Pharmacological modulation of gastric emptying rate of solids as measured by the carbon labelled octanoic acid breath test: influence of erythromycin and propantheline

B D Maes, M I Hiele, B J Geypens, P J Rutgeerts, Y F Ghoo, G Vantrappen

Abstract
The *C (13C or 14C) labelled octanoic acid breath test was recently developed to measure the gastric emptying rate of solids. This study aimed to investigate whether it is sensitive enough to detect pharmacologically induced changes in the gastric emptying rate. Nine healthy volunteers were studied in basal condition, after intravenous administration of 200 mg erythromycin, and after peroral administration of 30 mg propantheline. Erythromycin significantly enhanced gastric emptying in all subjects, with an increase of the gastric emptying coefficient (p=0.0043) in eight of nine and a fall in both the gastric half emptying time (p=0.0020) and the lag phase (p=0.0044) in all nine. Propantheline significantly reduced the gastric emptying rate, with a decreased gastric emptying coefficient (p=0.0007) and an increased gastric half emptying time (p=0.0168) in all subjects, but no change in the lag phase (p=0.1214). Further mathematical analysis showed that breath sampling at 15 minutes intervals over a four hour period is recommended to guarantee accuracy and the discriminative value of the breath test in various gastric emptying patterns. In conclusion the *C labelled octanoic acid breath test is sufficiently sensitive to show pharmacologically induced changes of gastric emptying rates of solids.

(Gut 1994; 35: 333–337)

Gastric emptying is susceptible to a wide variety of external influences, including drugs. Care should be taken when interpreting gastric emptying studies in patients taking drugs with a long biological half-life. On the other hand, gastrointestinal side effects of some drugs may prove to be of interesting clinical value, as was recently shown for some macrolide antibiotics.

A *C (13C or 14C) octanoic acid breath test was recently developed to measure the gastric emptying rate of solids. *C octanoic acid, a medium chain fatty acid, is readily solubilised in egg yolk. When cooked as an omelette it has proved to be as good a marker of the solid phase of a meal as the radioscintigraphic markers for gastric emptying studies. Once the egg yolk reaches the duodenum, rapid disintegration of the labelled solid phase occurs with subsequent absorption and preferential hepatic oxidation of *C octanoic acid to *CO₂. Since gastric emptying of the meal is the rate-limiting step in the whole process, the rate of *CO₂ excretion in the breath as a function of time can be used to measure the gastric emptying rate. In a validation study, with simultaneous radioscintigraphic and breath test measurements, an excellent correlation was found between the gastric emptying results of the radioscintigraphic method (lag phase, half emptying time) and those of the breath test (lag phase, half emptying time, and the gastric emptying coefficient) when using a solid standard test meal of 250 kcal. The breath test was both sensitive and specific when discriminating between normal and delayed gastric emptying.

In this study, we wanted to investigate the sensitivity of the *C labelled octanoic acid breath test in measuring even minor drug induced changes in the gastric emptying rate of solids in individual healthy volunteers. Two drugs with a known influence on gastrointestinal motor activity were used – erythromycin, which accelerates, and propantheline, which delays gastric emptying.

Methods

Subjects
Nine healthy volunteers (five men and four women; mean age 22 years, range 18 to 25 years) were studied. None had a history of gastrointestinal disease or surgery, or was taking any medication. The gastric emptying rate of a solid standard meal was measured by means of the 14C octanoic acid breath test.

Each subject was studied on three consecutive days in three different randomly applied test situations – without medication, 30 minutes after intravenous administration of 200 mg of erythromycin (erythromycin lactobionate, Abbott) in 250 ml of NaCl 0.9% over a 15 minute period, and 60 minutes after peroral administration of 30 mg of propantheline (propantheline bromide, Continental Pharma).

Materials
All tests were carried out after an overnight fast. The test meal consisted of two slices of white bread and an egg, the yolk of which was doped with 2 μCi of 14C octanoic acid, sodium salt (DuPont, NEN Reserarch, Boston, MA, USA). The egg yolk and white were cooked separately to avoid incorporation of octanoic acid into the protein structure of the white. All meals were consumed within a five minute period. The...
propantheline, with after pattern and 2: Mean (A)
of propantheline.

