptying studies measure the gastric transit time or gastric emptying rate over a constant time period, and these studies usually evaluate both the grinding phase (the time required to grind the solid meal into smaller particles) and the transport phase (the time required to evacuate the ground meal into the duodenum) after the solid test meal ingestion phase. The OBT after oral intake of a solid meal measures both these phases and the absorption and oxidation phases (the times required to absorb and oxidate the octanoic acid). Therefore, it does not necessarily reflect the process of gastric emptying. As far as we know no study has reported on the time required for each process (grinding, transport, absorption, and oxidation) during the OBT.

The aim of this study was to make an accurate interpretation of the OBT through assessment of each process by modifying the administration methods of a test meal.

Materials and methods

Subjects

Six asymptomatic healthy male volunteers (mean age: 33.2 years; range: 23–40 years) participated in this study. None of them had a history of abdominal surgery, nor were they taking any drugs that would affect their gastric motility. All of them provided informed consent for this study as approved by the Ethics Committee of Hiroshima University. They all submitted to upper gastrointestinal endoscopy to exclude those with organic disorders such as peptic ulcers, tumors, and esophagitis. Smoking was prohibited the day before and during both days of parameter measurements. We told the subjects to refrain from large quantities of alcohol, fats, and spices during the night before the examination.

Test meal

The test meal consisted of 180 g of commercially prepared egg with chicken soup (Otsuka, Tokyo, Japan) and was mixed with 100 g of cooked instant rice (Sato, Niigata, Japan) and 200 ml
of water. This is a popular Japanese dish that was prepared as a bowl of rice topped with a mixture of boiled chicken soup and scrambled eggs (280 g, protein 7.4 g, carbohydrate 63.0 g, fat 3.7 g, 273 kcal). The egg yolk was labeled with 100 mg of Na-\textsuperscript{13}C-octanoic acid.

**Stepped assessment**

After an overnight fast of at least 12 hr, a polyvinyl feeding tube (16 Fr) was introduced through the nose and secured to the subject's cheeks with adhesive tape. The position of the tip of the tube was checked fluoroscopically. The test meal was a meal ground with a mixer and administered via the tube. We set a minimum interval of 15 min between fixing the tube and administering the test meal. During this examination, subjects were in a sitting position, leaning slightly backwards.

During a seven-day period, all subjects were given the test meal in three different ways as follows:

1. usual oral intake of the test meal (within 15 min)
2. feeding the ground meal through a nasogastric tube (for 15 min)
3. feeding the ground meal through a nasoduodenal tube (for 15 min)

Breath samples were collected at the baseline before the meal and every 10 min for the first 2 hr, every 15-min for the next 1 hr, and every 30 min for another 3 hr. Samples collected in breath bags were analyzed to determine the isotopic enrichment by isotope selective non-dispersive infrared spectrometry with an on-line gas chromatographic purification system (Ghoos et al., 1993; Maes et al., 1994; Braden et al., 1995; Ziegler et al., 1996; Choi et al., 1997a; Choi et al., 1997b; Duan et al., 1997; Maes et al., 1997; Maes et al., 1998; Perri et al., 1998; Lee et al., 2000). Total CO\textsubscript{2} production was assumed to be 300 mmol/hr/m\textsuperscript{2} of body surface calculated with Haycock's formula (Haycock et al., 1978). Mathematical analysis, such as of gastric half emptying time (T1/2), lag phase (L-breath), and the gastric emptying coefficient (GEC), was performed with the model suggested by Ghoos et al. (1993). Then we used measured maximum \textsuperscript{13}C excretion time (Tmax-measured) as a useful parameter to simplify the \textsuperscript{13}C breath test for gastric emptying in accordance with a previous report by the working party of the Japan Society of Smooth Muscle Research (Nakata et al., 2002).

The statistical moments for the pulmonary excretion rate-time curve are defined as:

\[
M(\infty) = \int (dM/dt) dt \quad \text{eq. 1}
\]

\[
\text{MRT} = \int t (dM/dt) dt / \int (dM/dt) dt \quad \text{eq. 2}
\]

where dM/dt is the pulmonary excretion rate of \textsuperscript{13}C-CO\textsubscript{2}, M (\infty) is the total amount of \textsuperscript{13}C-CO\textsubscript{2} excreted in exhaled air to infinite time, and MRT is the mean residence time (Yamaoka et al., 1978). M (\infty) and MRT were calculated by linear trapezoidal integration with extrapolation of the time course curve to infinite time according to a monoexponential equation. This equation was determined by the least-squares method.

