Gut 1998;**43** (suppl 3):S28–S30

^{13}C octanoic acid breath test

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Although scintigraphy, a non-invasive procedure, is usually considered to be the reference technique for measuring gastric emptying in humans,[1] several drawbacks limit its application in routine practice. Expensive equipment is required and access to a nuclear medicine department, and the use of radioactive isotopes (generally ^{99m}Tc and ^{111}In) can produce low but significant irradiation.[2] It is difficult to repeat the technique at frequent intervals or to use it with certain patients such as children or pregnant women. However, these disadvantages are not involved when stable isotopes are used. In 1993, Ghoos *et al*[3] were the first to report a novel technique based on the use of ^{13}C octanoic acid, a medium chain fatty acid which is rapidly absorbed in the duodenum and metabolised in the liver.[4 5] Following oxidation, the resulting $^{13}CO_2$ is excreted into breath at a level which can easily be detected and measured by isotope ratio mass spectrometry.[6] After validation of the ^{13}C octanoic breath test in healthy subjects, the same authors developed several applications, including pathophysiological and pharmacological studies.[7–12] However, the test has not been validated on a large scale by other groups. Initial work of Choi *et al* was less promising,[13] but a recent report from the same team did find a statistically significant correlation between scintigraphy and breath test.[14]

The purpose of the international multicentric study reported in abstract 1 was twofold: firstly, to validate the accuracy and reproducibility of the test on a large scale by reference to gastric scintigraphy, regarded as the gold standard; and secondly, to define the reference values for clinical, pharmacological, and pathophysiological studies. To facilitate comparison with the Ghoos study, the mathematical model developed by their group was used,[3 15] but applied to different European countries including France, Italy, and Germany. Scintigraphic gastric emptying curves were calculated and fitted using a power exponential function (Weibell model) for the solid curves.[16] Results of solid gastric emptying measurements were expressed as half emptying time ($t_{1/2s}$) as previously reported by Lartigue *et al*.[17]

In abstract 2 a comparison was made of gastric emptying rates with and without an overnight fast and the conclusion was drawn that due to the lack of an apparent circadian rhythm, gastric emptying studies could be done at different times of day.

The application of the ^{13}C octanoic acid breath test to study gastric emptying in the paediatric population is described in abstract 3. The non-invasive nature of the test is ideal for this age group, but further standardisation of test meals and validation of methodology is required.

Abstract 4 describes a novel measurement of gastric emptying using ^{2}H octanoic acid. Deuterium enters the body water pool after oxidation of the substrate and is then slowly eliminated. This method has potential for measuring gastric emptying in addition to another event by a conventional ^{13}C breath test, such as fat digestion or oro-caecal transit time.

This work has been supported by a BIOMED project, by a grant from the "Société Nationale Française de Gastro Enterologie" and from the Délégation à la recherche clinique du CHU de Nantes. The authors thank the participants of their workshops for helpful discussions.

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(1) Measurement of gastric emptying of solids by ^{13}C octanoic acid breath test: a validation and reproducibility study