MEASURING TECHNIQUES
Breath samples were taken before the meal, at three minute intervals for a period of 90 minutes, and at 30 minute intervals from 90 to 240 minutes after ingestion of the meal. At each sampling point, the subjects exhaled into a liquid scintillation vial containing 2 ml of 1 M hyamine hydroxide and 2 ml of ethanol together with 1 drop of thymolphthalein solution. This amount of hyamine is neutralised by 2 mM of CO₂. The end point of neutralisation is indicated by decolouration of the indicator. After decolouration, 10 ml of scintillation cocktail (Hionic Fluor, Packard) were added and radioactivity was determined by liquid scintillation spectrometry (Packard Tri-Carb Liquid Scintillation Spectrometer, model 3375, Packard Instruments Inc, Downers Grove, IL, USA). CO₂ production was assumed to be 300 mmol/m² body surface area per hour. Body surface area was calculated using the weight–height formula of Haycock et al.² The results were expressed as the percentage of ¹⁴C recovery per hour.

MATHMATICAL AND STATISTICAL ANALYSIS OF THE RESULTS
The mathematical analysis of test results is described in a previous paper.¹ Briefly, the curves with the measured ¹⁴CO₂ recovery in breath, expressed as percentage excretion per hour of the given ¹⁴C dose, were fitted by two mathematical formulas as follows: (a) \( y = a \cdot e^{-k \cdot t} \), where \( y \) is the percentage of ¹⁴C excretion in breath per hour; \( t \) is the time in hours; and \( a \), \( b \), and \( c \) are regression estimated constants and (b) \( y = -\frac{m}{k} \cdot \frac{k}{1 - e^{-k \cdot t}} \), where \( y \) is the percentage of ¹⁴C excretion in breath per hour; \( t \) is the time in hours; and \( m \), \( k \), and \( \beta \) are regression estimated constants with \( m \) the cumulative ¹⁴C recovery when time is infinite. The results of this non-linear regression analysis (SAS: PROC NLIN (24) or EXCEL) allows calculation of three distinctive parameters describing the gastric emptying rate of solids, that is: (1) the gastric half emptying time \( t_{1/2} = \frac{60}{b} \left( \ln \left( 1 - e^{-\frac{t}{k}} \right) \right) \) in minutes, (2) the lag phase as defined by Siegel \( \left( t_{\text{lagb}} = \frac{60}{b} \left( \ln \left( -\frac{\ln \beta}{k} - 66 \right) \right) \right) \) in minutes and, (3) the gastric emptying coefficient (GEC = \( \ln(a) \)).

In each subject, the gastric half emptying time, lag phase, and gastric emptying coefficient after erythromycin and after propantheline were compared with the values obtained in the control study using paired comparisons \( t \) tests (SAS: PROC MEANS (24)).

To determine the minimum frequency of breath sampling needed to achieve accurate information about the gastric emptying rate, mathematical curve fitting was repeated for the following sampling intervals: six, nine, 12, 15 and 30 minutes. The calculated gastric half emptying time, lag phase, and gastric emptying coefficient of these five different sampling frequencies were compared with the corresponding values obtained by sampling at three minute intervals using paired comparisons \( t \) tests (24).

Results
Figure 1 illustrates a typical ¹⁴CO₂ breath excretion pattern in a subject studied in three test situations – (B) without medication, (A) after erythromycin and, (C) after propantheline. The drugs clearly affect the shape of the ¹⁴CO₂ excretion curve representing the percentage of the dose excreted per hour. Erythromycin increases not only the peak but also the slope of the ascending and descending limb of ¹⁴CO₂ excretion curve. With propantheline both the peak and the slope of the ascending and descend-
TABLE 1 The mean (SD) values of the different gastric emptying rate parameters in normal conditions and after the administration of erythromycin and propantheline. Also given is the value of the mathematical fitted curve through the mean data.