**Mean grinding time and mean gastroduodenal migration time**

To interpret the results, we defined two equations as follows:

\[
\text{MGT} = \text{MRT}_{\text{oral}} - \text{MRT}_{\text{nasogastric}} \quad \text{MGDTT} = \text{MRT}_{\text{nasogastric}} - \text{MRT}_{\text{nasoduodenal}}
\]
Fig. 1. The %\(^{13}\)C-dose/hr curves for each administration route of the stepped assessment.

where MGT (mean grinding time) is the mean time required for grinding the test meal, MRT\(_{oral}\) as MRT calculated from the results after oral ingestion of the test meal, MRT\(_{nasogastric}\) as MRT when fed through a nasogastric tube, MRT\(_{nasoduodenal}\) as MRT through a nasoduodenal tube, and MGD\(_T\) (mean gastroduodenal transport time) is the time required for the gastric emptying of the test meal including the grinding process.

**Statistical analysis**

Data was expressed as the mean ± SE. The statistical analysis of the data was performed using the Mann-Whitney U test, and \(P<0.05\) was considered to be statistically significant.

**Results**

Although all the subjects felt epigastric discomfort, none of the subjects had any severe symptoms or adverse events which caused them to drop out of the study. Figure 1 shows the %\(^{13}\)C-dose/hr curves after each administration. In these subjects, the peak times of the curves were nasoduodenal tube<nasogastric tube<oral intake feeding.

The parameters corresponding to gastric emptying are shown in Tables 1, 2, 3 and 4. In these subjects, the values of all of the parameters increased significantly with nasoduodenal tube<nasogastric tube<oral intake feeding. The time required for the absorption and dispersion of \(^{13}\)C was supposed to be 1.60 ± 0.20 hr (MRT), 1.03 ± 0.24 hr (T\(_{1/2}\)), 0.10 ± 0.08 hr (L-breath), 3.72 ± 0.46 hr (GEC), and 19.67 ± 2.11 min (T\(_{max}\)-measured). With these parameters for each administration route, we calculated MGT and MGD\(_T\) (Table 5). The results of MGT and MGD\(_T\) using MRT and T\(_{max}\)-measured became comparatively near in value.
Table 1 Result of each administration route of stepped assessment oral intake

<table>
<thead>
<tr>
<th></th>
<th>A</th>
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<th>D</th>
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<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT (hr)</td>
<td>3.75</td>
<td>3.03</td>
<td>3.55</td>
<td>2.78</td>
<td>3.35</td>
<td>3.31</td>
</tr>
<tr>
<td>Half-emptying time (hr)</td>
<td>2.42</td>
<td>2.60</td>
<td>2.43</td>
<td>2.40</td>
<td>2.49</td>
<td>2.66</td>
</tr>
<tr>
<td>L-breath (hr)</td>
<td>1.67</td>
<td>1.75</td>
<td>1.47</td>
<td>1.78</td>
<td>1.67</td>
<td>1.81</td>
</tr>
<tr>
<td>GEC (hr)</td>
<td>3.45</td>
<td>3.11</td>
<td>3.14</td>
<td>3.76</td>
<td>3.46</td>
<td>3.33</td>
</tr>
<tr>
<td>Tmax-measured (min)</td>
<td>135</td>
<td>120</td>
<td>115</td>
<td>135</td>
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</tr>
</tbody>
</table>

MRT; Mean residence time. L-breath; Lag phase of the breath test. GEC; Gastric emptying coefficient. Tmax-measured; measured maximum 13C excretion time.

Table 2 Result of each administration route of stepped assessment nasogastric tube

<table>
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<tr>
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<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT (hr)</td>
<td>2.45</td>
<td>2.86</td>
<td>2.23</td>
<td>1.91</td>
<td>2.35</td>
<td>3.03</td>
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<td>Half-emptying time (hr)</td>
<td>1.55</td>
<td>1.94</td>
<td>2.00</td>
<td>1.50</td>
<td>1.88</td>
<td>2.18</td>
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<tr>
<td>L-breath (hr)</td>
<td>1.06</td>
<td>1.12</td>
<td>1.40</td>
<td>1.04</td>
<td>1.12</td>
<td>1.38</td>
</tr>
<tr>
<td>GEC (hr)</td>
<td>4.10</td>
<td>3.76</td>
<td>3.91</td>
<td>4.17</td>
<td>3.51</td>
<td>3.47</td>
</tr>
<tr>
<td>Tmax-measured (min)</td>
<td>80</td>
<td>70</td>
<td>80</td>
<td>80</td>
<td>90</td>
<td>80</td>
</tr>
</tbody>
</table>

MRT; Mean residence time. L-breath; Lag phase of the breath test. GEC; Gastric emptying coefficient. Tmax-measured; measured maximum 13C excretion time.