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Background and aims: The ^{13}C octanoic breath test has recently been proposed as an alternative to scintigraphy for the study of gastric emptying of solids, although no large scale validation study has been conducted. Moreover, the reliability of this technique has been questioned, notably for the metabolism of ^{13}C octanoic. The purpose of the European multicentric study reported here was to validate the accuracy and reproducibility of the test as compared with gastric scintigraphy and to define the reference values. **Methods**: Sixty nine healthy subjects (40 men, 29 women; mean age 30 years, range 21–61) were studied at least once by the ^{13}C octanoic breath test (OBT). In 34 healthy subjects, gastric emptying was simultaneously measured by gastric scintigraphy, and the ^{13}C (OBT) was then repeated in 18 of these cases. Fifty four patients (30 men, 24 women; mean age 46 years, range 13–74) were studied according to the same procedure, including a simultaneous breath test and scintigraphy. Reasons for referral were non-ulcer dyspepsia (29 cases), gastro-oesophageal reflux disease (15 cases), post-surgical dyspepsia (seven cases), and diabetes mellitus (three cases). The test meal consisted of one scrambled egg, 50 g of ham, 10 g of butter, two slices of toast, 100 ml of orange juice, and 100 ml of water. For the breath test, egg yolk was doped with 91 mg of ^{13}C octanoic acid (Euriso-top, Saint-Aubin, France). For scintigraphy, egg whites were doped with 1.5 mCi ^{99m}Tc-colloid (TCK1 Cis-Bio). The yolk and egg whites were cooked separately. Total energy intake was 1354 kJ, and nutrient composition was 26 g carbohydrates (32%), 16 g fat (44%), and 19 g protein (24%). Scans and breath samples were obtained every 15 minutes for four hours and measurements of ^{13}C enrichment in breath were made using a gas chromatograph isotope ratio mass spectrometer (Delta S; Finnigan Matt, Bremen, Germany; ABCA, Europa Scientific, Crewe, UK). Results were expressed as the half time for gastric emptying. The scintigraphic half emptying times ($t_{1/2s}$) were derived from the power exponential formula of Siegel *et al*. The $^{13}CO_2$ excretion curves were analysed according to the formulas of Ghoos *et al* and the half emptying times ($t_{1/2b}$) were calculated. **Results**: The correlation between breath test and scintigraphic values was highly significant (r=0.744, p<0.001). The concordance of results of scintigraphy and breath test was good (Bland and Altman method). The reproducibility of the breath test was also good (CVinter=24%, CVintra=15%). The median, 90th, and 95th centiles for the breath test were respectively 89, 120, and 138 minutes. As compared with scintigraphy, breath test detected an abnormal gastric emptying with 67% sensitivity and 80% specificity. **Conclusion**: These results further validate the use of breath test as an accurate measurement of gastric emptying. Its excellent reproducibility makes it a method of choice for pharmacological studies, but its sensitivity, at least when scintigraphy is considered the gold standard, remains open to further investigations.

(2) Meal-to-meal variability of gastric emptying of solids in man

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Background: Gastric emptying studies in man are usually performed after an overnight fast. There is little information, however, about the variation of gastric emptying rate of meals on different periods of the same day. **Aim**: The aim of the present study was to investigate whether a standardised test meal is emptied from the stomach in the same way when ingested at various moments of the same day. **Methods**: After an overnight fast, nine healthy male volunteers were examined using the ^{13}C octanoic acid breath test. None of them was taking medication, nor had a medical or surgical history of gastrointestinal disease. The test meal consisted of one egg, doped with 91 mg of ^{13}C octanoic acid, two slices of white bread, and 150 ml of water. A second identical test meal was ingested four hours after the first test meal. Breath samples were taken before ingestion of the meal and at regular intervals thereafter over eight hours, and analysed for $^{13}CO_2$ concentration by isotope ratio mass spectrometry. Using non-linear regression methods, the $^{13}CO_2$ excretion curves were fitted to calculate three gastric emptying values—that is, the gastric emptying coefficient (GEC), the half emptying time ($t_{1/2}$), and the lag phase (tlag), as defined by Siegel *et al*. The results were compared using the Wilcoxon test. **Results**: The differences between the gastric emptying values of the meal ingested at breakfast and at noon were statistically not significant (GEC: p=0.54; $t_{1/2}$: p=0.17; tlag: p=0.35). **Conclusion**: There is no difference in gastric emptying rate of solids in man of identical meals ingested after an overnight fast and at noon of the same day. Because of the lack of an apparent circadian rhythm, gastric emptying studies can be done at different moments of the day. It has to be noted, however, that meal-to-meal variability is as equally large as day-to-day variability of solid gastric emptying rates.

(3) Measuring gastric emptying with the ^{13}C octanoic acid breath test in infants and children

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Impaired gastric emptying causes significant morbidity in the paediatric population with different clinical presentations in various age groups. In preterm neonates it remains a challenge to determine the optimal time to institute enteral feedings because their intestinal motility, and as a part thereof their gastric emptying, is incompletely developed. Older children and adolescents present with symptoms of dyspepsia and vomiting that are comparable with dyspepsia in adults. Thus, a better understanding of gastric emptying in children is needed to clarify developmental aspects and control mechanisms as well as pathophysiology.

The methods to study gastric emptying that are used in adults are not readily applicable to paediatrics. Most gastric emptying studies that were done in infants involve invasive methodology such as various marker dilution techniques and antroduodenal manometry. The results of non-invasive techniques such as applied potential tomography and ultrasound are difficult to quantify. Reported values for gastric emptying vary widely depending on the age and clinical status of the subjects and on test meal and methods.

The ^{13}C octanoic acid breath test offers a reliable and reproducible alternative to study gastric emptying safely in all age groups. Specific aspects of the methodology, such as test meal and sampling methods, require standardisation for various age groups. Also the test needs to be validated against other methods, especially because of the potential gastric absorption of medium chain triglycerides (octanoic acid) in young infants.