<table>
<thead>
<tr>
<th></th>
<th>GEC</th>
<th>t_{1/2} (min)</th>
<th>t_{lag} (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Mean (SD)</td>
<td>3.31 (0.36)</td>
<td>22.7 (13.75)</td>
</tr>
<tr>
<td></td>
<td>Fit of mean</td>
<td>3.29</td>
<td>27.19</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Mean (SD)</td>
<td>3.42 (1.24)</td>
<td>21.4 (1.86)</td>
</tr>
<tr>
<td></td>
<td>Fit of mean</td>
<td>3.48</td>
<td>2.16</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Mean (SD)</td>
<td>2.69 (0.56)</td>
<td>8.24 (1.74)</td>
</tr>
<tr>
<td></td>
<td>Fit of mean</td>
<td>2.72</td>
<td>37.26</td>
</tr>
</tbody>
</table>

GEC=gastric emptying coefficient; t_{1/2} (min)=half emptying time (min); t_{lag} (min)=lag time (min).

The difference in the mean 14CO2 excretion rate parameters after the administration of erythromycin and propantheline is shown in the table. It was observed that the mean values of the gastric emptying rate parameters were significantly increased after the administration of erythromycin. The difference in the mean values of the gastric emptying rate parameters was significant after the administration of propantheline. The difference in the mean values of the gastric emptying rate parameters was also significant after the administration of both drugs.

Discussion

We recently developed a breath test – the C octanoic acid breath test – to measure the gastric emptying rate of solids.17 Octanoic acid is fully retained in egg yolk during mixing and grinding in the stomach, but is rapidly liberated in the duodenum. Being a medium-chain fatty acid, it
is quickly absorbed and transported to the liver via the vena portae where it is rapidly oxidised (no carnitine required to enter the mitochondria) and extensively metabolised to CO₂ instead of being used in hepatic lipid synthesis. The rate of CO₂ excretion in breath mainly depends on gastric emptying of the C octanoic acid labelled test meal. The C labelled octanoic acid breath test has several advantages over other methods that measure the gastric emptying rate in humans. It is non-invasive and easy to perform for the patients. C octanoic acid means that the amount of radiation used is reduced considerably, and no radiation is involved with C octanoic acid as marker of the solid test meal. Moreover, the C labelled octanoic acid breath test makes it possible to do repeated gastric emptying studies, even in children and pregnant women.

In this study, we modulated gastric emptying pharmacologically in order to investigate the sensitivity of the test in normal subjects. Erythromycin, a potent stimulator of gastrointestinal activity, caused a shift in the CO₂ excretion curve to the left on the time axis, which can only be explained by an acceleration of gastric emptying. The acceleration included a shortening of both the lag phase and the gastric half emptying time in all subjects studied. The gastric emptying coefficient, an overall parameter for the gastric emptying rate was increased in all but one volunteer by erythromycin. In this subject, the basal gastric emptying rate was already very fast. As erythromycin, at the recommended dose of 200 mg, enhances gastric emptying to normal values in patients with gastroparesis diabeticorum, larger doses were not used to reduce side effects. This study showed that a dose of 200 mg of erythromycin accelerates gastric emptying in healthy volunteers, even in subjects with a very fast basal gastric emptying rate. Preparanale, a synthetic quaternary ammonium anticholinergic drug, delays gastric emptying of fluids in an oral dose of 30 mg, without causing major anticholinergic side effects. Our study showed that a single dose of 30 mg propantheline also delays gastric emptying of solids, with a fall in the gastric emptying coefficient and an increase of the gastric half emptying time in all subjects examined. However, the lag phase is not significantly altered. This is due to the early increase of the CO₂ excretion in most subjects after administration of propantheline (see Fig 2), probably caused by an initial relaxation of the pylorus, which at this dose is not sufficient to alter significantly the overall gastric emptying of solids. It would be interesting to study the effects of larger doses of propantheline.

Mathematical analysis of the breath sample data with simulation of different sampling intervals indicates that sampling at short intervals is needed in subjects with a rapid gastric emptying pattern, whereas sampling has to extend over a long period of time with very slow gastric emptying patterns. In this study, lengthening the sampling interval showed that the breath test parameters remained accurate and discriminative for up to 15 minutes. Therefore, sampling every 15 minutes for a four hour period seems to be the best schedule to ensure reliable results.