Table 3 Result of each administration route of stepped assessment duodenal tube

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT (hr)</td>
<td>1.53</td>
<td>1.96</td>
<td>1.62</td>
<td>1.58</td>
<td>1.33</td>
<td>1.59</td>
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<td>Half-emptying time (hr)</td>
<td>1.04</td>
<td>1.44</td>
<td>0.94</td>
<td>0.72</td>
<td>0.97</td>
<td>1.09</td>
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<tr>
<td>L-breath (hr)</td>
<td>0.04</td>
<td>0.01</td>
<td>1.20</td>
<td>0.06</td>
<td>0.09</td>
<td>0.22</td>
</tr>
<tr>
<td>GEC (hr)</td>
<td>3.60</td>
<td>3.49</td>
<td>4.39</td>
<td>3.57</td>
<td>3.57</td>
<td>3.33</td>
</tr>
<tr>
<td>Tmax-measured (min)</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

MRT; Mean residence time. L-breath; Lag phase of the breath test. GEC; Gastric emptying coefficient. Tmax-measured; measured maximum 13C excretion time.

Table 4 Comparison of parameters for each administration route of stepped assessment

<table>
<thead>
<tr>
<th></th>
<th>Oral intake</th>
<th>Nasogastric tube</th>
<th>Duodenal tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT (hr)</td>
<td>3.30 ± 0.35</td>
<td>2.47 ± 0.41</td>
<td>1.60 ± 0.20</td>
</tr>
<tr>
<td>Half-emptying time (hr)</td>
<td>2.50 ± 0.11</td>
<td>1.86 ± 0.25</td>
<td>1.03 ± 0.24</td>
</tr>
<tr>
<td>L-breath (hr)</td>
<td>1.69 ± 0.12</td>
<td>1.19 ± 0.16</td>
<td>0.10 ± 0.08</td>
</tr>
<tr>
<td>GEC (hr)</td>
<td>3.38 ± 0.24</td>
<td>3.82 ± 0.29</td>
<td>3.72 ± 0.46</td>
</tr>
<tr>
<td>Tmax-measured (min)</td>
<td>129 ± 3.75</td>
<td>80 ± 2.58</td>
<td>16.67 ± 2.11</td>
</tr>
</tbody>
</table>

MRT; Mean residence time. L-breath; Lag phase of the breath test. GEC; Gastric emptying coefficient. Tmax-measured; measured maximum 13C excretion time.

Discussion

Most gastric emptying studies including breath tests, have generally reflected the time required for the gastroduodenal transport of a test meal. However, the gastric emptying of a solid meal is composed of two phases: the time required for the stomach to grind the solid meal into particles small enough (1–2 mm in diameter) to pass through the pyloric region and the
Table 5 Comparison of MGT and MGDIT using each parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MGT</th>
<th>MGDIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT (hr)</td>
<td>0.82 ± 0.50</td>
<td>0.87 ± 0.38</td>
</tr>
<tr>
<td>Half-emptying time (hr)</td>
<td>0.64 ± 0.18</td>
<td>0.26 ± 0.29</td>
</tr>
<tr>
<td>L-breath (hr)</td>
<td>0.51 ± 0.24</td>
<td>0.92 ± 0.36</td>
</tr>
<tr>
<td>GEC (hr)</td>
<td>−0.45 ± 0.30</td>
<td>0.05 ± 0.23</td>
</tr>
<tr>
<td>Tmax-measured (min)</td>
<td>49.2 ± 8.0</td>
<td>63.33 ± 8.16</td>
</tr>
</tbody>
</table>

MRT: Mean residence time. L-breath: Lag phase of the breath test. GEC: Gastric emptying coefficient. Tmax-measured: measured maximum $^{13}$C excretion time.