We have adapted the methodology of the ^{13}C octanoic acid breath test to study preterm infants, neonates, and toddlers. In a study group of stable infants with bodyweight around 2 kg, the gastric emptying half time ranged from 17 to 100 minutes, with a mean of 56 minutes and the estimated gastric volume emptied/body surface area/hour ranged from 8.4 to 39.2 ml/0.1 $m^2 \times h$, with a mean of 19.1 ml/0.1 $m^2 \times h$. Validation studies against the dye dilution technique in a group of preterm infants clearly showed a similar trend in the half emptying times obtained by both methods (regression coefficient 0.495). Moreover, the results obtained with dye dilution suggested a shorter emptying time, as opposed to what could be speculated on the basis of possible gastric absorption of octanoic acid.

Various possibilities have been suggested as a test meal for toddlers. We found that toddlers will not accept the adult test meal consisting of scrambled eggs nor accept pancakes. A test meal consisting of bread with ^{13}C octanoic acid containing chocolate spread is welcomed by this age group and is easily prepared because individual portions of labelled chocolate spread can be stored.

It can be expected that the application of the non-invasive ^{13}C octanoic acid breath test to study gastric emptying in the paediatric population will enhance our understanding of the development and control mechanisms of gastrointestinal function and that the medical care of preterm infants, especially their nutritional support, will continue to improve. It is of major importance that standardised methodology be used in clinical research to allow for results to be compared.

(4) Measurement of gastric emptying by simultaneous dosing with ^{13}C and ^2H octanoic acid

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The purpose of this study was to compare measurements of gastric emptying following simultaneous administration of ^{13}C octanoic acid and ^2H octanoic acid. After oxidation of the substrate, deuterium rapidly enters the single body water pool from where it is slowly eliminated according to well established kinetics. This removes the complexity of multiple pool bicarbonate kinetics which are associated with the metabolism of the carbon labelled substrate. **Methods**: A healthy adult volunteer ingested the labelled octanoic acid on three separate occasions. The test meal consisted of one egg labelled with 91 mg of [1-^{13}C]octanoic acid and 455 mg of [$^2H_{15}$]octanoic acid, two slices of white bread (as toast), 7 g of butter, and 150 ml of water (total calorific intake 1237 kJ). The labelled material was mixed with the egg yolk and cooked separately from the white to ensure firm retention of the label in the acidic environment. Breath and saliva samples were collected immediately before the test meal and at 15 or 30 minute intervals thereafter for a six hour period. Additional samples of saliva only were collected at nine hours, 12 hours, 14 hours, and then every 24 hours for four days. Two weeks after the third test, total body water was measured from urine collected from the same subject following a dose of $H_2^{18}O$ (0.17 g/kg body weight). Measurements of ^{13}C, ^2H, and ^{18}O enrichments were made on VG Sira 10 isotope ratio mass spectrometers. **Results**: ^2H data were fitted to a model comprising a single compartment representing the total body pool with first order elimination kinetics. For ^{13}C the model is complicated by a second bidirectionally exchanging compartment, approximating to established bicarbonate kinetics. In both cases the rate of gastric emptying was modelled by an asymmetric triangular function which is fully characterised by the variables: t_1, the time of maximum rate of gastric emptying, and t_2 the time of its completion. Table 1 shows the derived values of these variables from least squares fitting of experimental data to the model. It will be seen that the characteristics of the derived input function are largely independent of the isotope used. Comparison of distribution volumes obtained from the ^2H data and the subsequent ^{18}O measurements indicated that, as expected, the octanoic acid is completely absorbed and oxidised. **Conclusions**: We have used data from two isotopes to derive an improved model for the octanoic acid gastric emptying test and subsequent metabolism. This method has potential for the measurement of gastric emptying by use of the deuterium label, in addition to another event by a conventional ^{13}C breath test, such as fat digestion or oro-caecal transit time.

Abstract 4, Table 1 Derived values of variables from least square fitting of experimental data to the model

Test	*Isotope*	*t_1 (hour)*	*t_2 (hour)*
1	^2H	0.01	3.77
1	^{13}C	0.51	3.50
2	^2H	0.10	4.06
2	^{13}C	0.60	4.18
3	^2H	1.34	2.81
3	^{13}C	1.48	2.80