### Table II

<table>
<thead>
<tr>
<th>Sampling interval (min)</th>
<th>GEC</th>
<th>t₅₀ (min)</th>
<th>t₅₀ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference</td>
<td>SD</td>
<td>Mean difference</td>
</tr>
<tr>
<td>3-6</td>
<td>0-01 (0-01)</td>
<td>0-36</td>
<td>-1-99 (2-07)</td>
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<tr>
<td>3-9</td>
<td>0-01 (0-02)</td>
<td>0-45</td>
<td>0-78 (5-08)</td>
</tr>
<tr>
<td>3-12</td>
<td>0-02 (0-03)</td>
<td>0-44</td>
<td>-3-85 (4-41)</td>
</tr>
<tr>
<td>3-15</td>
<td>0-04 (0-03)</td>
<td>0-22</td>
<td>-2-37 (2-53)</td>
</tr>
<tr>
<td>3-30</td>
<td>0-10 (0-06)</td>
<td>0-09</td>
<td>4-07 (6-35)</td>
</tr>
</tbody>
</table>

GEC = gastric emptying coefficient; t₅₀ (min) = half emptying time (min); t₅₀ (min) = lag time (min).

### Table III

<table>
<thead>
<tr>
<th>GEC (sampling interval (min))</th>
<th>t₅₀ (min) (sampling interval (min))</th>
<th>t₅₀ (min) (sampling interval (min))</th>
</tr>
</thead>
<tbody>
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<td>Normal:</td>
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<td>93 94 95 95 97 104</td>
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<td>82 83 80 82 80 81</td>
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<td>81 78 78 77 76 73</td>
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<tr>
<td>6</td>
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<td>54 54 14 13 14 13</td>
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<tr>
<td>7</td>
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<td>114 108 106 106 108 100</td>
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<tr>
<td>8</td>
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<td>49 46 48 46 47 48</td>
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<tr>
<td>9</td>
<td>3-43 3-42 3-42 3-39 3-40 3-40</td>
<td>67 67 67 67 67 67</td>
</tr>
</tbody>
</table>

**Table III Values of the gastric emptying coefficient (GEC), half emptying time (t₅₀), and lag phase (t₅₀) derived from mathematical curve fitting when taken into account three, six, nine, 12, 15, and 30 minute intervals sampling during the first 90 minutes of the breath test.**
We conclude that the *C labelled octanoic breath test is useful for measuring the gastric emptying rate of solids and is sensitive enough to detect pharmacological effects on gastric motor activity.

Pharmacological modulation of gastric emptying rate of solids as measured by the carbon labelled octanoic acid breath test: influence of erythromycin and propantheline.
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doi: 10.1136/gut.35.3.333

This slim book is written primarily for trainees in endoscopy to 'fill some of the gaps found in all training programmes'. In this, it undoubtedly succeeds though whether it will appeal to the wider audience hoped for by the author is in doubt. John Baillie's friendly, avant-garde style is one that the reader will be able to read for the most part, although wordy at times. The general layout is very similar to that of the major competitor in the field, Cotton and Williams. There are sections on endoscopes, sedation, the ASGE training guidelines, and teaching aids as well as chapters on gastroscopy and basic procedures, colonoscopy and, the best of all the procedure related sections, endoscopic retrograde cholangiopancreatography. There are helpful hints in many areas, written with humour and obviously much experience of the problems encountered by trainees. Some of them would be of help also to the more experienced trainee.

Trainees at varying stages of maturity to whom I have shown the book commented that the initial section seems suitable for those who have never seen an endoscope or an endoscopy unit but, thereafter, rapidly becomes redundant. This is perhaps inevitable in a book that intends to be comprehensive for beginners. Similar comments were made about parts of the upper gastrointestinal section. The colonoscopy section describes techniques, such as entering the ileocaecal valve that I cannot make work in practice. The book is illustrated by rather obscure diagrams, which hinder rather than help. Sadly the whole enterprise is weakened by poor photographs, some of which were so dark in my copy as to be almost useless. The quality of the diagrams is also disappointing. Illustrations are an important part of any guide such as this and their poor quality is a serious problem. The major rival in this market – Cotton and Williams – has had the benefit of revision through previous editions and was preferred by all the trainees who had seen both. I am sure that John Baillie's book would improve in subsequent iterations, and I hope that it will sell enough in the face of the competition to justify a second go.