time required for the transport of the test meal from the pylorus to the duodenum. In the present study we administered test meals to healthy subjects by various routes to clarify the time required for each phase of gastric emptying. The present study is the first study using the $^{13}$C-octanoic acid breath test to evaluate the stomach function of grinding a meal (gastric grinding time) and its function of transporting the ground meal (gastric transport time), independently. In all subjects, the values of all the parameters increased significantly in order of the nasoduodenal tube, the nasogastric tube, and oral intake feeding. However, in addition to the total gastric emptying rate, we found that there were some differences between the subjects in the parameters of each phase. Even if the total time of gastric emptying was equal, the times of the phases were not constant at all. Further evaluation of the two functions of the stomach, i.e., grinding and transport, in patients with delayed gastric emptying, such as those with functional dyspepsia, may make it possible to evaluate the difference between patients with lowered grinding ability and those with lowered emptying ability and could lead to a more accurate assessment of gastric emptying functions after ingestion of a solid meal. MGT is considered a parameter for evaluating grinding ability via chewing a whole buccal capsule as well as for intragastric food grinding.

The differences seen in the curve of $^{13}$CO$_2$ among the subjects after feeding through a duodenal tube indicated that each subject had his/her own time required for the metabolism of $^{13}$C substrate. The amount and ingredients of the food they took the day before the examination, as well as their liver function, might have produced these differences. Therefore, one must be careful in performing this examination and analyzing the results.

The time required for a solid meal to be ground in the stomach has been roughly determined by the radioisotope method, and the lag phase of the radioisotope method expresses the time when the first 10% of the test meal has been evacuated from the stomach (Choi et al., 1997b; Maes et al., 1998). This is the first study to calculate the absorption and disposition times after nasoduodenal tube administration of ground test meal admixed with $^{13}$C-octanoic acid. Nasoduodenal tube administration of $^{14}$C-octanoic acid (Ghoos et al., 1993) and $^{13}$C-acetic acid dissolved in water (Bradent et al., 1995) was performed to evaluate the times for absorption and disposition in two previous reports. In the present study, the times for absorption and dispersion of $^{13}$C-octanoic acid were 1.60 ± 0.20 hr (MRT), 1.03 ± 0.24 hr (T$_{1/2}$), 0.10 ± 0.08 hr (L-breath), 3.72 ± 0.46 hr (GEC) and 19.67 ± 2.11 min (Tmax-measured).

Ghoos et al. (1993) proposed that the lag phase, the gastric emptying coefficient (GEC), and
half-emptying time ($t_{1/2}$) be used as breath test markers and stated that gastric emptying function should be globally assessed based on all three parameters. In addition to these parameters, we employed mean residence time (MRT) as a fourth marker. Each parameter was calculated by the non-linear least-squares method according to the methods of Ghoos et al. (1993) and Yamaoka et al. (1978). MRT is a marker obtained by moment analysis, and it is one of the most commonly used parameters for analysis of the pharmacokinetic behavior of pharmaceutical products (Yamaoka et al., 1978). This marker, which does not require a complicated mathematical model and can be applied to the assessment of various emptying functions, is now expected to become a promising marker in the field of gastrointestinal physiology. MRT results showed that the gastric emptying time increased significantly in the order of feeding via a nasoduodenal tube, a nasoduodenal tube and oral intake of the test meal. In addition, there was little difference between individuals. MRT showed stable results with the parameter of Tmax-measured, and its utility as a gastric emptying evaluation parameter was proven. However, since this index does not have results which can be compared with those of the radioisotope method, which is the gold standard method of gastric emptying, evaluation of this matter requires further study. When the parameter of GEC is used, discrepancies between individuals and discrepancies in the results through different administrating routes are significant.

However, the working party of the Japanese Society of Smooth Muscle Research has proposed a reference for the standard method (Nakata et al., 2002) in which maximum $^{13}$C excretion time (Tmax-measured) is recommended as a useful parameter. In accordance with the previous report by the working party of the Japanese Society of Smooth Muscle Research, we have adopted this parameter as the fifth marker in the present study. This parameter obtained by the actual $^{13}$C excretion curve does not require a fitting curve or computed calculation. Diagnosis using Tmax-measured is considered more accurate than that using other parameters to simplify the breath test, but further studies are needed to confirm this parameter as an acceptable one for evaluation of gastric emptying. The results of MGT and MGDRT using MRT and Tmax were comparatively near in value. This is the first study to use MRT and Tmax-measured for the evaluation of gastric emptying.

In conclusion, by varying the administration route of a test meal containing $^{13}$C-octanoic acid, we may be able to assess each phase of gastric emptying of solids in detail, which will lead to a better understanding of gastroduodenal motility. However, we must pay careful attention to the individual differences in the absorption and metabolism of $^{13}$C-octanoic acid when evaluating results.

References