P D FAIRCLOUGH


This is a timely contribution to a rapidly developing field – indeed, the field in many areas has already left some of the chapters looking rather elderly. The book begins with detailed reviews of the neuromodulation of gastrointestinal immune and inflammatory responses and the immune modulation of epithelial function and of motor activity. The function of neutrophils and mast cells in an inflammatory response is well covered. Lymphocyte and macrophage functions and their control are not discussed as such but they are covered to a degree by an excellent review on cytokines – it is inevitable that at least three more interleukins have been described since it was written. The reviews of eicosanoids, nitric oxide, and platelet activation factor are good. Perhaps the only slight disappointment was the final chapter on the effects of glucocorticoids on gastrointestinal inflammation as it fails to go beyond rather standard information on the effect of these drugs on the release of mediators and cytokine and on an inflammatory response in general. The fascinating events at molecular level that lead to these effects are not discussed at all.

This book is not for the casual reader. It is a gold mine of information and the detailed referencing will be invaluable to the clinical investigator. Some of the chapters are hard going, largely because of a failure to write elegant English. My other criticism is that virtually every cell, protein, mediator or substance is abbreviated ab initio. A list of abbreviations (formulated by the mine of information) is given at the back but I looked through the book twice before finding it – at least there was suspense before finding what a FLAP was! Nevertheless, the book is well produced, well illustrated with line diagrams and experimental data, and provides excellent in depth reviews. My review copy is likely to disappear rapidly into the briefcases of eager research fellows.

P D JEWELL

*S-lipoxygenase activating protein.


These volumes represent a magnificent achievement and follow in the tradition set by its classic predecessor written by Professor John Goligher. It should not be regarded as the next edition of a previous text, even if it uses the same title, but an excellent new creation by Michael Keighley and Norman Williams.

Coloproctology is now emerging as a specialty, a nomenclature, and basic science, and the question has to be asked whether one or two authors can hope to cover all the subject matter. While the authors have covered much of the ground themselves they have assembled a small team of appropriate experts to assist them and so recognise the difficulty. On this occasion the experts cover other relevant disciplines such as genitourinary medicine, urology, gynaecology, colorectal surgery, and paediatrics. In a subsequent editions physicians, radiologists, clinical geneticists, and histopathologists will probably be required as the text will inevitably need to cover the surgically driven specialty as a whole rather than be devoted to surgical aspects only. Such recruitment will strengthen the weaker areas.

These general comments must not detract from the immense worth of these two volumes (they weigh 16 lb!). Not only are they well researched and referenced but they are also pleasingly written with good illustrations and detailed index. Of particular value are the chapters on functional problems and the surgical techniques for inflammatory bowel disease. The postscript on laparoscopic techniques is also excellent with its cautionary critique.

There is no doubt that these volumes will be used by many in this country and overseas and greatly assist in the promotion of coloproctology as a specialty. The authors deserve congratulations and it is to be hoped that they will be rewarded in its sales. They have laid an excellent foundation for the future.

J P S THOMSON

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NOTES

European venture

The North of England Gastroenterology Society has created a European Venture Fund through donations from industry to support younger members presenting original work at European meetings. Three travelling Fellowships were awarded in 1993 to Dr Mark Cotterill of Leigh Infirmary, Dr Michael Wright of the Royal Liverpool Hospital, and Miss Tasmin Greenwell of the Northern General Hospital. Their work was well received and stimulated much discussion. The Society plans to continue to support its younger members in this way.

Corrections

An error occurred in this paper by Dr Bart Maes et al (Gut 1994; 35: 335–7). The symbols in Figure 2 should have been e = after erythromycin, r = normal, A = after propantheline.

An editorial error occurred in this paper by Dr Bjorn Ostendorst et al (Gut 1994; 35: 382–70). The fourteenth line in the abstract should have read peripheral blood lymphocytes (not lamina propria lymphocytes).